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Comparative Effectiveness and Safety of Pharmacological Therapies for the Management of Crohn's Disease

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Prepared by:
[Redacted]

Investigators
[Redacted]

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Key Informants

[Redacted]

Technical Expert Panel

[Redacted]

AHRQ Contacts

Christine Chang, MD, MPH
Task Order Officer
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality
Rockville, MD

Structured Abstract

Objectives: The purpose of this review was to compare the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of moderate-to-severe Crohn's disease.

Data sources: We searched MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials from inception through June 2010.

Review methods: Two reviewers independently reviewed titles, abstracts and articles, and included English-language articles that reported on induction or maintenance of remission in placebo-controlled or head-to-head randomized controlled trials (RCTs). We also included observational studies with a comparison group if they reported on the safety of treatment. Two reviewers serially extracted study information using standardized forms and independently assessed study quality. Effectiveness was measured by induction and maintenance of remission. Remission was defined using the Crohn's disease activity index, mucosal healing, the absence of Crohn's disease hospitalizations or surgeries, reduction of steroids, fistula healing, and patient-reported outcomes. The safety outcomes of interest were mortality, occurrence of lymphomas and other cancers, infections, infusion and injection-site reactions, bone fractures, and growth in children.

Results: We included 140 studies involving 137,398 patients. For adults, we did not identify a single medication or class of medications that was most effective at inducing and maintaining remission, while producing the highest quality of life and the best safety profile. There was high strength of evidence that specific biologics were more effective than placebo at inducing or maintaining remission at some timepoints through 1 year. Adalimumab, certolizumab pegol, and natalizumab were effective at inducing remission. Adalimumab, certolizumab pegol, and infliximab were effective at maintaining remission. Moderate and high evidence existed for the biologics at other time points and measures of efficacy including mucosal healing, fistula response, decreasing steroids, hospitalizations and surgeries, and increasing beneficial patient-reported outcomes. There was also moderate strength of evidence that budesonide was more effective than placebo or mesalamine at inducing and maintaining remission up to 1 year. For children, the strength of evidence was low or insufficient to support the effectiveness of any medication in inducing or maintaining remission. No pediatric study reported on a serious adverse event such as mortality, progressive multifocal leukoencephalopathy, lymphoma, or other cancers.

Conclusions: Strong evidence exists for the short-term efficacy of adalimumab, certolizumab pegol, infliximab, natalizumab, and budesonide in decreasing disease activity in adults with Crohn's disease, but only weak or insufficient evidence exists on the safety and long-term effectiveness of treatment options.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Description of Disease 1
Interventions to Treat Crohn's Disease 1
Current Controversies in the Treatment of Crohn's Disease 2
Treatment Guidelines and Meta-Analyses on the Management of Crohn's Disease 2
Previous Systematic Reviews 2
Scope of the Evidence Report and Key Questions 2

Methods 7
Topic Development 7
Search Strategy 7
Study Selection 8
Data Abstraction 9
Quality Assessment 10
Applicability 11
Data Analysis and Synthesis 11
Data Entry and Quality Control 12
Rating the Body of Evidence 12

Results 14
Search Results 14
Adult Results 15
KQ1: Comparative Effectiveness of Therapies to Induce Remission 15
Key Points 15
Disease Activity Indexes – Ustekinumab and Natalizumab 15
Disease Activity Indexes – TNF-Alpha Inhibitors 15
Disease Activity Indexes – Thiopurines 16
Disease Activity Indexes – Methotrexate 17
Disease Activity Indexes – Corticosteroids 17
Disease Activity Indexes – Aminosalicylates 18
Mucosal Healing 18
Hospitalization 19
Surgeries 19
Reduction of Steroids 19
Fistula Response 19
Patient-Reported Outcomes 20
Ustekinumab 25
Study Design 25
Population Characteristics 25
Disease Activity Indexes 25
Natalizumab 28

Study Design 28
Population Characteristics 28
Disease Activity Indexes 29
TNF-Alpha Inhibitors 32
Study Design 32
Population Characteristics 32
Disease Activity Indexes 32
Thiopurines 40
Study Design 40
Population Characteristics 41
Disease Activity Indexes 41
Methotrexate 45
Study Design 45
Population Characteristics 45
Disease Activity Indexes 46
Corticosteroids 46
Study Design 47
Population Characteristics 47
Disease Activity Indexes 48
Aminosalicylates 54
Study Design 54
Population Characteristics 54
Disease Activity Indexes 55
Indirect Comparisons 57
Mucosal Healing 57
Reduction of Steroids 58
Fistula Response 58
Patient-Reported Outcomes 59
Quality Assessment 63
Applicability 63
Populations 63
Intervention 64
Comparisons 64
Outcomes 64
Timing 65
Setting 65
Other – Conflict of Interest 65
KQ2: Comparative Effectiveness of Therapies to Maintain Remission 66
Key Points 66
Disease Activity Indexes – Ustekinumab and Natalizumab 66
Disease Activity Indexes – TNF-Alpha Inhibitors 66
Disease Activity Indexes – Thiopurines 67
Disease Activity Indexes – Methotrexate 67
Disease Activity Indexes – Corticosteroids 67
Disease Activity Indexes – Aminosalicylates 68
Mucosal Healing 68

Hospitalizations....69
Surgeries....69
Reduction of Steroids....69
Fistula Response....69
Patient-Reported Outcomes....70
Ustekinumab....73
Natalizumab....73
Study Design and Population Characteristics....73
Disease Activity Indexes....73
TNF-Alpha Inhibitors....74
Study Design....74
Population Characteristics....75
Disease Activity Indexes....75
Thiopurines....82
Study Design....82
Population Characteristics....82
Disease Activity Indexes....83
Methotrexate....84
Study Design....84
Population Characteristics....84
Disease Activity Indexes....85
Corticosteroids....85
Study Design....85
Population Characteristics....86
Disease Activity Indexes....86
Aminosalicylates....93
Study Design....93
Population Characteristics....93
Disease Activity Indexes....94
Mucosal Healing....101
Hospitalizations....101
Surgeries....102
Reduction of Steroids....103
Fistula Response....103
Patient-Reported Outcomes....104
Quality Assessment....108
Applicability....108
Populations....108
Intervention....109
Comparisons....109
Outcomes....109
Timing....110
KQ3: Comparative Safety of Therapies....110
Key Points....110
Mortality....110
Hepatosplenic T-cell Lymphoma....111

Lymphoma 111
Cervical Cancer....111
All Cancers....111
Infections....112
Tuberculosis....112
Infusion- and Injection-Site Reactions....112
Bone Fractures 113
Study Design and Population Characteristics 116
Mortality 117
Biologics 117
Immunomodulators 123
Corticosteroids 126
Aminosalicylates....128
Studies Evaluating Patients with Inflammatory Bowel Disease....130
Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease 130
Progressive Multifocal Leukoencephalopathy (PML)....130
Lymphoma 131
Biologics 131
Immunomodulators 135
Corticosteroids 137
Studies Evaluating Patients with Inflammatory Bowel Disease....139
Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease 139
Hepatosplenic T-Cell Lymphoma....139
Cervical Cancer....141
Studies Evaluating Patients with Inflammatory Bowel Disease....141
Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease 141
Other Cancers....141
Biologics 141
Immunomodulators 146
Corticosteroids 149
Aminosalicylates....151
Studies Evaluating Patients with Inflammatory Bowel Disease....151
Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease 151
Case-Control Studies Designed to Examine Specific Cancers 152
Infections....154
Ustekinumab and Natalizumab 154
TNF-Alpha Inhibitors 158
Immunomodulators 170
Corticosteroids 176
Aminosalicylates....180
Studies Evaluating Patients with Inflammatory Bowel Disease....182
Case-Control Studies Designed to Examine Specific Infections....182

Tuberculosis 184
Infusion- and Injection-Site Reactions 186
Ustekinumab and Natalizumab 187
TNF-Alpha Inhibitors 189
Immunomodulators 195
Studies Evaluating Patients with Inflammatory Bowel Disease 196
Bone Fractures 196
Studies Evaluating Patients with Inflammatory Bowel Disease 198
Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease 198
Study Quality 198
Applicability 199
KQ4: Comparative Effectiveness of Treatmetns to Prevent Post-Operative Recurrence 199
Studies Included 199
Study Design and Population Characteristics 199
Randomized Controlled Trial 199
Observational Study 199
Study Results 200
Randomized Controlled Trial 200
Observational Study 200
Study Quality and Limitations 200
Randomized Controlled Trial 200
Observational Study 201
Applicability 201
Pediatric Results 201
KQ1: Comparative Effectiveness of Therapies to Induce Remission 201
Key Points 201
Study Design and Population Characteristics 204
Disease Activity Indexes 204
Mucosal Healing 205
Hospitalizations 205
Surgeries 206
Reduction of Steroids 206
Fistula Response 206
Patient-Reported Outcomes 206
Study Quality 206
Applicability 207
KQ2: Comparative Effectiveness of Therapies to Maintain Remission 207
Key Points 207
Study Design and Population Characteristics 210
Disease Activity Indexes 210
Mucosal Healing 210
Hospitalizations 210
Surgeries 210
Reduction of Steroids 211

Fistula Response 211
Patient-Reported Outcomes 211
Study Quality 211
Applicability 211
KQ3: Comparative Safety of Therapies.....211
Key Points.....211
Study Design and Population Characteristics 215
Mortality 215
Cancer 216
Serious Infections.....216
Tuberculosis.....216
Other Infections 216
Infusion- and Injection-site Reactions 217
Bone Fractures 217
Height Change 217
Weight Change.....219
Study Quality 220
Applicability 221
Comparative Effectiveness of Therapies in Subgroups 221
Key Points.....221
KQ1 – Induction of Remission 221
Baseline CRP 221
Baseline Corticosteroid Use.....222
Baseline Immunomodulator Use.....222
Prior TNF-Alpha Inhibitor Exposure.....222
KQ2 – Maintenance of Remission.....222

Discussion.....223
Key Findings and Implications 223
Summary of Key Findings for Adults.....223
Summary of Key Findings for Pediatrics.....223
Comparison to Other Systematic Reviews 224
Limitations 224
Future Research Needs 226

Abbreviations 229
References.....230

Tables

Table A. List of medications used for the treatment of Crohn's disease.....ES-2
Table B. List of outcomes considered for each Key Question concerning the comparative effectiveness and safety of medications for the treatment of Crohn's disease ES-5
Table C. Summary of the strength of evidence on the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of

inducing a remission as measured by a disease activity index at various time points ES-15
Table D. Summary of the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of maintaining remission as measured by a disease activity index at various time points ES-20
Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low ES-23
Table 1. List of medications used for treatment of Crohn's disease 4
Table 2. List of outcomes considered for each key question on the comparative effectiveness and safety of medications for treatment of Crohn's disease 6
Table 3. Inclusion and exclusion criteria for identifying eligible studies 9
Table 4. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* 22
Table 5. Randomized controlled trials comparing the effectiveness of ustekinumab with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease 27
Table 6. Randomized controlled trials comparing the effectiveness of natalizumab with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease 30
Table 7. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of inducing remission or response at week 2 in patients with Crohn's disease 34
Table 8. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of inducing remission or response at week 8 to 12 in patients with Crohn's disease 37
Table 9. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of inducing remission or response at week 24 to 26 in patients with Crohn's disease 39
Table 10. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease 44
Table 11. Randomized controlled trials comparing the effectiveness of methotrexate with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease 46
Table 12. Randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease 50
Table 13. Randomized controlled trials comparing the effectiveness of aminosalicylates with placebo in terms of inducing remission or response in patients with Crohn's disease 56
Table 14. Results from one randomized controlled trial comparing the effectiveness of azathioprine, infliximab, and a combination of infliximab and azathioprine in terms of Inflammatory Bowel Disease Questionnaire† results in patients with Crohn's disease 62

Table 15. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* 71
Table 16. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of maintaining remission or response at week 16 to 18 in patients with Crohn's disease 76
Table 17. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of maintaining remission or response at week 28 in patients with Crohn's disease 79
Table 18. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of maintaining remission or response at week 52 in patients with Crohn's disease 81
Table 19. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment in maintaining remission in patients with Crohn's disease 84
Table 20. Relapse* rates reported in randomized controlled trials comparing the effectiveness of methotrexate with placebo in patients with Crohn's disease 85
Table 21. Relapse rates reported in randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in patients with Crohn's disease 89
Table 22. Relapse rates reported in randomized controlled trials comparing the effectiveness of aminosalicylates with placebo in patients with Crohn's disease 95
Table 23. Randomized controlled trials comparing the effectiveness of infliximab with placebo in terms of patient-reported outcomes in patients with Crohn's disease 107
Table 24. Key findings and strength of the available evidence comparing pharmacologic therapies for the management of Crohn's disease in terms of safety-related outcomes 114
Table 25. Summary of reported mortality results in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease 118
Table 26. Summary of randomized controlled trials that did not report on mortality when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease* 118
Table 27. Summary of reported mortality results in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 123
Table 28. Summary of reported mortality results in randomized controlled trials comparing prednisone alone or in combination with placebo or another treatment in patients with Crohn's disease 126
Table 29. Summary of reported mortality results in randomized controlled trials and observational studies comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease 129

Table 30. Summary of lymphoma risk in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*.....132
Table 31. Summary of risk of lymphoma in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease.....138
Table 32. Demographic and survival characteristics of patients with Crohn's disease who developed hepatosplenic T-cell lymphoma.....140
Table 33. Medications used prior to diagnosis of hepatosplenic T-cell lymphoma in 37 unique patients with Crohn's disease.....140
Table 34. Summary of the risk of other cancers in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease* 142
Table 35. Summary of the risk of other cancers in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease* 147
Table 36. Summary of the risk of other cancers in randomized controlled trials and observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 150
Table 37. Summary of the risk of other cancers in a randomized controlled trial comparing an aminosalicylate with placebo in patients with Crohn's disease.....151
Table 38. Summary of the randomized controlled trials reporting no opportunistic infections when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease.....154
Table 39. Summary of other infections reported in observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease 163
Table 40. Summary of the risk of serious infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 171
Table 41. Summary of the risk of other infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease 171
Table 42. Summary of the risk of serious infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 177
Table 43. Summary of the risk of other infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease 177
Table 44. Summary of reported rates of tuberculosis in randomized controlled trials* comparing the safety of therapies for the management of Crohn's disease.....185
Table 45. Summary of the risk of bone fracture in studies comparing the safety of therapies for the management of Crohn's disease 197

Table 46. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission in children 203
Table 47. Summary of absolute disease activity scores in studies comparing the effectiveness of medications in inducing remission in children with Crohn's disease 205
Table 48. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease to maintain remission 209
Table 49. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of safety 214
Table 50. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of serious infections....216
Table 51. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of other infections....217
Table 52. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of height change 219
Table 53. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of weight change....220

Figures

Figure A. Treatment diagram....ES-3
Figure 1. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease 5
Figure 2. Summary of the literature search....14
Figure 3. Pooled relative risk of inducing remission* of Crohn's disease at weeks 2-4 comparing natalizumab with placebo 31
Figure 4. Pooled relative risk of inducing remission* of Crohn's disease at week 2 comparing a TNF-alpha inhibitor with placebo....35
Figure 5. Pooled relative risk of inducing remission* of Crohn's disease at week 8 comparing budesonide with another corticosteroid 53
Figure 6. Pooled relative risk of maintaining remission* of Crohn's disease at week 16 to 18 comparing a TNF-alpha inhibitor with placebo 77
Figure 7. Pooled relative risk of maintaining remission* of Crohn's disease at week 28 comparing a TNF-alpha inhibitor with placebo 80
Figure 8. Pooled relative risk of a relapse* of Crohn's disease at week 52 comparing budesonide with placebo....92
Figure 9. Pooled relative risk of a relapse* of Crohn's disease at weeks 15-19 comparing an aminosalicylate with placebo 98
Figure 10. Pooled relative risk of a relapse* of Crohn's disease at week 26 comparing an aminosalicylate with placebo 99
Figure 11. Pooled relative risk of a relapse* of Crohn's disease at weeks 48-52 comparing an aminosalicylate with placebo 100

Figure 12. Summary of Peto odds ratios of mortality among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease....119
Figure 13. Summary of Peto odds ratios of mortality among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease....124
Figure 14. Summary of Peto odds ratios of mortality among observational studies comparing a corticosteroid alone or in combination with another treatment in patients with Crohn's disease....127
Figure 15. Summary of Peto odds ratios of lymphoma among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease....133
Figure 16. Summary of Peto odds ratios of lymphoma among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease....136
Figure 17. Summary of Peto odds ratios of cancer risk among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease....143
Figure 18. Summary of Peto odds ratios of cancer among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease....148
Figure 19. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease....155
Figure 20. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease....156
Figure 21. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease....159
Figure 22. Summary of Peto odds ratios of serious infections among observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease....160
Figure 23. Summary of Peto odds ratios of opportunistic infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease....161
Figure 24. Summary of Peto odds ratios of other infections among randomized controlled trial comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease....162
Figure 25. Summary of Peto odds ratios of other infections among randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease....172
Figure 26. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease....178

Figure 27. Summary of Peto odds ratios of other infections in a randomized controlled trial comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease.....181
Figure 28. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing a biologic alone or in combination with another treatment in patients with Crohn's disease 188
Figure 29. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease 190
Figure 30. Summary of Peto odds ratios of infusion- and injection-site reactions among observational studies comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease 191

Appendixes

Appendix A: Detailed Electronic Database Search Strategies
Appendix B: Forms
Appendix C: List of Excluded Articles
Appendix D: Evidence Tables
Appendix E: Additional Meta-analyses
Appendix F: Summary of Studies Comparing the Safety of Pharmacologic Therapies Among Patients with Inflammatory Bowel Disease
Appendix G: Subgroup Analysis Table

Comparative Effectiveness and Safety of Pharmacologic Therapies for the Management of Crohn's Disease

Executive Summary

Background

The clinical management of Crohn's disease is complicated. Clinical practice guidelines for Crohn's disease recommend that clinicians take into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy. However, no universal treatment strategy exists for patients.[1] The lack of consensus about the best treatment strategy can result in confusion and frustration for the Crohn's disease patient as well as practitioners who treat Crohn's disease patients.

Description and Prevalence of the Disease

Crohn's disease is characterized by chronic inflammation that can occur anywhere in the gastrointestinal tract, but most often affects the small bowel and colon. Typical symptoms include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[2] Ten percent of Crohn's disease patients are children under the age of 17 years.[3]

Interventions to Treat Crohn's Disease

Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the natural history of the disease. Corticosteroids and 5-aminosalicylate acids such as sulfasalazine have been used since the middle of the last century to treat Crohn's disease. Immunomodulators (e.g., 6-mercaptopurine, azathioprine, and methotrexate) have been used for the treatment of Crohn's disease since the 1970s, although the use of these medications was not routine until the 1990s.[4] The first biologic tumor necrosis factor-alpha (TNF-alpha) inhibitor, infliximab, was approved by the Food and Drug Administration (FDA) for the treatment of Crohn's disease in adults in 1998. The FDA-approved TNF-alpha-inhibitor biologics also include adalimumab and certolizumab pegol.[1] Other biologic agents used for the treatment of Crohn's disease include natalizumab, which is FDA-approved for Crohn's disease in adults,[5] and ustekinumab, which is not FDA-approved for this indication (Table A).

Table A. List of medications used for the treatment of Crohn's disease

Class	Generic name	US trade name	Route	Half-life	Mechanism of Action	FDA approved for CD in adults	FDA approved for CD in children
Aminosalicylate	Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No
Aminosalicylate	Mesalamine	Asacol, Canasa, Pentasa, Lialda, Rowasa	Oral, rectal	2-15 hours	Inhibits reactions involving inosinic acid	No	No
Anti-metabolite	Azathioprine	Azasan; Imuran	Oral, intravenous	5- hours	Purine synthesis inhibitor	No	No
Anti-metabolite	Methotrexate	Methotrexate LPF	Intravenous, oral	3-15 hours	Works through adenosine receptor	No	No
Anti-metabolite	6-mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis and metabolism inhibitor	No	No
Biologic	Adalimumab	Humira	Subcutaneous	10-18 days	TNF-alpha inhibitor	Yes	No
Biologic	Infliximab	Remicade	Intravenous	9.8 days	TNF-alpha inhibitor	Yes	Yes
Biologic	Certolizumab pegol	Cimzia	Subcutaneous	~14 days	TNF-alpha inhibitor	Yes	No
Biologic	Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers	Yes	No
Biologic	Ustekinumab	Stelara	Subcutaneous	15-46 days	Interleukin-12 and interleukin-23 inhibitor	No	No
Corticosteroid	Prednisone prednisolone 6-methylpredisolone hydrocortisone budesonide	Cortef, Entocort	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm, where it upregulates anti-inflammatory genes	No	No

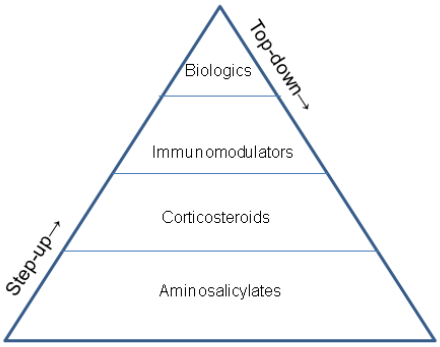
CD = Crohn's disease; FDA = Food and Drug Administration; TNF = tumor necrosis factor; US = United States

Current Uncertainties and Controversies in the Treatment of Crohn's Disease

The Institute of Medicine recently identified as one of its priorities for comparative effectiveness research the comparison of algorithms to treat Crohn's disease that introduce biologics at different time points in the disease course.[6] Some experts have considered the early use of immunomodulators and biologics ("top-down therapy"), rather than after the prolonged use of steroids ("step-up therapy"), with the expectation of better long-term outcomes. These experts have cautioned, however, that the long-term safety of these treatments, particularly when used in combination, remains unknown.[7 8] The use of immunomodulators and biologics from the onset of disease is frequently summarized in a disease treatment pyramid (Figure A).[9]

The treatment guidelines point to controversial areas in need of future research, including: treatments to achieve long-term remission, the benefits and harms of step-up versus top-down treatment strategies, and how to optimize the use of biologic agents, given that many patients' disease can be managed with non-biologic treatments.[1]

Figure A. Treatment diagram



Purpose of the Evidence Report

The purpose of this review is to compare the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of moderate-to-severe Crohn's disease. The specific key questions (KQ) of interest are:

KQ1: What is the comparative effectiveness of therapies alone or in combination used to <u>induce remission</u> in adults and children with moderate-to-severe Crohn's disease?

Remission is a decrease in or absence of Crohn's disease symptoms. Remission can be defined using the Crohn's disease activity index (CDAI), mucosal healing, the absence of Crohn's disease hospitalizations or surgeries, reduction of steroids, fistula healing, and patient-reported outcomes. We looked for data on remission rates at the following time points after randomization: (1) the first time point, (2) 2-4 weeks, (3) 8-12 weeks, (4) 12-16 weeks, (5) 22-30 weeks, (6) 48-54 weeks,

(7) 18-24 months, (8) the last pre-specified time point, and (9) last reported time point (Table B).

KQ2: What is the comparative effectiveness of therapies alone or in combination used to maintain remission in adults and children with moderate-to-severe Crohn's disease?

We looked for data on the maintenance of remission at the following time points after randomization: (1) the first time point, (2) 12-16 weeks, (3) 15-19 weeks, (4) 22-30 weeks, (5) 48-54 weeks, (6) 18-24 months, (7) the last pre-specified time point, and (8) the last reported time point.

KQ3: What is the comparative safety of therapies alone or in combination used in adults and children with moderate-to-severe Crohn's disease in terms of minimizing short- and long-term adverse effects?

The safety outcomes of interest were mortality, occurrence of lymphomas and/or other cancers, infections, infusion and injection-site reactions, bone fractures, and growth in children. We looked for data on these outcomes at the last reported time point.

KQ4: What is the comparative effectiveness of agents used to prevent post-operative recurrence in Crohn's disease as pertains to patient-reported outcomes?

The patient-reported outcomes of interest were: standard quality-of-life indices and specialty indices (Inflammatory Bowel Disease Questionnaire [IBDQ], Short Inflammatory Bowel Disease Questionnaire [SIBDQ]), and days of work or school missed. We looked for data on patient-reported outcomes at the following time points after randomization: (1) the first time point, (2) 12-16 weeks, (3) 48-54 weeks, (4) the last pre-specified time point, and (5) the last reported time point.

Table B. List of outcomes considered for each Key Question concerning the comparative effectiveness and safety of medications for the treatment of Crohn's disease

Key Question	Outcomes	Time points
KQ1	• Disease activity indexes (remission, response, CDAI, PCDAI, HBI, or other disease activity indexes) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (complete or partial fistula closure or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life indexes, IBDQ, days of work or school missed)	• First time point after randomization • 12 to 16 weeks after randomization • 48 to 54 weeks after randomization • Last pre-specified time point; and • Last reported time point
KQ2*	• Disease activity indexes (relapse, loss of response, CDAI, PCDAI, HBI, or other disease activity indexes) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (fistula recurrence or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life indexes, IBDQ, days of work or school missed)	• First time point after randomization • 12 to 16 weeks after randomization • 48 to 54 weeks after randomization • Last pre-specified time point; and • Last reported time point
KQ3	• Mortality • Lymphomas • Cervical cancer • Other cancers • Tuberculosis • Serious infections • Other infections • Infusion- and injection-site reactions • Bone fractures • Height and weight (for pediatric studies only)	• Last reported time point
KQ4	• Patient-reported outcomes (health-related quality of life indexes, IBDQ, days of work or school missed)	• First time point after randomization • 12 to 16 weeks after randomization • 48 to 54 weeks after randomization • Last pre-specified time point; and • Last reported time point

CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = Key Question; PCDAI = Pediatric Crohn's Disease Activity Index

KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for post-surgical patient-reported outcomes

Methods

Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of key informants to give input on the selection and refinement of the questions to be examined. In March 2010, we posted preliminary questions on the Agency for Healthcare Research and Quality (AHRQ) Web site for public comment. With the key informants, representatives of AHRQ, and public comments, we finalized the key questions listed above.

Search Strategy

We searched the following databases for primary studies from inception of this analysis through June 2010: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. We also reviewed the reference lists of each included article and relevant review articles. To assess the risk of two of the most serious and rare complications that may be associated with the treatment for Crohn's disease, hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we supplemented our primary search strategy by also searching for cases reported to the FDA's Adverse Event Reporting System (AERS).

Study Selection

Two reviewers independently reviewed titles and abstracts. Titles and abstracts were excluded when both reviewers agreed on exclusion. Differences regarding article inclusion were resolved through consensus adjudication. A third reviewer audited a random sample of abstract and article reviews to ensure consistency in the reviewing process. We included relevant English-language studies evaluating non-pregnant patients with moderate-to-severe Crohn's disease; for KQ3, we included a sensitivity analysis of studies that evaluated patients with inflammatory bowel disease, but did not report results separately for patients with Crohn's disease.

For KQ1 and KQ2 on induction and maintenance of remission, we included only randomized controlled trials (RCTs). Both placebo-controlled and head-to-head trials were eligible. We did not include RCTs that examined only the same medication administered at different time points or at different dosages. We did not include non-randomized trials. The outcomes of interest for KQ1 and KQ2 were chosen to represent important clinical and patient-centered outcomes.

For KQ3 (on safety), we included RCTs and observational studies. Specific safety outcomes were chosen on the basis of the severity of the outcome, impact on quality of life, and potential for safety to differ by medication class. Clinical outcomes were selected a priori for inclusion in the review. All RCTs that reported on safety-related outcomes were eligible. Observational studies were eligible if they reported: (1) clear comparison groups specified in the study aims or methods; (2) clear denominators (patients on groups of medications); and (3) clear numerators (patients who experienced the safety event of interest, according to group of medication). We also included studies

that reported an effect estimate or p-value for a safety outcome by medication use if they met criterion 1.

For KQ4, we focused on the comparative effectiveness of medications only in terms of patient-reported outcomes, because a rigorously conducted systematic review[10] recently assessed the other clinical outcomes associated with the use of medications to maintain remission after intestinal resection in patients with Crohn's disease.

Data Abstraction

For all articles, reviewers extracted information on general study characteristics, study participants, study eligibility criteria, interventions, outcome measures and their method of ascertainment, and the results of each outcome, including measures of variability. We abstracted information on subgroup analyses to understand how disease characteristics could modify the relationship between medications and remission, including baseline C-reactive protein or elevated inflammatory markers, medication history, concomitant use of medications during the trial, disease duration, disease location, and prior Crohn's disease-related surgery.

Quality Assessment

We used study quality assessment to help us understand differences in results between studies. For RCTs, the dual, independent review of article quality was based on the Cochrane Collaboration's Risk of Bias Tool.[11] For non-randomized observational studies, we selected items from the Downs and Black quality checklist.[12] Both quality assessment tools were supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13]

Applicability

We assessed the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings were typical of the treatment of individuals with Crohn's disease.

Data Synthesis and Meta-Analysis

We synthesized the evidence for children separately from adults for all Key Questions. For each Key Question, we created a set of detailed evidence tables containing the information abstracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least three studies) and studies were sufficiently homogenous with regard to study characteristics (population characteristics, intervention, comparison, outcome, and timing). For studies amenable to pooling for meta-analyses, we calculated pooled relative risks using a DerSimonian and Laird random effects model.[14] We looked for statistical heterogeneity between the studies in meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10; and (2) an I-squared statistic, with a value greater than 50 percent indicating substantial heterogeneity.[15] If

substantial statistical heterogeneity was found, we reconsidered the assumption of homogeneity with respect to the key study characteristics.

We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we conducted formal tests for publication bias using Begg's[16] and Eggers tests,[17] including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses were conducted using Intercooled STATA 9.2 (College Station, TX). When there were no head-to-head RCTs meeting the criteria for meta-analyses listed above, we conducted an indirect comparison on the odds ratio scale of the placebo-controlled meta-analyses using the common comparator placebo.[18 19]

When we were unable to pool studies for an outcome, we calculated and displayed risk ratios (RR) with 95% confidence intervals (CI) for the individual studies. For KQ1 and KQ2, we considered a difference to be clinically significant when there was a 10 percent absolute difference in the outcome between the groups compared, even when the difference was not statistically significant at a p-value less than 0.05. For the IBDQ (the most commonly employed outcome for patient-reported outcomes), we used an absolute difference in change from baseline of 17 points or greater.[20] In terms of adverse effects, when a study did not report an effect estimate, we calculated a Peto odds ratio if the combined number of events in each arm was greater than 5.[21 22] We also calculated incidence rate ratios for person-time data if the authors did not report an effect estimate or if the reported effect estimate appeared to contradict the reported events per person-time. We did not specify a standard for a clinically meaningful difference in the adverse events because the absolute rate was rare for most of the adverse events.

Rating the Body of Evidence

At the completion of our review, we graded the quantity, quality, and consistency of the evidence addressing the Key Questions by adapting an evidence-grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.[23] The evidence grade was based on the risk of bias, consistency, directness, and precision and was classified into four categories: high, moderate, low, and insufficient. If the evidence grade or direction of the effect differed at two time points of interest, we reported the evidence grade separately for each time point.

Results

Search Results

We identified 140 studies involving 137,398 patients who met our inclusion criteria for one or more of the Key Questions. Combining KQ1 and KQ2 yielded 90 publications of studies with 15,613 patients. For KQ3, we found 43 RCTs involving 9,139 Crohn's disease patients and 46 observational studies involving 121,649 inflammatory bowel disease patients. For KQ4, we found one RCT with 78 Crohn's disease patients. Four pediatric RCTs examined a total of 258 children, and five observational studies involving 397 children with Crohn's disease reported data for KQ1-3 but not KQ4. Sixty-seven percent of the RCTs and 44% of the observational studies reported pharmaceutical

company support or a potential conflict of interest for the authors. Nine percent of the studies did not report on conflict of interest.

The results of our systematic review are first reported according to KQ, then medication class. The pediatric results follow the results for adults. When a study compared multiple medication classes, our report of the study begins with the first medication in our ordered list of medication classes, which is organized according to the top-down approach in the treatment pyramid (Figure A). The medication classes are: biologics (ustekinumab, natalizumab, TNF-alpha inhibitor), immunomodulators (thiopurines, methotrexate), corticosteroids, and 5-aminosalicylate acids. When we were able to combine clinically homogenous studies for a meta-analysis, we have reported the results of that meta-analysis. For KQ1 and KQ2, the results for disease remission and response as measured by disease activity scores were generally consistent, with the response rates being greater than the remission rates. Here we summarize the remission results because remission was the outcome of interest in the Key Questions.

KQ1-2. Induction and Maintenance of Remission

Study characteristics. The duration of the 91 RCTs ranged from 2 weeks to 4 years. Most RCTs were multi-center (76 percent), with most sites located in Europe and North America and fewer than 10 multicenter or single-center RCTs in Africa, Australia, Israel, or Asia.

Most patients with active disease who were considered in KQ1 were identified using the CDAI (lower limit, 150 to 220; upper limit, 350 to 600; 43 studies). Most patients with inactive disease who were considered in KQ2 were also identified using the CDAI (upper limit, 120 to 220; 23 studies). The Harvey-Bradshaw Index was used in two studies, and the Van Hees index in one study. Twenty-two studies did not report a scoring system to identify disease activity. Most studies allowed patients to use other medications during the RCT, although many specified that patients were required to be on a stable dose at the time of randomization and considered patients to be treatment failures if major dose changes were made.

Population characteristics. Most RCTs that reported on race included predominately white participants. Among the minority of studies that reported race, 84 to 100 percent of the patients were white. The largest non-white racial group in any individual study was 10 percent African American,[24] 8 percent Asian,[25] 1 percent Hispanic,[26] and 7 percent unspecified other race.[27] The mean or median disease duration was reported in 159 study arms and ranged from 7 months to 14 years. Age at the time of randomization was reported in 190 study arms, and the mean and median ranged from 26 to 47 years. The minimum age reported in any one study was 14 years,[28] and the maximum age was 78 years.[29]

Remission results. Our analysis of evidence derived from more than one study and time point indicated that no medication or combination of medications had a clinically and statistically significant effect in inducing or maintaining remission in Crohn's disease at all time points (Tables C and D). Most monotherapy comparisons included three or more studies in which medications were grouped by class. Combination therapy comparisons included three or fewer studies for all comparisons. Despite the large number of studies, we were able to perform very few meta-analyses because of the

heterogeneity in the definition of the inclusion criteria and outcomes between studies. Recently published studies tended to define remission using the CDAI, with scores below 150 indicating remission and scores above 150 indicating active disease. Older studies, including the study for which the CDAI was developed,[30] tended to use disease activity indexes with or without clinical outcomes, such as the need for surgery or laboratory measures to indicate remission status. We found very few studies that reported on measures of remission other than the disease activity indices (e.g., mucosal healing, hospitalizations, surgeries, reduction of corticosteroid use, fistula response, or patient-reported outcomes).

We found high strength of evidence for the clinical effectiveness of particular medications at specific time points using a disease activity scale. Statistical significance was not required for an effect to be considered clinically significant, although comparisons with high strength of evidence tended to be statistically significant. For induction of remission, the strength of evidence was high that natalizumab was more effective than placebo at 2-4 weeks, adalimumab was more effective than placebo at 2-4 weeks, and certolizumab pegol was more effective than placebo at 22-30 weeks. For maintenance of remission, the strength of evidence was high that, among those who achieved response or remission during an open-label run-in period (using the study drug), infliximab and adalimumab were more effective than placebo at maintaining remission at 22-30 and 48-54 weeks, and adalimumab and certolizumab pegol was more effective than placebo at 15-19 weeks.

We also found high strength of evidence for the clinical effectiveness of particular medications at specific time points using the patient-reported outcome IBDQ for induction of remission and reduction of steroids for maintenance of remission (Table E). For induction of remission, the strength of evidence was high that infliximab was more effective than placebo at 4 weeks and that neither medication was favored comparing natalizumab to placebo at 12 weeks, adalimumab to placebo at 4 weeks, and certolizumab pegol to placebo at 12 and 26 weeks. For maintenance of remission, the strength of evidence was high that infliximab was more effective than placebo at leading to the discontinuation of steroids among patients in remission at 52 weeks. Moderate strength of evidence was found for 27 of the KQ1, 19 of the KQ2 comparison timepoints using any definition of remission.

Subgroup analyses. Our goal was to report on disease characteristics that might modify the relationship between medications and remission. However, only six of these analyses used a statistical test for heterogeneity to report the results and no consistent relationship was observed.

Applicability. Applicability was limited to patients with a long history of Crohn's disease. The relevance of the study findings beyond the clinical trial setting may be limited due to the lack of routine reporting on outcomes other than the CDAI. The applicability to newly diagnosed patients was limited because many of the trials included patients with at least 10 years of Crohn's disease prior to randomization who had previously used medications. Comparisons across studies were frequently not possible in a meta-analysis even within the same drug class as there was heterogeneity in medication dosing, route of administration, and trial duration or inclusion criteria. Different disease activity indices were used including multiple definitions of response and remission (including the requirement to be steroid-free) using a disease activity scale. The CDAI

was the most commonly used index, but it lacks specificity for Crohn's disease; activity scores are largely based on symptoms and correlate poorly with mucosal disease.[31] Many types of remission outcomes were not routinely reported including: mucosal healing, hospitalization, surgery, reduction of steroids, fistula response and patient-reported outcomes.

KQ3. Safety

Study characteristics of RCTs. Forty-three of 90 RCTs (48 percent) that reported efficacy also reported a safety outcome of interest according to treatment group. The only information on safety assessment for nearly all RCTs was that unspecified safety outcomes were ascertained at study visits. These RCTs made no mention of the ascertainment method (questionnaire, patient-initiated report) or blinding.

Study characteristics of the observational studies. Seven prospective (n = 26,973), 26 retrospective (n = 53,856), 11 case-control (n = 40,040), one cross-sectional (n = 207),[32] and one observational study of unclear study design (n = 573)[33] reported safety outcomes. A specific safety outcome of interest was a stated outcome of interest in all of the case-control and prospective studies. All of the retrospective studies aimed to assess safety, but the exact safety outcomes of interest were not specified in about half of the studies. No observational study mentioned active ascertainment or blinded assessment of safety outcomes.

Most observational studies occurred at single study centers. Most single- or multi-center studies took place in the United States, Europe, Canada, and/or Australia, with one study in Africa and no studies in Asia.

Population characteristics of the observational studies. The age and gender distribution was very inclusive, with some studies including patients of all ages (0 to 90 years) and studies of cervical cancer including exclusively female patients. Twenty-eight studies reported results for inflammatory bowel disease patients without separately reporting results for Crohn's disease patients.

In contrast to the RCTs, all activity levels and severities of Crohn's disease were included in most of the observational studies reporting safety. Most of the observational studies had no restrictions on previous medication use. Sixteen studies included only patients who had used infliximab. These 16 studies compared the safety of infliximab alone or in combination with other medications. Two retrospective studies required azathioprine use because they were designed to compare the effectiveness of azathioprine with or without concomitant aminosalicylate.[34 35]

Safety results. We found that no medication or combination of medications was consistently associated with adverse effects across the safety outcomes of interest (Table E). Meta-analysis was not done because very few safety outcomes had more than three studies that contributed to any monotherapy or combination therapy comparison, and when more than three studies were available, the inclusion criteria and study duration were too heterogeneous.

The most serious adverse events of interest, including mortality and lymphoma, occurred in fewer than 1 percent of patients in most of the cohort studies and RCTs. Cancer occurred in fewer than 5 percent of patients in most of the cohort studies and fewer than 1 percent of patients in the RCTs.

Hepatosplenic T-cell lymphoma is so rare that we identified only one case in the cohort studies and RCTs. No progressive multifocal leukoencephalopathy was identified in a cohort study or trial. A search of case reports, case series, and the FDA's AERS identified 45 cases of hepatosplenic T-cell lymphoma and one case of progressive multifocal leukoencephalopathy in Crohn's disease patients. The data from those reports was insufficient to support a causal relationship with any specific medication.

Serious and opportunistic infections also occurred in fewer than 5 percent of patients in most of the cohort studies and RCTs, although other infections occurred in 5 to 20 percent of patients and as many as 83 percent of patients in one RCT. Only six cases of tuberculosis were observed among the five RCTs that reported this outcome. However, many RCTs excluded patients with a history of tuberculosis, or patients were treated before enrollment.

Infusion and injection site reactions were reported only for biologics studies, with the exception of one RCT of intravenous azathioprine. Infusion reactions were reported in 0 to 40 percent of patients. Most RCTs reported that fewer than 20 percent of the randomized patients experienced infusion reactions.

Bone fractures were only reported for comparisons including steroids. Traumatic bone fractures were very rare. In one cross-sectional study, asymptomatic vertebral fractures measured by dual X-ray absorptometry (DXA) scan were observed in 24 percent of steroid-treated patients and 17 percent of those who did not use steroids in the previous year.[32]

The strength of evidence for nearly every comparison was insufficient or low. Frequently, no medication was favored among the comparisons with low strength of evidence. We found high strength of evidence for two safety comparisons, each from a single RCT and in both cases for an outcome of infusion and injection-site reactions. Oral azathioprine with placebo infusion was favored over intravenous infliximab, and placebo was favored over intravenous azathioprine. Moderate strength of evidence was found for two safety comparisons, each from a single RCT. A combination of prednisone and sulfasalazine was favored over prednisone alone for infections, and neither budesonide nor prednisolone was favored in terms of bone fractures.

Subgroup analyses. No study reported on subgroup analyses for the safety outcomes.

Applicability. Because there were fewer restrictions made on the patient populations, the observational studies likely apply to Crohn's disease patients of all disease activity and severity levels. The observational studies that reported safety outcomes of interest did not have as many inclusion criteria as the RCTs. Very few observational studies had disease activity or disease location exclusions. Despite the differences in inclusion and exclusion criteria between the RCTs and observational studies, we did not see meaningful differences in safety signals between the RCTs and observational studies. The studies that included all inflammatory bowel disease patients had safety findings similar to those of studies that included only Crohn's disease patients or reported results for both Crohn's disease and inflammatory bowel disease patients.

KQ4. Patient-Reported Outcomes After Surgery

We identified only one study that met the inclusion criteria for KQ4. This RCT compared azathioprine with mesalamine and reported on the IBDQ among patients who

had undergone ileocolonic anastomosis within 6 to 24 months prior to randomization. The strength of the evidence was high for no difference in the effect on the IBDQ between azathioprine and mesalamine.

KQ1-4 for Pediatrics

Study characteristics. Four studies were RCTs,[36-39] two were prospective cohort studies,[40 41] and three were retrospective cohort studies.[42-44] Studies were conducted in various countries (two in the United States, one in Canada, four in Europe, and two in Israel), and five studies were multi-centered. The length of followup ranged from 8 weeks to 18 months for RCTs and up to 3.6 years in an observational study.

Population characteristics. The mean age of patients ranged from 12 to 14 years, with a maximum age in one study of 22 years. The mean disease duration was 7 to 8 months as reported in two RCTs.[38 43] The mean age at diagnosis was 7 and 14 years as reported in two studies.[40 41] The majority of patients in the RCTs were male (RCT range, 60 to 69 percent; observational studies, 33 to 100 percent). Race was reported in two studies as 90 and 93 percent white.[37 43] The mean baseline pediatric Crohn's disease activity index (PCDAI) score was consistent with active disease in all studies (range, 27.6 to 45.7), although studies included patients with all disease activity levels.

Individual studies further restricted their patients in terms of disease location, disease duration, and/or medications allowed prior to and during the study. One study of budesonide versus prednisolone[38] included only patients with disease of the ileum or ascending colon. One study of 6-mercaptopurine and prednisone versus prednisone alone included only patients with a disease duration of fewer than 8 weeks.[37] Two studies[36 37] allowed patients no additional treatment during the study. Four studies examining 6-mercaptopurine and prednisone,[37] corticosteroids,[36 38] or mesalamine[39] excluded patients who had previously used an immunomodulator. Two studies measuring growth[43 44] excluded patients who had an illness or were taking any other medications that could affect growth or development.

Pediatric results. Few studies were designed to examine the efficacy and safety of Crohn's disease treatments in the pediatric population (younger than 18 years old). Four RCTs compared the efficacy of therapies alone or in combination in inducing or maintaining remission in children with Crohn's disease. Eight studies reported the comparative safety of therapies alone or in combination in children with Crohn's disease. Of these eight studies, most used height or weight change as their primary outcomes of interest. No study reported patient-reported outcomes after surgical resection.

The strength of evidence was insufficient or low for all but two comparisons in the pediatric population. The strength of evidence was moderate for no difference in the effectiveness of budesonide versus prednisolone in inducing remission. The strength of evidence also was moderate that prednisolone was favored over budesonide for infections.

We did not find any RCT of biologics in children that met the criteria for inclusion in this review. An RCT of maintenance therapy with on-demand infliximab in pediatric patients was not included because there was no comparison with another medication, only with the timing of infliximab administration.[45]

Pediatric applicability. The applicability of these studies was limited because few children were included, very few medications were compared, and the longest RCT was 18 months and the longest prospective study less than four years.

Table C. Summary of the strength of evidence on the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of inducing a remission as measured by a disease activity index at various time points

Comparison* (# of studies / # of participants)	Weeks 2-4 (immediate response)	Weeks 8-12 (induction)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
Ustekinumab IV vs. placebo (1 / 53)	Low SOE; favors ustekinumab (RD, 12%; G2 rate, 7%; RR, 2.6; CI, 0.6 to 12.2)	Low SOE; favors ustekinumab (RD, 16%; G2 rate, 11%; RR, 2.4; CI, 0.7 to 8.3)	Insufficient	Insufficient	Insufficient
Ustekinumab SC vs. placebo (1 / 51)	Low SOE; favors ustekinumab (RD,12%; G2 rate, 12%; RR, 2.1; CI, 0.6 to 7.4)	Low SOE; no difference (RD, 1%; G2 rate, 23%; RR, 1.0; CI, 0.4 to 2.8)	Insufficient	Insufficient	Insufficient
Ustekinumab IV vs. ustekinumab SC (1 / 27)	Low SOE; favors ustekinumab IV (RD, 8%; G2 rate, 0%)	Low SOE; favors ustekinumab IV (RD, 10%; G2 rate, 21%; RR, 1.4; CI, 0.4 to 5.2)	Insufficient	Insufficient	Insufficient
Natalizumab vs. placebo (3 / 1394)	High SOE, favors natalizumab (RD range, 4% to 31%; G2 rate range, 8% to 16%; pooled RR, 1.5; CI, 1.1 to 2.0)	Mod SOE, no difference (RD range, 6% to 13%; G2 rate range, 0% to 30%; RR range,1.2 to 1.5)	Insufficient	Insufficient	Insufficient
Natalizumab + infliximab vs. infliximab (1 / 79)	Low SOE, no difference (RD, 8%; G2 rate, 7%; RR, 2.1; CI, 0.5 to 9.1)	Low SOE, no difference (RD, 7%; G2 rate, 30%; RR, 1.2; CI, 0.6 to 2.4)	Insufficient	Insufficient	Insufficient
Infliximab vs. placebo (1 / 101)	Mod SOE, no difference (RD, 23%; G2 rate, 4%; RR, 6.4; CI, 0.9 to 45.3)	Mod SOE, no difference (RD, 16%; G2 rate, 8%; RR, 2.9; CI, 0.7 to 11.6)	Insufficient	Insufficient	Insufficient
Adalimumab vs. placebo (2 / 624)	High SOE, favors adalimumab (RD range, 10% to 15%; G2 rate range, 6% to 14%; RR range, 1.8 to 3.4)	Insufficient	Insufficient	Insufficient	Insufficient
Certolizumab pegol vs. placebo (3 / 1040)	Mod SOE, no difference (RD range, 5% to 16%; G2 rate range, 8% to 16%; RR range, 1.6 to 2.0)	Low SOE, no difference (RD range, 0% to 16%; G2 rate range, 11% to 32%; RR, 1.0 to 2.4)	High SOE, favors certolizumab pegol (RD, 11%; G2 rate, 18%; RR, 1.6; CI, 1.2 to 2.1)	Insufficient	Insufficient
Infliximab vs. azathioprine (1 / 339)	Insufficient	Mod SOE, favors infliximab (RD, 13%; G2 rate, 24%; RR, 1.5; CI, 1.1 to 2.2)	Mod SOE, favors infliximab (RD, 16%; G2 rate, 32%; RR, 1.5; CI, 1.2 to 2.0)	Insufficient	Insufficient

Table C. Summary of the strength of evidence on the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of inducing a remission as measured by a disease activity index at various time points (continued)

Comparison* (# of studies / # of participants)	Weeks 2-4 (immediate response)	Weeks 8-12 (induction)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
Infliximab + azathioprine vs. infliximab (1 / 338)	Insufficient	Mod SOE; favors infliximab + azathioprine (RD, 10%; G2 rate, 37%; RR, 1.3; CI, 1.0 to 1.6)	Mod SOE; favors infliximab + azathioprine (RD, 12%; G2 rate, 48%; RR, 1.2; CI, 1.0 to 1.5)	Insufficient	Insufficient
Infliximab + thiopurine vs. thiopurine (2 / 393)	Insufficient	Mod SOE; favors infliximab + azathioprine (RD range, 12% to 30%; G2 rate range, 24% to 48%; RR, 1.9)	Mod SOE; favors infliximab + azathioprine (RD range, 16% to 24%; G2 rate range, 26% to 32%; RR range, 1.5 to 1.9)	Insufficient	Insufficient
Infliximab + azathioprine vs. corticosteroids (1 / 129)	Insufficient	Insufficient	Low SOE, favors infliximab + azathioprine (RD, 24%; G2 rate, 36%; RR, 1.7; CI, 1.1 to 2.4)	Low SOE, favors infliximab + azathioprine (RD, 19%; G2 rate, 42%; RR, 1.5; CI, 1.0 to 2.1)	Low SOE, no difference (RD, 6%; G2 rate, 49%; RR, 1.1; CI, 0.8 to 1.5)
Infliximab + methotrexate vs. infliximab (1 / 19)	Low SOE, favors infliximab + methotrexate (RD, 39%; G2 rate, 25%; RR, 2.5; CI, 0.7 to 9.2)	Low SOE, favors infliximab + methotrexate (RD, 32%; G2 rate, 50%; RR, 1.6; CI, 0.8 to 3.5)	Low SOE, favors infliximab + methotrexate (RD, 17%; G2 rate, 38%; RR, 1.5; CI, 0.5 to 4.1)	Low SOE, favors infliximab + methotrexate (RD, 20%; G2 rate, 25%; RR, 1.8; CI, 0.5 to 7.1)	Insufficient
Thiopurines vs. placebo (2 / 194)	Insufficient	Insufficient[†]	Insufficient[‡]	Insufficient	Insufficient
Thiopurines vs. methotrexate (2 / 89)	Insufficient	Insufficient	Low SOE, no difference[§] (RD, 14%; G2 rate, 80%; RR, 1.2; CI, 0.9 to 1.6)	Insufficient	Insufficient
Thiopurines vs. corticosteroids (1 / 144)	Insufficient	Insufficient[‖]	Insufficient	Insufficient	Insufficient
Thiopurines vs. 5ASA (2 / 156)	Insufficient	Insufficient[¶‖]	Low SOE, favors thiopurines (RD, 80%; G2 rate, 14%; RR, 6.6; CI, 1.1 to 40.4)	Insufficient	Insufficient
Azathioprine IV vs. azathioprine oral (1 / 96)	Insufficient	Mod SOE, no difference** (RD range, 1% to 4%; G2 rate range, 24% to 27%; RR range, 1.0 to 1.4)	Insufficient	Insufficient	Insufficient

Table C. Summary of the strength of evidence on the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of inducing a remission as measured by a disease activity index at various time points (continued)

Comparison* (# of studies / # of participants)	Weeks 2-4 (immediate response)	Weeks 8-12 (induction)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
Thiopurines + corticosteroids vs. corticosteroids (3 / 186)	Insufficient	Low SOE, favors azathioprine + corticosteroids (RD, 10%; G2 rate, 63%; RR, 1.1; CI, 0.8 to1.6)	Low SOE, favors azathioprine + corticosteroids (RD, 10%; G2 rate, 28%; RR, 1.3; CI, 0.7 to 2.6)	Insufficient	Insufficient
Thiopurines + corticosteroids vs. methotrexate + corticosteroids (1 / 54)	Insufficient	Insufficient[††]	Low SOE, no difference (RD, 7%; G2 rate, 56%; RR, 1.1; CI, 0.7 to 1.8)	Insufficient	Insufficient
Methotrexate IM vs. placebo (1 / 141)	Insufficient	Insufficient[‡‡]	Insufficient	Insufficient	Insufficient
Methotrexate oral vs. placebo (1 / 52)	Insufficient	Insufficient	Insufficient[§§]	Insufficient	Insufficient
Methotrexate oral vs. 5ASA (1 / 22)	Insufficient	Insufficient	Low SOE, favors methotrexate (RD, 66%; G2 rate, 14%; RR, 5.6; CI, 0.9 to 35.0)	Insufficient	Insufficient
Budesonide vs. placebo (2 / 458)	Mod SOE, favors budesonide (RD range, 12% to 23%; G2 rate range, 11% to 12%; RR range, 2.2 to 2.9)	Mod SOE, favors budesonide (RD range, 16% to 20%; G2 rate range, 22% to 33%; RR range,1.5 to 2.1)	Insufficient	Insufficient	Insufficient
Corticosteroids[‖‖] vs. placebo (2 / 267)	Low SOE, favors corticosteroids (RD range, 4% to 14%; G2 rate range, 16% to 79%; RR range, 1.2 to 1.3)	Insufficient[¶¶]	Insufficient	Low SOE, favors corticosteroids (RD, 35%; G2 rate, 14%; RR, 3.5; CI, 1.8 to 7.2)	Low SOE, favors corticosteroids (RD, 25%; G2 rate, 9%; RR, 3.9; CI, 1.6 to 10.0)
Budesonide vs. corticosteroids[‖‖] (4 / 581)	Mod SOE, no difference (RD range, -10% to 0%; G2 rate range, 38% to 56%; RR range, 0.8 to 1.0)	Mod SOE, no difference (RD range, -13% to -2%; G2 rate range, 53% to 66%; pooled RR, 0.9; CI, 0.8 to 1.0)	Insufficient	Insufficient	Insufficient

Table C. Summary of the strength of evidence on the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of inducing a remission as measured by a disease activity index at various time points (continued)

Comparison* (# of studies / # of participants)	Weeks 2-4 (immediate response)	Weeks 8-12 (induction)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
Corticosteroids vs. 5ASA (6 / 617)	Low SOE, favors corticosteroids (RD range, 1% to 19%; G2 rate range, 5% to 87%; RR range, 1.0 to 4.6)	Low SOE, no difference[***] (RD range, -17% to 24%; G2 rate range, 45% to 79%; RR range, 0.8 to 1.5)	Insufficient	Low SOE, favors corticosteroids (RD, 19%; G2 rate, 30%; RR, 1.7; CI 1.0 to 2.7)	Low SOE, favors corticosteroids (RD, 12%; G2 rate, 22%; RR, 1.5; CI, 0.8 to 2.9)
Corticosteroids + 5ASA vs. placebo (1 / 114)	Low SOE, favors corticosteroids + 5ASA (RD, 19%; G2 rate, 79%, RR, 1.2; CI, 1.1 to 1.4)	Insufficient[†††]	Insufficient	Low SOE, favors corticosteroids + 5ASA (RD, 38%; G2 rate, 14%, RR, 3.8; CI, 1.9 to 7.5)	Low SOE, favors corticosteroids + 5ASA (RD, 27%; G2 rate, 9%, RR, 4.1; CI, 1.7 to 10.3)
Corticosteroids + 5ASA vs. corticosteroids (2 / 192)	Low SOE, no difference (RD, 5%; G2 rate, 93%; RR, 1.0; CI, 1.0 to 1.1)	Low SOE, favors corticosteroids + 5ASA (RD, 19%; G2 rate, 57%; RR, 1.3; CI, 1.0 to 1.8)[‡‡‡]	Insufficient	Low SOE, no difference (RD, 3%; G2 rate, 49%; RR, 1.1; CI, 0.7 to 1.6)	Low SOE, no difference (RD, 2%; G2 rate, 33%; RR, 1.0; CI, 0.6 to 1.8)
Corticosteroids + 5ASA vs. 5ASA (2 / 170)	Low SOE, favors corticosteroids + 5ASA (RD, 11%; G2 rate, 87%; RR, 1.1; CI, 1.0 to 1.3)	Low SOE, favors corticosteroids + 5ASA[§§§]	Insufficient	Low SOE, favors corticosteroids + 5ASA (RD, 22%; G2 rate, 30%; RR, 1.7; CI, 1.1 to 2.8)	Low SOE, favors corticosteroids + 5ASA (RD, 13%; G2 rate, 22%; RR, 1.6; CI, 0.9 to 3.0)
5ASA vs. placebo (7 / 744)	Low SOE, no difference (RD range, -8% to 8%; G2 rate range, 8% to 79%; RR range, 1.1; CI, 0.9 to 1.3)	Insufficient[‖‖‖]	Low SOE, favors 5ASA (RD, 55%; G2 rate, 8%; RR, 8.0; CI, 1.2 to 55.2)	Low SOE, favors 5ASA (RD, 16%; G2 rate, 14%; RR, 2.1; CI, 1.0 to 4.6)	Low SOE, favors 5ASA (RD, 12%; G2 rate, 10%; RR, 2.1; CI, 0.8 to 5.6)

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable

5ASA = aminosalicylates; CI = 95% confidence interval; G2 = group 2; IM = intramuscular; IV = intravenous; RD = risk difference; RR = relative risk; SC = subcutaneous; SOE = strength of evidence; vs. = versus

* Comparison is Group 1 versus Group 2. The risk difference (RD) was calculated as the percent of patients in Group 1 in remission minus the percent of patients in Group 2 in remission. Numbers greater than zero favor group 1 and numbers less than zero favor group 2. The risk ratio (RR) was calculated as the percent of patients in Group 1 in remission divided by the percent of patients in Group 2 in remission. Numbers greater than 1 favor Group 1 and numbers less than 1 favor group 2. Meta-analysis results of the risk ratio are presented as pooled risk ratios. If more than one study reported results for a particular comparison and time point but we were unable to conduct a meta-analysis, we presented the range.

[†] We did not identify any trials that compared thiopurines and placebo and evaluated remission at weeks 8-12. However, we identified one trial that evaluated this comparison in terms of remission at week 17. We found low strength of evidence that there is no difference between thiopurines and placebo at week 17 (RD, 5%; G2 rate, 48%; RR, 1.1; CI, 0.8 to 1.5).

[‡] We did not identify any trials that compared thiopurines and placebo and evaluated remission at weeks 22-30. However, we identified one trial that evaluated this comparison in terms of remission at week 38. We found low strength of evidence that there is no difference between thiopurines and placebo at week 38 (RD, -5%; G2 rate, 46%; RR, 0.9; CI, 0.5 to 1.6).

[§] Additionally, we identified one trial that evaluated 6-mercaptopurine with methotrexate in terms of remission at week 38. We found low strength of evidence that there is no difference between 6-mercaptopurine and methotrexate at week 38 (RD, 3%; G2 rate, 38%; RR, 1.1; CI, 0.6 to 2.0).
[‖] We did not identify any trials that compared thiopurines with corticosteroids and evaluated remission at weeks 8-12. However, we identified one trial that evaluated this comparison in terms of remission at week 17. We found low strength of evidence that azathioprine is less effective than prednisone in terms of remission at week 17 (RD, -24%; G2 rate, 77%; RR, 0.7; CI, 0.5 to 0.9).
[¶] We did not identify any trials that compared thiopurines with aminosalicylates and evaluated remission at weeks 8-12. However, we identified one trial that evaluated this comparison in terms of remission at week 17. We found low strength of evidence that there is no difference between thiopurines and aminosalicylates in terms of remission at week 17 (RD, 0%; G2 rate, 53%; RR, 1.0; CI, 0.7 to 1.4).
** Week 12 and week 16 data are presented.
[††] We did not identify any trials that compared a combination of thiopurines and corticosteroids with a combination of methotrexate and corticosteroids and evaluated remission at weeks 8-12. However, we identified one trial that evaluated this comparison in terms of remission at week 13. We found low strength of evidence that there is no difference between the two combination therapies in terms of remission at week 13 (RD, -11%; G2 rate, 44%; RR, 0.8; CI, 0.4 to 1.5).
[‡‡] We did not identify any trials that compared intramuscular methotrexate with placebo and evaluated remission at weeks 8-12. However, we identified one trial that evaluated this comparison in terms of remission at week 16. We found moderate strength of evidence favoring intramuscular methotrexate at week 16 (RD, 20%; G2 rate, 19%; RR, 2.1; CI, 1.1 to 3.9).
[§§]We did not identify any trials that compared oral methotrexate with placebo and evaluated remission at weeks 22-30. However, we identified one trial that evaluated this comparison in terms of remission at week 16. We found low strength of evidence that there is no difference between oral methotrexate and placebo at week 38 (RD, -8%; G2 rate, 46%; RR, 0.8; CI, 0.4 to 1.6).
[‖‖] Prednisone or 6-methylprednisolone
[¶¶] We did not identify any trials that compared corticosteroids (prednisone or 6-methylprednisolone) with placebo and evaluated remission at weeks 8-12. However, we identified two trials that evaluated this comparison in terms of remission at week 16-17. We found low strength of evidence favoring corticosteroids at weeks 16-17 (RD range, 17% to 38%; G2 rate range, 36% to 42%; RR range, 1.4 to 2.0).
*** Additionally, we identified 3 trials that compared corticosteroids with aminosalicylates and evaluated remission at weeks 16-17. We found low strength of evidence favoring corticosteroids in terms of remission at week 16-17 (RD range, 17% to 30%; G2 rate range, 28% to 57%; RR range, 1.3 to 2.0).
[†††] We did not identify any trials that compared a combination of corticosteroids and aminosalicylates with placebo and evaluated remission at weeks 8-12. However, we identified one trial that evaluated this comparison in terms of remission at week 16. We found low strength of evidence favoring a combination of corticosteroids and aminosalicylates in terms of remission at week 16 (RD, 34%; G2 rate, 64%; RR, 1.5; CI, 1.2 to 2.0).
[‡‡‡] Additionally, we identified one trial that compared a combination of corticosteroids and aminosalicylates with corticosteroids and evaluated remission at week 16. We found low strength of evidence that there is no difference between the therapies in terms of remission at week 16 (RD, 8%; G2 rate, 74%; RR, 1.1; CI, 0.9 to 1.4).
[§§§]We are unable to calculate a risk difference or a relative risk for this time point.
[‖‖‖] We did not identify any trials that compared aminosalicylates with placebo and evaluated remission at weeks 8-12. However, we identified five trials that evaluated this comparison in terms of remission at week 16-17. We found low strength of evidence favoring aminosalicylates at weeks 16-17 (RD range, 2% to 23%; G2 rate range, 18% to 36%; RR range, 1.1 to 2.0).

Table D. Summary of the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of maintaining remission as measured by a disease activity index at various time points

Comparison* (# of studies / # of participants)	Weeks 15-19 (4 months)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
Ustekinumab vs. placebo	Insufficient	Insufficient	Insufficient	Insufficient
Natalizumab vs. placebo (1 / 339)	Insufficient	Low SOE; favors natalizumab (RD, 25%; G2 rate, 30%; RR, 1.7; CI, 1.2 to 2.4)	Low SOE; favors natalizumab (RD, 33%; G2 rate, 22%; RR, 2.6; CI, 1.6 to 4.2)	Insufficient
TNF-alpha inhibitors vs. placebo (5 / 1340)	High SOE; favors TNF-alpha inhibitors (pooled RR, 1.8; CI, 1.5 to 2.2)	High SOE; favors TNF-alpha inhibitors (pooled RR, 2.1; CI, 1.7 to 2.7)	High SOE; favors TNF-alpha inhibitors	Insufficient
Infliximab vs. placebo (2 / 408)	Low SOE; favors infliximab (RD, 30%; G2 rate, 30%; RR 1.9; CI, 1.1 to 3.4)	High SOE; favors infliximab (RD range, 21% to 29%; G2 rate range, 21% to 35%; RR range, 1.8 to 2.0)	High SOE; favors infliximab (RD, 20%; G2 rate, 15%; RR, 2.3; CI, 1.4 to 3.7)	Insufficient
Adalimumab vs. placebo (2 / 504)	High SOE; favors adalimumab (RD range, 23% to 40%; G2 rate range, 21% to 51%, RR range, 1.7 to 2.1)	High SOE; favors adalimumab (RD range, 24% to 50%; G2 rate range, 17% to 38%; RR range, 2.3 to 2.4)	High SOE; favors adalimumab (RD range, 27% to 37%; G2 rate range, 12% to 44%; RR range, 1.8 to 3.3)	Insufficient
Certolizumab pegol vs. placebo (1 / 428)	High SOE; favors certolizumab pegol (RD, 19%; G2 rate, 29%; RR, 1.7; CI, 1.3 to 2.2)	Insufficient	Insufficient	Insufficient
Infliximab and azathioprine vs. infliximab alone (1 / 80)	Insufficient	Insufficient	Insufficient	Low SOE; no difference[†]
Infliximab and azathioprine vs. infliximab and IV hydrocortisone pretreatment (1 / 46)	Insufficient	Low SOE; no difference (RD, -9%; G2 rate, 88%; RR, 0.9; CI, 0.7 to 1.2)	Low SOE; no difference (RD, -5%; G2 rate, 84%; RR, 1.0; CI, 0.7 to 1.3)	Low SOE; no difference (RD, -5%, G2 rate, 77%; RR, 0.9; CI, 0.6 to 1.3)
Azathioprine vs. placebo (5 / 328)	Insufficient	Low SOE; favors azathioprine (RD, 40%; G2 rate, 40%; RR, 2.0; CI, 0.6 to 6.4)	Low SOE; favors azathioprine (RD range, 5% to 39%; G2 rate range, 47% to 64%; RR range, 1.1 to 1.8)	Low SOE; favors placebo[‡] (RD, -11%; G2 rate, 40%; RR, 0.7; CI, 0.5 to 1.2)
Azathioprine vs. corticosteroids (2 / 192)	Insufficient	Insufficient	Low SOE; favors azathioprine (RD range, 12% to 15%; G2 rate range, 57% to 64%; RR, 1.2)	Low SOE; no difference (RD, -3%, G2 rate, 32%; RR, 0.9; CI, 0.5 to 1.6)

Table D. Summary of the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of maintaining remission as measured by a disease activity index at various time points (continued)

Comparison* (# of studies / # of participants)	Weeks 15-19 (4 months)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
Azathioprine vs. sulfasalazine (1 / 112)	Insufficient	Insufficient	Low SOE; no difference (RD, 7%; G2 rate 62%; RR, 1.1; CI, 0.8 to 1.4)	Low SOE; no difference (RD, -2%; G2 rate, 31%; RR, 1.0; CI 0.5 to 1.7)
Methotrexate (intramuscular) vs. placebo (1 / 76)	Low SOE; favors methotrexate (RD, 13%; G2 rate, 58%; RR, 1.3; CI, 0.9 to 1.8)	Insufficient	Low SOE; favors methotrexate (RD, 26%; G2 rate, 39%; RR, 1.6; CI, 1.0 to 2.5)	Insufficient
Budesonide vs. placebo (6 / 587)	Low SOE; no difference (RD, 19%; G2 rate, 44%; RR, 1.4; CI, 0.9 to 2.3)	Low SOE; no difference (RD range, 15% to 23%; G2 rate range, 26% to 44%; RR range, 1.3 to 1.9)	Low SOE; no difference (RD range, -4% to 11%; G2 rate range, 33% to 43%; pooled RR, 1.0; CI, 0.8 to 1.1)	Insufficient
Corticosteroids (prednisone, 6-methylprednisolone) vs. placebo (3 / 298)	Low SOE; no difference (RD range, 0% to 16%; G2 rate range, 67% to 90%; RR range, 1.0 to 1.2)	Low SOE; no difference (RD range, -9% to 67%; G2 rate range, 22% to 88%; RR range, 0.9 to 4.0)	Low SOE; no difference (RD range, 0% to 13%; G2 rate range, 48% to 73%; RR range, 1.0 to 1.3)	Low SOE; no difference(RD range, 8% to 10%; G2 rate range, 33% to 59%; RR range, 1.1 to 1.3)
Budesonide vs. mesalamine (1 / 57)	Mod SOE; favors budesonide (RD, 35%; G2 rate, 45%; RR, 1.7; CI, 1.1 to 2.7)	Mod SOE; favors budesonide (RD, 39%; G2 rate, 24 RR, 2.5; CI, 1.2 to 5.0)	Mod SOE, favors budesonide (RD, 27%; G2 rate, 18%; RR, 2.5; CI, 1.0 to 6.1)	Insufficient
Corticosteroids (prednisone, 6-methylprednisolone) vs. 5ASA (2 / 248)	Low SOE; no difference (RD range, 4% to 6%; G2 rate range, 78% to 87%; RR range, 1.0 to 1.1)	Low SOE; no difference (RD range, -2% to 7%; G2 rate range, 73% to 83%; RR range, 1.0 to 1.1)	Low SOE; no difference (RD, 5%; G2 rate range, 56% to 67%; RR range, 1.0 to 1.1)	Low SOE; no difference (RD range, 6% to 9%; G2 rate range, 37% to 58%; RR range, 1.1 to 1.2)
6-Methylprednisolone and sulfasalazine vs. placebo (1 / 119)	Low SOE; no difference (RD, 0%; G2 rate, 68%; RR, 1.0; CI, 0.8 to 1.3)	Low SOE; no difference (RD, 2%; G2 rate, 65%; RR, 1.0; CI, 0.8 to 1.4)	Low SOE; no difference (RD, 5%; G2 rate, 48%; RR, 1.1; CI, 0.8 to 1.6)	Low SOE; no difference (RD, 1%; G2 rate, 32%; RR, 1.0; CI, 0.6 to 1.8)
Corticosteroids (prednisone, 6-methylprednisolone) and sulfasalazine vs. corticosteroids alone (2 / 181)	Low SOE; no difference (RD range,-15% to 0%; G2 rate range, 23% to 83%; RR range, 0.8 to 1.0)	Low SOE; no difference (RD range, -12% to -6%; G2 rate range, 23% to 80%; RR range, 0.7 to 0.8)	Low SOE; no difference (RD, -7%; G2 rate, 61%; RR, 0.9; CI, 0.6 to 1.2)	Low SOE; no difference (RD, -8%; G2 rate, 42%; RR, 0.8; CI, 0.5 to 1.3)
6-Methylprednisolone and sulfasalazine vs. sulfasalazine alone (1 / 119)	Low SOE; no difference (RD, -9%; G2 rate, 77%; RR, 0.9; CI, 0.7 to 1.1)	Low SOE; no difference (RD, -6%; G2 rate, 73%; RR, 0.9; CI, 0.7 to 1.2)	Low SOE; no difference (RD, -2%; G2 rate, 56%; RR, 1.0; CI, 0.7 to 1.3)	Low SOE; no difference (RD, -3%; G2 rate, 37%; RR, 0.9; CI, 0.6 to 1.5)

Table D. Summary of the comparative effectiveness of pharmacologic therapies for the management of Crohn's disease in terms of maintaining remission as measured by a disease activity index at various time points (continued)

Comparison* (# of studies / # of participants)	Weeks 15-19 (4 months)	Weeks 22-30 (6 months)	Weeks 48-54 (1 year)	Months 18-24 (long-term)
5ASA vs. placebo (14 / 1930)	Low SOE; no difference (RD range, -12% to 10%; G2 rate range, 41% to 90%; pooled RR of relapse, 0.8; CI, 0.7 to 1.1)	Low SOE; no difference (RD range, -5% to 22%; G2 rate range, 29% to 88%; pooled RR of relapse, 0.8; CI, 0.6 to 1.1)	Low SOE; favors 5ASA (RD range, -13% to 26%; G2 rate range, 18 to 74%; pooled RR of relapse, 0.7; CI, 0.6 to 1.0)	Low SOE; no difference (RD range, -17% to 14%; G2 rate, 33% to 59%; RR range, 0.6 to 1.4)

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable

5ASA = aminosalicylates; CI = 95% confidence interval; G2 = group 2; IM = intramuscular; IV = intravenous; RD = risk difference; RR = relative risk; SC = subcutaneous; SOE = strength of evidence; vs. = versus

* Comparison is Group 1 versus Group 2. The risk difference (RD) was calculated as the percent of patients in Group 1 in remission minus the percent of patients in Group 2 in remission. Numbers greater than zero favor group 1 and numbers less than zero favor group 2. The risk ratio (RR) was calculated as the percent of patients in Group 1 in remission divided by the percent of patients in Group 2 in remission. Numbers greater than 1 favor Group 1 and numbers less than 1 favor group 2. Meta-analysis results of the risk ratio are presented as pooled risk ratios. If more than one study reported results for a particular comparison and time point but we were unable to conduct a meta-analysis, we presented the range.

[†]This study reported on the percent of patients who required a change in the dosing schedule or stoppage of infliximab (RD, 5%, G2 rate, 55%; RR, 1.1; CI, 0.7 to 1.6).

[‡] Additionally, this trial reported on remission rates at week 78. We found moderate evidence favoring azathioprine in terms of remission at week 78 (RD, 13%; G2 rate, 79%; RR, 1.2; 95% CI, 1.0 to 1.4).

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Natalizumab vs. placebo	**Induction of remission.** No difference	Patient-reported outcomes	High	12 wks	12 pts¶ (15 pts‖)	NA
	Maintenance of remission. More effective	Patient-reported outcomes	Low	48 wks	19 pts¶ (-23 pts‖)	NA
	Safety. No difference	Mortality, lymphoma All cancers Infections Infusion and injection-site reactions	Low Low Low Low	12-52 wks 12-48 wks 12-48 wks 12-48 wks	< 5 events < 5 events -1 – 6% (2 – 56%) -2 – 4% (7 – 8%)	< 5 events < 5 events 0.3 – 1.3 0.8 – 1.5
Natalizumab and infliximab vs. infliximab alone	**Induction of remission.** No difference	Patient-reported outcomes	Low	10 wks	2 pts¶ (17 pts‖)	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Lymphoma All cancers Infections Infusion and injection-site reactions	Low Low Low Low	20 wks 20 wks 20 wks 20 wks	< 5 events < 5 events -3% (30%) < 5 events	< 5 events < 5 events 0.9 (0.3 to 2.5) < 5 events
Ustekinumab vs. placebo	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	All cancers Infections Infusion and injection-site reactions	Low Low Low	8 wks 8 wks 8 wks	< 5 events -8% (23%) < 5 events	< 5 events 0.6 (0.2 to 1.6) < 5 events

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence[†]	Time points	Absolute risk difference[‡] (% in group 2)	Relative risk[§] (95% CI)
TNF-alpha inhibitor vs. no TNF-alpha inhibitor	**Safety.** No difference	Cervical cancer	Low	26 wks 3 yrs**	NA	0.4** (0 to 225**)
		All cancers	Low	4-52 wks 2-12 yrs**	0% (1%) -2 – 1%** (2-5%**)	1.0 (0.2 to 5.3) 0.6 – 1.3**
		Infections	Low	4-52 wks 2-5 yrs**	-29 – 16% (1 – 83%) -3 – 1%** (1 – 9%**)	0.3 – 5.1 0.7 – 2.1**
		Tuberculosis	Low	4 – 52 wks	< 5 events	< 5 events
Infliximab vs. placebo	**Induction of remission.** More effective	Mucosal healing	Moderate	4 wks	7.7 pts[††] (0.9 pts[‡‡])	NA
		Fistula response	Moderate	6 wks	25 – 42% (13%)	2.9 – 4.3
		Patient-reported outcomes	High	4 wks	31 pts[¶] (5 pts[‖])	NA
	Maintenance of remission. More effective	Mucosal healing	Moderate	8 wks; 52 wks	31 - 43% (0 - 7%)	Wk 52, 7.0 (1.0 - 48.1)
		Hospitalizations	Moderate	40 wks	NA[§§]	NA[§§]
		Surgeries	Moderate	40 wks	NA[¶¶]	NA[¶¶]
		Reduction of steroids	High	52 wks	20% (9%)	OR, 4.2 (1.5 - 11.5)
		Fistula response	Moderate	40 wks	17% (19%)	1.9 (1.1 - 3.0)
		Patient-reported outcomes	Moderate	28 wks; 52 wks	Wk 28, 13 - 18 pts[¶] (14 pts[‖]) Wk 52, 13 - 21 pts[¶] (9 pts[‖])	NA
	Maintenance of remission. No difference	Patient-reported outcomes	Moderate	16 wks	10 - 22 pts[¶] (-8 - 4 pts[‖])	NA
	Safety. No difference	Mortality	Low	18-52 wks 2-4.4 yrs**	-0.8 - -7.4%** (2.4 - 8.4%**)	0.7 – 1.1**
		Lymphoma	Low	36-52 wks 2-4.5 yrs**	-0.2%** (0.5%**)	0.6 – 1.7**
	Safety. Less safe	Infusion and injection-site reactions	Low	18-52 wks	7 – 12% (3 – 9%)	2.3 – 3.2

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence[†]	Time points	Absolute risk difference[‡] (% in group 2)	Relative risk[§] (95% CI)
Adalimumab vs. placebo	**Induction of remission.** No difference	Fistula response Patient-reported outcomes	Low High	4 wks 4 wks	-17 – 58% (17%) 2 – 15 pts[¶] (15 pts[‖])	NA NA
	Maintenance of remission. More effective	Hospitalizations Surgeries Reduction of steroids	Moderate Moderate Moderate	52 wks 52 wks 26 wks; 52 wks	NA NA[‖‖] Wk 26, 29% (3%) Wk 52, 20% (6%)	HR, 0.3 (0.2 - 0.6) NA[‖] Wk 26, 10.5 (2.6 - 42.0) Wk 52, 4.25 (1.6 - 11.5)
	Maintenance of remission. No difference	Patient-reported outcomes	Moderate	22-24 wks; 52-56 wks	Wk 22-24, 14 – 19 pts[¶] (-10 - -19 pts[‖]) Wk 52-56, 14 – 22 pts[¶] (-10 - -25 pts[‖])	NA
	Safety. No difference	Mortality, lymphoma	Low	4-52 wks	< 5 events	< 5 events
	Safety. Less safe	Infusion and injection-site reactions	Low	4-52 wks	1 – 13% (10 – 16%)	1.1 – 2.0
Certolizumab pegol vs. placebo	**Induction of remission.** No difference	Fistula response Patient-reported outcomes	Low High	26 wks 12 wks 26 wks	-1% (31%) Wk 12, 11 pts[¶] (18 pts[‖]) Wk 26, 5 pts[¶] (21 pts[‖])	1.0 (0.6 – 1.7) NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality, lymphoma Infusion and injection-site reactions	Low Low	12-26 wks 12-26 wks	< 5 events -12 – 2% (3 – 15%)	< 5 events 0.2 – 1.7

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Infliximab vs. azathioprine	**Induction of remission.** More effective	Mucosal healing	Moderate	26 wks	Absence of ulcers, 13% (17%)	Absence of ulcers, 1.8 (1.1 – 3.1)
	Induction of remission. No difference	Patient-reported outcomes	Moderate	26 wks	9¶ (31‖)	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality , all cancers	Low	54 wks	< 5 events	< 5 events
		Infections	Low	54 wks	-1 – 1% (6 – 45%)	0.9 – 1.0
	Safety. Less safe	Infusion and injection-site reactions	Low	54 wks	11% (6%)	3.0 (1.5 – 6.1)
TNF-alpha inhibitor + immunomodulator vs. no therapy	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Lymphoma	Low	2 yrs**	NA	IRR, 1.5 events/py** (0.04 – 8.7**)
		All cancers	Low	2 yrs**	NA	IRR, 0.9 events/py** (0.6 – 1.4**)
		Infections	Low	2 yrs**	NA	IRR, 2.2 – 4.8**

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Infliximab + immunomodulator vs. infliximab alone	**Induction of remission.** More effective	Mucosal healing	Moderate	26 wks	Absence of ulcers, 14% (30%)	Absence of ulcers, 1.5 (1.0 – 2.1)
	Induction of remission. No difference	Patient-reported outcomes	Moderate	26 wks	5¶ (40‖)	NA
	Maintenance of remission. No difference	Mucosal healing	Low	104 wks	Absence of ulcers, 3% (61%)	Absence of ulcers, 1.1 (0.7 -1.6)
	Safety. No difference	Mortality	Low	1-2 yrs 12 wks-2 yrs**	< 5 events	< 5 events
		Lymphoma	Low	2 yrs**	< 5 events	< 5 events
		All cancers	Low	48-104 wks 2 yrs**	2%** (1%**)	3.1** (0.7 – 13.0**)
		Infections	Low	48-104 wks NR**	-1 – 30% (5 – 25%) -15%** (20%**)	0.8 – 3.2 0.1** (0.0 – 3.3**)
		Tuberculosis	Low	52 wks	NA	NA
		Infusion and injection-site reactions	Low	52-104 wks 52-140 wks**	-12 – 3% (5 – 17%) -27 – -7%** (22 – 41%**)	0.3 – 1.5 0.3 – 0.6**
Infliximab + immunomodulator vs. immunomodulator alone	**Induction of remission.** More effective	Mucosal healing	Moderate	26 wks	Absence of ulcers, 27% (17%)	Absence of ulcers, 2.7 (1.7 – 4.3)
	Induction of remission. No difference	Patient-reported outcomes	Moderate	26 wks	14¶ (31‖)	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality	Low	54 wks	< 5 events	< 5 events
		All cancers	Low	24-54 wks	< 5 events	< 5 events
		Infections	Low	52-54 wks	-3 – -2% (6 – 45%)	0.7 – 0.9
		Tuberculosis	Low	52 wks	< 5 events	< 5 events
		Infusion and injection-site reactions	Low	52-54 wks	-1% (6%)	0.9 (0.4 – 2.3)

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Infliximab + immunomodulator vs. corticosteroids	**Induction of remission.** More effective	Mucosal healing	Low	104 wks	Absence of ulcers, 43% (30%)	Absence of ulcers, 2.4 (1.2 – 4.6)
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality, lymphoma Infections	Low Low	2 yrs** 104 wks	< 5 events -8 – 3% (5 – 48%)	< 5 events 0.4 – 1.3
Infliximab + thiopurine vs. infliximab + methotrexate	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Infusion and injection-site reactions	Low	52 wks	1 – 4% (13 – 14%)	1.1 – 1.4
TNF-alpha inhibitor + immunomodulator + corticosteroids vs. no therapy	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Lymphoma All cancers Infections	Low Low Low	2 yrs** 2 yrs** 2 yrs**	NA NA NA	IRR, 0 events/py** (0 to 30.0**) IRR, 0.7 events/py** (0.1 to 2.1**) IRR, 4.1**
Infliximab + methotrexate vs. infliximab	**Induction of remission.** More effective	Patient-reported outcomes	Low	48 wks	22 pts¶ (28 pts‖)	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. NA	NA	Insufficient	NA	< 5 events	< 5 events

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Infliximab + corticosteroids vs. no therapy	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Lymphoma	Low	2 yrs**	NA	IRR, 0 events/py** (0 to 6.5**)
		All cancers	Low	2 yrs**	NA	IRR, 0.6 events/py** (0.3 to 1.0**)
		Infections	Low	2 yrs**	NA	IRR, 0.7 – 2.7**
Infliximab + corticosteroids vs. infliximab	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	All cancers	Low	2-9 yrs**	< 5 events	< 5 events
		Infusion and injection-site reactions	Low	2 yrs**	< 5 events	< 5 events
Immunomodulator vs. placebo	**Induction of remission.** No difference	Reduction of steroids	Low	16 wks	NA***	NA
		Fistula response	Low	17 wks	2% (11%)	
		Patient-reported outcomes	Low	8-16 wks	NA†††	NA
	Maintenance of remission. More effective	Reduction of steroids	Moderate	26 wks	NA‡‡‡	NA‡‡‡
	Safety. No difference	Mortality	Low	48 wks-2 yrs 2-7 yrs**	-0.4 – 1.4%** (0.9 - 6.9%**)	0.7 – 1.3**
		Lymphoma	Low	2-8 yrs**	-0.1 - 0.2%** (0.1 - 0.3%**)	0.3 – 3.3**
		Cervical cancer	Low	3 yrs**	NA	3.5** (0.8 – 14.5**)
		All cancers	Low	2 yrs 2-8 yrs**	0 – 3%** (1 – 4%**)	1.1 – 2.1**
		Infections	Low	48 wks-2 yrs 99 wks**	-5 – 13% (6 – 19%) 0%** (2%**)	0.5 – 2.0 1.0** (0.7 – 1.4**)
	Safety. Less safe	Infusion and injection-site reactions	High	16 wks	19% (2%)	5.8 (1.7 to 19.2)

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Azathioprine vs. methotrexate	**Induction of remission.** Less effective	Fistula response	Low	16 wks	-42% (67%)	0.4 (0.1 – 2.2)
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. NA	NA	Insufficient	NA	NA	NA
Azathioprine vs. corticosteroids	**Induction of remission.** Less effective	Fistula response	Low	16 wks	< 5 events	< 5 events
	Maintenance of remission. More effective	Mucosal healing	Moderate	52 wks	Absence of ulcers, 55% (5%)	Absence of ulcers, 11.5 (2.9-45.4)
	Safety. No difference	Mortality All cancers Infections	Low Low Low	1-2 yrs 2 yrs 78-104 wks	< 5 events < 5 events -23 – 18% (2 – 32%)	< 5 events < 5 events 0.3 – 3.0
Azathioprine vs. sulfasalazine	**Induction of remission.** Less effective	Fistula response	Low	16 wks	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality, all cancers	Low	2 yrs	< 5 events	< 5 events
		Infections	Low	2 yrs	-5 – 3% (4 – 29%)	0.6 – 1.7
Thiopurine and prednisone vs. placebo	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Lymphoma	Low	2 yrs**	NA	IRR, 0 events/py** (0 – 48.9**)
		All cancers	Low	2 yrs**	NA	IRR, 0 events/py** (0 – 1.4**)
		Infections	Low	2 yrs**	NA	IRR, 1.2 – 5.4 events/py**

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence[†]	Time points	Absolute risk difference[‡] (% in group 2)	Relative risk[§] (95% CI)
Azathioprine and prednisone vs. azathioprine	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality	Low	7 mos	< 5 events	< 5 events
Immunomodulator and corticosteroids vs. corticosteroids	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Infections	Low	16 – 28 wks	-1 – 3% (11 – 13%)	0.9 – 1.3
Thiopurine and ASA vs. thiopurine	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Lymphoma All cancers Infections	Low Low Low	4 yrs** 4 yrs** 4 yrs**	< 5 events < 5 events < 5 events	< 5 events < 5 events < 5 events
Methotrexate IM vs. placebo	**Induction of remission.** No difference	Patient-reported outcomes	Moderate	16 wks	15 pts[¶] (-8 pts[‖])	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. NA	NA	Insufficient	NA	NA	NA
Methotrexate oral vs. placebo	**Induction of remission.** No difference	Patient-reported outcomes	Low	12-16 wks 38 wks	NA[§§§]	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. NA	NA	Insufficient	NA	NA	NA

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence[†]	Time points	Absolute risk difference[‡] (% in group 2)	Relative risk[§] (95% CI)
Budesonide vs. placebo	**Induction of remission.** More effective	Patient-reported outcomes	Low	8 wks	7 – 30 pts[¶] (10 – 29 pts[‖])	NA
	Maintenance of remission. No difference	Patient-reported outcomes	Low	3 mos 6 mos 12 mos	Mos 3, 11 – 15 pts[¶] (-27 – -4 pts[‖]) Mos 6, 2 – 10 pts[¶] (-28 pts[‖]) Mos 12, 2 – 8 pts[¶] (-31 pts[‖])	NA
	Safety. NA	NA	Insufficient	NA	NA	NA
Prednisone vs. placebo	**Induction of remission.** More effective	Fistula response	Low	16 wks	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. Less effective	Mortality	Low	2 yrs 2-7 yrs**	0.3 – 0.7%** (0.6 – 6.9%**)	1.0 - 2.5**
	Safety. No difference	Lymphoma Cervical cancer All cancers Infections Bone fractures	Low Low Low Low Low	2-4 yrs** 3 yrs** 2 yrs** 8-104 wks 2 yrs** NR**	0%** (0.1%**) NA NA -6 – 19% (6 – 19%) 2 – 8%** (1 – 14%**) -1 – 7%** (1 – 17%**)	1.0** 2.8** (0.7 to 11.0**) IRR, 0 events/py** (0 – 0.7**) 0.2 – 2.9 1.7 – 2.9** 1.4 – 4.1**
Budesonide vs. prednisone	**Induction of remission.** No difference	Patient-reported outcomes	Moderate	8 wks	8 pts[¶] (26 pts[‖])	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Bone fractures	Moderate	2 yrs	-1% (2%)	0.7 (0.1 – 3.8)

Table E. Summary of the conclusions and strength of evidence on the comparative effectiveness and safety of pharmacologic therapies used in the management of adults with Crohn's disease for non-disease activity index outcomes where the strength of evidence was at least low (continued)

Comparison (group 1 vs. group 2)	Conclusions*	Outcomes reported	Strength of evidence†	Time points	Absolute risk difference‡ (% in group 2)	Relative risk§ (95% CI)
Prednisone vs. 5ASA	**Induction of remission.** No difference	Fistula response Patient-reported outcomes	Low Moderate	17 wks 2 wks 12 wks	8% (22%)	1.4 (0.3 – 6.3)
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality All cancers Infections	Low Low Low	2 yrs 2 yrs 2 yrs	< 5 events < 5 events -16 – 18% (3 – 29%)	< 5 events < 5 events 0.4 – 2.8
Corticosteroids + ASA vs. other treatment	**Induction of remission.** NA	NA	Insufficient	NA	NA	NA
	Maintenance of remission. NA	NA	Insufficient	NA	NA	NA
	Safety. No difference	Mortality Infections	Low Low	2 yrs 8 wks	< 5 events -28% (72%)	< 5 events 0.3 (0.1 – 0.8)
ASA vs. placebo	**Induction of remission**. More effective	Fistula response	Low	17 wks	NA	NA
	Maintenance of remission. No difference	Patient-reported outcomes	Low	48 wks	1 pt¶ (-14 pts‖)	NA
	Safety. No difference	Mortality Lymphoma Cervical cancer All cancers Infections	Low Low Low Low Low	48 wks-2 yrs 7 yrs** 4 yrs** 3 yrs** 2 yrs 2 yrs	-1.5%** (8.3%**) 0%** (0.1%**) NA NA 1 – 10% (13 – 19%)	aOR, 0.7** (0.5 to 1.1**) 1.0** (0.3 to 2.6**) 1.7** (0.3 to 8.0**) NA 1.1 – 1.8

ASA = aminosalicylates; CI = confidence interval; IM = intramuscular; IRR = incidence rate ratio; mos = months; NA = not applicable; NR = not reported; OR = odds ratio; pts = points; py = person-years; TNF = tumor necrosis factor; vs = versus; wks = weeks; yrs = years

* Conclusions are written comparing group 1 with group 2.

† The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

‡ The risk difference (RD) was calculated as the percent of patients in Group 1 in remission minus the percent of patients in Group 2 in remission. The risk difference was only calculated when at least 5 events occurred in a study.

§ The risk ratio (RR) was calculated as the percent of patients in Group 1 in remission divided by the percent of patients in Group 2 in remission. Unless reported in the study itself, only calculated when at least 5 events occurred in a study. The range of risk ratios is presented when there was more than one study where we were able to calculate a risk ratio.

¶ Inflammatory Bowel Disease Questionnaire (IBDQ) between-group difference in the change from baseline.
‖ Inflammatory Bowel Disease Questionnaire (IBDQ) change from baseline in Group 2.
** Data obtained from observational studies. All other data presented was obtained from randomized controlled trials.
†† Crohn's Disease Endoscopic Index of Severity (CDEIS) between-group difference in the change from baseline.
‡‡ Crohn's Disease Endoscopic Index of Severity (CDEIS) change from baseline in Group 2.
§§ There were 11 hospitalizations per 100 patients in the infliximab group and 31 hospitalizations per 100 patients in the placebo group ($P < 0.05$).
¶¶ There were 65 surgeries and procedures per 100 patients in the infliximab group and 126 surgeries and procedures per 100 patients in the placebo group.
‖‖ The rate of surgeries were 0.6% in the combined adalimumab groups and 3.8% in the placebo group.
*** Reduction in steroid dose from baseline, 7 mg for azathioprine and 12 mg for placebo.
††† Based on a variety of measures. For details, see the full report.
‡‡‡ The reduction in prednisone use from baseline was 9.4 mg among patients treated with azathioprine and 6.1 mg among patients treated with placebo.
§§§One study evaluated this comparison in terms of the Treatment Goal Score for Wellbeing at weeks 12-16 and 38. The scores rose to 1.2 and 2.7 points in the methotrexate group and to 1 and 1 point in the placebo group in the respective time points. The clinical and statistical significance of these increases are unclear.

Discussion

Summary of Key Findings for Adults

We did not identify a single medication or class of medications that was most effective at inducing and maintaining remission, while producing the highest quality of life and the best safety profile. We were able to identify medications that were efficacious in inducing or maintaining short-term (less than 1 year) remission according to the disease activity scales, with high strength of evidence for KQ1 and KQ2. We found that no medication or combination of medications was consistently associated with increased adverse effects across the safety outcomes of interest for KQ3. Only one RCT was identified that measured a patient-reported outcome after intestinal resection for KQ4, and no difference was found between the medications compared.

Summary of Key Findings for Children

Only eight studies were identified that reported on pediatric outcomes. The strength of evidence was low or insufficient to support the effectiveness of any medication in inducing or maintaining remission in pediatric Crohn's disease for KQ1 and KQ2. No pediatric study reported on a serious adverse event such as mortality, progressive multifocal leukoencephalopathy, lymphoma, or other cancers for KQ3. No pediatric study reported on a patient-reported outcome for KQ1, KQ2, or KQ4.

Comparison to Other Systematic Reviews

Other systematic reviews have reported on the efficacy and safety of treatments designed to induce or maintain remission in Crohn's disease.[6 46-55] The most recent systematic review was performed by the American College of Gastroenterology (ACG) Task Force.[53] The ACG Task Force review was similar to our review in that we applied similar inclusion criteria across medication classes. The strength of evidence and direction of the associations were generally consistent between our review and those of the ACG Task Force review, Cochrane reviews, and other reviews across the classes of medications. Compared to other recent reviews, we included multiple outcomes associated with treatment aimed at achieving remission; specifically included mortality, PML, HSTCL, other lymphomas and cancers, serious infections and infusion reactions; and we reviewed and graded the strength of evidence separately for safety and efficacy and according to clinically relevant time points.

Limitations

The major limitations in our review were: (a) the inability to perform meta-analyses of all comparisons, (b) potential measurement error, and (c) no established standard for a clinically meaningful difference in remission or safety related outcomes.

Other limitations should also be mentioned: (a) Many of the observational studies were not designed to examine the medication-outcome relationships that we abstracted from them, resulting in low study quality as a result of poor reporting and bias control for our comparison of interest. (b) A majority of the trials were sponsored by the manufacturers of the medications, a

situation that has been associated with the reporting of results that are more favorable than those of studies not supported by industry.[56] (c) Meta-analyses indicated publication bias, especially for corticosteroids and 5-aminosalicylate acids. (d) We excluded non-English articles. (e) We only included information from peer-reviewed journals, excluding information reported in abstract-only form, which has been shown to differ from the subsequent peer-reviewed articles.[57][58]

Future Research Needs

The major future research needs include: (a) evidence to support the induction and maintenance of remission in patients with complicated and severe Crohn's disease (defined later); (b) evidence to support the most effective treatment strategy over at least 5 years, instead of 1-2 years; (c) reporting on efficacy outcomes other than the CDAI, especially mucosal healing outcomes, as recommended by the FDA in 1995;[59] (d) ensuring that observational studies for safety are sufficiently long to allow observation of the outcomes produced by the treatment; (e) performing trials and safety studies in children; (f) incorporating patient-reported outcomes into post-surgical relapse studies; (g) comparing medications and medication classes head-to-head to provide evidence concerning the step-up versus the top-down treatment approach; and (h) performing more studies of newly diagnosed patients.

Additional future research needs include: (a) the inclusion of non-white patients in RCTs and safety studies; (b) performing head-to-head comparisons, especially for the biologics for which such studies were identified; (c) performing head-to-head trials of biologics and immunomodulators that include all thiopurine methyltransferase (TPMT) phenotypes, because an unacceptable TPMT metabolism level does not prohibit treatment in the clinical setting; (d) identifying treatments to induce and maintain remission in patients who do not respond to biologics, because these patients were excluded from many of the maintenance trials; (e) specifying safety outcomes in advance and including them as primary or secondary outcomes in RCTs; (f) clarifying whether safety outcomes associated with medication efficacy (such as disease flare and abscess) are safety outcomes or efficacy outcomes; (g) clearly accounting for the use of other medications in both RCTs and observational studies, so that the independent effect of the medication of interest is more clear; (h) accounting for other confounders in observational studies and examining the reasons for the imbalance in potential confounders in the setting of RCTs; (i) conducting and reporting subgroup analyses appropriately in pre-specified groups and using interaction terms; (j) consistently reporting outcomes in text and figures, especially for clinically relevant time points other than the primary outcome time point; and (k) in the case of extremely rare safety-related outcomes that are likely to be reported in case reports, such as progressive multifocal leukoencephalopathy or hepatosplenic T-cell lymphoma, emphasizing in these reports the criteria used to estimate the causal relationships, such as the McMaster Quality Assessment Scale of Harms.[60]

Opportunities for the Crohn's Disease Community to Address the Identified Limitations and Future Research Needs

The Crohn's disease community could address the limitations identified here by: (a) creating registries that include both adult and pediatric patients to measure safety outcomes that are unlikely to occur in RCTs, such as lymphoma and other cancers; (b) working collaboratively as a

community to create evidence-based treatment algorithms and guidelines based on the best available evidence, and updating the guidelines regularly as new evidence becomes available; (c) identifying the most important measures of remission and most important safety outcomes that should be measured in all RCTs; and (d) determining the need for RCTs of medications that are not currently approved for the treatment of Crohn's disease, such as immunomodulators, corticosteroids, and 5-aminosalicylate acids, possibly comparing these medications head-to-head and in combination to inform the top-down versus step-up treatment strategy. Ideally, the registries, guidelines, and RCTs should be performed in a manner that is independent of industry support and with minimal conflict of interest to prevent the biases that are sometimes inherent in industry-sponsored research.

Introduction

Background

Description of Disease

Crohn's disease is characterized by chronic full thickness inflammation that can occur anywhere in the gastrointestinal tract, but most often affects the small bowel and colon. Typical symptoms include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[2] Ten percent of Crohn's disease patients are children under the age of 17.[3]

The activity of Crohn's disease fluctuates over time, frequently leading to complications that require surgical intervention. One study estimated that during the first seven years after diagnosis, 20% of Crohn's disease patients will have active disease at least once each year, 67% will fluctuate between years of active disease and years in remission, and 13% will have no relapses after the initial disease episode.[61] The most common complications of Crohn's disease include fibrotic narrowing of the intestines (stricture) which can lead to obstruction, collections of pus in the abdomen or around the rectum (abscess), and spontaneous rupture of the bowel contents through the skin or other organs (fistula). In a cohort from Olmsted County, Minnesota, half of all patients had experienced at least one intestinal complication within 10 years of diagnosis.[62] Similarly, half of patients will require at least one surgical resection within 10 years of diagnosis when considering two reports from Olmsted County, Minnesota.[62]

Crohn's disease is thought to be caused by an inappropriate immune response to intestinal microbes in a genetically susceptible individual.[63] Usually, the diagnosis is established by endoscopy with biopsies showing focal ulcerations and acute and chronic inflammation consistent with Crohn's disease.

Interventions to Treat Crohn's Disease

Dr. Burrill Crohn's initial description of this disease suggested that it could be cured with wide surgical resection, which is now known to be false.[64] Medications are now used to treat the intestinal inflammation with the intent of altering the natural history of the disease. Sulfasalazine and corticosteroids have been used since the middle of the last century to treat Crohn's disease. Immunomodulators such as 6-mercaptopurine, azathioprine, and methotrexate have been considered for the treatment of Crohn's disease since the 1970s, although the use of these medications was not routine until the 1990s.[4] The first biologic tumor necrosis factor-alpha (TNF-alpha) inhibitor, infliximab, was approved for Crohn's disease in 1998. The Food and Drug Administration (FDA)-approved TNF-alpha inhibitor biologics also include adalimumab and certolizumab pegol.[1] Other biologic agents include natalizumab and ustekinumab. Table 1 summarizes the Crohn's disease medications (aminosalicylates, corticosteroids, immunomodulators, and biologics), their mechanisms of action, and FDA approval status.

Current Controversies in the Treatment of Crohn's Disease

One Institute of Medicine Comparative Effectiveness Research priority is to compare algorithms for Crohn's disease treatment that introduce biologics at different timepoints in the disease course.[65] Another controversy is the use of biologics in combination with immunomodulators. Early use of immunomodulators and biologics ("top-down therapy"), have been recently advocated rather than after prolonged use of steroids ("step-up therapy"), with the expectation of better long-term outcomes.[66] The benefits of this early treatment approach need to be weighed against the risks of increased immunosuppression, including lymphoma,[67] and expense and harms of over-treating the 40% of patients who will not receive an intestinal resection and 70% of patients who will not have aggressive, disabling disease.[2] The major challenge and focus of current research is improving the natural history of disease while minimizing adverse events and interventions, such as surgeries.[68]

Treatment Guidelines and Meta-Analyses on the Management of Crohn's Disease

Treatment guidelines exist for the management of Crohn's Disease, often combining evidence-based medicine with expert panel review when evidence-based research is sparse. In the United States, the American College of Gastroenterology, the American Gastroenterological Association, and the American Society of Colon and Rectal Surgeons publish management guidelines for Crohn's disease.[1 69-74] The treatment guidelines point to controversial areas in need of future research including: treatments to achieve long-term remission; the benefits and harms of step-up versus top-down treatment strategies; and further evidence on optimizing the use of biologic agents given that many patients' disease can be managed with traditional treatments. This report addresses these aims.

Previous Systematic Reviews

Meta-analyses have examined individual medications compared to placebo but few have compared medications directly. Numerous high-quality meta-analyses have compared aminosalicylates, corticosteroids, immunomodulators, and biologics to placebo (there are 43 meta-analyses for Crohn's disease; 18 from the Cochrane Collaboration). A recent high-quality meta-analysis of randomized control trials (RCTs) published through February 2009 examined the efficacy of treatments after surgical resection, but did not report on the quality of life effects.[10] Few meta-analyses reported quality of life, although quality of life remains a high priority topic for patients. The central question for patients and their caretakers is the comparison of medications to each other at relevant time points in the natural history of disease. This report focuses on these questions and includes comparison of combinations of medications.

Scope of the Evidence Report and Key Questions

As displayed in Figure 1, the purpose of this review is to compare the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of moderate-to-severe Crohn's disease. The specific key questions (KQ) of interest are:

KQ1: What is the comparative effectiveness of therapies alone or in combination used to induce remission in adults and children with moderate-to-severe Crohn's disease?

KQ2: What is the comparative effectiveness of therapies alone or in combination used to maintain remission in adults and children with moderate-to-severe Crohn's disease?

KQ3: What is the comparative safety of therapies alone or in combination used in adults and children with moderate-to-severe Crohn's disease in terms of minimizing short- and long-term adverse effects?

KQ4: What is the comparative effectiveness of agents used to prevent post-operative recurrence in Crohn's disease as pertains to patient-reported outcomes?

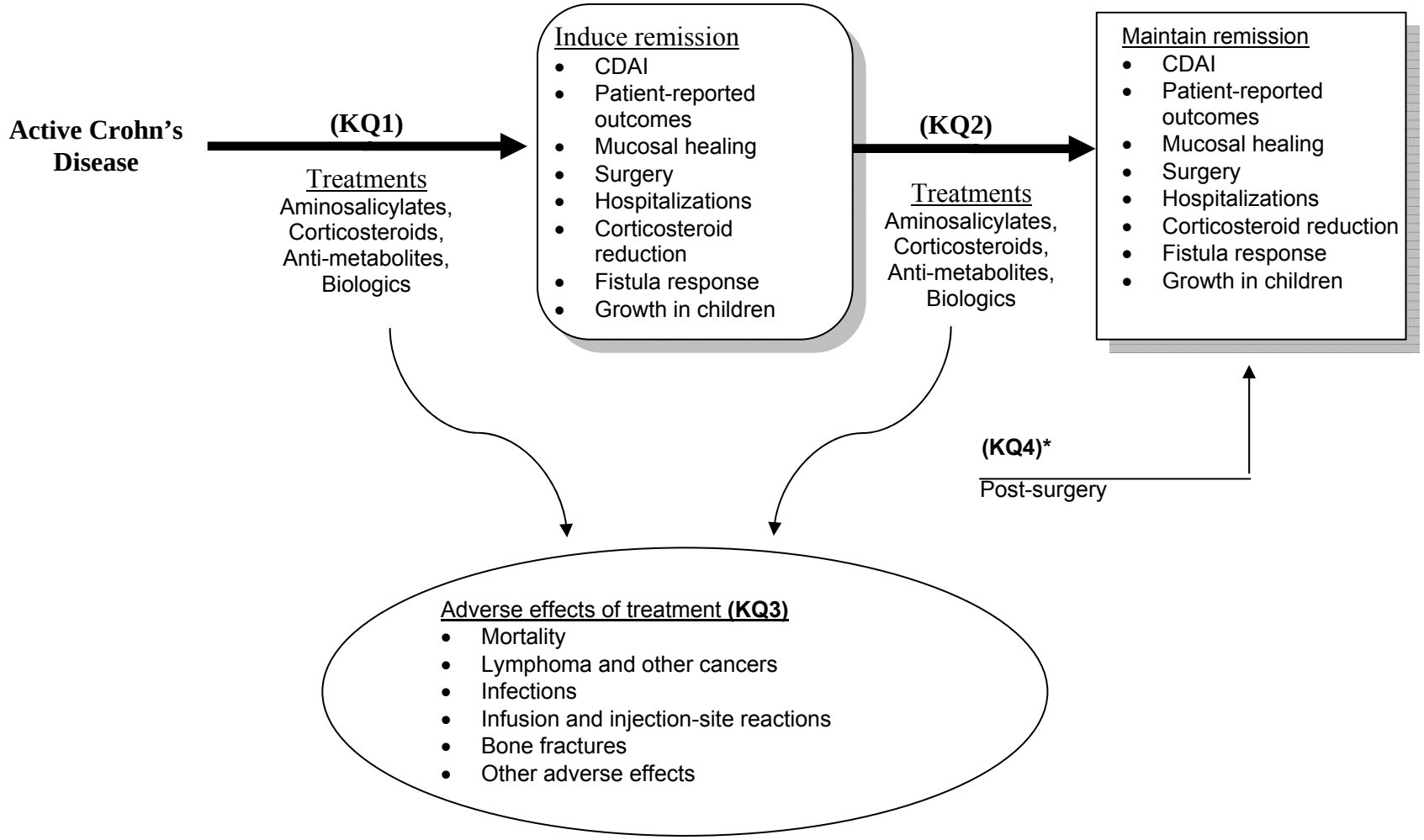
For each KQ, we aimed to evaluate specific outcomes as listed in Table 2.

Table 1. List of medications used for treatment of Crohn's disease

Class	Generic name	US trade name	Route	Half-life	Mechanism of Action	FDA approved for CD in adults	FDA approved for CD in children
Aminosalicylate	Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No
Aminosalicylate	Mesalamine	Asacol, Canasa, Pentasa, Lialda, Rowasa	Oral, rectal	2-15 hours	Inhibits reactions involving inosinic acid	No	No
Anti-metabolite	Azathioprine	Azasan; Imuran	Oral, intravenous	5- hours	Purine synthesis inhibitor	No	No
Anti-metabolite	Methotrexate	Methotrexate LPF	Intravenous, oral	3-15 hours	Works through adenosine receptor	No	No
Anti-metabolite	6-mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis and metabolism inhibitor	No	No
Biologic	Adalimumab	Humira	Subcutaneous	10-18 days	TNF-alpha inhibitor	Yes	No
Biologic	Infliximab	Remicade	Intravenous	9.8 days	TNF-alpha inhibitor	Yes	Yes
Biologic	Certolizumab pegol	Cimzia	Subcutaneous	~14 days	TNF-alpha inhibitor	Yes	No
Biologic	Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers	Yes	No
Biologic	Ustekinumab	Stelara	Subcutaneous	15-46 days	Interleukin-12 and interleukin-23 inhibitor	No	No
Corticosteroid	Prednisone, prednisolone, 6-methylpredisolone, hydrocortisone, budesonide	Cortef, Entocort	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm, where it upregulates anti-inflammatory genes	No	No

CD = Crohn's disease; FDA = Food and Drug Administration; TNF = tumor necrosis factor; US = United States

Figure 1. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease



*For KQ4, the only examined endpoint will be patient-reported outcomes.
CDAI = Crohn's Disease Activity Index; KQ = Key Question
KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for post-surgical patient-reported outcomes

Table 2. List of outcomes considered for each key question on the comparative effectiveness and safety of medications for treatment of Crohn's disease

Key Question	Outcomes
KQ1	• Disease activity indexes (remission, response, CDAI, PCDAI, HBI, or other disease activity indexes) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (complete or partial fistula closure or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life indexes, IBDQ, days of work or school missed)
KQ2	• Disease activity indexes (relapse, loss of response, CDAI, PCDAI, HBI, or other disease activity indexes) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (fistula recurrence or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life indexes, IBDQ, days of work or school missed)
KQ3	• Mortality • Lymphomas • Cervical cancer • Other cancers • Tuberculosis • Serious infections • Other infections • Infusion- and injection-site reactions • Bone fractures • Height and weight (for pediatric studies only)
KQ4	• Patient-reported outcomes (health-related quality of life indexes, IBDQ, days of work or school missed)

CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = key question; PCDAI = Pediatric Crohn's Disease Activity Index

KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for post-surgical patient-reported outcomes

Methods

This topic was nominated by a lay person with Crohn's disease who was frustrated by the lack of consensus among physicians about her treatment options after surgical resection. Her experience reflects the general lack of consensus about pharmacologic therapies for the management of Crohn's disease. Our Evidence-based Practice Center (EPC) established a team and a work plan to develop the evidence report. The project involved recruiting technical experts, formulating and refining the questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review and public comment.

Topic Development

At the beginning of the project, we recruited a panel of key informants to give input on the selection and refinement of the questions to be examined. The key informants included a clinical expert in the management of Crohn's disease from the Johns Hopkins University Division of Gastroenterology, a patient with Crohn's disease, external clinician-investigators having experience in research on treatment of Crohn's disease, and a pharmaceutical company representative. Our draft Key Questions were posted on AHRQ's website for public comment in March 2010.

With the key informants, representatives of AHRQ, and public comments, we developed the Key Questions that are presented in the Scope and Key Questions section of the Introduction. The final Key Questions focus on the comparative effectiveness and safety of individual and combined therapies for Crohn's disease, including biologics, immunomodulators, corticosteroids, and aminosalicylates, in terms of: (1) induction of remission, (2) maintenance of remission, (3) adverse effects, and (4) patient-reported outcomes after surgical resection.

We drafted a protocol to address these Key Questions. We then recruited a panel of technical experts, which included the key informants, an epidemiologist, and a pediatric gastroenterologist. With input from the technical expert panel and representatives from AHRQ, we finalized the protocol.

Search Strategy

We searched the following databases for primary studies from inception through June 2010: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject heading (MeSH) terms and text words of key articles identified a priori (Appendix A).

To identify additional studies, we reviewed the following material from the EPC Program's Scientific Resource Center:

- Medical and/or statistical reviews of natalizumab, infliximab, adalimumab, certolizumab pegol, hydrocortisone, prednisone, prednisolone, and mesalamine from the Food and Drug Administration (FDA) website,
- Health Canada Product Monographs for ustekinumab, natalizumab, infliximab, adalimumab, certolizumab pegol, azathioprine, 6-mercaptopurine, methotrexate, hydrocortisone, and 6-methylprednisolone,

- Public registries of clinical trials, including the Clinical Study Results website (www.clinicalstudyresults.org) and ClinicalTrials.gov (www.clinicaltrials.gov).

We also reviewed the reference lists of each included articles and relevant review articles.

To assess the risk of one of the most serious rare complications of treatment for Crohn's disease, hepatosplenic T-cell lymphoma, the primary search strategy was supplemented by also searching for cases reported to the FDA's Adverse Event Reporting System (AERS).

The results of the searches were downloaded and imported into ProCite® version 5 (ISI ResearchSoft, Carlsbad, CA). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in ProCite®. From ProCite, the articles were uploaded to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a web-based software package developed for systematic review data management. We used this database to track the search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

Two independent reviewers conducted title scans in parallel. For a title to be eliminated at this level, both reviewers had to indicate that it was ineligible (Appendix B, Title Review Form). If they disagreed, the article was promoted to the next level. The title review was designed to capture as many studies as possible that potentially reported on the efficacy or safety of therapies for the management of Crohn's disease.

Abstracts were reviewed independently by two investigators, and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 3 and the Abstract Review Form in Appendix B). Differences between investigators regarding abstract inclusion or exclusion were resolved through consensus adjudication.

Articles promoted on the basis of abstract review underwent another independent parallel review to determine if they should be included for data abstraction (Appendix B, Article Review Form). Differences regarding article inclusion were resolved through consensus adjudication. A third reviewer audited a random sample of abstract and article reviews to ensure consistency in the reviewing process.

For KQ1 and KQ2 to evaluate induction and maintenance of remission, we included randomized controlled trials (RCTs) exclusively. Both placebo-controlled and head-to-head trials were eligible. We did not include trials that examined only the same medication administered at different time points or at different dosages. The outcomes of interest for KQ1 and KQ2 were chosen to represent clinically important and patient-centered outcomes.

For KQ3 to evaluate the safety of treatment, we included RCTs and observational studies. Specific safety outcomes were chosen based on the severity of the outcome, impact on quality of life, and potential for safety to differ by medication class. Clinical outcomes were selected a priori for inclusion. All RCTs that reported on safety were eligible. Observational studies were eligible if they reported a relevant comparison group with clear numerators and denominators for each group or an effect estimate or p-value for a safety outcome by medication use. Because of the rarity and severity of hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we included all study types (including case reports) for these outcomes.

We found that a rigorously conducted systematic review[10] had recently assessed the efficacy and safety of medications to maintain remission of Crohn's disease after intestinal resection. Instead of duplicating that work, we limited the focus of KQ4 to the comparative effects of medications on patient-reported outcomes (which were not included in the previous review) as reported in RCTs and observational studies.

Table 3. Inclusion and exclusion criteria for identifying eligible studies

Population and condition of interest	• Included studies of human subjects of all ages with moderate-to-severe Crohn's disease • Excluded studies if they included only pregnant women. • Sensitivity analyses for all Key Questions included all levels of disease severity. Sensitivity analysis for KQ3 included any inflammatory bowel disease.
Interventions	• Included studies evaluating a Crohn's disease medication of interest (see Table 1) or combination of medications of interest compared with each other or with placebo.
Comparisons of interest	• Excluded studies that did not have a comparison group, where the comparison was either a medication or combination of medications of interest or placebo. o Excluded studies that compared a medication of interest to a medication not of interest (such as antibiotics or fish oil supplements). o Excluded studies that only evaluated the same medication given at different times or at different doses.
Outcomes	• Excluded studies that did not apply to the Key Questions. • Included the following outcomes for KQ 1 and 2: Crohn's disease activity index (CDAI), patient-reported outcomes representing quality of life, mucosal healing, surgery, hospitalizations, corticosteroid reduction, and fistula response. • Included the following harms of medications for KQ 3: mortality, lymphomas, cervical cancer, other cancers, tuberculosis, serious infections, other infections, infusion and injection-site reactions, bone fractures, and height and weight in children. • Included the following patient-reported outcomes for KQ 4: generic and disease-specific quality of life indices (e.g., IBDQ), and days of work or school missed.
Type of study	• Excluded articles not written in English, articles with no original data (reviews, editorials, comments, letters), and abstract-only publications. • Included studies with any sample size from any year that met all other criteria. • Included only RCTS for KQ 1 and 2. • Included all study designs with a comparison group, for KQ 3 and 4, including: RCTs, prospective and retrospective cohorts, crossover studies, and case-control studies. • Included all study types (including case reports) for hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy because these outcomes are very rare and frequently fatal.

IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = Key Question; RCT = randomized controlled trial

Data Abstraction

We used a systematic approach for extracting data to minimize the risk of bias in this process. We created standardized forms for data extraction, which were pilot tested. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

For all articles, reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, gender, race, duration of Crohn's disease, smoking status, disease severity, and disease location), eligibility criteria, interventions (e.g., route of administration and dosing), outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability. For KQ1, KQ2, and KQ4, we abstracted data on the following time points: (1) first time point after randomization or study start, (2) 12 to 16 weeks after randomization or study start; (3) 48 to 54

weeks after randomization or study start, and (4) last pre-specified time point. For KQ3, we abstracted data for the last reported time point only.

We abstracted information on subgroup analyses to understand how disease characteristics could modify the relationship between medications and remission The following characteristics were considered for subgroup analyses a priori because these characteristics are most clinically relevant: elevated baseline markers of inflammation (including CRP), baseline mucosal lesions, medications used at randomization (baseline), prior medication exposure, disease duration, disease location, and prior Crohn's disease-related surgery.

Each article underwent double review by study investigators for data abstraction. All information was abstracted into a graphical user interface of the DistillerSR database (Evidence Partners, Ottawa, Canada). The second reviewer confirmed the first reviewer's data abstraction within DistillerSR for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. If possible, reviewers abstracted relevant data from figures when it was not available in text or table format. Reviewers entered comments into the system whenever applicable. The DistillerSR database was used to maintain the data, as well as to generate Excel files which were used to create detailed evidence tables and summary tables.

Quality Assessment

We used study quality assessment to help us understand differences in results between studies. We used different quality assessment tools for RCTs and observational studies. For RCTs, the dual independent review of article quality was based on the Cochrane Collaboration's Risk of Bias Tool[11] and supplemented with items from the EPC Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13] The quality assessment for RCTs included items on: (1) adequate allocation sequence generation, (2) adequate allocation concealment, (3) blinding, (4) incomplete outcome data, (5) other potential threats to validity, (6) pharmaceutical support, (7) company involvement in the design, conduct, or reporting of the study, (8) loss to followup, and (9) an overall rating of the quality assessment. The overall study quality was assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[13]

For observational studies, we selected quality concepts from the Downs and Black quality checklist[12] and added items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13] Observational studies were assessed on: (1) clear description of main outcome to be measured, (2) clear description of patient characteristics, (3) clear description of interventions of interest, (4) clear description of the distributions of principal confounders, (5) recruitment of the different intervention groups from the same population, (6) handling of loss to followup, (7) adequate adjustment for confounding, (8) pharmaceutical support, (9) company involvement in the design, conduct, or reporting of the study, and (10) overall study quality. The overall study quality was assessed as "good" if the responses for items 1 to 7 were all "yes"; "fair" if most of the responses to items 1 to 4 were "yes" and all of the responses to items 5 to 7 were "yes"; and "poor" if none of the responses to items 1 to 4 were "yes" or any of the responses to items 5 to 7 were "no" or "unable to determine."

For the assessment of study quality, we had high consistency between the primary and secondary reviewers. Therefore, we report only the second reviewers' quality scores (the second reviewers generally had more research experience than the primary reviewers).

Applicability

Throughout the report, we discuss the applicability of studies in terms of the degree to which the study population (e.g., age, race, disease severity), interventions (e.g., dosing, frequency, duration), outcomes, and settings are typical of the treatment of individuals with moderate-to-severe Crohn's disease.

Data Analysis and Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information abstracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least 3 trials) and studies were sufficiently homogenous with respect to the population characteristics, intervention, comparison, outcome, and timing. When possible for KQ1 (induction of remission), we decided to conduct meta-analyses at the following clinically-relevant time points:

- 2 to 4 weeks (using the earliest available time point),
- 8 to 12 weeks (using earliest available time point),
- 22 to 30 weeks (using time point closest to week 26),
- 48 to 54 weeks (using latest available time point), and
- 18 to 24 months (using latest available time point).

For KQ2 (maintenance of remission), we conducted meta-analyses at these time points:

- 15 to 19 weeks (using latest available time point),
- 22 to 30 weeks (using time point closest to week 26),
- 48 to 54 weeks (using latest available time point), and
- 18 to 24 months (using latest available time point).

For KQ3 (adverse effects), the meta-analyses used the last reported time point available from at least 3 studies.

For studies amenable to pooling with meta-analyses, we calculated pooled relative risks using a DerSimonian and Laird random effects model.[14] We identified heterogeneity between the trials in all the meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10, and (2) an I-squared statistic with a value greater than 50% indicating substantial heterogeneity.[15] We did not report the pooled result if substantial heterogeneity was found. We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we conducted formal tests for publication bias using Begg's[16] and Eggers tests[17] including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses were conducted using STATA (Intercooled, version 9.2, StataCorp, College Station, TX).

When we were unable to pool trials for an outcome, we calculated and displayed risk ratios with 95% confidence intervals (CI) for the individual studies. For infrequent adverse effects, we calculated the Peto odds ratios when the combined number of events in each arm was greater than 5.[21 22]

We aimed to conduct indirect comparisons when there was an absence of head-to-head trials that met the criteria for meta-analysis. Indirect comparisons are a theoretically valid way to compare active treatments that have not been compared to one another in a head-to-head comparison. The underlying assumptions are that the populations, outcomes (type and length of follow-up), and treatment duration are comparable for randomized trials, which have a common comparator (i.e., placebo). We followed the established approach for indirect comparisons that keep randomization intact (ratio of pooled odds ratios of treatment versus placebo and of another treatment versus placebo) and calculated the precision (95% CI) based on the sum of the variances of the logarithmic form of the pooled odds ratios.[18] We based the indirect comparison on the pooled odds ratios rather than on pooled relative risks because of the more robust properties of odds ratios for making indirect comparisons.[19]

Data Entry and Quality Control

A second reviewer checked and resubmitted the data that had been abstracted into DistillerSR. Second reviewers were generally more experienced members of the research team. In addition, two additional investigators audited a random sample of the reviews to identify problems with data abstraction. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In addition, research assistants used a system of random data checks to assure data abstraction accuracy.

Rating the Body of Evidence

At the completion of our review, we graded the best available evidence addressing KQ 1 to 4 by adapting an evidence grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.[23] We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome for each population (i.e., adult versus pediatric). If necessary, we created separate evidence grades by time point. We assessed the potential for bias by study designs with RCTs considered best, followed by observational studies. We also evaluated the consistency, directness, and precision of the effects. Lastly, we considered other potential limitations to the strength of evidence, such as limited applicability.

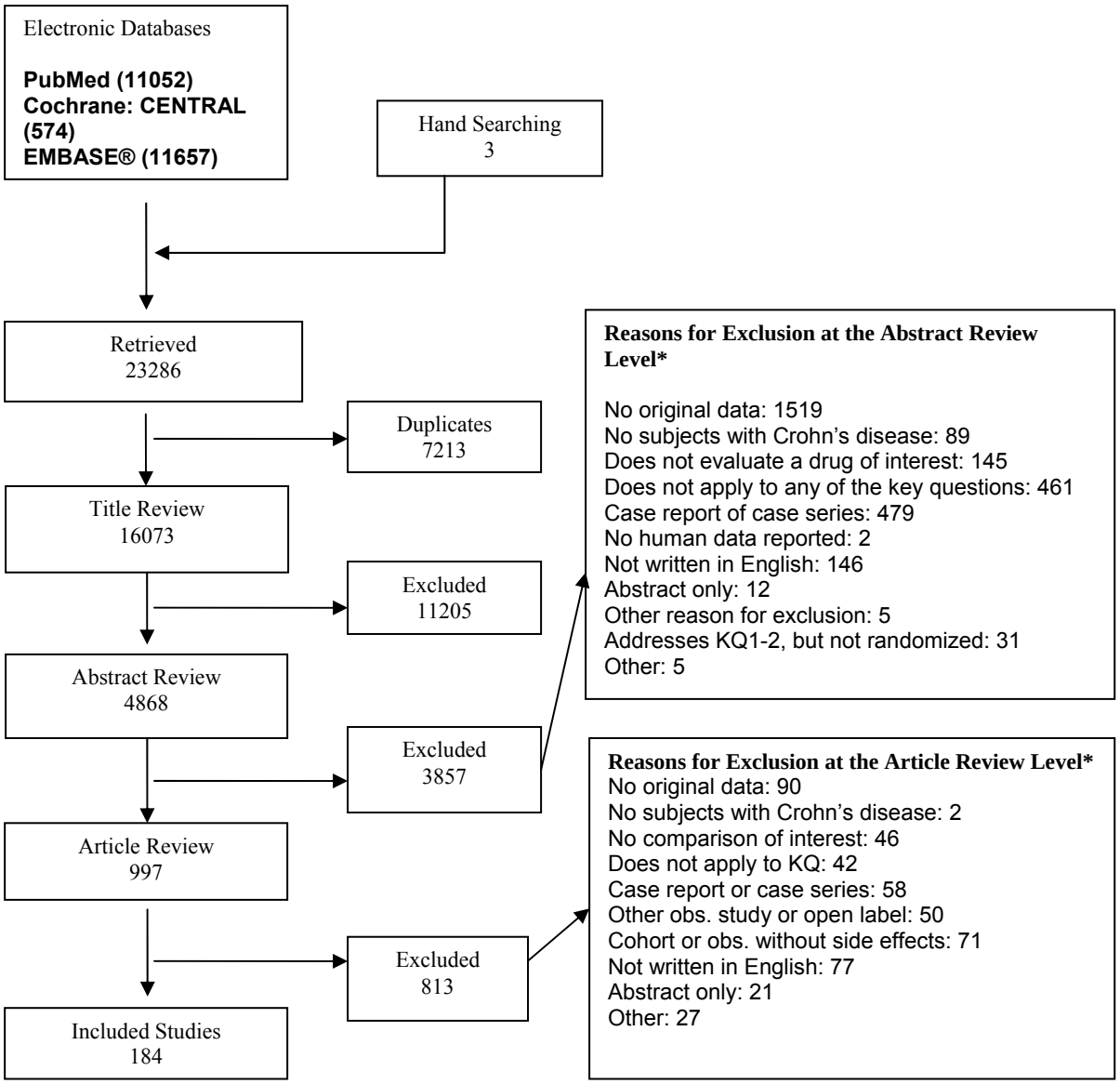
We classified the strength of evidence pertaining to KQ 1 to 4 into four basic categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (evidence is unavailable).

Results

Search Results

From our search, we retrieved 16073 unique records (Figure 2). After title and abstract review, 997 articles were deemed potentially relevant to review, and the full articles were retrieved. A total of 184 articles were included in this review (see Appendix C for list of excluded articles).

Figure 2. Summary of the literature search (number of articles)



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
CENTRAL = Central Register of Controlled Trials; obs = observational study

Adult Results

Key Question 1: What is the comparative effectiveness of therapies alone or in combination used to induce remission in adults with moderate-to-severe Crohn's disease?

Key Points

Disease Activity Indexes – Ustekinumab and Natalizumab

- The strength of evidence was low to demonstrate that one dose of intravenous ustekinumab (4.5 mg/kg) was more effective than placebo in inducing a remission at weeks 2 and 8 (absolute risk difference [RD] across time points, 12% to 16%; placebo rate, 7% to 11%).
- The strength of evidence was low to demonstrate no difference between subcutaneous ustekinumab (90 mg weekly for 4 weeks) and placebo in inducing a response or remission at week 8 (absolute RD, 1%; placebo rate, 23%).
  - The strength of evidence was low that subcutaneous ustekinumab was favored over placebo at week 2 (absolute RD, 12%; placebo rate, 12%).
- The strength of evidence was low to demonstrate that one dose of intravenous ustekinumab (4.5 mg/kg) was more effective than subcutaneous ustekinumab (90 mg weekly for 4 weeks) in inducing a remission at weeks 2 and 8 (absolute RD across time points: 8% to 10%; placebo rate, 0% to 21%).
- The strength of evidence was moderate to demonstrate no difference between natalizumab and placebo in inducing a response or remission at weeks 8 to 12 (absolute RD across time points: 6% to 13%; placebo rate, 0% to 30%).
  - The strength of evidence was high that natalizumab was more effective than placebo in inducing a remission at weeks 2 to 4 (pooled relative risk [RR], 1.5; 95% CI, 1.1 to 2.0).
- The strength of evidence was low to demonstrate no difference between the combination of natalizumab (300 mg every 4 weeks) and infliximab (5 mg/kg) and infliximab (5 mg/kg) alone in inducing a remission at weeks 2 and 10 (absolute RD across time points, 7% to 8%; infliximab alone rate, 7% to 30%).

Disease Activity Indexes – TNF-Alpha Inhibitors

- The strength of evidence was high to demonstrate that TNF-alpha inhibitors (infliximab, adalimumab, and certolizumab pegol) were more effective than placebo in inducing a remission at week 2 (pooled RR, 2.0; 95% CI, 1.4 to 2.8).
- The strength of evidence was moderate to demonstrate that one dose of infliximab was more effective than placebo in inducing a response, but not remission, at weeks 2 and 12 (absolute RD across time points, 10% to 33%; placebo rate, 4% to 8%).

- The strength of evidence was high to demonstrate that one dose of adalimumab (at 160 mg) was more effective than placebo in inducing a remission at week 2 (absolute RD, 0% to 15%; placebo rate, 6% to 14%).
- The strength of evidence was high to demonstrate that induction and maintenance dosing of certolizumab pegol was more effective than placebo at week 26 (absolute RD, 11%; placebo rate, 18%).
  - The strength of evidence was moderate that certolizumab pegol was more effective than placebo in inducing a response, but not remission, at week 2 (absolute RD, 5% to 31%; placebo rate, 8% to 16%).
  - The strength of evidence was low that there was no difference between the groups at weeks 8 to 12 (absolute RD, -7% to 19%; placebo rate, 11% to 32%).
- The strength of evidence was moderate to demonstrate that infliximab (5 mg/kg induction and maintenance) was more effective than azathioprine (2.5 mg/kg/day) in inducing a steroid-free remission at weeks 10 and 26 (absolute RD across time points, 13% to 16%; azathioprine rate, 24% to 32%).
- The strength of evidence was moderate to demonstrate that a combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg/day) was more effective than infliximab (5 mg/kg induction and maintenance) alone in inducing a steroid-free remission at weeks 10 and 26 (absolute RD across time points, 10% to 12%; infliximab alone rate, 37% to 48%).
- The strength of evidence was moderate to demonstrate that a combination of infliximab (5 mg/kg induction and maintenance) and a thiopurine (azathioprine or 6-mercaptopurine) was more effective than a thiopurine alone in inducing a steroid-free remission at weeks 10 to 12 and weeks 24 to 26 (absolute RD across time points, 12% to 30%; azathioprine rate, 24% to 48%).
- The strength of evidence was low to demonstrate no difference between the combination of infliximab (5 mg/kg induction only) and azathioprine (2-2.5 mg/kg/day) and corticosteroids alone in inducing a steroid-free remission at week 104 (absolute RD, 6%; corticosteroid rate, 49%).
  - The strength of evidence was low that the combination of infliximab and azathioprine was more effective than corticosteroids alone in inducing a steroid-free remission at weeks 26 and 52 (absolute RD across time points, 19% to 24%; corticosteroid rate, 36% to 42%).
  - This was the top-down versus step-up trial.
- The strength of evidence was low to demonstrate that a combination of infliximab (5 mg/kg at weeks 0 and 2) and methotrexate (intravenous weekly to week 5, then oral) was more effective than infliximab (5 mg/kg at weeks 0 and 2) alone in inducing a remission at weeks 2, 12, 24 and 48 (absolute RD across time points, 17% to 39%; infliximab rate, 25% to 50%).

Disease Activity Indexes – Thiopurines

- The strength of evidence was low to demonstrate no difference between thiopurines and placebo in inducing a remission at weeks 17 and 38 (absolute RD across time points, -5% to 5%; placebo rate, 46% to 48%).

- The strength of evidence was low to demonstrate no difference between 6-mercaptopurine and oral methotrexate in inducing a steroid-free remission at weeks 30 and 38 (absolute RD across time points, 3% to 14%; placebo rate, 38% to 80%).
- The strength of evidence was low to demonstrate that azathioprine (2.5 mg/kg/day) was less effective than prednisone in inducing a remission at week 17 (absolute RD, -24%; prednisone rate, 77%).
- The strength of evidence was low to demonstrate no difference between azathioprine (2.5 mg/kg/day) and sulfasalazine (1 g/15 kg/day) in inducing a remission at week 17 (absolute RD, 0%; sulfasalazine rate, 53%).
    - The strength of evidence was low to demonstrate that 6-mercaptopurine (1.5 mg/kg/day) was more effective than aminosalicylates (3 g/day) in inducing remission at week 30 (absolute RD, 80%; aminosalicylates rate, 14%).
- The strength of evidence was moderate to demonstrate no difference between intravenous azathioprine (40 mg/kg loading followed by 2 mg/kg/day oral) and oral azathioprine (2 mg/kg/day) in inducing a steroid-free remission at weeks 8 and 16 (absolute RD across time points, 1% to 4%; oral azathioprine alone rate, 24% to 27%).
- The strength of evidence was low to demonstrate that a combination of azathioprine (2.5 mg/kg/day) and corticosteroids was more effective than corticosteroids alone in inducing a remission at weeks 12 and 28 (absolute RD across time points, 10%; corticosteroid rate, 28% to 63%).
- The strength of evidence was low to demonstrate no difference between the combination of azathioprine (2 mg/kg/day) and prednisone (40 mg/day) and the combination of intravenous methotrexate (25 mg/day) and prednisone (40 mg/day) in inducing a steroid-free remission at weeks 13 and 26 (absolute RD across time points, -11% to 7%; combination methotrexate and prednisone rate, 44% to 56%).

Disease Activity Indexes – Methotrexate

- The strength of evidence was moderate to demonstrate that intramuscular methotrexate (25 mg a week) was more effective than placebo alone in inducing a steroid-free remission at week 16 (absolute RD, 20%; placebo rate, 19%).
- The strength of evidence was low to demonstrate no difference between oral methotrexate (12.5 mg a week) and placebo in inducing a remission in adults at week 38 (absolute RD, -8%; placebo rate, 46%).
- The strength of evidence was low to demonstrate that oral methotrexate (15 mg a week) was more effective than aminosalicylates in inducing a remission at week 30 (absolute RD, 66%; aminosalicylates rate, 14%).

Disease Activity Indexes – Corticosteroids

- The strength of evidence was moderate to demonstrate that budesonide was more effective than placebo in inducing a remission at weeks 2 and 8 (absolute RD across time points, -1% to 31%; placebo rate, 11% to 33%).
- The strength of evidence was low that other corticosteroids (prednisone, 6-methylprednisolone) were more effective than placebo in inducing a remission at weeks

2-3, 16-17, 54, and 104 (absolute RD across time points, 5% to 39%; placebo rate, 8% to 79%).

- The strength of evidence was low to demonstrate that corticosteroids (budesonide, prednisone, 6-methylprednisolone) were more effective than aminosalicylates in inducing a remission at weeks 2-3, 16-17, 54 and 104 (absolute RD across time points: 0% to 30%; aminosalicylates rate, 6% to 87%).
  - The strength of evidence was low that there was no difference between groups at week 12 (absolute RD, -18% to 2%; aminosalicylates rate, 41% to 79%).
- The strength of evidence was moderate to demonstrate no difference between corticosteroids (prednisone, prednisolone at 40 mg/day) and budesonide (9 mg a day) in inducing a remission at weeks 2 and 8 (pooled RR at week 8, 0.9; 95% CI, 0.8 to 1.0).
- The strength of evidence was low to demonstrate that the combination of 6-methylprednisolone (48 mg/day) and sulfasalazine (3 g/day) was more effective than placebo in inducing a remission at weeks 3, 16, 54, and 104 (absolute RD across time points, 19% to 47%; placebo rate, 8% to 79%).
- The strength of evidence was low to demonstrate no difference between the combination of corticosteroids (prednisone, 6-methylprednisolone) and sulfasalazine and corticosteroids alone in inducing at weeks 3, 16, 54, and 104 (absolute RD across time points, 2% to 8%; corticosteroid rate, 33% to 93%).
  - The strength of evidence was low that the combination of corticosteroids and sulfasalazine was more effective than corticosteroids alone at week 8 (absolute RD, 19%; corticosteroid rate, 57%).
- The strength of evidence was low to demonstrate that the combination of corticosteroids (prednisone, 6-methylprednisolone) and sulfasalazine was more effective than sulfasalazine alone in inducing a remission at weeks 3, 16, 54, and 104 (absolute RD across time points, 11% to 26%; sulfasalazine rate, 22% to 87%).

Disease Activity Indexes – Aminosalicylates

- The strength of evidence was low to demonstrate that aminosalicylates were more effective than placebo in inducing a response or remission at weeks 16-17, 26, 54 and 104 (absolute RD across time points, 2% to 55%; placebo rate, 14% to 36%).
  - The strength of evidence was low that there was no difference between the groups at weeks 2-3 (absolute RD, -8% to 8%; placebo rate, 8% to 79%).

Mucosal Healing

- The strength of evidence was moderate to demonstrate that infliximab was more effective than placebo in achieving mucosal healing at week 4 (absolute between-group difference in the change from baseline in Crohn's disease endoscopic index of severity [CDEIS] score, 7.7; placebo difference, 0.9).
- The strength of evidence was moderate to demonstrate that infliximab (5 mg/kg induction and maintenance) and placebo was more effective than azathioprine (2.5 mg/kg daily) in achieving mucosal healing at week 26 (absolute RD in percentage of patients who achieved absence of mucosal ulcers, 13%; azathioprine and placebo rate, 17%).

- The strength of evidence was moderate to demonstrate that a combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg daily) was more effective than infliximab (5 mg/kg induction and maintenance) and placebo in achieving mucosal healing at week 26 (absolute RD in percentage of patients who achieved absence of mucosal ulcers, 14%; infliximab and placebo rate, 30%).
- The strength of evidence was moderate to demonstrate that a combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg daily) was more effective than azathioprine (2.5 mg/kg daily) and placebo in achieving mucosal healing at week 26 (absolute RD in percentage of patients who achieved absence of mucosal ulcers, 27%; azathioprine and placebo rate, 17%).
- The strength of evidence was low to demonstrate that a combination of infliximab (5 mg/kg induction only) and azathioprine (2-2.5 mg/kg/day) was more effective than corticosteroids alone in achieving mucosal healing at week 104 (absolute RD in percentage of patients with no ulcers, 43%; corticosteroid rate, 30%).

Hospitalization

- We did not find any studies comparing the effectiveness of various pharmacologic therapies for the management of Crohn's disease in terms of hospitalizations. The evidence for this outcome was insufficient.

Surgeries

- We did not find any studies comparing the effectiveness of various pharmacologic therapies for the management of Crohn's disease in terms of surgeries. The evidence for this outcome was insufficient.

Reduction of Steroids

- The strength of evidence was low to demonstrate no difference between azathioprine (3 mg/kg/day) and placebo in reducing steroids at 16 weeks (reduction in steroid dose from baseline was 7 mg and 12 mg, respectively).

Fistula Response

- The strength of evidence was moderate to demonstrate that infliximab was more effective than placebo in healing fistulas at week 6 in patients with actively draining fistulas (absolute RD in fistula closure, 25% to 42%; placebo rate, 13%).
- The strength of evidence was low to demonstrate no difference between adalimumab and placebo in healing fistulas at week 4 in patients with actively draining fistulas (absolute RD in fistula closure, -17% to 58%; placebo rate, 17%).
- The strength of evidence was low to demonstrate no difference between certolizumab pegol (400 mg subcutaneous induction and maintenance) and placebo in healing fistulas at week 26 in patients with actively draining fistulas (absolute RD in fistula closure, -1%; placebo rate, 31%).

- The strength of evidence was low to demonstrate no difference between azathioprine (2.5 mg/kg/day) and placebo in healing fistulas at week 17 in patients with actively draining fistulas (absolute RD in perianal fistula response, 2%; placebo rate, 11%).
    - For comparisons of azathioprine versus prednisone and sulfasalazine, see Table 4.
- The strength of evidence was low to demonstrate that azathioprine (2 mg/kg/day) was less effective than methotrexate (25 mg intravenous/week) in healing fistulas at 26 weeks in patients with actively draining fistulas (absolute RD in fistula closure, -42%; methotrexate rate, 67%).
- The strength of evidence was low to demonstrate that prednisone is more effective than placebo in healing fistulas at 17 weeks in patients with actively draining fistulas (absolute RD in fistula closure, 19%; placebo rate, 11%).
    - For comparisons of prednisone versus sulfasalazine, see Table 4.
- The strength of evidence was low to demonstrate that sulfasalazine (1 g/15 kg) was more effective than placebo in healing fistulas at 17 weeks in patients with actively draining fistulas (absolute RD in fistula closure, 11%; placebo rate, 11%).

Patient-Reported Outcomes

- The strength of evidence was high to demonstrate no difference comparing natalizumab (300 mg intravenous every 4 weeks) and placebo in improving patient-reported outcomes at week 12 (absolute between-group difference in change in mean IBDQ from baseline, 12; placebo change in IBDQ, 15).
- The strength of evidence was low to demonstrate no difference between a combination of natalizumab (300 mg intravenous every 4 weeks) with infliximab (5 mg/kg) and a combination of infliximab (5 mg/kg) with placebo in improving patient-reported outcomes at 10 weeks in patients who were previously failing infliximab monotherapy (absolute between-group difference in change in mean IBDQ from baseline, 2; combination infliximab and placebo change in IBDQ, 17).
- The strength of evidence was high to demonstrate that infliximab was more effective than placebo in improving patient-reported outcomes at week 4 (absolute between-group difference in change in mean IBDQ from baseline, 31; placebo change in IBDQ, 5).
- The strength of evidence was high to demonstrate no difference comparing adalimumab with placebo in improving patient-reported outcomes at week 4 (absolute between-group difference in change in mean IBDQ from baseline, 2 to 15; placebo change in IBDQ, 15).
- The strength of evidence was high to demonstrate no difference comparing certolizumab pegol with placebo in improving patient-reported outcomes at week 12 and 26 (absolute between-group difference in change in mean IBDQ from baseline across time points, 5 to 11; placebo change in IBDQ, 18 to 21).
- The strength of evidence was moderate to demonstrate no difference comparing infliximab (5 mg/kg induction and maintenance) with azathioprine (2.5 mg/kg/day) in improving patient-reported outcomes at 26 weeks (absolute between-group difference in change in mean IBDQ from baseline, 9; azathioprine change in IBDQ, 31).
- The strength of evidence was moderate to demonstrate no difference comparing the combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5mg/kg/day) with infliximab (5 mg/kg induction and maintenance) and placebo in

improving patient-reported outcomes at 26 weeks (absolute between-group difference in change in mean IBDQ from baseline, 5; infliximab change in IBDQ, 40).

- The strength of evidence was moderate to demonstrate no difference comparing the combination of infliximab (5 mg/kg induction and maintenance) and azathioprine (2.5 mg/kg/day) with azathioprine (2.5 mg/kg/day) and placebo in improving patient-reported outcomes at 26 weeks (absolute between-group difference in change in mean IBDQ from baseline, 14; azathioprine change in IBDQ, 31).
- The strength of evidence was low to demonstrate that a combination of infliximab (5 mg/kg at weeks 0 and 2) and methotrexate (intravenous weekly to week 5, then oral) was more effective than infliximab (5 mg/kg at weeks 0 and 2) alone in improving patient-reported outcomes at 48 weeks (absolute between-group difference in change in mean IBDQ from baseline, 22; infliximab alone change in IBDQ, 28).
- The strength of evidence was low to demonstrate no difference between azathioprine and placebo in improving patient-reported outcomes in adults at 8 to 16 weeks (multiple patient-reported outcome scales were employed [see text]).
- The strength of evidence was moderate to demonstrate no difference between intramuscular methotrexate (25 mg/week) and placebo in improving patient-reported outcomes at 16 weeks (absolute between-group difference in change in mean IBDQ from baseline, 15; placebo change in IBDQ, -8).
- The strength of evidence was low to demonstrate that there was no difference between oral methotrexate (12.5 mg weekly) and placebo in improving patient-reported outcomes at 12 to 16 weeks, as well as at 38 weeks (absolute between-group difference in change in Treatment Score for Wellbeing from baseline across time points, 0.2 to 1.7; placebo change in Treatment Score for Wellbeing, 1 for both time points).
- The strength of evidence was low to demonstrate that budesonide at a dose of 9 mg or more daily was more effective than placebo in improving patient-reported outcomes at 8 weeks (absolute between-group difference in change in IBDQ from baseline, 7 to 30; placebo change in IBDQ, 10 to 29).
- The strength of evidence was moderate to demonstrate no difference between prednisone (taper starting with 40 mg daily) and budesonide (9 mg daily) in improving patient-reported outcomes at 8 weeks (absolute between-group difference in change in mean IBDQ from baseline, 8; budesonide change in IBDQ, 26).
- The strength of evidence was moderate to demonstrate no difference between prednisone (taper starting at 40 mg daily) and aminosalicylates (Salofalk 1 g three times daily) in improving patient-reported outcomes at 2 and 12 weeks (absolute between-group difference in improvement in Quality of Life Index from baseline across time points, 4% to 16%; Salofalk improvement in Quality of Life Index, 7% to 33%).

Table 4 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 1.

Table 4. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission*

Comparison	Disease activity index	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
Ustekinumab IV vs. placebo	Favors ustekinumab; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Ustekinumab SC vs. placebo	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Ustekinumab IV vs. ustekinumab SC	Favors IV ustekinumab; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Natalizumab vs. placebo	Favors neither; Moderate SOE†	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; High SOE
Natalizumab + infliximab vs. infliximab	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low SOE
TNF vs. placebo	Favors TNF; High SOE‡	N/A	N/A	N/A	N/A	N/A	N/A
Infliximab vs. placebo	Favors infliximab; Moderate SOE	Favors infliximab; Moderate SOE	Insufficient	Insufficient	Insufficient	Favors infliximab; Moderate SOE	Favors infliximab; High SOE
Adalimumab vs. placebo	Favors adalimumab; High SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low SOE	Favors neither; High SOE
CP vs. placebo	Favors CP; High SOE§	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low SOE	Favors neither; High SOE
Infliximab vs. azathioprine	Favors infliximab; Moderate SOE	Favors infliximab; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Moderate SOE
Infliximab + azathioprine vs. infliximab	Favors infliximab + azathioprine; Moderate SOE	Favors infliximab + azathioprine; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Moderate SOE
Infliximab + azathioprine vs. azathioprine	Favors infliximab + azathioprine; Moderate SOE	Favors infliximab + azathioprine; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Moderate SOE
Infliximab + azathioprine vs. steroids	Favors neither; Low SOE‖	Favors infliximab + azathioprine; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Infliximab + methotrexate vs. infliximab	Favors infliximab + methotrexate; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors infliximab + methotrexate; Low SOE
Thiopurines vs. placebo	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Favors neither; Low SOE	Favors neither; Low SOE	Favors neither; Low SOE¶
Thiopurines vs. methotrexate	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors methotrexate; Low SOE	Insufficient

Table 4. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison	Disease activity index	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
Thiopurines vs. steroids	Favors steroid; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors steroids; Low SOE	Insufficient
Thiopurines vs. ASA	Favors neither; Low SOE**	Insufficient	Insufficient	Insufficient	Insufficient	Favors ASA; Low SOE[††]	Insufficient
Thiopurines (IV + oral) vs. thiopurines (oral)	Neither favored; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. steroids	Favors thiopurines + steroids; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. methotrexate + steroids	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (IM) vs. placebo	Favors methotrexate; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Moderate SOE
Methotrexate (oral) vs. placebo	Favors neither; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low SOE
Methotrexate (oral) vs. ASA	Favors methotrexate; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. placebo	Favors budesonide; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors budesonide; Low[‡‡]
Steroids (not budesonide) vs. placebo	Favors steroids; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Favors steroids; Low SOE	Insufficient
Steroids vs. ASA	Favors steroids; Low SOE[§§]	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low SOE	Favors neither; Moderate SOE[‖‖]
Budesonide vs. other steroids	Favors neither; Moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Moderate SOE
6-methyl-prednisolone + sulfasalazine vs. placebo	Favors 6-methylprednisolone + sulfasalazine; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids	Favors neither; Low SOE[¶¶]	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table 4. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison	Disease activity index	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
Steroids + sulfasalazine vs. sulfasalazine	Favors steroids + sulfasalazine; Low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
ASA vs. placebo	Favors ASA; Low SOE***	Insufficient	Insufficient	Insufficient	Insufficient	Favors ASA; Low SOE	Insufficient

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable

ASA = aminosalicylates; CP = certolizumab pegol; IM = intramuscular; IV = intravenous; SC = subcutaneous; SOE = strength of evidence; Steroid = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor

* All other comparisons and outcomes were graded as insufficient since there were no eligible studies.

† Favors natalizumab with high evidence at weeks 2-4.

‡ Based on meta-analysis of TNF-alpha inhibitors versus placebo at 2 weeks.

§ Favors certolizumab pegol with moderate evidence for response only at week 2; favors neither with low evidence at weeks 8-12.

‖ Top-down versus step-up trial; Favors combination infliximab and azathioprine with low evidence at weeks 26 and 52. Based on 104 week data; only 10 patients remaining in study.

¶ Outcome based upon "feeling better" in 2 studies, Treatment Goal Score for Wellbeing in one study.

** Favors 6-mercaptopurine with low evidence at week 30.

†† Azathioprine versus sulfasalazine

‡‡ Only the larger of the 2 included studies was clinically significant.

§§ Favors neither with low evidence at week 12.

‖‖ Used McMaster University Quality of Life scale – favors prednisone with moderate evidence at week 2.

¶¶ Favors the combination of steroids and sulfasalazine with low evidence at week 8.

*** Five of seven studies were clinically significant; Favors neither with low evidence at weeks 2-3.

Ustekinumab

Two randomized controlled trials (reported in one article), comprising 131 total participants, assessed the efficacy of ustekinumab (subcutaneous and intravenous) versus placebo, as well as ustekinumab intravenous versus ustekinumab subcutaneous in inducing clinical remission.[75]

Study Design

The first trial included 104 patients, and compared ustekinumab (intravenous and subcutaneous preparations) with placebo in a double-blind fashion.[75] Although designed as a crossover study, we are concerned about the possibility of a carryover effect, the inadequacy of the washout period, and the lack of within individual comparisons in the analysis. Therefore, we analyzed data only up to the point of crossover (8 weeks). The second trial included only primary or secondary non-responders to infliximab and compared ustekinumab subcutaneous with ustekinumab intravenous in an open-label fashion in inducing remission.[75]

These trials included Crohn's disease patients with active disease defined as a minimum Crohn's Disease Activity Index (CDAI) of 150 to 220, to a maximum of 450 (Appendix D, Evidence Table 2).[75] These trials evaluated remission (CDAI < 150) and response (CDAI drop of 100 and 70 points). These trials included only "adults," but did not specify a minimum age. These trials took place in multiple centers across North America starting in 2004. In the first trial, prior treatment with at least one pharmacologic therapy for Crohn's disease (aminosalicylates, corticosteroids, thiopurines, antibiotics, methotrexate, or TNF-alpha inhibitor therapy) was required. In the second trial, prior infliximab exposure was a requirement for inclusion.

Population Characteristics

A total of 131 patients were randomized in the 2 trials (Appendix D, Evidence Table 3).[75] The proportion of male participants in each study arm ranged from 48% to 60%. Race was not reported. Smoking status (defined as "current" smoker) was reported and ranged between 27% and 50% across the study arms. Mean age at enrollment ranged between 37 and 44 years. Mean duration of disease ranged between 11 and 13 years. Disease location was only reported for ileal and colonic distributions and was as follows: ileal location ranged between 70% and 85%, and colonic location between 54% and 74%. Baseline mean CDAI ranged from 292 and 325 points. Concurrent medication use was as follows: aminosalicylate use ranged between 36% and 52% across all arms, antibiotic use ranged from 4% to 8%, corticosteroids use ranged between 27% and 40%, methotrexate use ranged from 4% to 12%, and thiopurine use ranged between 16% and 35% across all arms. Only prior TNF-alpha inhibitor (infliximab) use was reported and ranged from 31% to 100% of participants across study arms.

Disease Activity Indexes

Ustekinumab versus placebo. The first trial,[75] comprising 104 participants, compared ustekinumab subcutaneous and ustekinumab intravenous with placebo in inducing remission at 2 to 8 weeks. Intravenous ustekinumab was clinically favored over placebo (i.e., the difference could be considered clinically significant), although there were no statistically significant

differences in remission or response (70- or 100-point drop in baseline CDAI) rates at 2 or 8 weeks. Subcutaneous ustekinumab was neither clinically nor statistically favored over placebo at weeks 2 or 8 (Table 5; Appendix D, Evidence Table 4).

Ustekinumab subcutaneous versus ustekinumab intravenous. The second trial,[75] comprising 27 patients, compared intravenous ustekinumab with subcutaneous ustekinumab in inducing remission at 2 and 8 weeks. In this open-label study, there were no clinically or statistically significant differences in remission or response rates at any time points between the two modes of administration (Table 5; Appendix D, Evidence Table 4).

Table 5. Randomized controlled trials comparing the effectiveness of ustekinumab with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison (dose), n	Remission rate (%) (CDAI<150)	Response rate (%) (100-pt CDAI drop)	Response rate (%) (70-pt CDAI drop)
Sandborn, 2008[75]	**2**	Ustekinumab (4.5 mg IV once), 26	Placebo IV, 27	**19% vs 7%**	**31% vs 22%**	**39% vs 22%**
	8	Ustekinumab (4.5 mg IV once), 26	Placebo IV, 27	**27% vs 11%**	**50% vs 26%**	**50% vs 30%**
Sandborn, 2008[75]	**2**	Ustekinumab (90 mg sc every wk for 4 wks), 25	Placebo sc, 26	**24% vs 12%**	**36% vs 23%**	**44% vs 42%**
	8	Ustekinumab (90mg sc every wk for 4 wks), 25	Placebo sc, 26	**24% vs 23%**	**48% vs 35%**	**48% vs 50%**
Sandborn, 2008[75]	**2**	Ustekinumab (4.5 mg IV once), 14	Ustekinumab (90 mg sc every wk for 4 wks), 13	**8% vs 0%**	**39% vs 0%**	**39% vs 7%**
	8	Ustekinumab (4.5 mg IV once), 14	Ustekinumab (90 mg sc every wk for 4 wks), 13	**31% vs 21%**	**39% vs 36%**	**54% vs 43%**

CDAI = Crohn's Disease Activity Index; IV = intravenous; mg = milligrams; pt = point; sc = subcutaneous; vs = versus; wk = week

Natalizumab

Four trials, comprising 1523 participants, assessed the efficacy of natalizumab, alone or in combination with infliximab, in inducing remission in Crohn's disease patients with active disease. Three trials[25 26 76] evaluated natalizumab versus placebo, while one trial[27] evaluated combination of natalizumab and infliximab versus infliximab and placebo.

Study Design

All four RCTs only included Crohn's disease patients with active disease defined as a minimum CDAI of 150 to 220 (Appendix D, Evidence Table 2).[25-27 76] All were double-blind studies. All but one study[25] used natalizumab at 300mg administered intravenously every 4 weeks through week 8. One study[25] evaluated a single dose of intravenous natalizumab at 3 mg/kg. Three studies took place in North America,[26 27 76] two took place in Europe,[26 76] two in Australia,[26 76] and two in Africa.[26 76] Three studies were multicenter in design, while one was not reported.[25] All studies except one[25] reported the starting year of enrollment, ranging from 2001 to 2004. The median study duration was 9 weeks (range, 8 weeks to 12 weeks). All studies included only adults with a minimum age of 18 years. All studies used the CDAI as the primary outcome measure of remission and response. All studies used CDAI less than 150 as the definition of remission. One study[26] reported a 100-point drop in CDAI as a measure of response to treatment, and two[26 76] reported a 70-point drop in CDAI as a response measure. One study[27] required that all patients have active disease (CDAI > 150) while taking infliximab at randomization. No studies included steroid-dependent patients. One study[26] only included patients with an elevated C-reactive protein ([CRP] > 2.7 mg/L). Two studies[26 76] excluded patients who had received any TNF-alpha inhibitor therapy within 3 to 4 months of the study. One study[25] excluded patients receiving treatment with methotrexate, cyclosporine, or tacrolimus.

Population Characteristics

A total of 1523 patients were randomized across the four studies (Appendix D, Evidence Table 3). The proportion of male participants in each study arm ranged from 39% to 63%. Three studies reported on race characteristics[25-27] with Caucasian patients comprising between 85% and 95% of all participants. Smoking status (defined as >10 cigarettes per day) was reported in two studies[26 76] and ranged between 19% and 24% in prevalence. Mean age at enrollment was reported in all studies, and ranged between 34 and 39 years. Mean duration of disease was reported in all studies and ranged between 8.5 and 12.5 years. Disease location was reported in all studies: ileal location was reported in all studies except one[25] and ranged between 15% and 27%, ileocolonic location between 28% and 56%, colonic location between 22% and 30%, and perianal location (reported in one study[25]) 28% and 33%. Baseline CDAI was reported for all studies, with mean CDAI ranging from 244 and 30 points. Concurrent medication use was as follows: aminosalicylates use ranged between 37% and 75% across all studies, antibiotic use ranged from 5% to 19% across all studies except one,[25] corticosteroids use ranged between 27% and 75% across all studies, methotrexate use ranged from 3% to 4% in two studies,[27 76] and thiopurines use ranged between 17% and 33% across all studies except one.[26] Prior medication use was reported by two studies,[26 76] with 38% to 50% of participants having used TNF-alpha

inhibitor therapy prior to the study. In another study,[27] per inclusion criteria, 100% of participants had prior infliximab exposure.

Disease Activity Indexes

Four RCTs,[25-27 76] comprising 1523 participants, assessed the efficacy of natalizumab, alone or in combination with infliximab, in inducing remission in Crohn's disease patients with active disease. Table 6 summarizes the efficacy of each treatment in inducing remission at 2 through 12 weeks (see also Appendix D, Table 4).

Natalizumab versus placebo. Three trials, comprising a total of 1394 patients, compared natalizumab intravenous with placebo in inducing remission in active Crohn's disease patients.[25 26 76] Only in one trial[26] of 459 patients was intravenous natalizumab clinically and statistically superior to placebo. In this trial, the natalizumab intravenous (300 mg every 4 weeks) arm had significantly higher rates of remission compared with placebo ($P < 0.01$ at all time points for remission, 70-point response, and 100-point response) at all time points (2, 8, and 12 weeks). Notably, this was the only study to include only patients with elevated CRP levels, thus minimizing patients with mostly functional disease. Remission rates were not significant in two trials.[25 76] In the smaller trial[25] of 30 patients, only one dose (3 mg/kg) of natalizumab intravenous was administered and remission rates were assessed at 2 weeks. Although remission rates were clinically different (39% natalizumab versus 8% placebo), the study was underpowered and did not show statistical significance. Another trial[76] was larger (905 patients), and administered the same regimen as the other large trial.[26] Absolute remission and response rates were similar to the other large natalizumab trial;[26] however, compared with placebo, results were neither clinically nor statistically significant.

When the week 2-4 data from the three RCTs was pooled, we found a significantly increased rate of remission for natalizumab compared with placebo (pooled RR, 1.5; 95% CI, 1.1 to 2.0) (Figure 3). There was no statistical heterogeneity across the three trials (I-squared, 0) and no study significantly influenced results. At weeks 8-12, the remission rate with natalizumab was neither clinically nor statistically different from the remission rate with placebo. Because the treatment arm in one trial[25] only received one dose of natalizumab, we chose not to perform a meta-analysis at weeks 8-12 due to study heterogeneity (per protocol a minimum of 3 studies is necessary for a meta-analysis; however, if a meta-analysis was performed using the two larger trials,[26 76] the results would likely look similar to those at weeks 2-4).

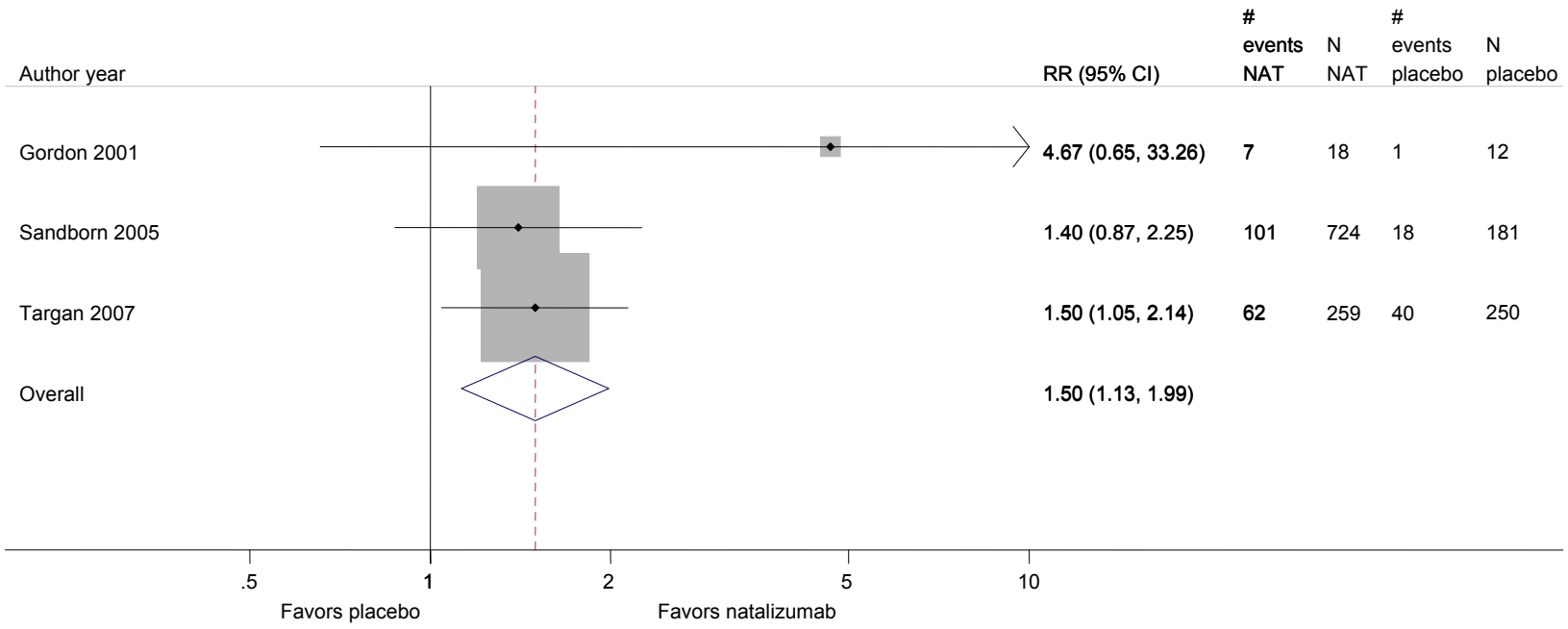
Combination of natalizumab and infliximab versus infliximab alone. One trial of 79 participants with active Crohn's disease on infliximab therapy at trial outset, compared a combination of natalizumab and infliximab with infliximab and placebo in inducing remission.[27] Inclusion criteria dictated that patients had to be on maintenance infliximab and with a CDAI greater than 150 at randomization. There was no clinically or statistically significant benefit in adding intravenous natalizumab 300 mg every 4 weeks to infliximab in inducing remission at 2 and 10 weeks. This study may have represented a particularly medically refractory population.

Table 6. Randomized controlled trials comparing the effectiveness of natalizumab with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease

Author, year	Followup (weeks)	Main Intervention (dose), n	Comparison (dose), n	Remission rate (%) (CDAI<150)	Response rate (%) (100-pt CDAI drop)	Response rate (%) (70-pt CDAI drop)
Targan, 2007[26]	4	Natalizumab (300 mg IV every 4 wks until wk 8), 259	Placebo, 250	24% vs 16%*	39% vs 27%*	51% vs 37%*
	8	Natalizumab (300 mg IV every 4 wks until wk 8), 259	Placebo, 250	32% vs 21%*	48% vs 33%*	56% vs 40%*
	12	Natalizumab (300 mg IV every 4 wks until wk 8), 259	Placebo, 250	38% vs 25%*	49% vs 31%*	60% vs 44%*
Sandborn, 2005[76]	2	Natalizumab (300 mg IV every 4 wks until wk 8), 724	Placebo, 181	14% vs 10%	NR	40% vs 33%
	8	Natalizumab (300 mg IV every 4 wks until wk 8), 724	Placebo, 181	34% vs 28%	NR	57% vs 50%
	10	Natalizumab (300 mg IV every 4 wks until wk 8), 724	Placebo, 181	37% vs 30%	NR	56% vs 49%
Gordon, 2001[25]	2	Natalizumab (3 mg/kg IV once), 18	Placebo, 12	39% vs 8%	NR	NR
	12	Natalizumab (3 mg/kg IV once), 18	Placebo, 12	11% vs 0%	NR	NR
Sands, 2007[27]	2	Natalizumab (300 mg IV at wks 0, 4, 8) + infliximab (5 mg/kg IV at wk -2 and 6), 52	Infliximab (5 mg/kg IV at wk -2 and 6), 27	15% vs 7%	NR	NR
	10	Natalizumab (300 mg IV at wks 0, 4, 8) + infliximab (5 mg/kg IV at wk -2 and 6), 52	Infliximab (5 mg/kg IV at wk -2 and 6), 27	37% vs 30%	NR	NR

*Statistically significant at 0.05 alpha level;
CDAI = Crohn's Disease Activity Index; IV = intravenous; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; pt = point; vs = versus; wk = week

Figure 3. Pooled relative risk of inducing remission* of Crohn's disease at weeks 2-4 comparing natalizumab with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Weeks 2-4

CI = confidence interval; NAT = natalizumab; RR = relative risk
* In all studies, remission was defined as a Crohn's Disease Activity Index less than 150.
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.36 with 2 degrees of freedom (p = 0.51)
I-squared statistic = 0%

TNF-Alpha Inhibitors

Ten studies evaluated the effectiveness of a TNF-alpha inhibitor as monotherapy or in combination with another drug to induce remission. Six studies compared TNF-alpha inhibitor monotherapy with placebo: one evaluated infliximab,[77] two evaluated adalimumab,[78 79] and three evaluated certolizumab pegol.[80-82] One study compared infliximab with azathioprine.[83] Four studies compared TNF-alpha inhibitor combination therapy with another therapy: two studies[83 84] compared a combination of infliximab and a thiopurine to thiopurines alone, while one study[83] compared a combination of infliximab and azathioprine to infliximab alone. Schroder et al. studied the combination of infliximab and methotrexate versus infliximab alone.[85] Another study compared the combination of infliximab and azathioprine to corticosteroids.[86]

Study Design

Per our inclusion criteria, all ten studies were RCTs (Appendix D, Evidence Table 2). Only one was not blinded.[86] Five studies took place in North America, while nine took place in Europe. All but one study[85] was multicenter in design. The starting year of enrollment was between 1995 and 2005. The median study duration was 18 weeks (range, 4 weeks to 104 weeks). All studies included adults ages 18 or older. Only one study took patients as young as 16.[86] All studies were restricted to patients with active Crohn's disease. Eight of ten studies required a minimum CDAI of 200 to 220 at entry. Eight of ten studies defined remission as a CDAI less than 150, while three studies evaluated steroid-free remission (CDAI < 150).[83 84 86] Three studies evaluated response defined as a CDAI drop of 70 or more points, while five studies evaluated a response defined as a CDAI drop of 100 or more points. In terms of prior medication use, patients in one study[79] had to have lost response to or have been intolerant of infliximab in the past. Another study[85] demanded that patients be corticosteroid resistant or dependent in addition to having a history of resistance or intolerance to azathioprine. In one study[84] patients had to be on at least 10 mg of prednisone, and had to have active disease despite being on thiopurines for the last 6 months (thiopurine failures). In three studies,[78 83 85] prior TNF-alpha inhibitor use was prohibited. In two studies,[83 86] prior thiopurine use was prohibited, while one study[86] also forbid prior corticosteroid use. Only one study[86] restricted the duration of disease to be 4 years or less.

Population Characteristics

A total of 2,493 patients were randomized across the studies (Appendix D, Evidence Table 3). Males comprised 43 % of the participants. Only two studies[83 86] commented on the percentage of Caucasians, which ranged from 84% to 99% among all arms. Smoking (varying definitions) was reported in five studies[78-80 83 86] and ranged between 31% and 43%. Mean age at enrollment ranged between 29 and 40 years. Mean duration of disease ranged between 8 and 13.6 years. However, in one study[83] median duration of disease was only 2.3 years, while in another[86] the patients were newly diagnosed. In terms of disease location, ileal only location ranged between 7% and 68%, ileocolonic location between 5% and 68%, and colonic location between 9% and 36%. Baseline CDAI was reported for all but one study.[81] Mean CDAI ranged from 251 to 330 points. Concurrent medication use was as follows: aminosalicylates use ranged between 18% and 68%, antibiotic use ranged between 5% and 14%, corticosteroids use ranged from 22% to 100%,

methotrexate use was 1% to 7%, thiopurines use was 26% to 44%, and TNF-alpha inhibitor use was 17% to 30% (although for one study,[79] per inclusion criteria, 100% of patients had to have had prior infliximab exposure).

Disease Activity Indexes

Week 2. A total of 7 RCTs[77-82 85] involving 1,797 patients were analyzed at this time point. At week 2, patients across all studies had received only one infusion or injection. Table 7 summarizes the effects of TNF-alpha inhibitor therapy in terms of inducing remission and response at week 2 (see also Appendix D, Evidence Table 4).

TNF-alpha inhibitor versus placebo. Six of the RCTs compared a TNF-alpha inhibitor versus placebo.[77-82] Patients with moderate to severe Crohn's disease were twice as likely to achieve remission by week 2 with a TNF-alpha inhibitor as with placebo (RR, 2.0; 95% CI, 1.4 to 2.8; $P < 0.001$) (Figure 4). No one study significantly influenced results. Although there was no substantial statistical heterogeneity found in the meta-analysis (I-squared, 18%), heterogeneity in study design was observed. Three different TNF-alpha inhibitor agents were used (infliximab, adalimumab, and certolizumab pegol). Although all three medications have a unique make-up, we believe that the mechanism of action for all three is similar. Additionally, prior TNF-alpha inhibitor exposure was variable across studies: in two studies[77 78] patients were naïve to TNF-alpha inhibitor treatment, in three studies[80-82] prior TNF-alpha inhibitor use was allowed, and in one study[79] all patients had to have either lost response to or were intolerant of TNF-alpha inhibitors. For all studies that included TNF-alpha inhibitor experienced patients, primary non-responders were excluded. We decided to explore the effects of TNF-alpha inhibitor on remission among patients who were naïve to treatment[77 78] and those who were previously treated with another TNF-alpha inhibitor.[79-82] For both TNF-alpha inhibitor treatment-naïve and experienced patients, the relative risk of remission at week 2 remained at 2; however, this estimate was not statistically significant for treatment-naïve patients (see Appendix E).

Meta-analyses for week 2 response rates for the six RCTs comparing TNF-alpha inhibitor versus placebo were also significant. The relative risk for 100-point response was 1.8 (95% CI, 1.4 to 2.1) and for 70-point response was 1.6 (95% CI, 1.3 to 1.9) (see Appendix E).

Combination of a TNF-alpha inhibitor and another therapy versus another therapy. One small open-label study (n = 19) compared the effectiveness of inducing remission of a combination of infliximab and methotrexate with infliximab monotherapy, and showed no statistically significant differences in remission rate (64% versus 25%; $P = 0.16$).[85] This study did not report response rates.

Table 7. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of inducing remission or response at week 2 in patients with Crohn's disease

Author, year	Main intervention (dose), n	Comparison (dose), n	Remission rate (%) (CDAI<150)	Response rate (%) (100-pt CDAI drop)	Response rate (%) (70-pt CDAI drop)
Targan, 1997[77]	Infliximab (5 mg/kg IV once), 26	Placebo, 24	37% vs 4% ($P > 0.05$)	NR	75% vs 17% ($P < 0.001$)
	Infliximab (10 mg/kg IV once), 23	Placebo, 24	20% vs 4% ($P > 0.05$)	NR	50% vs 17% ($P < 0.01$)
	Infliximab (20 mg/kg IV once), 28	Placebo, 24	20% vs 4% ($P > 0.05$)	NR	52% vs 17% ($P < 0.01$)
Hanauer, 2006[78]	Adalimumab (40 mg sc once), 74*	Placebo, 74	14% vs 14% ($P > 0.05$)	21% vs 15% ($P > 0.05$)	44% vs 30% ($P > 0.05$)
	Adalimumab (80 mg sc once), 75†	Placebo, 74	20% vs 14% ($P > 0.05$)	37% vs 15% (P =0.002)	55% vs 30% (P = 0.003)
	Adalimumab (160 mg sc once), 76‡	Placebo, 74	24% vs 14% ($P > 0.05$)	31% vs 15% (P = 0.019)	45% vs 30% ($P > 0.05$)
Sandborn, 2007[79]	Adalimumab (160 mg sc once), 159‡	Placebo, 166	21% vs 6% ($P < 0.001$)	37% vs 18%(P NR)	52% vs 33% (P NR)
Schreiber, 2005[81]	Certolizumab pegol (100 mg sc once), 74	Placebo, 73	18% vs 8% ($P > 0.05$)	30% vs 15% (P = 0.033)	NR
	Certolizumab pegol (200 mg sc once), 72	Placebo, 73	10% vs 8% ($P > 0.05$)	31% vs 15% (P = 0.026)	NR
	Certolizumab pegol (400 mg sc once), 72	Placebo, 73	18% vs 8% ($P > 0.05$)	33% vs 15% (P = 0.01)	NR
Sandborn, 2007[80]	Certolizumab pegol (400 mg sc once), 331§	Placebo, 328	13% vs 8% ($P > 0.05$)	25% vs. 14% ($P < 0.05$)	35% vs 25% ($P < 0.05$)
Winter, 2004[82]	Certolizumab pegol (5 mg/kg IV once), 25	Placebo, 25	35% vs 16% ($P > 0.05$)	65% vs 50% ($P > 0.05$)	NR
	Certolizumab pegol (10 mg/kg IV once), 17	Placebo, 25	47% vs 16% (P = 0.041)	65% vs 50% ($P > 0.05$)	NR
	Certolizumab pegol (20 mg/kg IV once), 23	Placebo, 25	20% vs 16% ($P > 0.05$)	55% vs 50% ($P > 0.05$)	NR
Schroder, 2006[85]	Infliximab (5 mg/kg IV once) + methotrexate (20 mg IV every wk), 11‖	Infliximab (5 mg/kg once), 8	64% vs 25% (P = 0.16)	NR	NR

IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; sc = subcutaneous injections; vs = versus; wk = week

* 40 mg sc week 0, 20 mg sc week 2;

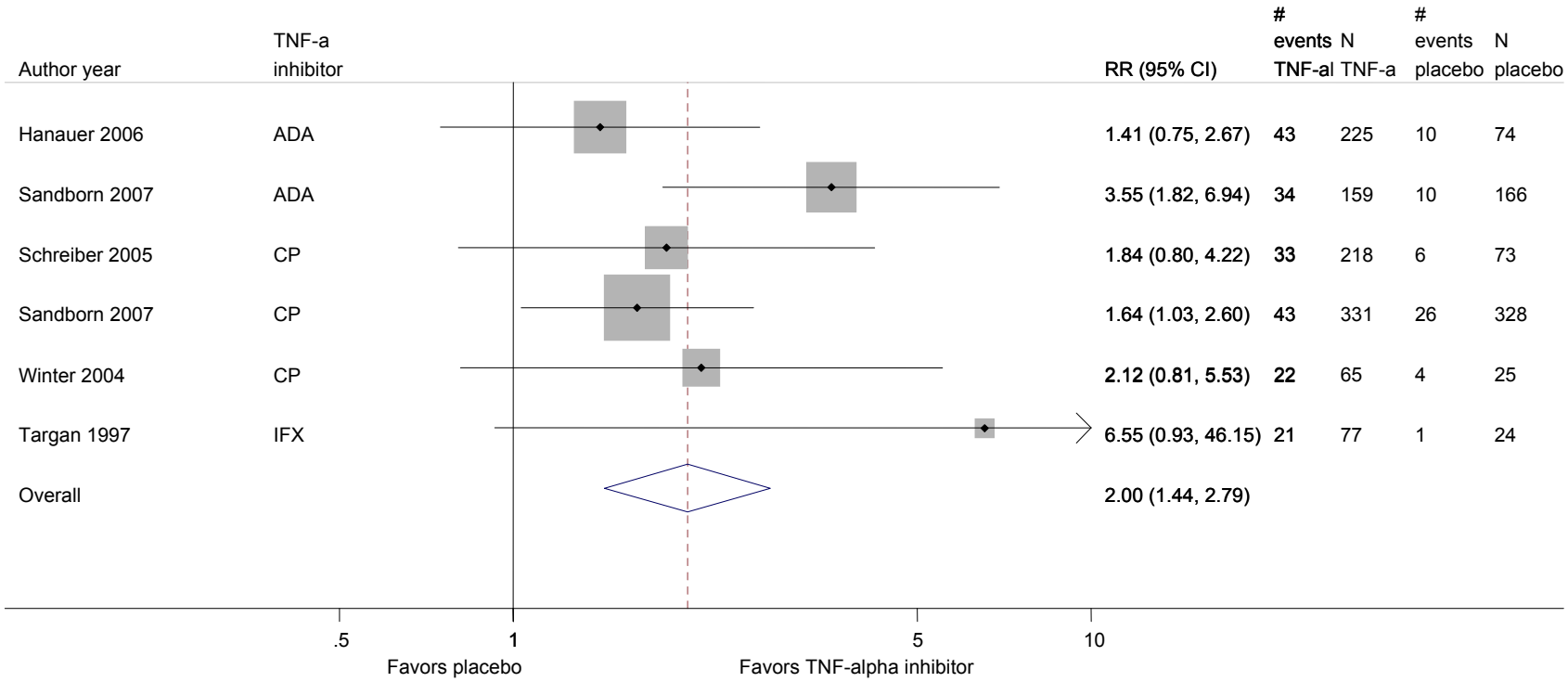
† 80 mg sc week 0, 40 mg sc week 2;

‡160 mg sc week 0, 80 mg sc week 2;

§ 400 mg sc at 0, 2, and 4 weeks, then every 4 weeks;

‖ Infliximab 5mg/kg IV at 0 and 2 weeks, methotrexate 20mg IV every wk through week 5 and 20 mg orally every week after week 5

Figure 4. Pooled relative risk of inducing remission* of Crohn's disease at week 2 comparing a TNF-alpha inhibitor with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 2

ADA = adalimumab; CI = confidence interval; CP = certolizumab pegol; IFX = infliximab; RR = relative risk; TNF-a = tumor necrosis factor-alpha inhibitor
* In all studies, remission was defined as a Crohn's Disease Activity Index less than 150. Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 6.11 with 5 degrees of freedom (p = 0.30)
I-squared statistic = 18%

Weeks 8 to 12. A total of 7 RCTs[77 80-85] involving 1,628 patients were analyzed at this time point. Table 8 summarizes the effects of TNF-alpha inhibitor therapy in terms of inducing remission and response at weeks 8 to 12.

TNF-alpha inhibitor versus placebo. Four RCTs were examined representing infliximab and certolizumab pegol.[77 80-82] Only one study[81] comparing certolizumab pegol to placebo reported clinically and statistically higher rates of remission and response compared to placebo. Two of the other studies[77 82] were underpowered and were designed to administer only one dose of drug at week 0. Thus, by 8 to 12 weeks one might expect a decrement in remission and response rates. In addition, because maintenance therapy has become the standard of care in the administration of TNF-alpha inhibitor agents (discussed in KQ2), we felt that the results for all but one[80] are not applicable to standard practice; therefore, a meta-analysis was not performed.

TNF-alpha inhibitor versus another therapy. In one study,[83] infliximab and placebo was found to be clinically and statistically superior to azathioprine and placebo for the induction of steroid-free remission at week 10. At this time point, one would not expect complete clinical response among patients randomized to azathioprine and placebo. Rates for response were not reported.

Combination TNF-alpha inhibitor and another therapy versus another therapy. In one study,[83] the combination of infliximab and azathioprine was found to be clinically and statistically superior to azathioprine and placebo for the induction of steroid-free remission at week 10. Response rates were not reported. At this time point, one would not expect complete clinical response among patients randomized to the azathioprine and placebo arm.[87] Another study[84] that compared a combination of infliximab and thiopurine with thiopurine and placebo at 12 weeks found clinically and statistically higher steroid-free remission rates in the combination infliximab and thiopurine arm. Notably, all of the patients in this study had been on a thiopurine agent for at least 6 months, implying that it was not effective in this population in the first place.

One study[83] found that the combination of infliximab and azathioprine was clinically superior to infliximab and placebo, although statistical significance was not met.

Results for Schroder et al. (comparing a combination of infliximab and methotrexate with infliximab alone) favored combination therapy at 12 weeks, although the results were not statistically significant.[85]

Table 8. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of inducing remission or response at week 8 to 12 in patients with Crohn's disease

Author, year	Followup (weeks)	Main Intervention (dose), n	Comparison (dose), n	Remission rate (%) (CDAI<150)	Response Rate (%) (100-pt CDAI drop)	Response Rate (%) (70-pt CDAI drop)
Targan, 1997[77]	12	Infliximab (5 mg/kg IV once), 27	Placebo, 24	30% vs 8% ($P > 0.05$)	NR	48% vs 12% (*P* NR)
		Infliximab (10 mg/kg IV once), 27	Placebo, 24	18% vs 8% ($P > 0.05$)	NR	29% vs 12% (*P* NR)
		Infliximab (20 mg/kg IV once), 28	Placebo, 24	25% vs 8% ($P > 0.05$)	NR	46% vs 12% (*P* NR)
Schreiber, 2005[81]	8	Certolizumab pegol (100 mg sc once), 74	Placebo, 73	29% vs 11% ($P < 0.01$)	44% vs 25% ($P < 0.05$)	NR
		Certolizumab pegol (200 mg sc once), 72	Placebo, 73	20% vs 11% ($P > 0.05$)	40% vs 25% ($P > 0.05$)	NR
		Certolizumab pegol (400 mg sc once), 72	Placebo, 73	30% vs 11% ($P < 0.01$)	48% vs 25% ($P < 0.01$)	NR
Sandborn, 2007[80]	8	Certolizumab pegol (400 mg sc at 0, 2, 4 weeks), 331*	Placebo, 328	24% vs 19% ($P > 0.05$)	35% vs. 29% ($P > 0.05$)	43% vs 39% ($P > 0.05$)
Winter, 2004[82]	8	Certolizumab pegol (5 mg/kg IV once), 25	Placebo, 25	37% vs 32% ($P > 0.05$)	52% vs 60% ($P > 0.05$)	NR
		Certolizumab pegol (10 mg/kg IV once), 17	Placebo, 25	36% vs 32% ($P > 0.05$)	57% vs 60% ($P > 0.05$)	NR
		Certolizumab pegol (20 mg/kg IV once), 23	Placebo, 25	25% vs 32% ($P > 0.05$)	43% vs 60% ($P > 0.05$)	NR
Colombel, 2010[83]	10	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks), 169[†]	Azathioprine (2.5 mg/kg orally daily), 170	37% vs 24% ($P = 0.006$)[‡]	NR	NR
Colombel, 2010[83]	10	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks) + azathioprine (2.5 mg/kg orally daily),169[†]	Azathioprine (2.5 mg/kg orally daily), 170	47% vs 24% ($P < 0.001$)[‡]	NR	NR
Lemann, 2006[84]	12	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks) + azathioprine or 6-mercaptopurine, 25[§]	Azathioprine or 6-mercaptopurine, 29[§]	64% vs 34% ($P = 0.03$)[‡]	NR	NR
Colombel, 2010[83]	10	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks) + azathioprine (2.5 mg/kg orally daily), 169[†]	Infliximab (5 mg/kg IV at 0, 2, and 6 weeks), 169	47% vs 37% ($P = 0.07$)[‡]	NR	NR
Schroder, 2006[85]	12	Infliximab (5 mg/kg IV at 0 and 2 weeks) + methotrexate (20 mg IV every wk), 11[‖]	Infliximab (5 mg/kg once), 8	82% vs 50% ($P = 0.32$)	NR	NR

CDAI = Crohn's Disease Activity Index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; pt = point; sc = subcutaneous injections; vs = versus; wk = week

* 400 mg sc at 0, 2, and 4 weeks, then every 4 weeks

[†] Infliximab 5 mg/kg IV at 0, 2, and 6 weeks then every 8 weeks

[‡] Steroid-free remission

[§] Azathioprine orally 2-3 mg/kg/day or 6-mercaptopurine orally 1-1.5 mg/kg/day

[‖] Methotrexate 20 mg IV every week through week 5 and 20 mg orally every week after week 5

Weeks 24 to 26. A total of 5 RCTs[80 83-86] involving 1,377 patients were analyzed at this time point. Table 9 summarizes the effects of TNF-alpha inhibitor therapy in terms of inducing remission and response at weeks 24 through 26.

TNF-alpha inhibitor versus placebo. One study[80] found that certolizumab pegol given on a scheduled basis is clinically and statistically more effective than placebo in inducing a response and remission at 26 weeks.

TNF-alpha inhibitor versus another therapy. In one study,[83] infliximab and placebo was found to be clinically and statistically superior to azathioprine and placebo for the induction of remission at week 26. Rates for response were not reported.

Combination TNF-alpha inhibitor and another therapy versus another therapy. In one study,[83] the combination of infliximab and azathioprine was found to be clinically and statistically superior to azathioprine and placebo for the induction of steroid-free remission at week 26. Response was not reported. By 26 weeks, response to azathioprine would be expected to be complete. Of note, this study excluded patients with intermediate levels (<50% percentile) of thiopurine methyltransferase enzyme activity. Studies have suggested that higher levels of thiopurine methyltransferase correlate with poorer response to thiopurines.[88] Another study[84] that compared a combination of infliximab and thiopurine with thiopurine found combination therapy was clinically, but not statistically favored compared with azathioprine or 6-mercaptopurine when patients who had not achieved remission after at least 6 months of thiopurine therapy. When the 58 patients who had not previously used thiopurines were analyzed, the result was clinically and statistically significant (24-week steroid-free remission 63% versus 32%, $P = 0.02$).

Results for Schroder et al. (comparing a combination of infliximab and methotrexate with infliximab alone) favored combination therapy at 24 weeks, although the results were not statistically significant.[85]

D'Haens et al.[86] was different from the other studies listed. It attempted to compare early top-down therapy with step-up therapy. At entry, patients were newly diagnosed, and were naïve to corticosteroids, thiopurines, and TNF-alpha inhibitor therapy. Patients were randomized to receive either the combination of infliximab (given at 0, 2, and 6 weeks) and azathioprine (top-down therapy), or a taper with corticosteroids (step-up therapy). The latter was called step-up therapy because patients in the corticosteroids (prednisolone or budesonide) arm were given azathioprine if they relapsed after a second course of corticosteroids, or were given infliximab if they continued to have active disease. In this non-blinded study, the primary outcome was steroid-free remission. At week 26, a clinically and statistically higher proportion of patients in the top-down group were in steroid-free remission than the corticosteroid group.

Table 9. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of inducing remission or response at week 24 to 26 in patients with Crohn's disease

Author, year	Followup (weeks)	Main Intervention (dose), n	Comparison (dose), n	Remission rate (%) (CDAI<150)	Response Rate (%) (100-pt CDAI drop)	Response Rate (%) (70-pt CDAI drop)
Sandborn, 2007[80]	26	Certolizumab pegol (400 mg sc at 0, 2, 4 wks, then every 4 wks), 331	Placebo, 328	29% vs 18% (P < 0.05)	37% vs 27% (P < 0.05)	43% vs 29% (P < 0.05)
Colombel, 2010[83]	26	Infliximab (5 mg/kg IV at 0, 2, 6 wks, then every 8 wks), 169	Azathioprine (2.5 mg/kg orally daily), 170	48% vs 32% (P = 0.006)*	NR	NR
Colombel, 2010[83]	26	Infliximab (5 mg/kg IV at 0, 2, 6 wks, then every 8 wks) + azathioprine (2.5 mg/kg orally daily),169	Azathioprine (2.5 mg/kg orally daily), 170	60% vs 32% (P < 0.001)*	NR	NR
Lemann, 2006[84]	24	Infliximab (5 mg/kg IV at 0, 2, 6 wks) + azathioprine or 6-mercaptopurine, 24†	Azathioprine or 6-mercaptopurine, 27†	50% vs 26% (P = 0.08)*	NR	NR
Colombel, 2010[83]	26	Infliximab (5mg/kg IV at 0, 2, 6 wks, then every 8 wks) + azathioprine (2.5 mg/kg orally daily), 169	Infliximab (5 mg/kg IV at 0, 2, 6 wks, then every 8 wks), 169	60% vs 48% (P = 0.02)*	NR	NR
D'Haens, 2008[86]	26	Infliximab (5 mg/kg IV at 0, 2, 6 wks) + azathioprine (2 – 2.5 mg/kg orally daily), 65	Methylprednisolone (32 mg orally daily with taper), or budesonide (9 mg orally daily with taper), 64	60% vs 36% (P = 0.006)	NR	NR
Schroder, 2006[85]	24	Infliximab (5 mg/kg IV at 0, 2 wks) + methotrexate (20 mg IV every wk), 11‡	Infliximab (5 mg/kg IV once), 8	55% vs 38% (P = 0.65)	NR	NR

CDAI = Crohn's Disease Activity Index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; pt = point; sc = subcutaneous injections; vs = versus; wk = week

* Steroid-free remission

† Azathioprine orally 2-3 mg/kg/day or 6-mercaptopurine orally 1-1.5 mg/kg/day

‡ Methotrexate 20 mg IV every week through week 5 and 20 mg orally every week after week 5

Later time points (after 26 weeks). The primary endpoint for one trial was 26 weeks.[83] After this time point, patients were given the option of enrolling in an extension study (through week 50) in which they would continue their assigned therapy in a blinded manner. This extension was not evaluated.

Results for Schroder et al. (comparing a combination of infliximab and methotrexate with infliximab alone) favored combination therapy at 48 weeks (remission rate, 45% versus 25%), although the results were not statistically significant.[85]

One study comparing a top-down strategy (combination infliximab and azathioprine) versus a step-up strategy (starting with corticosteroids, and then escalating therapy as needed) was carried out to 104 weeks.[86] Up until 52 weeks, patients in the top-down arm experienced higher rates of steroid-free remission than the step-up strategy: 60% versus 36% ($P = 0.006$) at week 26 and 62% versus 42% at week 52 ($P = 0.03$). However, by week 104, there was no clinically or statistically significant difference between the groups: 55% versus 49%.

Thiopurines

Eight RCTs evaluated the effectiveness of thiopurines (azathioprine or 6-mercaptopurine) as monotherapy or in combination with other therapies to induce remission.[89-96]

Study Design

Per our inclusion criteria, all eight studies were RCTs (Appendix D, Evidence Table 2). Doses of thiopurines were as follows: four studies used azathioprine 2.5 mg/kg per day administered orally. One study used azathioprine 2 mg/kg per day,[95] one used 6-mercaptopurine 50 mg per day administered orally,[94] one used 6-mercaptopurine 1.5 mg/kg per day,[90] and another used azathioprine 2 mg/kg per day orally, with one group also receiving azathioprine 40 mg intravenously once prior to initiation of oral therapy.[96] Six studies used CDAI as the relevant outcome, one used CDAI score as one of several outcomes in an aggregate "treatment success" outcome,[89] and one used Harvey-Bradshaw Index (HBI).[94] All studies except one[90] included only Crohn's disease patients, with active disease defined as CDAI greater than 150 to 200 or HBI of 7 or greater. One study[90] included patients with both ulcerative colitis and Crohn's disease but presented remission rates for Crohn's disease patients separately (subgroup analysis, randomization not stratified by ulcerative colitis versus Crohn's disease). Three studies took place in North America,[89 93 96] four took place in Europe,[89 90 92 97] two in Africa,[89 91] one in Israel,[94] and one in Russia.[89] Four studies[89 93 94 96] were multicenter in design, while four[90-92 95] were not. All studies except one[91] reported the starting year of enrollment, ranging from 1971 to 2004. The median study duration was 17 weeks (range, 12 weeks to 52 weeks). All studies included only adults with a minimum age of 18 years, with three exceptions: one study included adults with a minimum age of 17,[94] two included a minimum age of 15,[90 91] and one did not report minimum age.[93] Remission was defined as follows: five studies used CDAI less than 150, one used CDAI less than 150 as only one of several outcomes in an aggregate "treatment success" outcome,[89] one[90] used CDAI less than 150 with steroid-free status and normal serum orosomucoid concentrations as additional requirements for remission, one only assessed CDAI if several other outcomes were achieved as part of a rank-sum model,[93] and one used an HBI of 3 or less and being steroid-free.[94] Four studies[90 94-96] required that remission be steroid-free; another study[89] included being steroid-free as part of an aggregate "treatment success" outcome.

In terms of prior medication use, one study[90] required that patients be steroid-dependent at randomization with no definition of steroid-dependence, while two others[94 95] defined corticosteroid-dependence as 7.5 mg to 10 mg a day of prednisone for four out of the last 12 months, and one[96] defined steroid-dependence as prednisone at 20 mg/day or more for at least 4 weeks. Two studies prohibited prior use TNF-alpha inhibitors,[89 96] and two excluded patients with prior thiopurine use.[92 96]

Population Characteristics

A total of 753 participants were randomized across the eight studies (Appendix D, Evidence Table 3). One study[90] included patients with Crohn's disease and ulcerative colitis, but only baseline characteristics for those with Crohn's disease are presented here. The proportion of male participants in each study arm ranged from 21% to 66%, with two studies[90 92] not reporting gender. One study reported on race characteristics[93] with Caucasian patients comprising between 90% and 94% of all participants across the four study arms. Smoking status was reported in five studies and ranged between 24% and 86% in prevalence. Age at enrollment was reported in all studies except one,[90] and ranged between 27 to 38 years (mean) and 32 to 40 years (median). Duration of disease was reported in all studies and ranged between 3.2 to 8.4 years (mean) and 0.6 to 7.1 years (median). Disease location was reported in all studies: ileal location ranged between 5% and 86%, ileocolonic location between 25% and 67%, colonic location between 9% and 61%, and perianal lesions ranged between 14% and 25%. Baseline CDAI was reported for all seven studies using this index, with mean CDAI ranging from 191 and 290, and median CDAI ranging from 244 and 301 points. In the study that used HBI,[94] mean HBI scores ranged from 7.8 to 9 across the three study arms. Concurrent medication use was as follows: aminosalicylates use ranged between 63% and 72% across the three arms of one study,[94] and corticosteroids use ranged between 73% and 100% across three studies.[91 94 95] Prior medication use was as follows: aminosalicylates use in three studies[92 93 95] ranged from 29% to100% of participants, antibiotic use was 7% across two arms of one study,[95] corticosteroids use ranged from 25% to 100% (indicating treatment with corticosteroids as a requirement for study entry) across five studies,[91-95] and immunomodulator (thiopurine or methotrexate) use ranged between 7% and 27% across both arms of two studies.[94 95]

Disease Activity Indexes

Eight different studies, comprising a total of 753 participants, assessed the efficacy of thiopurine therapy in inducing remission in those with active Crohn's disease.[89-96] Table 10 summarizes the efficacy of thiopurines in inducing remission and response in Crohn's disease patients with active disease (see also Appendix D, Table 4).

Thiopurines versus placebo. Two trials, comprising 194 participants, compared thiopurines to placebo in inducing remission in those with active disease.[93 94] Neither study showed any clinically or statistically significant difference in remission rates between thiopurines and placebo groups at 17 and 38 weeks, respectively. One study[94] with 58 participants included only recently steroid-dependent patients and used the HBI to assess steroid-free remission at 38 weeks. The other study[93] with 136 patients used the CDAI, but only after assessing several other outcomes in a rank-sum model.

Thiopurines versus methotrexate. Two trials including 89 participants compared thiopurine with methotrexate therapy.[90 94] One trial of 58 participants[94] compared 6-mercaptopurine and placebo to oral methotrexate and placebo in steroid-dependent patients with active Crohn's disease defined by an HBI of 7 or greater. At 38 weeks, there was no clinically or statistically significant difference in remission rates (defined by HBI of 3 or less and steroid-free status at any point in the study) between the two groups.

In the other study[90] of 31 participants, the group randomized to 6-mercaptopurine 1.5 mg/kg/day had higher remission rates (94%) than those randomized to oral methotrexate 15 mg/week (80%) at 30 weeks; however, significance levels were not reported. Results represent a subgroup analysis, and blinding was not reported in this study.

Thiopurines versus corticosteroids. One arm of a larger trial, comprising 144 participants, compared azathioprine with prednisone.[93] At 17 weeks, patients on azathioprine had a clinically lower rate of remission than patients on prednisone, although the results were not statistically significant. However, the assessment of remission was limited, including only those who had achieved several other outcomes in a rank-sum model.

Thiopurine versus aminosalicylates. Two studies including 156 participants compared thiopurine with aminosalicylate therapy.[90 93] One arm of a larger study, comprising 133 participants, compared azathioprine with sulfasalazine therapy in inducing remission in those with active disease (CDAI > 150).[93] There was no clinically or statistically significant difference in remission rates between the groups at 17 weeks, although the assessment of remission was limited, including only those who had achieved several other outcomes in a rank-sum model.

In the other study of 23 participants,[90] the group receiving 6-mercaptopurine 1.5 mg/kg/day had significantly higher remission rates (94%) than the group receiving aminosalicylate 3 g/day (14%) at 30 weeks ($P < 0.001$). Results represented a subgroup analysis, and blinding was not reported in this study.

Combination of intravenous and oral thiopurines versus oral thiopurines. One trial of 96 steroid-dependent participants with active Crohn's disease assessed whether a loading dose of azathioprine intravenous combined with an oral regimen of daily azathioprine would yield higher remission rates compared to an oral regimen alone.[96] Prednisone therapy was standardized in all participants to 20 mg per day during a 2-week period prior to randomization. There were no clinically or statistically significant differences in steroid-free remission rates between the two groups at 2, 8, 12, or 16 weeks.

Combination of thiopurines and corticosteroids versus corticosteroids alone. Three trials[89 91 92] comprising 186 participants compared azathioprine and prednisolone combination therapy with prednisolone and placebo (in all trials, steroids were tapered) in inducing remission in those with active Crohn's disease. Study duration ranged from 12 to 28 weeks; active disease was defined variably as CDAI greater than 150, 200, or 220. One study[92] in which prednisolone was tapered, but continued at a maintenance dose of 10 mg daily through study end, showed significant findings with twice as many patients receiving azathioprine and prednisolone combination therapy (76%) achieving remission at 16 weeks than those receiving prednisolone and placebo (38%, $P = 0.03$). The two studies[89 91] which evaluated steroid-free remission showed

a modest clinical benefit in favor of combination therapy with azathioprine and prednisone, although results were not statistically significant. Notably, one study[91] of 63 patients evaluated two endpoints. At 12 weeks, steroid-free remission rates were 73% and 63% respectively, in the group receiving the combination of azathioprine and prednisolone compared with the group receiving prednisolone and placebo. After 12 weeks, only patients in steroid-free remission were followed for an additional 12 months (azathioprine versus placebo). While the results favored azathioprine over placebo at this later time point, the results were not included in either KQ1 or KQ2 (although the study evaluated maintenance, patients were not re-randomized).

Combination of thiopurines and corticosteroids versus combination of methotrexate and corticosteroids. One trial, comprising 54 steroid-dependent participants with active Crohn's disease, compared a combination of azathioprine and prednisone with a combination of intravenous methotrexate and prednisone.[95] There were no statistically significant differences in remission rates between the two groups at either 13 or 26 weeks. It should be noted that patients were not blinded in this study, thus possibly biasing results.

Table 10. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison (dose), n	Remission/Response definition	Remission/ Response rate (%)
Reinisch, 2008[89]	28	Azathioprine (2.5 mg/kg/day) + prednisone (1 mg/kg/day or ≥ 40 mg/day then taper after response), 50	Prednisone (1 mg/kg/day or ≥ 40 mg/day then taper after response), 28	Treatment success*	38% vs 28%
Mate-Jimenez, 2000[90]	30	6-Mercaptopurine (1.5 mg/kg/day), 16	Methotrexate (15 mg/wk oral), 15	CDAI < 150 and steroid-free and normal serum orosomucoid concentrations	94% vs 80%
	30	6-Mercaptopurine (1.5 mg/kg/day), 16	Aminosalicylates (3 g/day), 7	CDAI<150 and steroid-free and normal serum orosomucoid concentrations	94% vs 14%†
Candy, 1995[91]	12	Azathioprine (2.5 mg/kg/day) + prednisolone (1 mg/kg/day then taper), 33	Prednisolone (1 mg/kg/day then taper), 30	CDAI <150 and steroid-free	73% vs 63%
Ewe, 1993[92]	16	Azathioprine (2.5 mg/kg/day) + prednisolone (60 mg/day then taper), 21	Prednisolone (60 mg/day then taper), 21	CDAI<150 and 60-pt drop in CDAI	76% vs 38%†
Oren, 1997[94]	38	6-mercaptopurine (50 mg/day), 32	Methotrexate (12.5 mg/wk oral), 26	HBI 3 and steroid-free	41% vs 38%
	38	6-mercaptopurine (50 mg/day), 32	Placebo, 26	HBI 3 and steroid-free	41% vs 46%
Summers, 1979[93]	17	Azathioprine (2.5 mg/kg/day), 59	Prednisone (0.25-0.75 mg/kg/day), 85	CDAI<150‡	53% vs 77%
	17	Azathioprine (2.5 mg/kg/day), 59	Sulfasalazine (1 g/15 kg/day), 74	CDAI<150‡	53% vs 53%
	17	Azathioprine (2.5 mg/kg/day), 59	Placebo, 77	CDAI<150‡	53% vs 48%
Sandborn, 1999[96]	8	Azathioprine (IV 40 mg/kg loading dose followed by azathioprine oral 2 mg/kg/day), 51	Azathioprine (oral 2 mg/kg/day), 45	CDAI <150 and steroid-free	25% vs 24%
	16	Azathioprine (IV 40 mg/kg loading dose followed by azathioprine oral 2 mg/kg/day), 51	Azathioprine (oral 2 mg/kg/day), 45	CDAI <150 and steroid-free	31% vs 27%
Ardizzone, 2003[95]	13	Azathioprine (2 mg/kg/day) + prednisone (40 mg/day), 27	Methotrexate (25 mg/wk) + prednisone (40 mg/day), 27	CDAI≤150 and steroid-free	33% vs 44%
	26	Azathioprine (2 mg/kg/day) + prednisone (40 mg/day), 27	Methotrexate (25 mg/wk) + prednisone (40 mg/day), 27	CDAI≤150 and steroid-free	63% vs 56%

*Treatment success was defined as absence of treatment failure, which encompassed: patients who prematurely discontinued the study drug due to unsatisfactory therapeutic effect; patients who failed to achieve steroid-free remission (i.e., CDAI total score ≥150) by the end of month 3; patients who used steroids after the end of month 3; patients who used any prohibited efficacy-related treatment; and patients with a relapse (i.e., any CDAI score ≥150 points and a minimum increase in the CDAI score ≥70 compared with the score at the beginning of remission) recorded after the end of month 3.

†Significant at 0.05 alpha level

‡CDAI Remission was only assessed after subjects had attained other outcomes in a rank-sum model

CDAI = Crohn's Disease Activity Index; IV = intravenous, kg = kilogram; mg = milligram; pt = point; wk = week

Methotrexate

Three studies evaluated the effectiveness of methotrexate as monotherapy to induce remission.[90 94 98] Two studies[94 98] compared methotrexate with placebo while one study[90] compared methotrexate with aminosalicylates. Two studies[90 94] used oral methotrexate between 12.5 mg and 15 mg weekly, while one study[98] used intramuscular methotrexate at 25 mg a week.

Study Design

Per our inclusion criteria, all three studies were RCTs (Appendix D, Evidence Table 2). All studies except one[90] were restricted to patients with Crohn's disease. One study[90] with 22 participants included both ulcerative colitis and Crohn's disease patients, with no stratification by disease type at randomization. Results for Crohn's disease patients was presented as part of a subgroup analysis. Two studies used CDAI as the relevant outcome, while one used HBI.[94] One study took place in North America,[98] one took place in Europe,[90] and the last took place in Israel.[94] Two of the studies were multicenter in design.[94 98] All studies reported the starting year of enrollment, ranging between 1992 and 1994. The median study duration was 39 weeks (range, 16 weeks to 106 weeks). All studies included only steroid-dependent patients, except one[94] which only required prior steroid use for at least 4 of the prior 12 months. In one study,[98] patients who had a baseline prednisone dose under 20 mg daily raised their prednisone up to 20 mg daily for 2 weeks following randomization. One study included adults ages 17 or older,[94] one included those 15 and older,[90] and one did not specify an age range.[98] Two studies defined remission as a CDAI less than 150 and steroid-free[90 98] with one of these studies also including normal serum orosomucoid concentrations as a necessary criterion for remission.[90] One study defined remission as a reduction of HBI to 3 and steroid-free.[94] In terms of prior medication use, only one study prohibited prior use of immunomodulators.[94]

Population Characteristics

A total of 215 patients were randomized across the three studies (Appendix D, Evidence Table 3). The proportion of male participants in each study arm ranged from 46% to 55%. No studies reported on race characteristics. Smoking status was reported in all studies and ranged between 24% and 86% across all study arms. Mean age at enrollment was reported in all but one study,[90] and ranged between 33 and 38 years. Mean duration of disease was reported in all studies and ranged between 4 years to 12 years. Disease location was reported in all studies: ileal location ranged between 17% and 50%, ileocolonic location between 25% and 64%, colonic location between 14% and 40%, and perianal location between 14% and 20%. Baseline CDAI was reported for two studies[90 98] with mean CDAI ranging from 181 and 215 points. In the study that used HBI,[94] mean baseline HBI scores ranged from 7.8 to 9 across both study arms. Concurrent medication use was as follows: aminosalicylates use ranged between 69% and 72% across two arms of one study,[94] and corticosteroids use ranged between 73% and 80% one study,[94] while corticosteroids use was 100% across the other two studies.[90 98] Prior immunomodulator (thiopurines or methotrexate) use ranged between 12% and 15% across both arms of one study.[94]

Disease Activity Indexes

A total of three RCTs involving 215 patients were analyzed.[90 94 98] Table 11 summarizes the effects of methotrexate therapy in terms of inducing remission and response (see also Appendix D, Evidence Table 4).

Methotrexate versus placebo. Two trials included steroid-dependent participants or patients who had had at least 4 months of corticosteroids use in the last year.[94 98] Methotrexate was superior to placebo in inducing steroid-free remission in only one study (16 weeks endpoint; $P = 0.03$).[98] This study used the highest dose of methotrexate (25 mg per week), and used intramuscular therapy, whereas the other study[94] in which no clinically or statistically significant difference in remission rates was found, used lower methotrexate doses (12.5 mg per week) administered orally. Additionally, all patients in Feagan et al.[98] were on a minimum of prednisone 20 mg daily at randomization; not all patients in Oren et al.[94] were on corticosteroids at baseline.

Methotrexate versus aminosalicylates. One study[90] compared methotrexate with aminosalicylates in steroid-dependent patients. A substantially higher proportion of Crohn's disease patients receiving oral methotrexate 15 mg per week achieved steroid-free remission (defined as CDAI < 150 and normal serum orosomucoid concentrations) than patients receiving 3 g per day of aminosalicylates therapy (80% versus 14%; $P < 0.01$). However, given the small sample size, and the fact that this was a subgroup analysis, the results should be interpreted with caution.

Table 11. Randomized controlled trials comparing the effectiveness of methotrexate with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison (dose), n	Remission/Response definition	Remission/ Response rate, %
Feagan, 1995[98]	16	Methotrexate (25 mg IM/week), 94	Placebo, 47	CDAI<150 and steroid-free	39% vs 19% (P = 0.025)
Oren, 1997[94]	38	Methotrexate (12.5 mg oral/week), 26	Placebo, 26	HBI of 3 and steroid-free at any time during study	38% vs 46% (NS)
Mate-Jimenez, 2000*[90]	30	Methotrexate (15 mg oral /week), 15	Aminosalicylates (3 g/day), 7	CDAI<150 and steroid-free and normal serum orosomucoid concentrations	80% vs 14% (P < 0.01)

CDAI = Crohn's Disease Activity Index; g = grams; HBI = Harvey-Bradshaw Index; IM = intramuscular; mg = milligrams; NS = not significant; vs = versus
* Subgroup analysis

Corticosteroids

Fourteen RCTs assessed the benefit of corticosteroids therapy (alone or in combination) versus placebo or other therapies in inducing remission. One study[99] included participants with both active (CDAI > 150) and inactive (CDAI < 150) disease at randomization; patients with active disease were analyzed as part of a subgroup analysis. Three studies[93 100 101] evaluated corticosteroids (budesonide, prednisone) versus placebo. Four studies[102-105] evaluated budesonide versus prednisone or prednisolone. Five studies[93 106-109] evaluated corticosteroids (budesonide,

prednisone, 6-methylprednisolone) versus aminosalicylates. One study[110] evaluated a combination of prednisone and sulfasalazine versus prednisone alone, and one study[111] evaluated a combination of prednisone and sulfasalazine versus sulfasalazine alone.

Study Design

Per our inclusion criteria, all fourteen studies were RCTs (Appendix D, Evidence Table 2). All studies used CDAI as the relevant outcome, except one[111] which used both CDAI and the Van-Hees Activity Index (VHAI). All studies only included Crohn's disease patients with active disease defined as CDAI greater than 150 to 200, with the exception of one[111] which defined patients with active disease as a VHAI greater than 140. Another trial[99] included participants with both active (CDAI > 150) and inactive (CDAI < 150) disease at randomization; only the patients with active disease will be analyzed in this section. Five studies took place in North America,[93 100 101 109 110] eight took place in Europe,[99 102 104-108 111] one in Africa,[106] one in Israel,[103] and two in Australia.[104 106] All studies were multicenter in design. Seven studies reported the starting year of enrollment, ranging from 1971 to 1995. The median study duration was 11 weeks (range, 2 weeks to 104 weeks). All studies included only adults with a minimum age of 18 years, with the following exceptions: one study included adults with a minimum age of 15,[94] one did not list a minimum age and only reported "adults" as included,[102] and four did not report whether the study was restricted to adult patients.[93 108 110 111] No studies required that patients be steroid-dependent at randomization, and steroid-free remission was not a requirement in any study. Remission was defined as CDAI less than 150 in all studies except two;[99 111] one study also used a 60-point drop in CDAI from baseline as an additional requirement for remission,[108] and one only assessed CDAI if several other outcomes were achieved as part of a rank-sum model.[93] One study[99] defined response to therapy as an absence of "failure and relapse," a category comprising early withdrawal from the study, need for repeat induction therapy, and multiple clinical and CDAI criteria.[A] One study[111] assessed response to therapy, defined as the relative change in VHAI and CDAI from baseline. All corticosteroids were administered orally. In terms of prior medication use, two studies prohibited use of immunomodulators (thiopurines or methotrexate) or corticosteroids in the 3 months prior to the trial,[100 103 107] one study prohibited any treatment for Crohn's disease in the month prior to the trial,[109] and one study[111] prohibited patients with a "need for antibiotics or corticosteroids."

Population Characteristics

All of the following statistics exclude one study[99] due to its inclusion of both those with active and inactive disease in the baseline population. Therefore, results on only thirteen studies are reported here. A total of 1778 patients were randomized across the thirteen studies (Appendix D, Evidence Table 3). The proportion of male participants in each study arm ranged from 23% to 66%. Two studies reported on race characteristics[93 110] with Caucasian patients comprising between 86% and 94% of all participants across the five study arms. Smoking status was

[A] "Failure and relapse" included study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60 point decrease after end of all three treatment cycles).

reported in three studies[101 103 107] and ranged between 30% and 58% in prevalence. Age at enrollment was reported in all studies, and ranged between 26 to 41 years (mean) and 30 to 38 years (median). Duration of disease was reported in all studies except two[110 111] and ranged between 2.4 to 11.9 years (mean) and 4.6 to 9.2 years (median). Disease location was reported in all but three studies:[100 104 105] ileal location ranged between 23% and 100%, ileocolonic location between 12% and 66%, and colonic location between 0% and 94%. Baseline CDAI was reported for all studies, with mean CDAI ranging from 236 and 305 points and median CDAI ranging between 220 and 293 points. One study[111] reported baseline VHAI scores, ranging from 173 to 178 across both study arms. Concurrent medication use was as follows: aminosalicylates use ranged between 50% and 58% across two arms of one study.[102] Prior medication use was as follows: aminosalicylates use in six studies[93 103 106 107 110 111] ranged from 10% to 81% of participants, antibiotic use was 28% to 35% across two arms of one study,[103] and corticosteroids use ranged from 0% to 52% across seven studies.[93 101-103 109-111]

Disease Activity Indexes

Table 12 summarizes the effects of corticosteroids on in terms of inducing remission or response (see also Appendix D, Evidence Table 4).

Corticosteroids versus placebo. Four trials, comprising 725 participants, compared corticosteroids with placebo in inducing remission.[93 99-101] In one trial[93] the assessment of remission by CDAI was limited, including only those who had first achieved several other outcomes in a rank-sum model.

Clinically and statistically higher remission rates were seen for budesonide over placebo at 2 weeks[100] and 8 weeks.[101] In one study[101] only daily budesonide doses of 9 mg or more were effective. In one study,[93] the results clinically and statistically favored prednisone over placebo at 17 weeks. In an analysis of another study,[99] the group receiving methylprednisolone (48 mg/day with taper) had significantly higher rates of being free of "failure and relapse" than the group receiving placebo through the two years of the study (33% versus 8% at two years; $P < 0.001$).[B] Caution should be used in interpreting this subgroup analysis.

Corticosteroids versus another corticosteroid. Four trials, including 581 participants, compared budesonide to other corticosteroids (prednisone, prednisolone) in the ability to induce remission through 2 to 10 weeks of therapy.[102-105] Total daily doses for budesonide in all trials were 9 mg, and those for prednisolone or prednisone were 40 mg. Overall there were no consistent clinical differences in remission rates between budesonide and prednisolone or prednisone. One trial[102] evaluated reduction in mean CDAI, and not rates of remission. Three trials[102 103 105] were included in a meta-analysis (Figure 5) of induction of remission with budesonide versus prednisolone or prednisone at 8 weeks. There was no significant difference in pooled remission rates at 8 weeks (RR of inducing remission, 0.88; 95% CI, 0.76 to 1.02). There was no significant heterogeneity (I-squared, 0%).

[B] "Failure and relapse" included study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60 point decrease after end of all three treatment cycles).

Corticosteroids versus aminosalicylates. Six studies, including 617 participants, compared corticosteroids with aminosalicylates therapy in inducing remission.[93 99 106-109] In one trial,[93] the assessment of remission by CDAI was limited, including only those who had first achieved several other outcomes in a rank-sum model.

Only one trial[106] showed a statistically significant difference in remission rates between corticosteroids and aminosalicylates. This was also the only trial that compared budesonide with aminosalicylates, with those on budesonide achieving higher rates of remission at 8, 12, and 16 weeks (62% versus 36% at 16 weeks, $P < 0.001$) than those on aminosalicylates. Otherwise, doses of aminosalicylates were comparable between studies. In another study,[99] the group receiving methylprednisolone (48 mg/day with taper) had higher rates of being free of "failure and relapse" than the group receiving sulfasalazine (3 g/day) through two years of follow-up, but significance levels were not reported. Data from this study represented a subgroup analysis. A meta-analysis was attempted for corticosteroids versus aminosalicylates using 3 studies.[106 107 109] However, it was not included because of significant statistical heterogeneity (I-squared, 64%). This occurred because of the isolated significant findings of one study.[106]

Combination of corticosteroids and aminosalicylates versus placebo. In one study[99] patients receiving combination therapy with methylprednisolone (48 mg/day with taper) and sulfasalazine (3 g/day) had significantly higher rates of being free of "failure and relapse" than the group receiving placebo through the two years of the study (35% versus 8% at two years; $P < 0.001$). Data from this study represented a subgroup analysis.

Combination of corticosteroids and aminosalicylates versus corticosteroids alone. Two trials[99 110] including 192 participants compared a combination of corticosteroids and aminosalicylates versus corticosteroids alone.

One study of 89 participants[110] compared a combination of prednisone and sulfasalazine with prednisone alone. Combination therapy was favored over prednisone at week 8; however, results were not statistically significant. In an analysis of the other study,[99] at 16 weeks and beyond (to 104 weeks) the group receiving combination therapy with methylprednisolone (48 mg/day with taper) and sulfasalazine (3 g/day) had equal chances of being free of "failure and relapse" compared with the group receiving 6-methylprednisolone (48 mg/day with taper) alone. Data from this study represented a subgroup analysis.

Combination of corticosteroids and aminosalicylates versus aminosalicylates alone. Two trials[99 111] including 170 participants compared a combination of corticosteroids and aminosalicylates with aminosalicylates alone. One study of 60 participants[111] compared the combination of prednisone and sulfasalazine with sulfasalazine alone, and found a significant difference between the groups in the relative change in VHAI scores at the 2 to 6 week time point (70% versus 87% of initial values, respectively; $P = 0.001$ between treatment groups favoring combination therapy). There was no statistically significant difference between the groups in the relative change in either CDAI at 2 to 6 weeks or VHAI or CDAI from baseline at 12 to 16 weeks.

In one other study,[99] the group receiving combination therapy with 6-methylprednisolone (48 mg/day with taper) and sulfasalazine (3 g/day) had higher rates of being free of "failure and

relapse" than the group receiving sulfasalazine (3 g/day) alone through two years of follow-up, but significance levels were not reported. Data from this study represented a subgroup analysis.

Table 12. Randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison (dose), n	Remission/Response definition	Remission/ Response rate (%)
Tremaine, 2002[100]	2	Budesonide (9 mg/day), 80	Placebo, 41	CDAI<150	31% vs 13%*
		Budesonide (4.5 mg twice daily), 79	Placebo, 41	CDAI<150	40% vs 13%*
	8	Budesonide (9 mg/day), 80	Placebo, 41	CDAI<150	48% vs 33%
		Budesonide (4.5 mg twice daily), 79	Placebo, 41	CDAI<150	53% vs 33%
Greenberg, 1994[101]	2	Budesonide (1.5 mg twice daily), 67	Placebo, 66	CDAI<150	10% vs 11%
		Budesonide (4.5 mg twice daily), 61	Placebo, 66	CDAI<150	32% vs 11%
		Budesonide (7.5 mg twice daily), 64	Placebo, 66	CDAI<150	28% vs 11%
	8	Budesonide (1.5 mg twice daily), 67	Placebo, 66	CDAI<150	33% vs 20%
		Budesonide (4.5 mg twice daily), 61	Placebo, 66	CDAI<150	51% vs 20%*
		Budesonide (7.5 mg twice daily), 64	Placebo, 66	CDAI<150	43% vs 20%*
Malchow, 1984[99]	3	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	Absence of "failure and relapse"**	93% vs 79%
	16	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	Absence of "failure and relapse"**	75% vs 36%
	54	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	Absence of "failure and relapse"**	49% vs 14%
	104	6-methylprednisolone (48 mg/day with taper), 47	Placebo, 58	Absence of "failure and relapse"**	33% vs 8%*
Summers, 1979[93]	2	Prednisone (0.5-0.75 mg/kg), 85	Placebo, 77	CDAI<150[†]	20% vs 15%
	17	Prednisone (0.5-0.75 mg/kg), 85	Placebo, 77	CDAI<150[†]	59% vs 42%*
Tillinger, 1998[102]	2	Budesonide (9 mg/day), 12	Prednisolone (48 mg/day), 12	Mean change in CDAI	-74 vs -106
Bar-Meir, 1998[103]	8	Budesonide (9 mg/day), 100	Prednisone (40 mg/day), 101	CDAI<150	51% vs 53%
Campieri, 1997[104]	2	Budesonide (4.5 mg twice daily), 58	Prednisolone (40 mg/day), 61	CDAI≤150	27% vs 37%
		Budesonide (9 mg/day), 61	Prednisolone (40 mg/day), 61	CDAI≤150	48% vs 37%
	8	Budesonide (4.5 mg twice daily), 58	Prednisolone (40 mg/day), 61	CDAI≤150	48% vs 60%
		Budesonide (9 mg/day), 61	Prednisolone (40 mg/day), 61	CDAI≤150	60% vs 60%
Rutgeerts, 1994[105]	2	Budesonide (9 mg/day), 86	Prednisolone (40 mg/day), 86	CDAI≤150	45% vs 56%
	10	Budesonide (9 mg/day), 86	Prednisolone (40 mg/day), 86	CDAI≤150	53% vs 66%
Thomsen, 1998[106]	8	Budesonide (9 mg/day), 93	Mesalamine (4 g/day), 89	CDAI<150	69% vs 45%*
	16	Budesonide (9 mg/day), 93	Mesalamine (4 g/day), 89	CDAI<150	62% vs 36%*
Prantera, 1999[107]	3	6-methylprednisolone (40 mg/day), 31	Aminosalicylates (4 g/day), 35[‡]	CDAI<150	61% vs 46%
		6-methylprednisolone (40 mg/day), 31	Aminosalicylates (4 g/day), 28[§]	CDAI<150	61% vs 61%
	12	6-methylprednisolone (40 mg/day), 31	Aminosalicylates (4 g/day), 35[‡]	CDAI<150	61% vs 60%
		6-methylprednisolone (40 mg/day), 31	Aminosalicylates (4 g/day), 28[§]	CDAI<150	61% vs 79%
Gross, 1995[108]	2	6-methylprednisolone (48 mg/day), 16	Aminosalicylates (4.5 g/day), 15	CDAI<150 and 60-pt drop in CDAI	56% vs 40%

Table 12. Randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease (continued)

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison (dose), n	Remission/Response definition	Remission/ Response rate (%)
Malchow, 1984[99]	3	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	Absence of "failure and relapse"**	93% vs 87%
	16	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	Absence of "failure and relapse"**	75% vs 57%
	54	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	Absence of "failure and relapse"**	49% vs 30%
	104	6-methylprednisolone (48 mg/day with taper), 47	Sulfasalazine (3g/day), 54	Absence of "failure and relapse"**	33% vs 22%
Summers, 1979[93]	3	Prednisone (0.5-0.75 mg/kg/day), 85	Sulfasalazine (1.5 mg/15 kg/day), 74	CDAI<150**	25% vs 6%
	17	Prednisone (0.5-0.75 mg/kg/day), 85	Sulfasalazine (1.5 mg/15 kg/day), 74	CDAI<150**	59% vs 29%
Rijk, 1991[111]	2-6	Sulfasalazine (6 g/day then 4g/day if side effects appeared)	Prednisone (30 mg/day with taper) + sulfasalazine (6 g/day then 3g/day if side effects appeared), 30	Percent of initial Van-Hees Activity Index value	87% vs 70%*
	2-6	Sulfasalazine (6 g/day then 4g/day if side effects appeared)	Prednisone (30 mg/day with taper) + sulfasalazine (6 g/day then 3g/day if side effects appeared), 30	Percent of initial CDAI value	75% vs 65%
	12-16	Sulfasalazine (6 g/day then 4g/day if side effects appeared)	Prednisone (30 mg/day with taper) + sulfasalazine (6 g/day then 3g/day if side effects appeared), 30	Percent of initial Van-Hees Activity Index value	70% vs 63%
	12-16	Sulfasalazine (6 g/day then 4g/day if side effects appeared)	Prednisone (30 mg/day with taper) + sulfasalazine (6 g/day then 3g/day if side effects appeared), 30	Percent of initial CDAI value	76% vs 65%
Malchow, 1984[99]	3	Placebo, 58	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	79% vs 98%
	16	Placebo, 58	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	36% vs 83%
	54	Placebo, 58	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	14% vs 52%
	104	Placebo, 58	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	8% vs 35%*

Table 12. Randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in terms of inducing remission or response in patients with Crohn's disease (continued)

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison (dose), n	Remission/Response definition	Remission/ Response rate (%)
Malchow, 1984[99]	3	Sulfasalazine (3g/day), 54	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	87% vs 98%
	16	Sulfasalazine (3g/day), 54	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	57% vs 83%
	54	Sulfasalazine (3g/day), 54	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	30% vs 52%
	104	Sulfasalazine (3g/day), 54	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	22% vs 35%
Malchow, 1984[99]	3	6-methylprednisolone (48 mg/day with taper), 47	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	93% vs 98%
	16	6-methylprednisolone (48 mg/day with taper), 47	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	75% vs 83%
	54	6-methylprednisolone (48 mg/day with taper), 47	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	49% vs 52%
	104	6-methylprednisolone (48 mg/day with taper), 47	6-methylprednisolone (48 mg/day with taper) + Sulfasalazine (3g/day), 56	Absence of "failure and relapse"**	33% vs 35%
Singleton, 1979[110]	8	Prednisone (0.25-0.75 mg/kg/day), 43	Prednisone (0.25-0.75 mg/kg/day) + sulfasalazine (1 g/15 kg/day), 46	CDAI<150	57% vs 76%

CDAI = Crohn's Disease Activity Index; g = grams; kg = kilograms; mg = milligrams; pt = point; vs = versus

*Significant at the 0.05 alpha level. For Malchow 1984,[99] significance level refers to difference in rates over entire period of study (0 to 104 weeks)

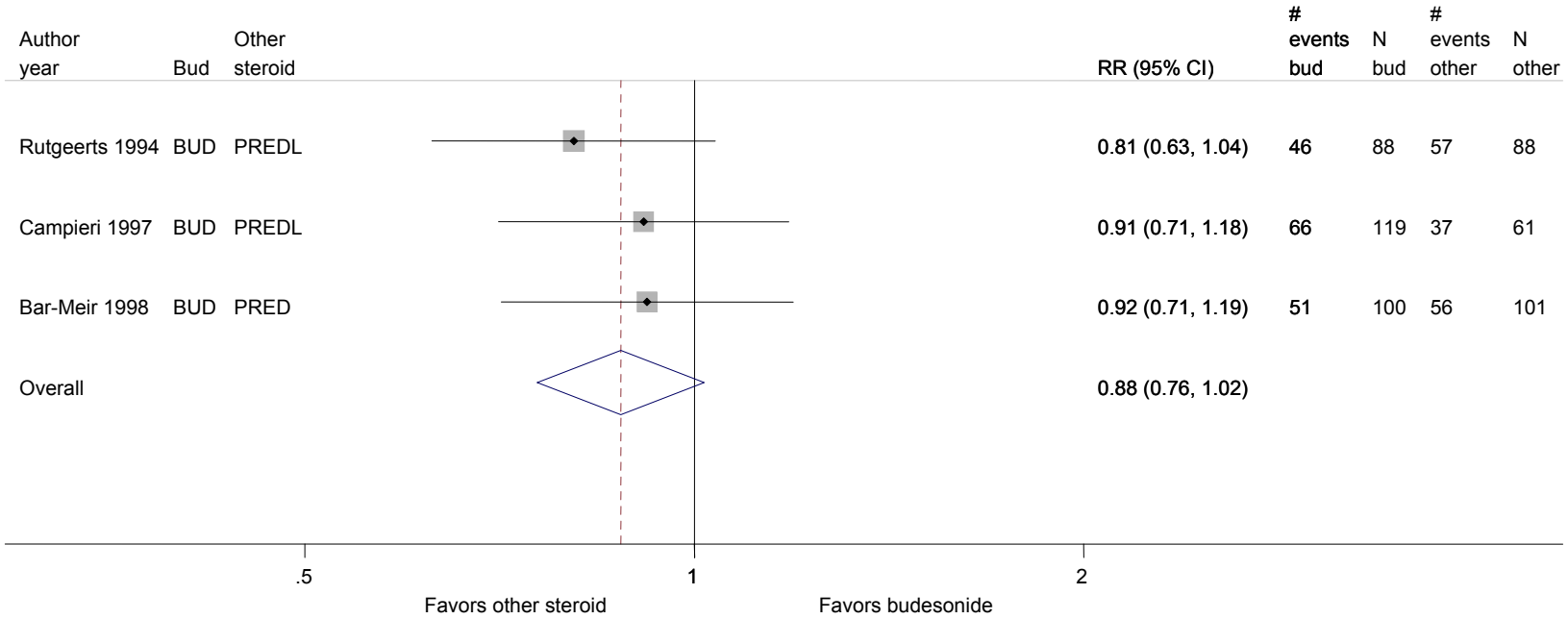
**Failure and relapse" defined by study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60 point decrease after end of all three treatment cycles)

[†]One component of a Wilcoxon rank sum test set of outcomes.

[‡]Tablets

[§] Granules

Figure 5. Pooled relative risk of inducing remission* of Crohn's disease at week 8 comparing budesonide with another corticosteroid



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 8

BUD = budesonide; CI = confidence interval; PRED = prednisone; PREDL = prednisolone; RR = relative risk; Steroid = corticosteroid
* In all studies, remission was defined as a Crohn's Disease Activity Index less than 150. Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.65 with 2 degrees of freedom (p = 0.72)
I-squared statistic = 0%

Aminosalicylates

Seven studies evaluated the effectiveness of aminosalicylates as monotherapy to induce remission using various disease activity indexes as outcome measures.[93 99 112-116] Three studies evaluated sulfasalazine at doses between 1 g/15 kg and 6 g a day,[93 99 115] two studies evaluated mesalamine (Asacol) between 1 g to 4 g a day,[112 116] and two studies evaluated mesalamine (Pentasa) at 1.5 g a day.[113 114]

Study Design

Four studies used CDAI as the relevant outcome,[93 112 114 116] one used HBI,[113] one used both CDAI and HBI,[116] one used a generic "activity index",[115] and one[99] used the absence of "failure and relapse" (a composite outcome) as the relevant outcome.[C] Three studies required a minimum CDAI of 150 at entry. Two studies defined active disease based on clinical criteria,[113 114] one of which[114] allowed patients with CDAI less than 150 to participate as long as they fulfilled the clinical criteria for active disease. One study[99] included participants with both active (CDAI>150) and inactive (CDAI<150) disease at randomization; patients with active disease were analyzed as part of a subgroup analysis.

Per our inclusion criteria, all seven studies were RCTs (Appendix D, Evidence Table 2). Three studies took place in the United States,[93 112 116] three took place in Europe,[99 114 115] while one did not report study location.[113] Five studies were multicenter in design, one was not[112] and one did not report whether it was multicenter or not.[113] Only three studies reported the starting year of enrollment, ranging between 1971 and 1977.[93 99 115] The median study duration was 16 weeks (range, 6 weeks to 26 weeks). Five studies included adults ages 18 years or older, and two[93 114] included those ages 15 and older. No studies demanded that patients be corticosteroids resistant or dependent. Three studies defined remission as a CDAI less than 150[93 112 116] with two of these studies also requiring a 50- to 70-point drop in CDAI as a necessary criterion for remission.[112 116] One study[114] defined remission as CDAI decrease of more than 33% from baseline. One study defined remission as a decrease in HBI of 2 points or more,[113] and another as a decrease in the "activity index – AI" of 25% or more.[115] One study[99] defined response to therapy as an absence of "failure and relapse," a category comprising early withdrawal from the study, need for repeat induction therapy, and multiple clinical and CDAI criteria.[C] In terms of prior medication use, no prior medications were prohibited. Two studies prohibited prior Crohn's disease surgery.[112 117]

Population Characteristics

All of the following statistics exclude one study[99] due to its inclusion of both those with active and inactive disease in the baseline population. Therefore, results on only six studies are reported here. A total of 632 participants were randomized across the six studies (Appendix D, Evidence Table 3). The proportion of male participants in each study arm ranged from 27% to

[C] "Failure and relapse" included study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60 point decrease after end of all three treatment cycles)

67%. Only two studies[93 112] commented on the percentage of Caucasians, which ranged from 93% to 100% among all arms. Smoking ("smoker") was only reported in one study[116] and ranged between 29% and 50% across all four arms. Mean age at enrollment was reported in four studies, and ranged between 30 and 37 years, while median age at enrollment was reported in two studies and ranged between 31 and 38 years. Duration of disease was reported in all studies except one[115] and ranged between 3.4 and 9.9 years (mean) and 3.5 and 7 years (median). Disease location was reported in all but one study:[112] ileal-only location ranged between 23% and 65%, ileocolonic location between 5% and 66%, and colonic location between 11% and 39%. Baseline CDAI was reported for all but one study.[113] CDAI ranged between 165 and 277 (mean) and 153 and 177 (median). The value of 153 was derived from the study[114] that included participants with CDAI less than 150. In the two studies that used HBI,[113 116] mean HBI scores ranged from 5.0 to 9.8. One study[116] assessed the VHAI at baseline, with scores ranging from 154 to 158 across the four study arms. Concurrent medication use, including corticosteroids, was not reported in any of the studies. Prior medication use was as follows: aminosalicylates use ranged between 8% and 51% across three studies,[93 115 116] and prior corticosteroids use ranged from 8% to 38% across the same three studies.

Disease Activity Indexes

Aminosalicylates versus placebo. A total of seven RCTs involving 744 patients were analyzed.[93 99 112-116] Table 13 summarizes the effects of aminosalicylate therapy in terms of inducing remission and response (see also Appendix D, Evidence Table 4). Five of seven studies clinically favored aminosalicylates over placebo; however, only three studies attained statistical significance.[99 115 116] In these two of these three studies, the highest daily dose of aminosalicylates (4 g and 6 g) was administered. In a study assessing three different doses of aminosalicylates,[116] the remission rate almost doubled between the 2 g/day and 4 g/day dose. Another study to reach significance was small (n = 26), and a unique "activity index" was used to measure remission, in which only a 25% reduction in initial score was required for remission.[115] If the CDAI less than 150 definition of remission was applied to this study it is not clear if it would remain significant. In one study[99] that randomized both active and inactive patients at randomization, the 112 patients with active disease were analyzed separately as part of a subgroup analysis. In this study, the group receiving sulfasalazine (3 g/day) had significantly higher rates of being free of "failure and relapse" than the placebo group through the two years of the study (22% versus 8%, $P < 0.05$).[D] Studies that failed to attain statistical significance may have been underpowered. Because of the extensive variability in drugs, doses, outcome definitions, and outcome time points, a meta-analysis was not performed.

[D] "Failure and relapse" included study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60 point decrease after end of all three treatment cycles).

Table 13. Randomized controlled trials comparing the effectiveness of aminosalicylates with placebo in terms of inducing remission or response in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (dose), n	Total dose (g/day)	Comparison, n	Remission/Response definition	Remission/ Response rate (%)
Mahida, 1990[113]	6	Pentasa (500 mg every 8 hr), 20	1.5	Placebo, 20	HBI 2-pt drop	40% vs 35%
Tremaine, 1994[112]	16	Mesalamine (800 mg every 6 hr), 20	3.2	Placebo, 18	CDAI<150 and 70-pt drop	45% vs 22%
Rasmussen, 1987[114]	2	Pentasa (1500 mg every 24 hr), 30	1.5	Placebo, 37	CDAI decrease by >33%	0% vs 8%
	16	Pentasa (1500 mg every 24 hr), 30	1.5	Placebo, 37	CDAI decrease by >33%	27% vs 25%
Malchow, 1984[99]	3	Sulfasalazine (3 g/day), 54	3	Placebo, 58	Absence of "failure and relapse"**	87% vs 79%
	16	Sulfasalazine (3 g/day), 54	3	Placebo, 58	Absence of "failure and relapse"**	57% vs 36%
	54	Sulfasalazine (3 g/day), 54	3	Placebo, 58	Absence of "failure and relapse"**	30% vs 14%
	104	Sulfasalazine (3 g/day), 54	3	Placebo, 58	Absence of "failure and relapse"**	22% vs 8%*
Singleton, 1993[116]	16	Mesalamine (1 g every 24 hr), 80	1	Placebo, 80	CDAI≤150 and 50-pt drop	23% vs 18%
		Mesalamine (2 g every 24 hr), 75	2	Placebo, 80	CDAI≤150 and 50-pt drop	24% vs 18%
		Mesalamine (4 g every 24 hr), 75	4	Placebo, 80	CDAI≤150 and 50-pt drop	43% vs 18%*
Summers, 1979[93]	17	Sulfasalazine (1 g/15 kg every 24 hr), 74	1 g/15 kg	Placebo, 77	CDAI<150 through study end[†]	42% vs 30%
Van Hees, 1981[115]	26	Sulfasalazine (1.5 g every 6 hr), 13	6	Placebo, 13	"Activity Index" decrease by ≥ 25%	62% vs 7%*

CDAI = Crohn's Disease Activity Index; g = gram; HBI = Harvey-Bradshaw Index; hr = hour; kg = kilogram; mg = milligram; pt = point; vs = versus

* Significant difference at 0.05 alpha level. For Malchow 1984,[99] significance level refers to difference in rates over entire period of study (0 to 104 weeks)

** "Failure and relapse" defined by study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60 point decrease after end of all three treatment cycles)

[†]CDAI remission was only assessed after subjects had attained other outcomes in a rank-sum model

Indirect Comparisons

Natalizumab versus TNF-alpha inhibitors. In the absence of head-to-head trials comparing TNF-alpha inhibitors and natalizumab, we conducted an indirect comparison using the common comparator placebo. Indirect comparisons are a theoretically valid way to compare active treatments that have not been compared to one another in a head-to-head comparison. The underlying assumptions are that the populations, outcomes (type and length of followup) and treatment duration are comparable for randomized trials, which have a common comparator. We judged the six trials comparing TNF-alpha inhibitors versus placebo and the three trials comparing natalizumab versus placebo to be comparable enough to be included in an indirect comparison. The trials included comparable populations and had remission at weeks 2 to 4 defined as a CDAI less than 150 as the outcome.

The pooled odds ratio of TNF-alpha inhibitors versus placebo for remission at weeks 2 to 4 was 2.28 (95% CI, 1.53 to 3.39; I-squared, 25%) and 1.63 (95% CI, 1.16 to 2.28, I-squared, 0%) for natalizumab versus placebo (Figures 3 and 4, which were presented earlier in the chapter). The indirect comparison showed an odds ratio of 1.40 (95% CI, 0.83 to 2.36) for TNF-alpha inhibitors versus natalizumab, which was not statistically significant.

Mucosal Healing

In all cases, mucosal healing was a secondary endpoint and represented a subset of the original study group (Appendix D, Evidence Table 4).

Biologics versus placebo. One study with 30 participants (a subgroup of patients from Targan et al.)[77] compared infliximab with placebo for this outcome.[118] Crohn's disease endoscopic index of severity (CDEIS) was significantly improved in the infliximab group (all doses, from 5 mg/kg to 20 mg/kg) at 4 weeks compared to baseline (mean change of 7.7; $P < 0.001$). The mean change in CDEIS for placebo was 0.9 (P = NS). Notably, the baseline CDEIS was higher in the infliximab group (13.0) compared to placebo (8.4).

Biologics versus immunomodulators. One study[83] compared infliximab and placebo with azathioprine and placebo for this outcome. At baseline, 309 out of 508 patients for this comparison had mucosal lesions and were evaluated again at the primary endpoint. Thirty percent (28 out of 93) of the infliximab and placebo group had no mucosal ulcers at 26 weeks, compared with 17% (18 out of 109) of the azathioprine and placebo group ($P = 0.02$).

Combination of a biologic and another therapy versus another therapy. One study[86] compared the combination of infliximab (induction only) and azathioprine with budesonide or 6-methylprednisolone (top-down versus step-up trial). Forty-nine out of 129 patients underwent colonoscopy at the end of the follow-up period. At 104 weeks, rates of clinical remission were not different between the two groups; however, rates of mucosal healing (i.e., no ulceration at endoscopy) at the same time point were significantly higher in the combination infliximab and azathioprine arm (73% versus 30%; $P = 0.003$).

One study[83] compared combination infliximab and azathioprine with infliximab and placebo, as well as with azathioprine and placebo. At baseline, 309 out of 508 patients for this comparison had mucosal lesions and were evaluated again after the primary endpoint. Rates of mucosal

healing (no ulcers) at 26 weeks were 47 out of 107 (44%) for the combination of infliximab and azathioprine, 28 out of 93 (30%) for infliximab and placebo ($P = 0.06$ compared to combination infliximab and azathioprine), and 18 out of 109 (17%) for azathioprine and placebo ($P < 0.001$ compared with the combination of infliximab and azathioprine).

One study[84] compared a combination of infliximab and a thiopurine with a thiopurine alone in a group of 113 steroid-dependent Crohn's disease patients. These analyses were performed both on patients with active disease (CDAI > 150) who had been on a thiopurine prior to randomization, as well as on thiopurine-naïve patients who had both active and inactive disease. Of the 20 patients who underwent colonoscopy at baseline and at 24 weeks, the CDEIS decrease from baseline to week 24 was significantly greater in the infliximab and thiopurine group compared with the thiopurine alone group (6.9 versus 1.2; $P < 0.05$). However, the number of patients with no ulceration at week 24 was neither clinically nor statistically significantly different between the two groups (27% versus 33%).

Reduction of Steroids

Thiopurines versus placebo. One study with 26 participants showed no clinical or statistical difference in the reduction of steroid use between azathioprine and placebo.[119] Reduction in steroid dose from baseline was 7 mg and 12 mg, respectively (Appendix D, Evidence Table 4).

Fistula Response

Biologics versus placebo. Three studies with 233 participants with draining fistulas were included for this outcome.[24 78 80] They considered three different comparisons: infliximab (5 mg/kg or 10 mg/kg versus placebo administered at 0, 2 and 6 weeks (N = 94),[24] adalimumab at three different doses versus placebo at 4 weeks (N = 32),[78] and certolizumab pegol (400 mg subcutaneous every 4 weeks) versus placebo at 26 weeks (N = 107).[80] Infliximab was the only TNF-alpha inhibitor to evaluate fistula healing (perianal and abdominal) as a primary endpoint. For infliximab, fistula response (the primary endpoint) at 6 weeks was 68%, 56% and 26% for 5 mg/kg, 10 mg/kg, and placebo, respectively ($P = 0.002$ and $P = 0.02$ compared to placebo).[24] Fistula closure rates were 55%, 38%, and 13%, respectively ($P = 0.001$ and $P = 0.04$ compared to placebo). Perianal disease activity index (PDAI) scores were lower at 2 weeks compared to baseline, but not at 18 weeks. There was no clinical or statistical difference in fistula response (75%, 20%, 8%, and 33% at 40 mg/20 mg, 80 mg/40 mg, 160 mg/80 mg doses) or complete fistula closure (75%, 0%, 0%, and 17%, respectively) for adalimumab versus placebo at week 4.[78] Similarly, there was no difference in complete fistula closure for certolizumab pegol versus placebo at week 26 (30% versus 31%).[80]

Thiopurines versus placebo. One study compared azathioprine at 2.5 mg/kg daily with placebo.[120] Seventeen patients had draining perianal disease at the time of randomization. Rate of fistula response was no different between groups (13% versus 11%).

Thiopurines versus another therapy. One study with 54 total participants compared azathioprine to methotrexate. Ten patients had active perianal fistulizing disease.[95] At week 26, closure was attained in one out of four patients in the azathioprine group and four out of six patients in the methotrexate group ($P > 0.05$).

Corticosteroids versus placebo. One study compared prednisone with placebo.[120] Nineteen patients had draining perianal disease at the time of randomization. Rate of fistula response was higher in the prednisone group (30% versus 11%; $P > 0.05$).

Aminosalicylates versus placebo. One study compared sulfasalazine daily with placebo.[120] Eighteen patients had draining perianal disease at the time of randomization. Rate of fistula response was higher in the sulfasalazine arm (22% versus 11%; $P > 0.05$).

Patient-Reported Outcomes

All studies below used the Inflammatory Bowel Disease Questionnaire (IBDQ) as their outcome measure unless reported otherwise. Clinical significance was based on an IBDQ delta of 17 or greater between treatment groups (Appendix D, Evidence Table 4).

Biologics versus placebo. Seven studies with 2,219 total participants addressed this outcome.[25 26 77-81]

Two studies compared natalizumab to placebo. At week 4, insufficient data was provided to determine whether natalizumab was superior to placebo.[25] In one study of 509 participants, mean IBDQ rose from 124 to 151 in the natalizumab arm and from 123 to 138 in the placebo arm at week 12 ($P < 0.001$).[26]

One study compared infliximab to placebo; infliximab was found to be both clinically and statistically superior to placebo at week 4.[77] Mean IBDQ rose from 118 to 154 in the infliximab arm and from 128 to 133 in the placebo arm.

Two studies compared adalimumab to placebo; adalimumab was statistically but not clinically superior to placebo at week 4.[78 79] In one study,[78] mean IBDQ rose from 127-129 up to 146-158 across all treatment arms, and from 131 up to 146 in the placebo arm (statistically significant for the 80/40 mg and the 160/80 mg adalimumab arms only). In another study,[79] mean IBDQ rose from 120 to 150 in the adalimumab arm and 124 to 139 in the placebo arm.

Two studies compared certolizumab pegol to placebo; certolizumab pegol was statistically but not clinically superior to placebo at weeks 12 and 26.[80 81] In one study,[81] baseline mean IBDQ scores for the treatment arms were 132, 123, and 127, while the baseline placebo IBDQ score was 123. The final IBDQ score at week 12 was 156 in the combined treatment arms and 141 in the placebo arm. In another study of 662 participants,[80] the mean IBDQ at 26 weeks rose 26 points in the certolizumab arm and 21 points in the placebo arm ($P = 0.03$); absolute IBDQ scores were not reported.

Biologics versus another therapy. One trial with 508 participants compared infliximab 5 mg/kg intravenous (induction and maintenance) and placebo with azathioprine (2.5 mg/kg daily) and placebo at 26 weeks.[83] This comparison favored infliximab and placebo to a statistically, but not clinically significant degree (Table 14).

Combination of biologic and another therapy versus another therapy. One trial with 508 participants compared the combination of infliximab and azathioprine with either azathioprine and placebo or infliximab and placebo at 26 weeks.[83] Statistical significance was achieved for the comparison of combination infliximab and azathioprine, versus both azathioprine and

placebo, as well as infliximab and placebo (Table 14). However, the absolute difference in mean IBDQ change from baseline was not clinically significant.

One study with 79 participants compared the combination of infliximab and natalizumab with infliximab and placebo.[27] At 10 weeks, mean IBDQ rose from 138 to 157 in the group receiving a combination of infliximab and natalizumab and from 133 to 150 in the group receiving infliximab and placebo. This comparison was neither clinically nor statistically significant.

One study with 19 participants compared the combination of infliximab and methotrexate with infliximab alone.[85] The comparison favored the combination of infliximab and methotrexate: at 48 weeks, the mean IBDQ score rose from 113 to 163 in the infliximab and methotrexate arm and from 107 to 135 in the infliximab alone arm (statistical significance not provided).

Thiopurines versus placebo. Three studies with 116 participants compared azathioprine to placebo.[94 119 122] One study[94] used the Treatment Goal Score for Wellbeing where at week 0 everyone starts out with a score of 0; a difference was found at 12-16 weeks (1.2 for 6-mercaptopurine versus 1 for placebo) and at 38 weeks (1.3 versus 1). However, no measures of variance were given and it was unclear whether this score difference was clinically significant. One cross-over study showed no improvement in patient-reported quality of life ("feeling better") with azathioprine compared to placebo; in both arms, 6 patients reported symptomatic improvement, while 5 reported no change.[119] In one study,[122] after 8 weeks, no patients reported subjective improvement in their symptoms with azathioprine or placebo. More patients reported that their symptoms were worse with azathioprine versus placebo and fewer patients reported that their symptoms were unchanged with azathioprine versus placebo. However, azathioprine can take up to 16 or more weeks to become clinically effective; additionally, a validated scale was not employed.[87]

Methotrexate versus placebo. Two trials with a total of 193 participants compared methotrexate to placebo. In one study,[98] patients with active disease despite chronic prednisone use were randomized to receive intramuscular methotrexate or placebo. At 16 weeks, the mean IBDQ rose from 162 to 169 in the methotrexate arm, and dropped from 159 to 151 in the placebo ($P < 0.002$). Another study using oral methotrexate[94] employed the Treatment Goal Score for Wellbeing where at week 0 everyone starts out with a score of 0. Scores at 12-16 weeks were 1.2 for methotrexate versus 1 for placebo, and 2.7 versus 1 at 38 weeks. No measures of variance were given and it was unclear whether this score difference was clinically significant.

Corticosteroids versus placebo. Two trials with 458 participants compared budesonide to placebo.[100 101] In the larger study of 258 participants,[101] at 8 weeks mean IBDQ rose from 131 to 138 in the 3 mg/day arm, 125 to 165 in the 9 mg/day arm, 130 to 155 in the 15 mg/day arm, and 130 to 140 in the placebo arm. Both 9 mg/day and 15 mg/day arms had results that were clinically and statistically significant when compared with the placebo arm. In a study of 200 patients,[100] the change in IBDQ score from baseline values (not provided) was 36 in the 9 mg/day arm, 34 in the 4.5 mg oral twice daily arm, and 29 in the placebo arm at 8 weeks; this was neither clinically or statistically significant.

Table 14. Results from one randomized controlled trial comparing the effectiveness of azathioprine, infliximab, and a combination of infliximab and azathioprine in terms of Inflammatory Bowel Disease Questionnaire† results in patients with Crohn's disease

Time point	Azathioprine‡ (N=170)	Infliximab‡ (N=169)	P-value (azathioprine vs infliximab)	Infliximab + azathioprine‡ (N=169)	P-value (infliximab + azathioprine vs infliximab)	P-value (infliximab + azathioprine vs azathioprine)
Baseline	122.1 ± 29.7	126.7 ± 30.3	ND	125.3 ± 28.9	ND	ND
Change from baseline						
Week 2	20.1 ± 24.3	27.7 ± 26.1	0.007	31.4 ± 29.6	0.31	<0.001
Week 10	31.0 ± 31.7	37.8 ± 35.6	0.10	42.4 ± 34.7	0.15	0.002
Week 26	31.4 ± 35.4	39.9 ± 36.6	0.05	45.2 ± 35.8	0.13	<0.001

ND = not done; vs = versus

* Data are from Colombel 2010.[83]

† The Inflammatory Bowel Disease Questionnaire ranges from 32 to 224 points, with higher scores indicating improvements in health-related quality of life.[121]

‡Data are mean ± standard deviation.

Corticosteroids versus another corticosteroid. One trial with 201 participants compared prednisone and placebo with budesonide and placebo.[103] At 8 weeks, mean IBDQ rose from 130 to 164 in the prednisone arm and 136 to 162 in the budesonide arm; this was neither clinically nor statistically significant. Additionally, there were no differences in the Short Form-36 (SF-36) mental score and physical score.

Corticosteroids versus another treatment. One trial with 50 participants compared prednisone with aminosalicylates using the McMaster University Quality of Life Index.[109] At two weeks, improvement in the Quality of Life Index was 23% in the prednisone arm and 7% in the aminosalicylates arm ($P < 0.005$). At 12 weeks, the improvement was 37% and 33%, respectively ($P > 0.05$).

Quality Assessment

Out of the 53 trials included in this report that addressed KQ1, all were randomized controlled trials with parallel arm design (Appendix D, Evidence Table 5). Among these 53 RCTs, 57% adequately generated their allocation sequence. Sixty-four percent of these RCTs adequately concealed their allocation of participants into the different study arms. Sixty-six percent were described as being double blinded while 34% were not double blinded or not report on blinding. Sixty-eight percent of these studies reported withdrawals and dropouts while 32% had incomplete outcome data. Forty-three percent of these RCTs had some form of threat to the validity of results that they reported. Sixty-six percent and 34% of these RCTs received pharmaceutical support and company involvement in the design, conduct or reporting of the study, respectively. Among these 53 trials, 27% were rated as good quality, 48% as fair quality, and 25% as poor quality.

There were two studies[90 99] where data could be extracted for active Crohn's disease only as a subgroup analysis. These results should be interpreted with caution.

Applicability

Populations

- The vast majority of studies enrolled only Caucasians; African Americans, Hispanics, and Asians were not well represented.
- The median age at enrollment in most studies ranged between 25 and 40 years of age. Older populations were not well represented.
- Smoking was not consistently reported. There is some evidence that smoking can affect drug efficacy. Additionally, smoking has been shown to affect surgical rates (one of our endpoints).[123]
- Mean duration of disease, with the exception of a few studies,[83 86] was long (often greater than 10 years). There is growing evidence that patients with a shorter duration of disease are more responsive to medications.[124] Also, patients with a long duration of disease frequently have complications of stricturing or fistulization,[125] which can affect hospitalization and surgical rates.

- For KQ1, most studies reported on patients with a minimum CDAI score of 220 (moderate disease cutoff). However, some studies only required a minimum CDAI of 150 (mild disease cutoff) and patients were not stratified by disease severity.
- Most studies used the CDAI. The CDAI takes into account frequency of diarrhea, abdominal pain, rating of general well-being, extraintestinal manifestation, use of anti-diarrheals, abdominal mass, and hematocrit. Many of the mentioned symptoms are not unique to Crohn's disease, and could be seen with other common concurrent conditions such as irritable bowel syndrome. Most studies did not document the presence of mucosal disease prior to randomization. The effect size in those with mucosal disease is probably different from that reported for all patients (with or without mucosal disease).
- Very few patients were medication naïve at the time of randomization. Most had received steroids or other medications, thus contributing to baseline population heterogeneity. Also, some patients were steroid dependent or resistant at the time of entry; this probably represents a sicker population.

Intervention

- The studies had significant heterogeneity.
  - Different doses of the same medications were used. Often the medications were under-dosed, particularly with regard to thiopurines.
  - Different delivery systems were used, including oral and intramuscular methotrexate, making comparisons difficult. In some cases, as for intravenous certolizumab pegol and intravenous azathioprine, routes that are not used in practice were evaluated in the studies. Even among oral aminosalicylates agents, different formulations were characterized by different delivery systems (pH dependent, microgranule, or other).
  - For studies where patients were started on corticosteroids at randomization, protocols for corticosteroid tapering were variable between studies.
- In some studies,[77 81 82] particularly with TNF-alpha inhibitor agents, one dose or only induction dosing was given without further maintenance dosing. Largely because of the results of episodic versus maintenance therapy, the standard of care is to continue maintenance therapy in those who respond.[1] This limits the chance of developing human anti-chimeric antibodies to TNF-alpha inhibitors along with loss of response and injection and infusion reactions.[126 127]

Comparisons

- In patients who were corticosteroid dependent at the time of randomization, corticosteroids were not counted as an active intervention, in an effort to differentiate them from studies where corticosteroids were explicitly designated as an active intervention.

Outcomes

- Some older studies used rank outcome (where other clinical variables including x-ray results, clinical signs such as fever were accounted for) which are not used in more

modern designs.[93 99] Other studies used indexes such as VHAI[111] that are not commonly used in research or clinical practice.

- Improvement in CDAI is non-specific for Crohn's disease; it can go down as a result of improvement in irritable bowel-type symptoms. This helps to explain the overall high placebo response, often exceeding 30%.
- Some studies looked at steroid-free remission, while others did not. This was often complicated by studies where steroids were part of the active intervention. Steroid-free remission is a different endpoint from remission still on steroids.
- Increasingly, mucosal healing is becoming increasingly recognized as an important outcome. However, it is unknown whether improvement in endoscopic disease is as important as complete mucosal healing (absence of ulceration). Also, for patients with mostly small bowel disease that cannot be easily evaluated with ileocolonoscopy, there is no agreement on how to quantify mucosal healing.
- Overall, many of the studies had incomplete reporting of many of our predetermined outcomes, including: mucosal healing, hospitalizations, surgery, reduction of steroids, and fistula response.

Timing

- For KQ1, most study endpoints ended at around 12 weeks. Few studies looked beyond 26 weeks as their primary endpoint. This is a particularly important limitation for studies of thiopurines and methotrexate as these drugs often take over 12 weeks to become clinically active.

Setting

- Most studies took place in North America and Europe. Thus, results may not necessarily be transferred to other locales.

Other – Conflict of Interest

- Almost half of studies had some pharmaceutical company input into study design, conduct, or reporting. Additionally, because participating study centers received incentives for enrolling patients, it is possible that some patients were enrolled inappropriately (e.g., the patient with a high CDAI, but no visible mucosal disease), thus biasing the results.

Key Question 2: What is the comparative effectiveness of therapies alone or in combination used to maintain remission in adults with moderate-to-severe Crohn's disease?

Key Points

Disease Activity Indexes – Ustekinumab and Natalizumab

- The strength of evidence was insufficient for ustekinumab in terms of maintaining remission. We did not find any studies evaluating the effectiveness of ustekinumab for this outcome.
- The strength of evidence was low to demonstrate that natalizumab (300 mg every 4 weeks) was more effective than placebo in maintaining remission at weeks 24 and 48 (following randomization) among patients who achieved at least a response during a natalizumab induction study (week 24 absolute RD, 25%; placebo rate, 30%; week 48 absolute RD, 33%; placebo rate, 22%).

Disease Activity Indexes – TNF-Alpha Inhibitors

- The strength of evidence was high to demonstrate that TNF-alpha inhibitors (infliximab, adalimumab, and certolizumab pegol) were more effective than placebo in maintaining remission at weeks 16 to 18 (pooled RR, 1.8; 95% CI, 1.5 to 2.2), week 28 (pooled RR, 2.1; 95% CI, 1.7 to 2.7), and week 52 among patients who had at least a response to open-label TNF-alpha inhibitors.
- The strength of evidence was high to demonstrate that infliximab was more effective than placebo in maintaining a remission at weeks 28 and 52 among patients who had at least a response to open-label infliximab (range in week 28 absolute RD, 18% to 29%; placebo rate range, 21% to 35%; range in week 52 absolute RD, 15% to 25%; placebo rate: 15%).
  - The strength of evidence was low that infliximab was more effective than placebo at week 16 (absolute RD, 30%; placebo rate, 30%).
- The strength of evidence was high to demonstrate that adalimumab was more effective than placebo in maintaining a remission at weeks 16, 28, and 52 among patients who had at least a response to open-label adalimumab (range in week 16 absolute RD, 22% to 40%; placebo rate range, 21% to 51%; range in week 28 absolute RD, 20% to 60%; placebo rate range, 17% to 38%; range in week 52 absolute RD, 24% to 39%; placebo rate range, 12% to 44%).
- The strength of evidence was high to demonstrate that certolizumab pegol (400 mg every 4 weeks) was more effective than placebo in maintaining a remission at week 18 among patients who had at least a response to open-label certolizumab pegol (absolute RD, 19%; placebo rate, 29%).
- The strength of evidence was low to demonstrate that there was no difference between the combination of infliximab (5 mg/kg every 8 weeks) and azathioprine (2-2.5 mg/kg daily) and infliximab (5 mg/kg every 8 weeks) alone in maintaining remission at 104 weeks among patients who have been in remission on infliximab and azathioprine

(absolute difference [with regard to need for infliximab stoppage or change in dosage interval], 5%; infliximab alone rate, 55%).

- The strength of evidence was low to demonstrate that there was no difference between the combination of infliximab (5 mg/kg every 8 weeks) and azathioprine (2-2.5 mg/kg daily) and infliximab (5 mg/kg every 8 weeks) with intravenous hydrocortisone pretreatment in maintaining remission at 6, 12, and 24 months among patients with steroid-dependent disease (range in absolute RD across time points, -9% to -5%; infliximab and hydrocortisone rate range, 77% to 88%).

Disease Activity Indexes – Thiopurines

- The strength of evidence was low to demonstrate that azathioprine was more effective than placebo in maintaining remission at weeks 24 and 52 (week 24 absolute RD, 40%; placebo rate, 40%; range in week 52 absolute RD, 5% to 39%; placebo rate, 47% to 64%).
  - The strength of evidence was moderate that azathioprine (1.7 mg/kg daily) was more effective than placebo at week 78 (absolute RD, 13%; placebo rate, 79%).
  - The strength of evidence was low that placebo was more effective than azathioprine (1 mg/kg daily) at week 104 (absolute RD, -11%; placebo rate, 40%).
- The strength of evidence was low to demonstrate that azathioprine was more effective than corticosteroids at week 52 (range in absolute RD, 12% to 15%; corticosteroid rate range, 57% to 64%).
  - The strength of evidence was low that there was no difference between azathioprine and corticosteroids in maintaining remission at weeks 104 (absolute RD, -3%; corticosteroid rate, 32%).
- The strength of evidence was low to demonstrate that there was no difference between azathioprine (1 mg/kg daily) and sulfasalazine (1-2 g/15 kg) in maintaining remission at weeks 52 and 104 (range in absolute RD across time points, -2% to 7%; sulfasalazine rate range, 31% to 62%).

Disease Activity Indexes – Methotrexate

- The strength of evidence was low to demonstrate that intramuscular methotrexate (15 mg weekly) was more effective than placebo in maintaining remission at weeks 16 and 40 (week 16 absolute RD, 13%; placebo rate, 58%; week 40 absolute RD, 26%; placebo rate, 39%).

Disease Activity Indexes – Corticosteroids

- The strength of evidence was low to demonstrate no difference between budesonide and placebo in maintaining remission at weeks 13, 19, 26, and 52 (week 52 pooled RR, 1.0; 95% CI, 0.8 to 1.1).
- The strength of evidence was low to demonstrate no difference between other corticosteroids (prednisone, 6-methylprednisolone) and placebo in maintaining remission at weeks 17 to 19, 26, 54, and 104 (absolute RD across time points, -9% to 67%; placebo rate, 22% to 90%).

- The strength of evidence was moderate to demonstrate that budesonide (6 mg daily) was more effective than mesalamine (3 g daily) in maintaining remission at weeks 16, 26, and 52 (week 16 absolute RD, 35%; mesalamine rate, 45%; week 26 absolute RD, 39%; mesalamine rate, 24%; week 52 absolute RD, 27%; mesalamine rate, 18%).
- The strength of evidence was low to demonstrate no difference between other steroids (prednisone, 6-methylprednisolone) and aminosalicylates in maintaining remission at weeks 17 to 19, 26, 54, and 104 (absolute RD across time points, -2% to 9%; aminosalicylates rate, 37% to 87%).
- The strength of evidence was low to demonstrate no difference between 6-methylprednisolone (8 mg daily) and sulfasalazine (3 g daily) combination therapy and placebo, as well as to sulfasalazine (3 g daily) alone in maintaining remission at weeks 19, 26, 54, and 104 (combination 6-methylprednisolone and sulfasalazine versus placebo absolute RD across time points, 0% to 5%; placebo rate, 32% to 68%; combination 6-methylprednisolone and sulfasalazine versus sulfasalazine absolute RD, -2% to -9%; sulfasalazine rate, 37% to 77%).
- The strength of evidence was low to demonstrate no difference between a combination of corticosteroids (prednisone, 6-methylprednisolone) and sulfasalazine and corticosteroids (prednisone, 6-methylprednisolone) alone in maintaining remission at weeks 19, 26, 54, and 104 (absolute RD across time points, -16% to 0%; corticosteroid rate, 22% to 84%).

Disease Activity Indexes – Aminosalicylates

- The strength of evidence was low to demonstrate no difference between aminosalicylates and placebo in maintaining remission at weeks 16 to 19 (pooled RR, 0.8; 95% CI, 0.7 to 1.1), week 26 (pooled RR, 0.8; 95% CI, 0.6 to 1.1), and week 104 (absolute RD across time points, -17% to 14%; placebo rate, 32% to 59%).
    - The strength of evidence was low that aminosalicylates were more effective than placebo at weeks 48 to 54 (weeks 48 to 52 pooled RR, 0.7; 95% CI, 0.6 to 1.0), and at week 208.
        - This was based on a meta-analysis of four studies.

Mucosal Healing

- The strength of evidence was moderate to demonstrate that infliximab was superior to placebo in achieving mucosal healing at weeks 8 and 52 in patients who have achieved at least a response to open-label drug (week 8 absolute RD for absence of ulcers, 31%; placebo rate, 0%; week 52 absolute RD, 43%; placebo rate, 7%).
- The strength of evidence was low to demonstrate that there was no difference at week 104 between a combination of infliximab and azathioprine and infliximab alone in achieving mucosal healing in patients who have been in remission on infliximab and azathioprine (absolute RD for absence of ulcers, 3%; infliximab rate, 61%).
- The strength of evidence was moderate to demonstrate that azathioprine was superior to budesonide in achieving mucosal healing at week 52 in adults with Crohn's disease participating in a maintenance trial (absolute RD for absence of ulcers, 55%; budesonide rate, 5%).

Hospitalizations

- The strength of evidence was moderate to demonstrate that infliximab was superior to placebo in decreasing Crohn's disease-related hospitalization rates during a 40-week period in patients with active fistulizing disease who have achieved fistula response to open-label drug (Crohn's disease-related hospitalizations per 100 patients, 11 hospitalizations in the infliximab group and 31 hospitalizations in the placebo group).
- The strength of evidence was moderate to demonstrate that adalimumab was superior to placebo in decreasing Crohn's disease-related hospitalization rates during a 52-week period in patients who have achieved at least a response to open-label drug (HR, 0.4; 95% CI, 0.2 to 0.7).

Surgeries

- The strength of evidence was moderate to demonstrate that infliximab was superior to placebo in decreasing surgical rates during a 40-week period in patients with active fistulizing disease who had achieved fistula response to open-label drug (number of surgeries and procedures, 65 for infliximab and 126 for placebo).
- The strength of evidence was moderate to demonstrate that adalimumab was superior to placebo in decreasing surgical rates during a 52-week period in patients who had achieved at least a response to open-label drug (surgery rates, 0.3% for adalimumab group and 4.1% for placebo group).

Reduction of Steroids

- The strength of evidence was high to demonstrate that infliximab was superior to placebo in reducing corticosteroid use at week 52 in patients who had achieved at least a response to open-label drug (discontinuation of steroids while in remission, OR, 4.2; 95% CI, 1.5 to 11.5).
- The strength of evidence was moderate to demonstrate that adalimumab was superior to placebo in maintaining a steroid-free state at weeks 26 and 52 in patients who had achieved at least a response to open-label drug and were able to come off steroids (week 26 absolute RD in steroid-free state, 27% to 32%; placebo rate, 3%; week 52 absolute RD in steroid-free state, 17% to 23%; placebo rate, 6%).
- The strength of evidence was moderate to demonstrate that azathioprine was superior to placebo in reducing steroid use at week 26 in adults with Crohn's disease participating in a maintenance trial (absolute reduction in prednisone use from baseline, 9.4 mg; placebo reduction, 6.1 mg).

Fistula Response

- The strength of evidence was moderate to demonstrate that infliximab was superior to placebo in closing fistulas at week 40 in adults with Crohn's disease who had achieved an initial fistula response to open-label drug (absolute RD, 17%; placebo rate, 19%).

Patient-Reported Outcomes

- The strength of evidence was low to demonstrate that natalizumab was superior to placebo in improving patient-reported outcomes in patients participating in a maintenance trial at week 48 (absolute between-group difference in change in mean IBDQ from randomization, 19 points; placebo mean change IBDQ, -23 points).
- The strength of evidence was moderate to demonstrate that infliximab was superior to placebo in improving patient-reported outcomes at weeks 28 and 52 in patients who had achieved at least a response to open-label drug (week 28 absolute between-group difference in change in mean IBDQ from baseline [prior to open-label run-in], 13 to 18 points; placebo mean change in IBDQ, 14 points; week 52 between-group difference, 13 to 21 points; placebo mean change: 9 points).
    - The strength of evidence was moderate that there was no difference between infliximab and placebo at week 16 (absolute between-group difference in change in mean IBDQ from baseline [prior to open-label run-in], 10 to 22 points; placebo mean change, -8 to 4 points).
- The strength of evidence was moderate to demonstrate no difference between adalimumab and placebo in improving patient-reported outcomes at weeks 22 to 24 and 52 to 56 in patients who had achieved at least a response to open-label drug (week 22 to 24 absolute between-group difference in change in mean IBDQ from randomization, 14 to 19 points; placebo mean change, -10 to -19 points; week 52 to 56 absolute between-group difference in change in mean IBDQ from randomization, 14 to 22 points; placebo mean change, -10 to -25 points).
- The strength of evidence was low to demonstrate that there was no difference between corticosteroids (budesonide) and placebo in improving patient-reported outcomes in patients participating in a maintenance trial at 3, 6, 9, or 12 months (absolute between-group difference in change in mean IBDQ from baseline, 2 to 15 points; placebo mean change, -4 to -31 points).
- The strength of evidence was moderate to demonstrate that budesonide was superior to mesalamine in improving patient-reported outcomes at 12 months in patients participating in a maintenance trial (absolute between-group difference in change in mean IBDQ, 30 to 36 points; mesalamine mean change, -51 to -76 points).
- The strength of evidence was low to demonstrate that there was no difference between mesalamine and placebo in improving patient-reported outcomes in patients participating in a maintenance trial at week 48 (absolute between-group difference in change in mean IBDQ, 1; placebo mean change, -14).

Table 15 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Evidence Table 6.

Table 15. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to maintain remission*

Comparison	Disease activity index	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
Natalizumab vs. placebo	Favors natalizumab; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors natalizumab; Low
TNF vs. placebo	Favors TNF; High	NA	NA	NA	NA	NA	NA
Infliximab vs. placebo	Favors infliximab; High*	Favors infliximab; Moderate	Favors infliximab; Moderate†	Favors infliximab; Moderate†	Favors infliximab; High	Favors infliximab; Moderate	Favors infliximab; Moderate‡
Adalimumab vs. placebo	Favors adalimumab; High	Insufficient	Favors adalimumab; Moderate	Favors adalimumab; Moderate	Favors adalimumab; Moderate	Insufficient	Favors neither; Moderate
CP vs. placebo	Favors CP; High	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Infliximab + azathioprine vs. infliximab	Favors neither; Low	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Infliximab + azathioprine vs. infliximab + steroids (premed)	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. placebo	Favors azathioprine; Low§	Insufficient	Insufficient	Insufficient	Favors azathioprine; Moderate	Insufficient	Insufficient
Azathioprine vs. steroids	Favors azathioprine; Low‖	Favors azathioprine; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. sulfasalazine	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate vs. placebo	Favors methotrexate; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. placebo	Favors neither; Low¶	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low
Steroids (other) vs. placebo	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. ASA	Favors budesonide; Moderate	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors budesonide; Moderate
Steroids (other) vs. ASA	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + ASA vs. placebo	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table 15. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison	Disease activity index	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
Steroids + ASA vs. ASA	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + ASA vs. steroids	Favors neither; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
ASA vs. placebo	Favors neither; Low**‖ (2)	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors neither; Low

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

* All other comparisons and outcomes were graded as insufficient since there were no eligible studies.

ASA = aminosalicylates; CP = certolizumab pegol; NA = not applicable; evidence grading was not conducted for this comparison and outcome; Steroids = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor; vs. = versus

* Low evidence at week 16.

† Confined to patients with fistulizing disease.

‡ Moderate evidence that there is no difference between infliximab and placebo at week 16.

§ Moderate evidence at week 78; Low evidence that placebo more effective than azathioprine at week 104

‖ Low evidence that there is no difference between azathioprine and placebo at week 104

¶ Based on meta-analysis for budesonide versus placebo at week 52.

** Based on composite of 14 included studies, not the 3 studies included in a 52 week meta-analysis (which was clinically and statistically significant); Low evidence that ASA is more effective than placebo at weeks 48-54 and week 208.

Ustekinumab

We did not find any RCTs that compared ustekinumab with placebo or another treatment in terms of maintaining remission in patients with Crohn's disease.

Natalizumab

Study Design and Population Characteristics

One placebo-controlled RCT evaluated the effects of natalizumab on maintenance of remission (Appendix D, Evidence Tables 7 and 8).[76] This maintenance trial followed an induction trial reported in the same publication and included 339 natalizumab treated responders (> 70 point decrease from baseline CDAI and absolute CDAI < 220) at weeks 10 and 12.[76] The natalizumab induction responders were randomized stratified by disease activity (mildly active or remission), use of corticosteroids, and use of immunomodulators to continue the induction natalizumab dose of 300 mg intravenous infusion every 4 weeks (n = 168) or receive a placebo intravenous infusion every 4 weeks (n = 171) for an additional 44 weeks with followup through 48 weeks. Fifteen randomized patients were excluded from analysis along with all induction placebo patients who were randomized for the maintenance trial. Patients were imbalanced ($P < 0.05$) in sex, baseline CDAI, and smoking status. Concomitant medications allowed during the study period included aminosalicylates, corticosteroids, immunomodulators, and antibiotics.

Disease Activity Indexes

Natalizumab versus placebo. Details of the results are presented in Appendix D, Evidence Table 9.

Week 2. CDAI was not reported.

Weeks 10 to 12. At week 12, 72% of natalizumab and 50% of placebo-treated patients had a sustained response (< 70-point CDAI change from week 0 of the maintenance trial, CDAI < 220, and no use of rescue medications); 60% of natalizumab and 40% of placebo-treated patients had a sustained remission (CDAI < 150) among those with CDAI < 150 at week 0 of the maintenance trial.[76]

Weeks 24 to 26. The primary study endpoint was reported at week 24.[76] Sustained response was reported in 61% of natalizumab and 28% of placebo patients at week 24 ($P < 0.001$). The overall remission rate (not sustained) at week 24 was 55% versus 30% ($P < 0.05$). The sustained remission at week 24 of those in remission at week 0 was 44% of 130 natalizumab and 26% of 120 placebo patients ($P = 0.003$).

Last reported time point. At week 48, sustained response was reported in 54% of natalizumab and 20% of placebo patients.[76] The overall remission rate (not sustained) at week 48 was 55% versus 22% ($P < 0.02$). The sustained remission at week 48 of those at remission at week 0 was 39% of natalizumab and 15% of placebo patients.

TNF-Alpha Inhibitors

Seven studies evaluated the effectiveness of a TNF-alpha inhibitor as monotherapy or in combination with another drug to maintain remission. Five of the studies compared TNF-alpha inhibitor monotherapy with placebo: two evaluated infliximab,[126 128] two evaluated adalimumab,[129 130] and one evaluated certolizumab pegol.[131] One study evaluated maintenance of remission with a combination of infliximab and azathioprine versus infliximab with hydrocortisone pretreatment prior to the infliximab infusion.[132] Another study[133] examined a combination of infliximab and azathioprine versus infliximab alone for the maintenance of remission in patients with previously controlled disease on combination infliximab and azathioprine for at least 6 months.

Study Design

Per our inclusion criteria, all seven studies were RCTs (Appendix D, Evidence Table 7). All but one study[133] used a run-in period whereby all patients received open-label drug (the same drug being studied for maintenance) prior to randomization. Patients demonstrating at least a clinical response (CDAI drop of 70 to 100 points) were randomized to receiving drug versus placebo. Duration of the run-in period ranged between 2 and 12 weeks.

Two studies were set up whereby induction of remission occurred as part of a prior study. In one study of infliximab versus placebo,[128] patients who responded to infliximab or placebo from a prior induction study[77] were randomized. In one study of adalimumab,[130] patients from the adalimumab induction study[78] who attained remission (in either adalimumab or placebo arms) were eligible to participate. Thus, in both studies[128 130] a small number of patients were enrolled who were responders to placebo and had not received open-label drug.

Each of the largest of the maintenance trials for infliximab,[126 134] adalimumab,[129 135] and certolizumab pegol[131] were set up such that patients who relapsed after an initial response were eligible to crossover and receive study drug at 8, 12, and an unspecified number of weeks after randomization, respectively. However, for disease activity endpoints, patients were considered failures and withdrawn from the study if they participated in the crossover portion.

Four out of seven trials took place in North America,[126 128-130] while six out of seven took place in Europe.[126 128-130 132 133] All of the studies but one[132] was multicenter in design. The starting year of enrollment ranged between 1995 and 2004. Following randomization, the median study duration was 52 weeks (range, 18 weeks to 104 weeks). All studies were limited to adult patients with Crohn's disease, although one study[133] included patients 16 years and older. In five studies, an inclusion criteria at the start of the trial (before the run-in) was a CDAI of 220 to 450.[126 128-131] In two studies,[130 132] prior TNF-alpha inhibitor use was not permitted. Prior TNF-alpha inhibitor exposure was permitted in two studies[129 131] (range of prior users, 24% to 50%), although patients with a history of primary non-response or severe reaction to TNF-alpha inhibitors were excluded. Because infliximab was the first approved TNF-alpha inhibitor agent for Crohn's disease, patients in the two infliximab trials[126 128] would not have received TNF-alpha inhibitors prior to the induction or run-in period. Per inclusion criteria, all patients in one study had prior exposure to infliximab.[133]

Population Characteristics

A total of 1,516 patients were randomized across all studies (Appendix D, Evidence Table 8). Males comprised 43% of participants. Response to open-label induction was 68% in the first infliximab maintenance trial,[128] 59% for the largest infliximab maintenance trial,[126] 64% for the largest adalimumab maintenance trail,[129] and 64% for the only certolizumab trial.[131] The remission rate of those who enrolled from the primary adalimumab induction trial[78] into a subsequent maintenance study[130] was 20%. Race was only reported in one study,[136] which was more than 90% Caucasians. Of studies that reported current smokers, rates ranged from 32% to 45%. Median duration of disease ranged from 5 to 12 years. Mean age at enrollment ranged between 34 to 38 years old. Disease location distribution was as follows: ileal (16% to 30%), ileocolonic (46% to 62%), colonic (17% to 39%). Mean CDAI after the run-in period ranged from 152 to 170, reflecting that some patients attained a remission while others attained only a response. Rates of concomitant aminosalicylates were 38% to 74%, corticosteroids use 21% to 56%, thiopurine use 11% to 42%, methotrexate use 0% to 12%.

Disease Activity Indexes

Week 16-18. A total of four RCTs involving 1,055 patients were analyzed at this time point (see Appendix D, Evidence Table 9).[128-131]

TNF-alpha inhibitors versus placebo. All four studies compared a TNF-alpha inhibitor with placebo. Table 16 summarizes the effects of TNF-alpha inhibitor therapy versus placebo in terms of maintaining a remission and response at weeks 16 to 18. All four studies included an open-label run-in period prior to randomization. In three studies,[128 129 131] patients who achieved a response (CDAI drop of 70 or 100 points) were then randomized to receive drug or placebo. Combining these three studies revealed that the TNF-alpha inhibitor agent was more effective than placebo in maintaining remission (RR, 1.8; 95% CI, 1.5 to 2.2; $P < 0.001$) (Figure 6). No one study significantly influenced results. Although there was no substantial statistical heterogeneity found in the meta-analysis (I-squared, 0%), heterogeneity in study design was observed. Three different TNF-alpha inhibitors agents were used (infliximab, adalimumab, and certolizumab pegol). Although all three medications have a unique make-up, we believe that the mechanism of action for all three is similar. Additionally, prior TNF-alpha inhibitor exposure was variable across studies; in two studies[129 131] some patients had prior TNF-alpha inhibitor exposure, while in one study[128] there was no prior TNF-alpha inhibitors exposure. Although one study[130] also studied adalimumab versus placebo for maintenance, the remission and response rates were considerably higher because only those patients who attained remission (CDAI < 150) in the induction trial[78] were eligible to participate. Therefore, this study was not included in the meta-analysis.

When all randomized patients were included for the adalimumab trial,[129] adalimumab remained clinically and statistically favored compared with placebo. Remission rates at 16 weeks were 45%, 40%, and 26% for 40 mg every other week, 40 mg weekly, and placebo ($P < 0.05$ for each arms versus placebo).[135]

In one study which evaluated infliximab versus placebo for fistula healing,[137] patients could have active or inactive disease at randomization; 59% of both infliximab and placebo arms had a baseline CDAI at randomization greater than 150. At weeks 16 and 40 after randomization, there

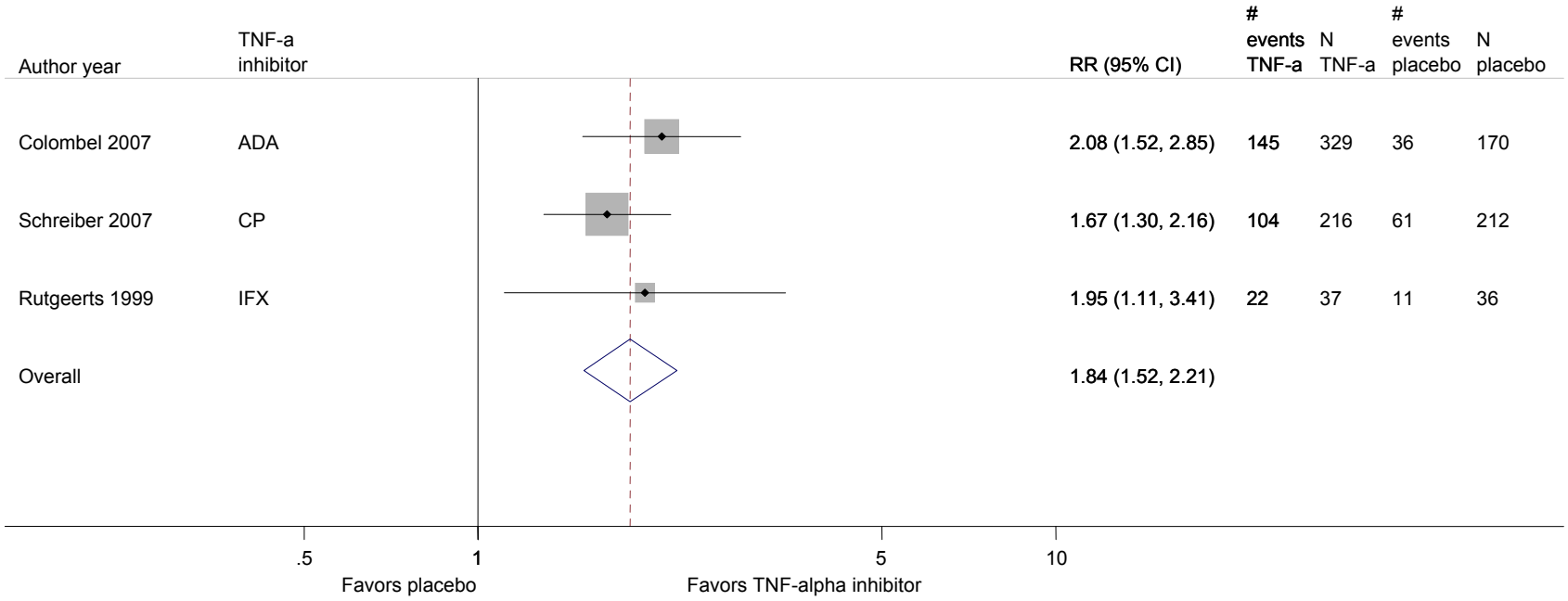
was not a clinically meaningful difference for the change in CDAI between infliximab and placebo, although the results were statistically significant.

Table 16. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of maintaining remission or response at week 16 to 18 in patients with Crohn's disease

Author, year	Main intervention (dose), n	Comparison, n	Remission rate (CDAI<150), %	Response rate, 100-pt CDAI drop, %	Response rate, 70-pt CDAI drop, %
Rutgeerts, 1999[128]	Infliximab (10 mg/kg IV every 8 wks), 37	Placebo, 36	60% vs 30% (*P* NR)	NR	73% vs 58% (*P* > 0.05)
Colombel, 2007[129]	Adalimumab (40 mg sc every 2 wks), 172	Placebo, 170	43% vs 21% (*P* = 0.001)	NR	NR
	Adalimumab (40 mg sc every wk), 157	Placebo, 170	45% vs 21% (*P* = 0.001)	NR	NR
Sandborn, 2007[130]	Adalimumab (40 mg sc every 2 wks), 19	Placebo, 18	91% vs 51% (*P* > 0.05)	94% vs 61% (*P* < 0.05)	95% vs 83% (*P* > 0.05)
	Adalimumab (40 mg sc every wk), 18	Placebo, 18	83% vs 51% (*P* = 0.006)	84% vs 61% (*P* > 0.05)	95% vs 83% (*P* > 0.05)
Schreiber, 2007[131]	Certolizumab pegol (400 mg sc every 4 wks), 216	Placebo, 212	48% vs 29% (*P* < 0.001)	63% vs 36% (*P* < 0.001)	NR

CDAI = Crohn's disease activity index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; sc = subcutaneous injections; vs = versus; wk = week

Figure 6. Pooled relative risk of maintaining remission* of Crohn's disease at week 16 to 18 comparing a TNF-alpha inhibitor with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 16

ADA = adalimumab; CI = confidence interval; CP = certolizumab pegol; IFX = infliximab; RR = relative risk; TNF-a = tumor necrosis factor-alpha inhibitor
* In all studies, remission was defined as a Crohn's Disease Activity Index less than 150.
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.17 with 2 degrees of freedom (p = 0.56)
I-squared statistic = 0%

Week 28. A total of 5 RCTs involving 1,101 patients were analyzed at this time point (see Appendix D, Evidence Table 9).[126 128-130 132]

TNF-alpha inhibitors versus placebo. Four studies met this criteria.[126 128-130] Table 17 summarizes the effects of TNF-alpha inhibitor therapy versus placebo in terms of maintaining remission and response at week 28. All four studies included an open-label run-in period prior to randomization. In 3 studies,[126 128 129] patients who achieved a response (CDAI drop of 70 or 100 points) were then randomized to receive drug or placebo. Combining these three studies revealed that the TNF-alpha inhibitors agent was more effective than placebo in maintaining remission (RR, 2.1; 95% CI, 1.7 to 2.7; $P < 0.001$; Figure 7). No one study significantly influenced results. Although no substantial statistical heterogeneity was found in the meta-analysis (I-squared, 0%), heterogeneity in study design was observed. Two different TNF-alpha inhibitors agents were used (infliximab and adalimumab). Although both medications have a unique make-up, we believe that the mechanism of action for all three is similar. Additionally, prior TNF-alpha inhibitor exposure was variable across studies; in one study[129] some patients had prior TNF-alpha inhibitor exposure, while in two studies[126 128] there was no prior TNF-alpha inhibitor exposure. Although one study[130] also studied adalimumab versus placebo for maintenance, the remission and response rates were considerably higher because only those patients who attained remission (CDAI < 150) in the induction trial[78] were eligible to participate. Therefore, this study was not included in the meta-analysis.

In contrast to the responders only analysis, the analysis of all randomized patients for the infliximab trial,[126] showed no clinical or statistical difference in rates of clinical remission between groups at week 28 (40% versus 32%).[134] In the analysis of all randomized patients for the adalimumab trial[129] the results were consistent with the responders only analysis. Remission rates at week 28 were 47%, 48%, and 34% for 40 mg every other week, 40 mg weekly, and placebo ($P < 0.05$ for both arms versus placebo).[135]

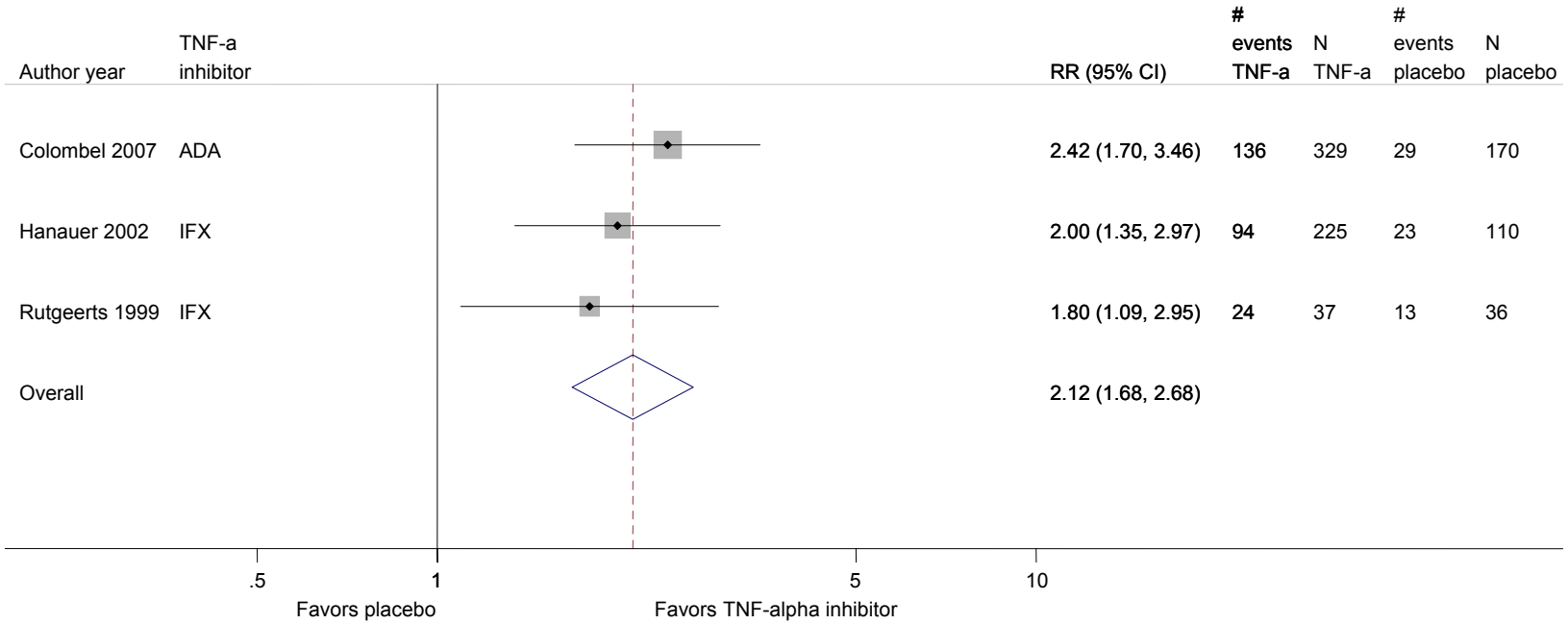
Combination of a TNF-alpha inhibitor and another treatment versus another therapy. One study of 46 participants[132] examined the maintenance of a combination of infliximab and azathioprine versus infliximab with hydrocortisone premedication. At 6 months, rates of remission were 79% and 88% in each arm ($P > 0.05$). However, the groups were not well balanced with respect to prior Crohn's medication use - all of the patients in the infliximab and azathioprine arm were azathioprine naïve, whereas only 6 out of 23 patients in the infliximab and corticosteroids arm were azathioprine naïve.

Table 17. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of maintaining remission or response at week 28 in patients with Crohn's disease

Author, year	Main intervention (dose), n	Comparison, n	Remission rate (CDAI<150), %	Response rate, 100-pt CDAI drop, %	Response rate, 70-pt CDAI drop, %
Rutgeerts, 1999[128]	Infliximab (10 mg/kg IV every 8 wks), 37	Placebo, 36	64% vs 35% (*P* NR)	NR	70% vs 46% (*P* > 0.05)
Hanauer, 2002[126]	Infliximab (5 mg/kg IV every 8 wks), 113	Placebo, 110	39% vs 21% (*P* = 0.003)	NR	55% vs 27% (*P* = 0.0002)
	Infliximab (10 mg/kg IV every 8 wks), 112	Placebo, 110	45% vs 21% (*P* = 0.002)	NR	60% vs 27% (*P* < 0.0001)
Colombel, 2007[129]	Adalimumab (40 mg sc every 2 wks), 172	Placebo, 170	37% vs 17% (*P* = 0.001)	NR	NR
	Adalimumab (40 mg sc every wk), 157	Placebo, 170	46% vs 17% (*P* = 0.001)	NR	NR
Sandborn, 2007[130]	Adalimumab (40 mg sc every 2 wks), 19	Placebo, 18	83% vs 38% (*P* > 0.05)	79% vs 50% (*P* > 0.05)	93% vs 71% (*P* > 0.05)
	Adalimumab (40 mg sc every wk), 18	Placebo, 18	98% vs 38% (*P* > 0.05)	99% vs 50% (*P* < 0.05)	99% vs 71% (*P* < 0.05)

CDAI = Crohn's disease activity index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; sc = subcutaneous injections; vs = versus; wk = week

Figure 7. Pooled relative risk of maintaining remission* of Crohn's disease at week 28 comparing a TNF-alpha inhibitor with placebo



Pooled Relative Risk and 95% Confidence Intervals of Remission at Week 28

ADA = adalimumab; CI = confidence interval; IFX = infliximab; RR = relative risk; TNF-a = tumor necrosis factor-alpha inhibitor
* In all studies, remission was defined as a Crohn's Disease Activity Index less than 150.
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 1.06 with 2 degrees of freedom (p = 0.59)
I-squared statistic = 0%

Week 52. A total of four RCTs involving 935 patients were analyzed at this time point (see Appendix D, Evidence Table 9).[126 129 130 132]

TNF-alpha inhibitors versus placebo. Three studies met this criteria.[126 129 130] Table 18 summarizes the effects of TNF-alpha inhibitor therapy versus placebo in terms of maintaining remission and response at week 52. All three studies included an open-label run-in period prior to randomization. In 2 studies,[126 129] patients who achieved a response (CDAI drop of 70 or 100 points) were then randomized to receive drug or placebo. Remission rates at 52 weeks ranged from 36% to 41% for TNF-alpha inhibitor agents and 12% to 15% for placebo; results were highly significant. A meta-analysis was not performed because there were only two comparable studies with available data at this time point. Remission and response rates were significantly higher for one study[130] evaluating adalimumab versus placebo because only those patients who attained remission (CDAI < 150) in the induction trial[78] were eligible to participate.

In the analysis of all randomized patients for infliximab there was no clinical or statistical difference in rates of clinical remission between groups at 52 weeks (41% versus 35%).[134] These results are in contrast to the clinically and statistically significant 52-week results reported for the responders to open-label drug.[126] In the analysis of all randomized patients for the adalimumab trial at 52 weeks, remission rates were 51%, 49%, and 38% ($P < 0.05$ for each arm versus placebo).[135] These results are consistent with the responders only results.[129]

Combination TNF-alpha inhibitors and another therapy versus another therapy. One study of 46 participants[132] examined the maintenance of a combination of infliximab and azathioprine versus infliximab with hydrocortisone premedication. At 12 months, rates of remission were 79% and 84% in each arm ($P > 0.05$). However, there were wide discrepancies in prior azathioprine exposure.

Table 18. Randomized controlled trials comparing the effectiveness of TNF-alpha inhibitor therapy with placebo or another treatment in terms of maintaining remission or response at week 52 in patients with Crohn's disease

Author, year	Main intervention (dose), n	Comparison, n	Remission rate (CDAI<150), %	Response rate, 100-pt CDAI drop, %	Response rate, 70-pt CDAI drop, %
Hanauer, 2002[126]	Infliximab (5 mg/kg IV every 8 wks), 113	Placebo, 110	30% vs 15% (P = 0.007)	NR	39% vs 18% (P = 0.0001)
	Infliximab (10 mg/kg IV every 8 wks), 112	Placebo, 110	40% vs 15% (P = 0.002)	NR	47% vs 18% (P < 0.0001)
Colombel, 2007[129]	Adalimumab (40 mg sc every 2 wks), 172	Placebo, 170	36% vs 12% (P = 0.001)	NR	NR
	Adalimumab (40 mg sc every wk), 157	Placebo, 170	41% vs 12% (P = 0.001)	NR	NR
Sandborn, 2007[130]	Adalimumab (40 mg sc every 2 wks), 19	Placebo, 18	79% vs 44% (P < 0.05)	79% vs 56% (P > 0.05)	79% vs 72% (P > 0.05)
	Adalimumab (40 mg sc every wk), 18	Placebo, 18	83% vs 44% (P < 0.05)	89% vs 56% (P < 0.05)	89% vs 72% (P > 0.05)

CDAI = Crohn's disease activity index; IV = intravenous infusion; mg = milligrams; mg/kg = milligrams per kilogram; NR = not reported; sc = subcutaneous injections; vs = versus; wk = week

Week 104. Two RCTs involving 126 patients were analyzed at this time point (see Appendix D, Evidence Table 9).[132 133]

Combination TNF-alpha inhibitors and another therapy versus another therapy. One study of 46 participants[132] examined the maintenance of a combination of infliximab and azathioprine versus infliximab with hydrocortisone premedication. At 24 months, rates of remission were 72% and 77% in each arm ($P > 0.05$). However, there were wide discrepancies in prior azathioprine exposure.

One study[133] examined Crohn's patients who were in an extended remission (>6 months) on combination infliximab and azathioprine. Patients were then randomized to continue or discontinue the azathioprine. Patients were studied out to 104 weeks. Twenty-four out of 40 (60%) patients in the azathioprine continuation arm and 22 out of 40 (55%) patients in the discontinuation arm required a change in the infliximab dosing interval or stoppage of infliximab (their primary outcome).

Thiopurines

Six studies were identified and are listed in Table 19: Five studies[29 93 138-140] compared azathioprine with placebo, two studies[93 141] compared azathioprine with corticosteroids, and one study[93] compared azathioprine with sulfasalazine. No studies used 6-mercaptopurine.

Study Design

Per our inclusion criteria, all six studies were RCTs (Appendix D, Evidence Table 7). In all studies, patients were in remission at the time of randomization. All trials were multicenter with five trials[29 138-141] conducted in Europe, and one in US.[93] The years of enrollment ranged from 1971 to 2009. In one study the azathioprine dose was 1 mg/kg/day,[93] in two studies the dose was 2.0 mg/kg/day,[139 142] and in one study the dose was 2.0 to 2.5 mg/kg/day.[141] Prior to randomization, patients were in remission for one month,[141] 6 months,[29] 24 months,[140] or 42 months.[138] Two studies[93 139] did not report duration of remission prior to randomization. In three studies,[29 138 140] patients had to have been in remission on azathioprine. Study duration ranged between 6 months and 18 months. Relapse was defined by CDAI scores in four studies[93 138 140 141] while two studies used an unnamed disease activity score.[29 139]

One study required steroid dependence for entry, but with a prednisone dose less than 30 mg.[141] One study[140] excluded patients receiving corticosteroids or aminosalicylates at the time of randomization. One study[138] excluded patients taking more than 10 mg of prednisone in addition to any immunosuppressant, aminosalicylates or antibiotic. The remainder allowed prednisone or aminosalicylates at study entry. Three studies excluded patients with previous surgery.[138 140 141] One study excluded patients with left-sided colonic disease.[141]

Population Characteristics

Half of the patients were males (Appendix D, Evidence Table 8). The mean ages ranged from 28 to 40 years and the median ages ranged from 31 to 47 years. Race was reported in one study (92% Caucasian).[93] All studies reported mean duration of disease at randomization ranging from 2 to 11 years. Mean CDAI ranged from 39 to 132 across all reporting study arms. Two studies reported smoking histories ranging from 42% to 92%.[138 141] In studies that reported disease distribution, ileal involvement ranged from 3% to 60%, ileocolonic 11% to 67%, and colonic 7%

to 63%. Concomitant steroid use ranged from 5% to 100% across study arms, while concomitant aminosalicylates use was not reported in any studies.

Disease Activity Indexes

Azathioprine versus placebo. A total of five studies[29 93 138-140] with 328 patients compared azathioprine to placebo (Appendix D, Evidence Table 9). Three studies[29 138 140] involving 163 patients assessed the effectiveness in those patients who were in remission on at least 6 months of azathioprine (range 6 to 42 months). Two of these studies totaling 80 participants found azathioprine to be clinically and statistically superior to placebo.[29 140] One study[138] found that azathioprine was clinically, but not statistically more effective than placebo. A couple explanations are possible: First, this study included lower doses of azathioprine (1.7 mg/kg/day), which is also the mean dose the patients were on prior to randomization. Second, the patients had been in remission for a long time (at least 42 months) and overall remission rates were higher in both treatment and placebo arms compared to the other studies.

Only one study[139] included steroid-dependent patients at randomization (involved steroid tapering). Results were clinically but not statistically significant; however, only 10 total patients were included.

One study[93] involving 155 patients included patients who had inactive disease within the year before randomization (induced medically or surgically). Results were based on a unique rank outcome. No differences between azathioprine and placebo were found at 1 year; results minimally favored placebo at 2 years (neither result statistically significant). However, the azathioprine was under-dosed at 1 mg/kg/day. Additionally, post-operative patients may behave differently from those who are medically induced into remission.

Azathioprine versus corticosteroids. Two studies[93 141] with 192 patients were included. In both studies, the remission rate at one year was higher (not statistically significant) in the azathioprine arm[93 141] and no different in one study at two years.[93] In one study,[93] the azathioprine was under-dosed at 1 mg/kg/day. Results in this study were also based on a unique rank outcome model.

Azathioprine versus sulfasalazine. One study[93] with 115 patients was included. No effect was seen. Patients receiving azathioprine were under-dosed at 1mg/kg/day. Results in this study were also based on a unique rank outcome model.

Table 19. Randomized controlled trials comparing the effectiveness of thiopurines with placebo or another treatment in maintaining remission in patients with Crohn's disease

Author, year	Time point	Main intervention (dose), n	Comparison, n	Remission rate, %	Other
Lemann, 2005[138]	18 mos	Azathioprine (median dose 1.7 mg/kg), 40	Placebo, 43	92% vs 79% (*P* = 0.195)	Duration of remission 17.3 mos vs 15.9 mos
Villien 2004[140]	12 mos	Azathioprine (median dose 2.1 mg/kg), 14	Placebo, 15	86% vs 47% (*P* < 0.043)	NA
O'Donoghue 1978[29]	12 mos	Azathioprine (2 mg/kg/d), 24	Placebo, 27	95% vs 59% (*P* < 0.01)	Activity Score 0.63 vs 2.48 (P < 0.05)
Willoughby, 1971[139]	24 wks	Azathioprine (2 mg/kg/d), 5	Placebo, 5	80% vs 40% (*P* NR)	Activity grade difference 1.2 vs 6.8
Mantzanis 2009[141]	12 mos	Azathioprine (2.0-2.5 mg/kg/d),38	Budesonide (6-9 mg/d), 39	79% vs 64% (*P* < 0.2)	NA
Summers, 1979[143]	1 yr	Azathioprine (1 mg/kg/d), 54	Placebo, 101	69% vs 64%*	NA
	2 yr	Azathioprine (1 mg/kg/d), 54	Placebo, 101	29% vs 40%*	
	1 yr	Azathioprine (1 mg/kg d), 54	Sulfasalazine (1-2 g/15 kg), 58	69% vs 62%*	
	2 yr	Azathioprine (1 mg/kg d), 54	Sulfasalazine (1-2 g/15 kg), 58	29% vs 31%*	
	1 yr	Azathioprine (1 mg/kg/d), 54	Prednisone (1-4 mg/kg), 61	1 yr: 69% vs 57%*	
	2 yr	Azathioprine (1 mg/kg/d), 54	Prednisone (1-4 mg/kg), 61	2 yr: 29% vs 32%*	

d = day; g = gram; kg = kilogram; mg = milligrams; mos = months; NA = not applicable; vs = versus; wks = weeks; yr = year
*Used rank-sum model

Methotrexate

One study[144] comparing intramuscular methotrexate to placebo with 76 patients was included (Table 20; Appendix D, Evidence Table 9).

Study Design

Per our inclusion criteria, the study was an RCT (Appendix D, Evidence Table 7). All patients were adults with Crohn's disease who were in a steroid-free remission (CDAI < 150) at entry. Remission was achieved through weekly methotrexate at 25 mg intramuscular weekly for a period of 16 to 24 weeks. The study participants were randomized to receive weekly intramuscular injections of either 15 mg of methotrexate or placebo for a period of 40 weeks. The primary outcome measure was relapse, defined as an increase in the CDAI of at least 100 points or the initiation of steroids or antimetabolite.

Population Characteristics

A total of 76 patients participated (Appendix D, Evidence Table 8). Males ranged from 40% to 61% across both arms. Mean age ranged from 32 to 38 years. Forty-two percent to 50% were smokers. Mean duration of disease ranged from 4 to 8 years. Mean CDAI ranged from 84 to 94.

Ranges of disease location were as follows: ileal disease 31% to 45%, ileocolonic disease 28% to 44%, and colonic disease 25% to 28%. Prior thiopurine use was less than 5% in both arms.

Disease Activity Indexes

One RCT[144] evaluated the difference between methotrexate and placebo in maintaining remission in patients with moderate-to-severe Crohn's disease. Relapse rates were consistently higher in the placebo group across time points. However, this was only statistically significant at 40 weeks.

Table 20. Relapse* rates reported in randomized controlled trials comparing the effectiveness of methotrexate with placebo in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (dose), n	Comparison, n	Relapse rate, %
Feagan, 2000[144]	4	Methotrexate (15 mg/wk IM), 36	Placebo, 40	10 vs 20%
	16	Methotrexate (15 mg/wk IM), 36	Placebo, 40	29 vs 42%
	40	Methotrexate (15 mg/wk IM), 36	Placebo, 40	35 vs 61%†

* Relapse was defined as a 100-point increase in Crohn's disease activity index or initiation of steroid or anti-metabolite.
†Difference in relapse rates significant at 0.05 alpha level
IM = intramuscular; mg/wk = milligrams per week; vs = versus

Corticosteroids

Study Design

A total of eleven studies evaluated the efficacy of corticosteroids in maintaining remission in patients with inactive Crohn's disease using various disease activity indexes (Appendix D, Evidence Table 7). Ten studies compared corticosteroids with placebo.[93 99 110 145-151] Seven trials used budesonide 3 mg to 6 mg per day, two trials used prednisone 0.25 mg/kg per day alone or in combination with an aminosalicylate,[93 110] and two trials used 6-methylprednisolone 0.25mg/kg per day to 8 mg per day, alone or in combination with an aminosalicylate.[99 151] Two studies[93 152] compared corticosteroids with aminosalicylates, and one study[110] compared a combination of corticosteroids and aminosalicylates with aminosalicylates alone. One study[99] included both those with active (CDAI > 150) and inactive disease (CDAI < 150) at randomization, but only relapse rates in the population with inactive disease at randomization were analyzed below (as part of a subgroup analysis).

All studies were RCTs. Four trials were conducted in the US and North America, seven in Europe, one in Australia, one in Asia, and one in Africa. All were multicenter trials except one.[152] Enrollment dates were reported by seven trials, and were conducted between 1971 and 1996. Six trials had run-in periods from 4 to 12 weeks in duration, where remission was induced as part of a separate prior trial comparing corticosteroids with placebo;[110 145 147-150] in one study[110] the run-in period was part of the same study comparing corticosteroids or corticosteroids and aminosalicylates. Five trials did not have a run-in period,[93 99 146 151 152] with one trial[152] requiring all patients to taper their corticosteroids dose before beginning the trial. Median study duration was 52 weeks (range from 13 to 104 weeks).

All studies included only patients with CDAI less than or equal to 150, except two. One study[146] defined inactive disease as having a CDAI less than or equal to 200, while another[99]

included patients with both active (CDAI ≥ 150) and inactive (CDAI < 150) disease initially, and then analyzed separately. Two studies[145 148] required a minimum duration of remission beyond the induction period, from 8 to 10 weeks. Two studies required patients to be steroid-dependent.[146 152] All studies reported a minimum age of inclusion of 18 years, with three exceptions[93 110 151] which did not report a minimum age. No studies required any other prior medication use aside from what is mentioned above. One study[152] excluded patients who had been maintained on mesalamine or azathioprine at the time of enrollment. Another study[145] excluded patients who had received mesalamine at any time, or immunomodulator or corticosteroids at the time of the initial run-in study.[100] All studies used CDAI as the outcome measure. No studies used alternative activity indexes.

Population Characteristics

All of the following statistics exclude one study[99] due to its inclusion of both those with active and inactive disease in the baseline population. Therefore, results on only ten studies are reported here. A total of 1028 patients were randomized across all study arms (Appendix D, Evidence Table 8). The proportion of male participants in each study arm ranged from 22% to 67%. Only two studies[93 146] reported on race, with Caucasian participants making up 91% to 98% across all study arms. Smoking (with no definition given) was only reported in one study[152] and ranged between 82% and 86% across both study arms. Mean age at enrollment was reported in six studies, and ranged between 32 and 41 years. Mean duration of disease was reported in seven studies and ranged between 3 to 9 years. Disease location was reported in seven studies: ileal location ranged between 33% and 89%, ileocolonic location between 11% and 49%, and colonic location between 0% and 33%. Perianal location was not reported in any trial. Mean baseline CDAI was reported for all but two studies,[110 151] ranging from 65 to 139. Concurrent medication use was reported in only one study:[146] aminosalicylates use in 48% to 49% of participants and thiopurine use in 9% to 15% of participants across both study arms. Prior thiopurine use was reported in one study[152] in 41% to 43% of all participants across both study arms. Of the six trials where patients were in an induction study involving corticosteroids, corticosteroid frequency ranged from 80% to 100% across arms of five studies. In one study[110] corticosteroids use prior to entry ranged from 47% to 52% across arms.

Disease Activity Indexes

A total of eleven studies evaluated the efficacy of corticosteroids in maintaining remission in patients with inactive Crohn's disease using CDAI as the outcome measure (Table 21; Appendix D, Evidence Table 9). In one study,[99] which included both those with active and inactive disease at randomization, only relapse rates in the population already in remission at randomization were analyzed. Otherwise, results from this study are included in other sections (KQ1, KQ1/2).

Corticosteroids versus placebo. Nine studies, including 854 participants, compared corticosteroids with placebo.[93 99 145-151] All studies used budesonide 3 mg to 6 mg per day with the exception of three studies, two of which[99 151] used 6-methylprednisolone and one[93] which used prednisone. Three out of the nine studies[146 149 151] involving a total of 225 participants showed a clinically and statistically significant difference in relapse rates at 12 to 26 weeks between those on corticosteroids and placebo. Only one study[149] evaluated patients at one year:

there was no difference between budesonide and placebo; however this study had significant inequalities in baseline budesonide use between arms at randomization. One small study[151] of 18 patients found significantly lower relapse rates in those patients on 6-methylprednisolone 0.25 mg/kg per day than placebo at 26 weeks. Patients had to have an abnormal laboratory index at entry. Most patients in this study discontinued 6-methylprednisolone prior to the endpoint (per protocol), and only patients still on treatment were included in the relapse rate (i.e., not an intention-to-treat analysis).

A meta-analysis was conducted on five studies[145 147-150] comparing budesonide 3 mg to 6 mg per day with placebo at 52 weeks (Figure 8). All studies had a run-in period, consisting of a prior clinical trial, in which patients received budesonide, corticosteroids, or placebo for induction. Results showed no significant benefit of budesonide over placebo (RR of relapse, 1.0; 95% CI, 0.8 to 1.1). There was no significant heterogeneity among the studies (I-squared, 0). However, definitions of relapse varied. While all studies defined relapse as CDAI greater than 150, with or without a 60-point increase from baseline, three[145 147 149] included other clinical criteria, such as an acute deterioration in clinical status. One study,[93] which also included patients induced with corticosteroids or placebo prior to the trial, was not included in the meta-analysis due to the fact that relapse (CDAI > 150) was calculated as part of a unique rank outcome method.

Corticosteroids versus aminosalicylates. Three studies,[93 99 152] involving 305 participants, included comparisons of corticosteroid therapy with aminosalicylates in maintaining remission from 16 to 104 weeks. In one partially blinded study[152] of steroid-dependent patients, there was a significant difference in relapse rates between those on budesonide 6 mg per day and those on mesalamine 3 g per day at 52 weeks (55% versus 82%, respectively; $P = 0.05$). In another study,[99] those with inactive disease randomized to 6-methylprednisolone 8 mg per day had relapse rates no different from those randomized to sulfasalazine 3 g per day (subgroup analysis). In yet another study[93] there was no significant overall difference in relapse rates between prednisone and aminosalicylates groups at any time points. This study evaluated an outcome-ranking model, where other variables other than CDAI were required for relapse. Notably, one study[152] employed the highest relative steroid dose relative to the other two studies.

Combination of corticosteroids and aminosalicylates versus placebo. In one study[99] of 119 participants, among those with inactive disease at randomization, there was no difference in relapse rates through 104 weeks between those on 6-methylprednisolone 8 mg per day and sulfasalazine 3 g per day combination therapy and those on placebo (subgroup analysis).

Combination of corticosteroids and aminosalicylates versus corticosteroids alone. Two studies,[99 110] including 181 participants, compared a combination of corticosteroids and aminosalicylates with corticosteroids alone in maintaining remission of Crohn's disease. One study[110] compared a combination of prednisone 0.25 mg/kg per day and sulfasalazine 1 mg/15kg per day with prednisone 0.25 mg/kg per day alone in maintaining remission. There was no difference in relapse rates through 26 weeks. In another study,[99] among those with inactive disease at randomization, the group on 6-methylprednisolone 8 mg/day and sulfasalazine 3 g/day combination therapy had higher relapse rates through 104 weeks than those on 6-methylprednisolone 8 mg/day alone (subgroup analysis), but significance levels were not reported.

Corticosteroids/aminosalicylates versus aminosalicylates alone. In one study[99] of 119 participants, there was no difference in relapse rates through 104 weeks in those randomized to combination 6-methylprednisolone 8 mg/day and sulfasalazine 3 g/day compared with those randomized to sulfasalazine 3 g/day alone (subgroup analysis).

Table 21. Relapse rates reported in randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (daily dose), n	Comparison (daily dose), n	Relapse definition	Relapse rate (%)
Hanauer, 2005[145]	13	Budesonide (6 mg), 54	Placebo, 54	CDAI ≥ 150 and ≥ 60-pt increase in CDAI from baseline or clinical deterioration	25 vs 38%
	26	Budesonide (6 mg), 54	Placebo, 54	CDAI ≥ 150 and ≥ 60-pt increase in CDAI from baseline or clinical deterioration	40 vs 55%
	52	Budesonide (6 mg), 54	Placebo, 54	CDAI ≥ 150 and ≥ 60-pt increase in CDAI from baseline or clinical deterioration	47 vs 58%
Cortot, 2001[146]	13	Budesonide (6 mg), 59	Placebo, 58	CDAI > 200 and ≥ 60-pt increase in CDAI from baseline	32 vs 65%*
Ferguson, 1998[147]	52	Budesonide (3 mg), 26	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or any deterioration requiring a different medication or surgery	46 vs 60%
	52	Budesonide (6 mg), 22	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or any deterioration requiring a different medication or surgery	48 vs 60%
Gross, 1998[148]	52	Budesonide (3 mg), 84	Placebo, 95	CDAI > 150 on 2 consecutive weeks	67 vs 65%
Lofberg, 1996[149]	12	Budesonide (3 mg), 31	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	45 vs 44%
	12	Budesonide (6 mg), 32	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	19 vs 44%*
	19	Budesonide (3 mg), 31	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	49 vs 57%
	19	Budesonide (6 mg), 32	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	25 vs 57%
	26	Budesonide (3 mg), 31	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	59 vs 75%
	26	Budesonide (6 mg), 32	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	42 vs 75%
	52	Budesonide (3 mg), 31	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	74 vs 63%
	52	Budesonide (6 mg), 32	Placebo, 27	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline, or acute deterioration in status	59 vs 63%
Greenberg, 1996[150]	52	Budesonide (3 mg), 33	Placebo, 36	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline	70 vs 67%
	52	Budesonide (6 mg), 36	Placebo, 36	CDAI > 150 and ≥ 60-pt increase in CDAI from baseline	61 vs 67%

Table 21. Relapse rates reported in randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in patients with Crohn's disease (continued)

Author, year	Followup (weeks)	Main intervention (daily dose), n	Comparison (daily dose), n	Relapse definition	Relapse rate (%)
Malchow, 1984[99]	19	6-Methylprednisolone (8 mg), 66	Placebo, 52	CDAI > 150 or clinical deterioration	16 vs 32%
	26	6-Methylprednisolone (8 mg), 66	Placebo, 52	CDAI > 150 or clinical deterioration	20 vs 35%
	54	6-Methylprednisolone (8 mg), 66	Placebo, 52	CDAI > 150 or clinical deterioration	40 vs 52%
	104	6-Methylprednisolone (8 mg), 66	Placebo, 52	CDAI > 150 or clinical deterioration	57 vs 68%
	19	6-Methylprednisolone (8 mg), 66	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	16 vs 23%
	26	6-Methylprednisolone (8 mg), 66	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	20 vs 27%
	54	6-Methylprednisolone (8 mg), 66	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	40 vs 45%
	104	6-Methylprednisolone (8 mg), 66	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	57 vs 63%
	19	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	32 vs 23%
	26	6-Methylprednisolone (8 mg) + sulfasalazine (3 g/d), 56	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	33 vs 27%
	54	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	47 vs 45%
	104	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Sulfasalazine (3 g), 63	CDAI > 150 or clinical deterioration	66 vs 63%
	19	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Placebo, 52	CDAI > 150 or clinical deterioration	32 vs 32%
	26	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Placebo, 52	CDAI > 150 or clinical deterioration	33 vs 35%
	54	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Placebo, 52	CDAI > 150 or clinical deterioration	47 vs 52%
	104	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	Placebo, 52	CDAI > 150 or clinical deterioration	66 vs 68%
	19	6-Methylprednisolone (8 mg/d) + sulfasalazine (3 g/d), 56	6-Methylprednisolone (8 mg), 66	CDAI > 150 or clinical deterioration	32 vs 16%
	26	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	6-Methylprednisolone (8 mg), 66	CDAI > 150 or clinical deterioration	33 vs 20%
	54	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	6-Methylprednisolone (8 mg), 66	CDAI > 150 or clinical deterioration	47 vs 40%

Table 21. Relapse rates reported in randomized controlled trials comparing the effectiveness of corticosteroids with placebo or another treatment in patients with Crohn's disease (continued)

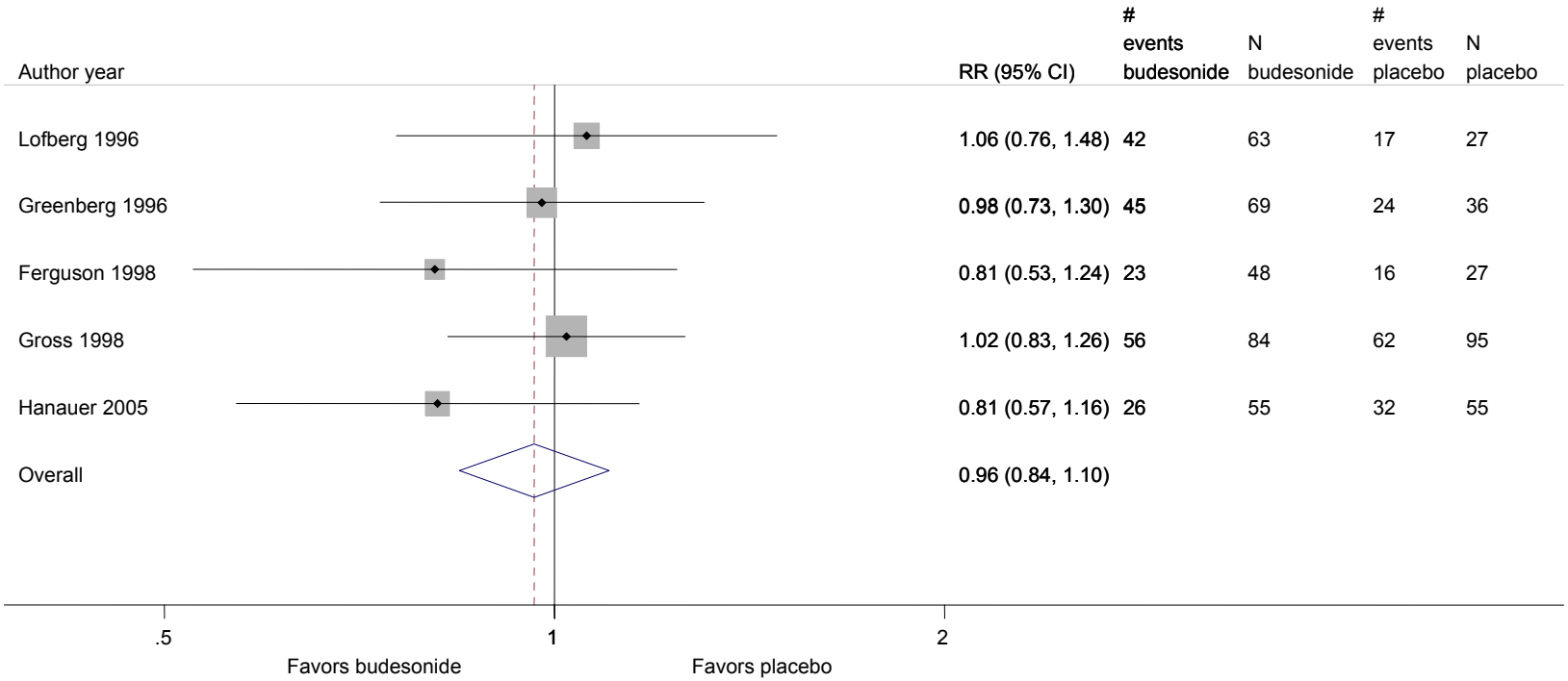
Author, year	Followup (weeks)	Main intervention (daily dose), n	Comparison (daily dose), n	Relapse definition	Relapse rate (%)
Malchow, 1984[99]	104	6-Methylprednisolone (8 mg) + sulfasalazine (3 g), 56	6-Methylprednisolone (8 mg), 66	CDAI > 150 or clinical deterioration	66 vs 57%
Brignola, 1988[151]	26	6-Methylprednisolone (0.25 mg/kg), 9	Placebo, 9	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 weeks	11 vs 78%*
Summers, 1979[93]	17	Prednisone (0.25 mg/kg), 61	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	10 vs 10%
	26	Prednisone (0.25 mg/kg), 61	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	20 vs 12%
	54	Prednisone (0.25 mg/kg), 61	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	28 vs 28%
	104	Prednisone (0.25 mg/kg), 61	Placebo, 101	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	32 vs 41%
	17	Prednisone (0.25 mg/kg), 61	Sulfasalazine (0.5 mg/kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	10 vs 13%
	26	Prednisone (0.25 mg/kg), 61	Sulfasalazine (0.5 mg/kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	20 vs 18%
	54	Prednisone (0.25 mg/kg), 61	Sulfasalazine (0.5 mg/kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	28 vs 33%
	104	Prednisone (0.25 mg/kg), 61	Sulfasalazine (0.5 mg/kg), 58	CDAI > 150 and ≥ 100-pt increase in CDAI for 2 consecutive weeks, or a need for surgery, development of a fistula, fever, or radiologic progression	32 vs 41%
Mantzaris, 2003[152]	16	Budesonide (6 mg), 29	Mesalamine (3 g), 28	CDAI > 150 and ≥ 100-pt increase in CDAI	20 vs 55%
	26	Budesonide (6 mg), 29	Mesalamine (3 g), 28	CDAI > 150 and ≥ 100-pt increase in CDAI	37 vs 76%
	52	Budesonide (6 mg), 29	Mesalamine (3 g), 28	CDAI > 150 and ≥ 100-pt increase in CDAI	55 vs 82%
Singleton, 1979[110]	19	Prednisone (0.25 mg/kg) + sulfasalazine (1 mg/15 kg), 29	Prednisone (0.25 mg/kg), 30	CDAI > 150 (Wilcoxon rank sum test)†	77 vs 77%
	26	Prednisone (0.25 mg/kg) + sulfasalazine (1 mg/15 kg), 29	Prednisone (0.25 mg/kg), 30	CDAI>150 (Wilcoxon rank sum test)†	84 vs 78%

CDAI = Crohn's Disease Activity Index; mg = milligrams; kg = kilograms; pt = points; vs = versus

* Significant at the 0.05 alpha level.

†In this study, relapse (CDAI>150 and CDAI 100 point increase) was one component of a Wilcoxon rank sum test set of outcomes.

Figure 8. Pooled relative risk of a relapse* of Crohn's disease at week 52 comparing budesonide with placebo



Pooled Relative Risk and 95% Confidence Intervals of Relapse at Week 52

CI = confidence interval; RR = relative risk
* In all studies, relapse was defined as a Crohn's Disease Activity Index more than 150 with at least a 60-point increase from baseline. Ferguson 1998, Lofberg 1996, and Hanauer 2005 also defined relapse to include clinical deterioration.
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.12 with 4 degrees of freedom (p = 0.72)
I-squared statistic = 0%

Aminosalicylates

Study Design

Fourteen studies compared aminosalicylates versus placebo in maintaining remission in patients with inactive Crohn's disease using various disease activity indexes (Appendix D, Evidence Table 7).[93 99 153-164] One study[99] included both those with active (CDAI > 150) and inactive disease (CDAI < 150) at randomization, but only relapse rates in the population with inactive disease at randomization were analyzed below (as part of a subgroup analysis).

All studies were RCTs. Ten trials were conducted in Europe, four in North America and the US, two in Asia, and one in Africa. All were multicenter trials except two,[162 163] and one[164] which did not report this. Eleven studies used mesalamine (Asacol® – 3 studies; Pentasa® – 4 studies; mesalamine (other) – 4 studies), one used sulfasalazine, and one used olsalazine. Mesalamine doses ranged from 1 to 4 grams daily. The starting year of enrollment was between 1971 and 2000. Three trials[153 156 157] had run-in periods involving induction of remission with 6-methylprednisolone or prednisone for 4 to 8 weeks. Median study duration was 52 weeks (range, 6 to 208 weeks).

Twelve studies included only patients with a CDAI less than 150, one with a CDAI less than 120,[164] and one with a HBI less than 4.[159] Five studies required a minimum duration of remission prior to the study, ranging from 4 weeks to 24 months.[154 159 160 162 164] No studies required patients to be steroid-dependent or resistant. Seven studies reported a minimum age of inclusion of 18, with two[157 160] including those 15 and over, and the remaining studies not reporting a minimum age. Regarding medication use in the 1 to 3 months prior to the studies, four studies[154 160 162 164] excluded patients who had used corticosteroids within this time frame, four[154 156 158 160] excluded those with immunomodulator use, and one study[155] excluded those with recent thiopurine or cyclosporine use.

Population Characteristics

All of the following statistics exclude one study[99] due to its inclusion of both those with active and inactive disease in the baseline population (Appendix D, Evidence Table 8). Therefore, results on only thirteen studies are reported here. Another study[155] did not distinguish between those patients in medical remission and those in surgical remission when reporting population characteristics, so statistics on both groups are included in the totals below.

A total of 1825 patients were randomized across all study arms. The proportion of male participants in each study arm ranged from 39% to 70%. Only one study[93] reported on race, with Caucasian participants making up 94% to 98% across both study arms. Smoking ("smoker" or "present smoker") was reported in three studies[155 156 159] and ranged between 18% and 38%. Mean age at enrollment was reported in six studies, and ranged between 29 and 40 years. Mean duration of disease was reported in all seven studies and ranged between 3 and 7 years. Disease location was reported as follows: ileal location ranged between 11% and 100%, ileocolonic location between 18% and 91%, and colonic location between 9% and 97%. Perianal location was reported in one trial[160] and ranged from 11% to 14%. Baseline CDAI was reported for all but four studies.[153 159 160 164] Mean CDAI ranged from 48 to 89 points. One study[159] reported mean HBI values, ranging from 2.2 to 2.3 across the two arms. No concurrent medication use was

reported in any study. Prior corticosteroid use ranged from 13% to 94% across three studies.[157 162 163] In one study,[159] 82% to 87% of patients were on an aminosalicylate at study entry.

Disease Activity Indexes

Aminosalicylates versus placebo. Fourteen studies, including 1,930 participants, compared aminosalicylate compounds to placebo in maintaining remission (Table 22; Appendix D, Evidence Table 9).[93 99 153-164] One study[99] included both patients with active and inactive Crohn's disease at randomization; patients with inactive disease were analyzed separately. Most of the studies included a small number of participants, from 40[153] to 328.[154]

Only four studies included information on statistical significance.[99 156 158 161] There was only one study[161] of 125 participants in which the difference in relapse rates between the aminosalicylates 2.4 g/day (34%) and placebo (55%) groups reached statistical significance (P = 0.02) at 52 weeks. There was no visible dose response curve with higher doses of aminosalicylates corresponding to lower relapse rates relative to placebo. Absolute relapse rates (most commonly defined by an increase in CDAI to >150) varied widely with a range of 14% to 78% for placebo and 0% to 71% for the groups receiving aminosalicylates.

Three studies[153 156 157] had a run-in period consisting of corticosteroid administration for 4 to 8 weeks to induce remission prior to randomization. There were no significant differences between aminosalicylates and placebo groups in the maintenance of remission in these studies.

A meta-analysis was performed on aminosalicylates versus placebo at several prespecified time points (Figures 9-11). Because of significant heterogeneity in designs and outcomes, only four studies[154 155 161 162] were included. The included studies used different formulations of aminosalicylates (mesalamine (Asacol®, Pentasa®), olsalazine) at doses of 2 to 3 grams daily. All studies used the CDAI for outcome assessment, although outcome definitions varied (see table). Studies excluded from the meta-analysis included those that did not use CDAI as an outcome, those that had a steroid run-in period prior to randomization, as well as studies that employed a rank outcome design that cannot be easily compared to other studies. Additionally, one study[163] used a laboratory index as part of its inclusion criteria and outcome, and was therefore not included in the meta-analysis.

We found that across all time points, aminosalicylates were better than placebo; however, these results were only statistically significant at weeks 48-52. The relative risk of a relapse comparing an aminosalicylate with placebo was 0.8 (95% CI, 0.7 to 1.1) at weeks 15 to 19; 0.8 (95% CI, 0.6 to 1.1) at week 26; and 0.7 (95% CI, 0.6 to 1.0) at weeks 48 to 52 (Figures 9-11). There was no significant statistical heterogeneity across time points (I-squared range, 0% to 33%). Notably, the largest study included in the meta-analysis evaluated olsalazine. Consisting of two aminosalicylates molecules joined by an azo bond and cleaved by bacteria in the colon, olsalazine can cause a secretory type diarrhea in about 15% of patients, and is therefore infrequently used in practice.[165] Therefore, the applicability of this study can be questioned. Additionally, the results of this meta-analysis were at odds with the overall conclusion (based on the 14 included studies) that there was no difference in efficacy for maintenance between aminosalicylates and placebo.

Table 22. Relapse rates reported in randomized controlled trials comparing the effectiveness of aminosalicylates with placebo in patients with Crohn's disease

Author, year	Followup (weeks)	Main intervention (daily dose), n	Comparison, n	Relapse definition	Relapse rate (%)
Prantera, 2005[153]	52	Mesalamine Asacol® (4 g), 23	Placebo, 17	CDAI > 150 or withdrawal from study for other reasons	87 vs 82%
Mahmud, 2001[154]	19	Olsalazine (2 g), 167	Placebo, 161	CDAI > 150 or 60-pt increase in CDAI and clinical criteria	25 vs 25%
	26	Olsalazine (2 g), 167	Placebo, 161	CDAI > 150 or 60-pt increase in CDAI and clinical criteria	27 vs 25%
	52	Olsalazine (2 g), 167	Placebo, 161	CDAI > 150 or 60-pt increase in CDAI	24 vs 26%
Sutherland, 1997[155*]	48	Mesalamine Pentasa® (3 g), 87	Placebo, 93	CDAI > 150 and 60-pt increase in CDAI, or physician-diagnosed disease flare, hospitalization for disease flare, or need for corticosteroids therapy	31 vs 42%
Arber, 1995[159]	52	Mesalamine[†] (1 g), 28	Placebo, 31	HBI > 4	27 vs 55%
Gendre, 1993[160]	104	Mesalamine Pentasa® (2 g), 80	Placebo, 81	CDAI > 250 or CDAI between 150 and 250 with 50-pt increase for 2 weeks	36 vs 42%
Prantera, 1992[161]	12	Mesalamine Asacol® (2.4 g), 64	Placebo, 61	CDAI > 150 and 100-pt increase in CDAI	12 vs 22%
	26	Mesalamine Asacol® (2.4 g), 64	Placebo, 61	CDAI > 150 and 100-pt increase in CDAI	28 vs 41%
	52	Mesalamine Asacol® (2.4 g), 64	Placebo, 61	CDAI > 150 and 100-pt increase in CDAI	34 vs 55%[‡]
Brignola, 1992[162]	16	Mesalamine Pentasa® (2 g), 21	Placebo, 22	CDAI > 150 for 2 weeks or 100-pt increase in CDAI	52 vs 59%
Bresci, 1995[163]	52	Mesalamine Asacol® (2.4 g), 32	Placebo, 31	CDAI ≥ 150 or 100-pt increase in CDAI and LI ≥ 100 – cumulative[§]	16 vs 29%
	104	Mesalamine Asacol® (2.4 g), 32	Placebo, 31	CDAI ≥ 150 or 100-pt increase in CDAI and LI ≥ 100 – cumulative[§]	47 vs 61%
	208	Mesalamine Asacol® (2.4 g), 32	Placebo, 31	CDAI ≥ 150 or 100-pt increase in CDAI and LI ≥ 100 – cumulative[§]	53 vs 71%
Wellmann, 1988[164]	52	Mesalamine (not reported), 31	Placebo, 35	CDAI > 150	32 vs 40%
Summers, 1979[93]	17	Sulfasalazine (0.5 g/15 kg), 58	Placebo, 101	CDAI > 150 and 100-pt increase in CDAI or clinical criteria	13 vs 10%
	26	Sulfasalazine (0.5 g/15 kg), 58	Placebo, 101	CDAI > 150 and 100-pt increase in CDAI or clinical criteria	18 vs 12%
	54	Sulfasalazine (0.5 g/15 kg), 58	Placebo, 101	CDAI > 150 and 100-pt increase in CDAI or clinical criteria	33 vs 28%
	104	Sulfasalazine (0.5 g/15 kg), 58	Placebo, 101	CDAI > 150 and 100-pt increase in CDAI or clinical criteria	41 vs 41%

Table 22. Relapse rates reported in randomized controlled trials comparing the effectiveness of aminosalicylates with placebo in patients with Crohn's disease (continued)

Author, year	Followup (weeks)	Main intervention (daily dose), n	Comparison, n	Relapse definition	Relapse rate (%)
de Franchis, 1997[156]	17	Mesalamine‖(3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	29 vs 17%
	26	Mesalamine‖ (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	34 vs 32%
	26 (ITT analysis)	Mesalamine‖ (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	41 vs 41%
	52	Mesalamine‖ (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	58 vs 52%
	52 (ITT analysis)	Mesalamine‖ (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	66 vs 59%
	104	Mesalamine‖ (3 g), 58	Placebo, 59	CDAI > 150 and 60-pt increase in CDAI and increase in at least 2 of 3 acute phase reactants	75 vs 58%
Modigliani, 1996[157]	12	Mesalamine Pentasa® (4 g), 65	Placebo, 64	CDAI > 150 and 100-pt increase in CDAI or failure to discontinue steroids	18 vs 27%
	19	Mesalamine Pentasa® (4 g), 65	Placebo, 64	CDAI > 150 and 100-pt increase in CDAI or failure to discontinue steroids	35 vs 42%
	26	Mesalamine Pentasa® (4 g), 65	Placebo, 64	CDAI > 150 and 100-pt increase in CDAI or failure to discontinue steroids	49 vs 71%
	52	Mesalamine Pentasa® (4 g), 65	Placebo, 64	CDAI > 150 and 100-pt increase in CDAI or failure to discontinue steroids	71 vs 78%
Malchow, 1984[99]	19	Sulfasalazine (3 g), 63	Placebo, 52	"Failure and relapse"¶	23 vs 32%
	26	Sulfasalazine (3 g), 63	Placebo, 52	"Failure and relapse"¶	27 vs 35%
	54	Sulfasalazine (3 g), 63	Placebo, 52	"Failure and relapse"¶	45 vs 52%
	104	Sulfasalazine (3 g), 63	Placebo, 52	"Failure and relapse"¶	63 vs 68%
Thomson, 1995[158]	13	Mesalamine‖ (3 g), 102	Placebo, 105	CDAI > 150 and 60-pt increase in CDAI	13 vs 18%**
	26	Mesalamine‖ (3 g), 102	Placebo, 105	CDAI > 150 and 60-pt increase in CDAI	20 vs 25%**
	52	Mesalamine‖ (3 g), 102	Placebo, 105	CDAI > 150 and 60-pt increase in CDAI	27 vs 32%**
	13	Mesalamine‖ (3 g), 36	Placebo, 43	CDAI > 150 and 60-pt increase in CDAI	19 vs 20%††
	26	Mesalamine‖ (3 g), 36	Placebo, 43	CDAI > 150 and 60-pt increase in CDAI	22 vs 26%††
	52	Mesalamine‖ (3 g), 36	Placebo, 43	CDAI > 150 and 60-pt increase in CDAI	40 vs 26%††

CDAI = Crohn's Disease Activity Index; g = grams; HBI = Harvey-Bradshaw Index; ITT = intention-to-treat; LI = Laboratory Index; pt = points; vs = versus

* Remission rates reported only for patients in medical (as opposed to surgical) remission at beginning of study.

† Rafassal is the brand name of mesalamine used in this study.

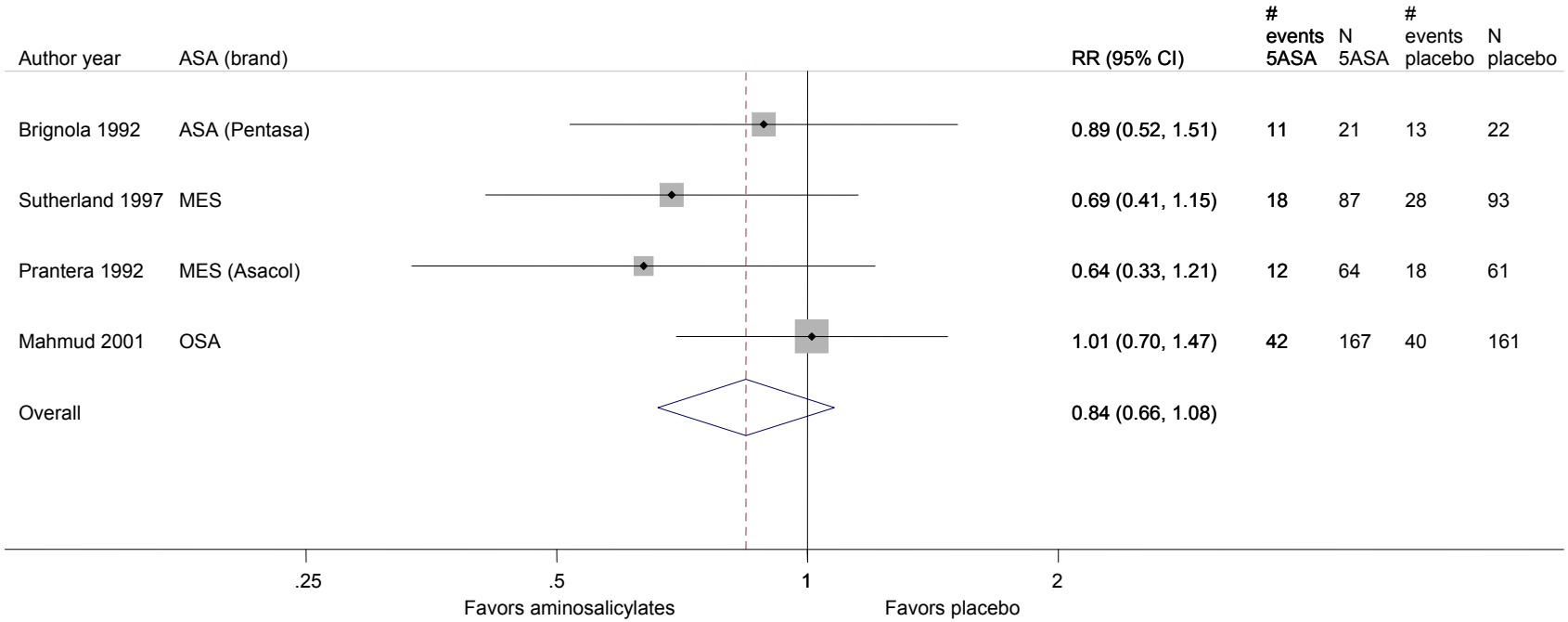
‡ Significant at the 0.05 alpha level

§ LI - laboratory index (-26 + (1.3 X erythrocyte sedimentation rate) + (0.03 X white blood cell) + (5.5 X C-reactive protein) + (0.08 X alpha-1-antitrypsin)

‖Claversal is the brand name of mesalamine used in this study.

¶ "Failure and relapse" included study withdrawal, need for repetition of induction therapy, and multiple clinical criteria (death due to Crohn's disease, fever for more than 2 weeks, need for Crohn's disease surgery, development of new fistulas or abscesses, or disease worsening by endoscopy or radiography) and CDAI criteria (increase of 100 points during first treatment, any increase during second treatment, and failure to achieve score less than 150 or 60-point decrease after end of all three treatment cycles).
**Ileocolitis/colitis only
†† Ileitis only

Figure 9. Pooled relative risk of a relapse* of Crohn's disease at weeks 15-19 comparing an aminosalicylate with placebo



Pooled Relative Risk and 95% Confidence Intervals of Relapse at Weeks 15-19

ASA = aminosalicylates; CI = confidence interval; MES = mesalamine; OSA = olsalazine; RR = relative risk

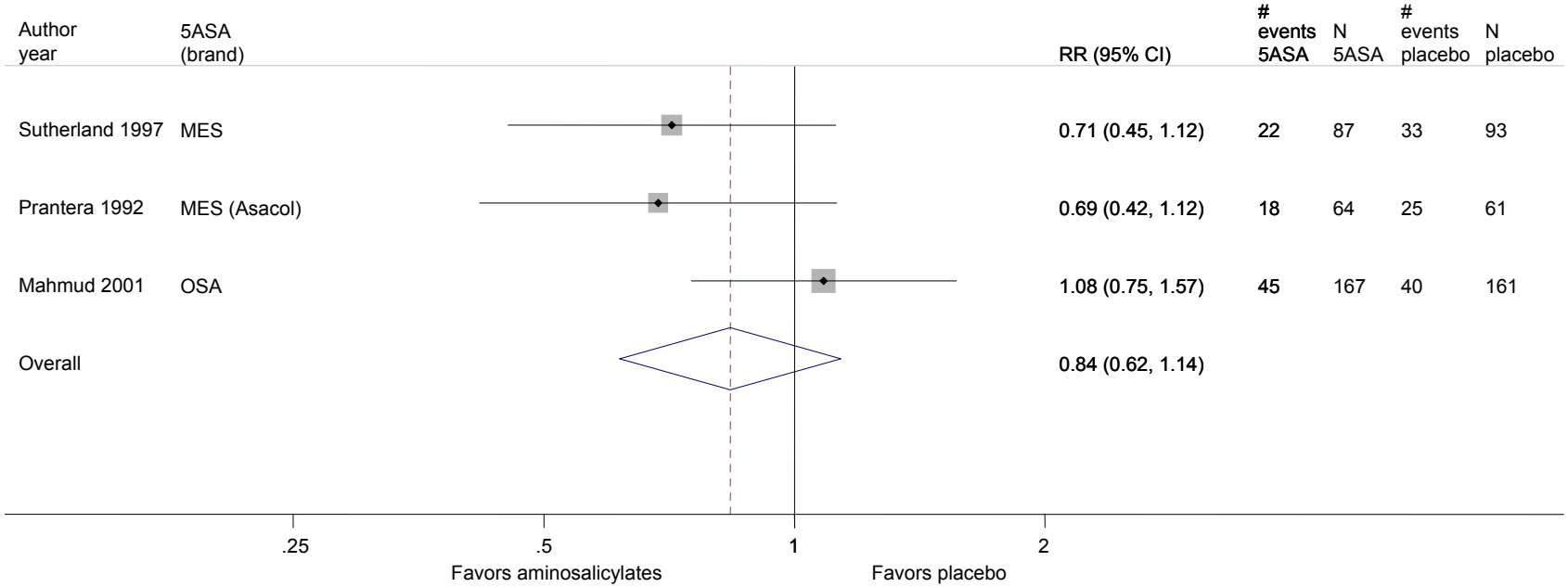
* Relapse was defined as a Crohn's Disease Activity Index more than 150 with at least a 100-point increase from baseline or a Crohn's Disease Activity Index more than 150 for more than 2 weeks in Brignola 1992; a Crohn's Disease Activity Index more than 150 with at least a 60-point increase from baseline or a diagnosed flare-up or a need for corticosteroids or hospitalization in Sutherland 1997; a Crohn's Disease Activity Index more than 150 with at least a 100-point increase from baseline in Prantera 1992; and a Crohn's Disease Activity Index more than 150 or a 60-point increase from baseline with clinical criteria in Mahmud 2001.

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 2.30 with 3 degrees of freedom (p = 0.51)

I-squared statistic = 0%

Figure 10. Pooled relative risk of a relapse* of Crohn's disease at week 26 comparing an aminosalicylate with placebo



Pooled Relative Risk and 95% Confidence Intervals of Relapse at Week 26

5ASA = aminosalicylates; CI = confidence interval; MES = mesalamine; OSA = olsalazine; RR = relative risk

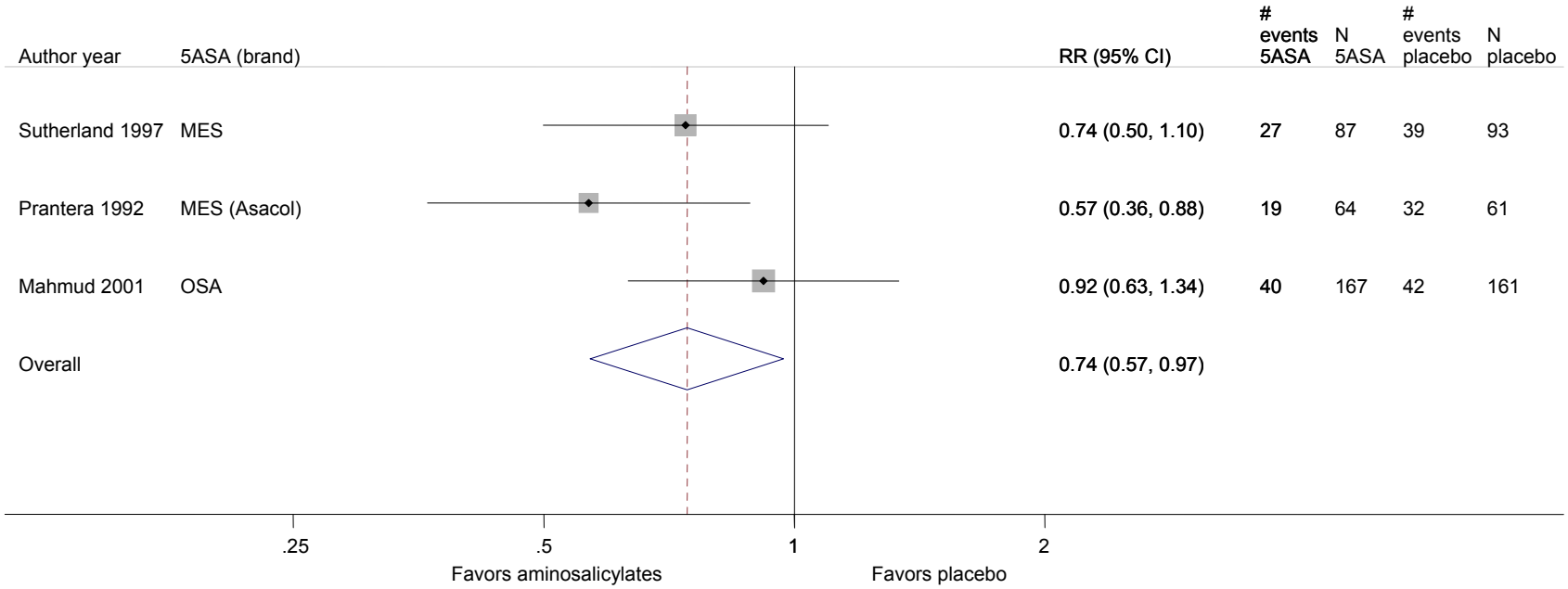
* Relapse was defined as a Crohn's Disease Activity Index more than 150 with at least a 60-point increase from baseline or a diagnosed flare-up or a need for corticosteroids or hospitalization in Sutherland 1997; a Crohn's Disease Activity Index more than 150 with at least a 100-point increase from baseline in Prantera 1992; and a Crohn's Disease Activity Index more than 150 or a 60-point increase from baseline with clinical criteria in Mahmud 2001.

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 3.00 with 2 degrees of freedom (p = 0.22)

I-squared statistic = 33%

Figure 11. Pooled relative risk of a relapse* of Crohn's disease at weeks 48-52 comparing an aminosalicylate with placebo



Pooled Relative Risk and 95% Confidence Intervals of Relapse at Weeks 48-52

5ASA = aminosalicylates; CI = confidence interval; MES = mesalamine; OSA = olsalazine; RR = relative risk
* Relapse was defined as a Crohn's Disease Activity Index more than 150 with at least a 60-point increase from baseline or a diagnosed flare-up or a need for corticosteroids or hospitalization in Sutherland 1997; a Crohn's Disease Activity Index more than 150 with at least a 100-point increase from baseline in Prantera 1992; and a Crohn's Disease Activity Index more than 150 with at least a 60-point increase from baseline in Mahmoud 2001.
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 2.65 with 2 degrees of freedom (p = 0.27)
I-squared statistic = 25%

Mucosal Healing

All results were based on a subset of the original randomized cohort, and represented secondary endpoints (Appendix D, Evidence Table 9).

Infliximab versus placebo. One study compared infliximab versus placebo among 81 patients with ulceration at baseline.[166] All patients received one dose of infliximab at 5 mg/kg intravenous; responders were then randomized to continue to receive infliximab or placebo. Patients who initially responded then lost response could receive infliximab on an as needed basis after 12 weeks; these patients were included in the analysis. A significantly higher proportion of week 2 responders in the combined (5 mg/kg and 10 mg/kg) scheduled maintenance group had complete mucosal healing at weeks 8 (31% versus 0%, $P = 0.01$) and 52 (50% versus 7%, $P = 0.007$) compared with the placebo arm. Additionally, significantly greater improvement in the CDEIS occurred with scheduled maintenance compared with the placebo arm at week 8 ($P < 0.001$) and week 52 ($P = 0.026$). Notably, because patients in the placebo arm may have also received infliximab after week 12, the applicability of the results at 52 weeks is questionable. When all randomized patients were analyzed, the results remained clinically and statistically significant. Fifty-eight of 81 patients underwent repeat endoscopy at 52 weeks; 44% had complete mucosal healing (absence of ulcers) in the infliximab arm compared with 18% in the placebo arm ($P = 0.04$).

Combination of a TNF-alpha inhibitor and another therapy versus another therapy. One open-label study with 80 participants who had disease controlled for 6 or more months on a combination of infliximab and an immunomodulator were randomized to continue combination therapy or infliximab alone.[133] There was no difference between groups. At the end of the study (104 weeks), 49 out of 60 (82%) patients who continued to be on infliximab received a colonoscopy. Sixteen out of 25 (64%) participants on a combination of infliximab and immunomodulators showed an absence of ulcers, compared with 14 out of 23 (61%) participants on infliximab alone.

Thiopurines versus corticosteroids. One study with 77 participants compared azathioprine to budesonide at 52 weeks.[141] The rate of complete mucosal healing (absence of ulcers) was 60% in the azathioprine arm and 5% in the budesonide arm ($P < 0.0001$). Comparisons of CDEIS also favored azathioprine.

Hospitalizations

Infliximab versus placebo. One study[167] with 306 total patients with draining fistulas received open-label induction with infliximab. Response (50% reduction in the number of draining fistulas) was assessed 10 and 14 weeks after starting induction. The 195 total responders were randomized to infliximab or placebo. Eight weeks after randomization, all patients who had lost response (both arms) could receive infliximab. The mean number of total Crohn's disease-related hospitalization days during the study (to week 40 after randomization) among responders was 0.5 in the infliximab group, compared to 2.5 among the placebo group; the number of Crohn's disease-related hospitalizations per 100 patients among responders was 11 in the infliximab group, compared to 31 among controls. Both comparisons were statistically significant at $P <$

0.05. Notably, patients in the placebo group who crossed over to receive infliximab were not censored from the analysis.

One study[134] evaluated the rate of hospitalization in 573 participants who were randomized to receive maintenance infliximab versus placebo after an open-label run in period. At 52 weeks, the rates of Crohn's disease-related hospitalization per 100 patients were 23, 24, and 38 in the 5 mg/kg infliximab, 10 mg/kg infliximab, and placebo arms ($P < 0.05$ for both comparisons). Placebo patients who crossed-over into the active drug group were included in the analysis.

Adalimumab versus placebo. One study[136] with 778 total participants compared adalimumab to placebo at 52 weeks with regard to Crohn's disease-related and all-cause hospitalizations. Among week 4 responders to open-label adalimumab (n = 499), adalimumab every other week and weekly maintenance therapies were associated with a 14.3% and 5.6% risk of 12 month hospitalization compared to 24.8% for placebo ($P < 0.02$ for both comparisons to placebo). The 12-month risk of Crohn's disease-related hospitalizations was 9.7% and 2.8%, respectively, compared with 13.4% for placebo ($P < 0.01$ for weekly versus placebo and $P = 0.12$ for every other week versus placebo). When the analysis combined the groups receiving weekly and every other week dosing, the HR was 0.4 (95% CI, 0.2 to 0.7). Notably, patients with lack of efficacy or loss of response at 8 weeks after randomization could receive open-label adalimumab.

The same study[136] also reported data for all randomized patients which included responders and non-responders to open-label drug. At 52 weeks, hazard ratios for Crohn's disease-related hospitalizations for the adalimumab every other week group and the adalimumab every week group compared with placebo were 0.5 (95% CI, 0.3 to 0.9) and 0.3 (95% CI, 0.2 to 0.7). Results for all-cause hospitalization were similar. Placebo patients who crossed-over to receive open-label adalimumab were included in the analysis.

Surgeries

Infliximab versus placebo. One study with 195 total responders (among 306 total randomized patients with fistulas) compared infliximab with placebo (see description for Hospitalizations: infliximab versus placebo).[167] Among patients who responded to open-label infliximab, those who were randomized to receive infliximab maintenance had a significantly decreased number of all surgeries and procedures (65 versus 126 surgeries; $P < 0.05$) as well as major surgeries (2 versus 11 surgeries; $P < 0.05$), compared with those who received placebo. Notably, patients in the placebo group who crossed over to receive infliximab were not censored from the analysis.

One study[134] evaluated the rate of hospitalization in 573 responders and non-responders randomized to infliximab versus placebo after an open-label run in period. At 52 weeks, the number of patients requiring Crohn's disease-related intra-abdominal surgeries in the 5 mg and 10 mg scheduled infliximab groups, combined, was 11 of 385, compared with 14 of 188 in the placebo group (RR for the combined group, 0.4; 95% CI, 0.2 to 0.8). Placebo patients who crossed-over into the active drug group were included in the analysis.

Adalimumab versus placebo. One study with 778 total participants compared adalimumab to placebo at 52 weeks with regard to Crohn's disease-related surgeries among 4-week responders to open-label adalimumab (n = 499) (except for abscess drainage and seton placement).[136] Major surgery rates were 0.6% for every other week dosing, 0% for weekly dosing, and 4.1% for

placebo (combined adalimumab versus placebo $P < 0.005$). Notably, patients with lack of efficacy or loss of response at 8 weeks after randomization could receive open-label adalimumab and were not censored from the analysis.

The same study[136] also reported results for all randomized patients including both responders and non-responders to open-label drug with similar results. At 52 weeks, fewer Crohn's disease-related surgeries occurred in the adalimumab every other week, weekly, and combined maintenance groups compared with placebo (0.4, 0.8, and 0.6 versus 3.8 per 100 patients; $P < 0.05$ for all comparisons versus placebo). Placebo patients who crossed-over to receive open-label adalimumab were included in the analysis.

Reduction of Steroids

Infliximab versus placebo. One study with 335 participants who responded to open-label infliximab compared infliximab (5 mg every 8 weeks or 10 mg every 8 weeks) with placebo.[126] At week 22, the median corticosteroid dose was lower in the combined infliximab groups (0 mg per day) than in the placebo group (10 mg per day). At 52 weeks, three times as many patients in the infliximab groups combined had discontinued corticosteroids while in remission compared with placebo (29% versus 9%, OR, 4.2; 95% CI, 1.5 to 11.5).

A different publication reported the results for all randomized patients, including responders and non-responders, at different timepoints.[134] At week 30, a clinically and statistically greater proportion of patients in the 5 mg/kg and 10 mg/kg scheduled infliximab treatment groups had their doses of corticosteroids tapered and remained free of corticosteroids throughout the study (44% and 47%, respectively) compared with the proportion of such patients in the placebo group (29%).

Adalimumab versus placebo. One study[129] with 499 responders to open-label adalimumab were randomized to placebo, 40 mg of adalimumab every other week, and 40 mg of adalimumab weekly. Of the 198 total patients who discontinued steroids, the proportion of individuals who remained steroid-free at 26 weeks was 3%, 35%, and 30%, respectively ($P < 0.001$ for both adalimumab groups compared to placebo); at week 52, the proportions were 6%, 29% ($P < 0.001$ for comparison to placebo), and 23% ($P = 0.008$ for comparison to placebo).

Azathioprine versus placebo. One study with 20 participants compared azathioprine to placebo for this outcome.[168] Average baseline daily prednisone dose was 19 mg in the azathioprine group and 17 mg in placebo. The study compared the numerical reduction (in grams) in dose of steroid between the groups at 26 weeks. Patients on azathioprine had a 15.5 mg mean reduction in steroids compared to 6.1 mg for patients given placebo ($P < 0.05$).

Fistula Response

TNF-alpha inhibitors versus placebo. One study[137] with 306 participants was included and compared infliximab with placebo for fistula healing. All of the patients had a fistula for at least 3 months' duration and received open-label induction with infliximab as part of the study. Response (50% reduction in the number of draining fistulas) was assessed 10 and 14 weeks after starting induction. The 195 total responders were randomized to infliximab or placebo. Eight weeks after randomization, all patients who had lost response (both arms) could receive

infliximab. The time to loss of response was significantly longer for patients who received infliximab maintenance therapy than for those who received placebo maintenance (more than 40 weeks versus 14 weeks, $P < 0.001$). At week 40 after randomization, the proportion of patients in the placebo group with complete fistula healing (complete absence of draining fistulas) was 19%, compared with 36% in the infliximab group ($P = 0.009$).

Two maintenance studies, one for adalimumab[129 169] and one for certolizumab pegol[131] examined fistula response among the patients with draining fistulas at baseline. In the study evaluating adalimumab,[129] fistula closure was evaluated among all included patients (both responders and non-responders with regard to disease activity indexes). Complete healing rates for the combined adalimumab group versus placebo was 31% versus 15% at week 28 (not statistically significant) and 33% versus 13% at week 52 ($P < 0.05$). In the study evaluating certolizumab pegol versus placebo,[131] fistula closure among responders (with regard to disease activity, not fistula response) was evaluated. Fifty-eight of 425 patients had draining fistulas at baseline. Closure at 18 weeks was 54% in the certolizumab pegol group and 43% in the placebo group.

Patient-Reported Outcomes

All patient-reported outcomes in this section used the IBDQ unless stated otherwise.

Natalizumab versus placebo. One trial[170] included 339 patients with Crohn's disease who had responded during an induction study with natalizumab. Participants were re-randomized in a maintenance trial (second portion of the study) in which they received natalizumab 300 mg intravenous (N = 168) or placebo (N = 171) every 4 weeks for 48 additional weeks. During maintenance study, IBDQ and SF-36 scale scores of patients re-randomized to natalizumab remained stable, while those re-randomized to placebo worsened. Forty-eight weeks after the initiation of maintenance therapy, the mean change in IBDQ and SF-36 (physical component score [PCS] and mental component score [MCS]) from the induction trial baseline was significantly higher for those who continued to receive natalizumab over placebo ($P < 0.001$ for both IBDQ, SF-36). At 48 weeks, the mean total IBDQ score dropped from 184 to 180 in the natalizumab arm and from 179 to 156 in the placebo arm.

TNF-alpha inhibitors versus placebo. Five studies with 1,157 participants compared TNF-alpha inhibitors to placebo, for varying outcomes.[128-130 137 171] Three studies compared infliximab to placebo.[128 137 171] Infliximab was favored over placebo in a clinically and statistically significant manner for this outcome for both IBDQ and SF-36. In the two larger studies,[137 171] patients who crossed over from the placebo to active drug were still included in the analysis. In the largest study,[171] absolute IBDQ and SF-36 scores are not reported; only the mean difference from baseline (prior to the open-label run-in period) is provided (baseline groups were well matched, however). The analysis of all randomized patients including responders and non-responders to the run-in period treatment[171] was published separately.[134] At 52 weeks, the proportion of patients in the 5 mg/kg and 10 mg/kg infliximab groups with an IBDQ greater than 170 was 38% and 46%, compared with 35% in the placebo group (RR in the 5 mg/kg arm, 1.1; 95% CI, 0.8 to 1.6; RR in the 10 mg/kg arm, 1.3; 95% CI, 0.9 to 1.8). One study[137] looked exclusively at fistulizing Crohn's disease. See Table 23 below.

Two studies with 554 participants compared adalimumab to placebo.[130 172] In one study of 499 participants who were responders to open-label run in adalimumab,[172] mean IBDQ scores were higher in the adalimumab treated arms; however, the change did not reach clinical significance. At 22 weeks, mean IBDQ dropped from 168 to 158 in the placebo arm, rose from 171 to 177 in the adalimumab 40 mg every other week arm ($P < 0.0001$ compared with placebo), and rose from 167 to 171 in the adalimumab 40 mg every week arm ($P < 0.001$). Results were identical at week 52. Similar results were obtained for other patient-related outcomes at 52 weeks, including the Zung Self-Rating Depression Scale, functional assessment of chronic illness therapy (FACIT)-Fatigue Scale Scores, SF-36 PCS, SF-36 MCS, and abdominal pain visual analog scale (VAS). Notably, in this study, patients who were primary non-responders to adalimumab or lost response could receive open-label drug after week 12, thus potentially biasing the results. As with infliximab, patients who crossed over into the open-label drug as soon as 8 weeks after randomization were still included in the analysis. The analysis of all randomized patients from this study[172] was published separately.[135] At 52 weeks, compared with baseline, the improvement in both adalimumab groups (every week and every other week) was 3 points on the IBDQ scale, compared with 11 points in the placebo group. This result was statistically, but not clinically significant.

In another study of adalimumab versus placebo,[130] of 55 patients who had achieved clinical remission during an adalimumab induction study,[78] the mean IBDQ score at 24 weeks dropped from 181 to 176 in the adalimumab 40 mg every other week arm, stayed even at 192 in the adalimumab 40 mg every week arm, and dropped from 187 to 168 in the placebo group ($P < 0.005$ for adalimumab 40 mg every week versus placebo). At 56 weeks, final IBDQ scores were 178, 186, and 162, respectively (results not statistically significant).

Corticosteroids versus placebo. Two studies with 122 participants compared budesonide with placebo.[146 150] One trial[146] examined steroid-dependent patients and compared 6 mg of budesonide daily with placebo. At week 13, mean IBDQ score rose from 162 to 169 in the budesonide arm and dropped from 158 to 154 in the placebo arm. This was statistically ($P = 0.025$), but not clinically significant. In another study[150] patients who had participated in an 8-week induction trial of budesonide were randomly assigned to receive placebo or budesonide at doses of 3 mg or 6 mg daily for 1 year. For the budesonide arm, IBDQ progressed from 185 to 170 to 159 to 156 at baseline, 3 months, 6 months and 12 months, respectively. Progression in the budesonide 6mg arm was as follows: 184 to 172 to 166 to 161, and progression in the placebo arm was as follows: 181 to 154 to 153 to 150. The treatment arm was not different from placebo at any time point.

Corticosteroids versus aminosalicylates. One study with 57 steroid-dependent participants compared budesonide (6 g daily) to mesalamine (Salofalk) 1 gram every 8 hours.[152] The study was only blinded to investigators. In the budesonide arm, the mean IBDQ score progressed from 188 to 173 to 152 to 148 at baseline, 4 months, 6 months, and 1 year. Progression for the mesalamine arm was as follows: mean of 186 to 135 to 120 to 110, respectively. Across time points, the difference between arms was clinically and statistically significant ($P = 0.0001$).

Aminosalicylates versus placebo. One 48-week study with 246 Crohn's disease patients who were in remission compared mesalamine (Pentasa®, 750 mg every 6 hours) to placebo for maintenance of remission.[155] At the last visit (early termination or study completion), mean

IBDQ dropped from 193 to 180 in the mesalamine arm, while it dropped from 193 to 179 in the placebo arm. This was neither clinically or statistically significant. Notably, randomized patients had achieved remission through surgical as well as medical means.

Table 23. Randomized controlled trials comparing the effectiveness of infliximab with placebo in terms of patient-reported outcomes in patients with Crohn's disease

Author, year	Outcome definition	Followup (weeks)	Main intervention (dose), n	Comparison, n	Mean difference from baseline (Infliximab)	Mean difference from baseline (placebo)	P-value
Feagan, 2003[171]	IBDQ	28	Infliximab (5 mg/kg every 8 wks), 107	Placebo, 109	27.1	14	< 0.05
	IBDQ	28	Infliximab (10 mg/kg every 8 wks), 111	Placebo, 109	31.7	14	< 0.01
	IBDQ	52	Infliximab (5 mg/kg every 8 wks), 107	Placebo, 109	22.1	8.9	< 0.05
	IBDQ	52	Infliximab (10 mg/kg every 8 wks), 111	Placebo, 109	30.2	8.9	< 0.001
	SF-36 PCS	28	Infliximab (5 mg/kg every 8 wks), 107	Placebo, 109	7.3	3.1	< 0.01
	SF-36 PCS	28	Infliximab (10 mg/kg every 8 wks), 111	Placebo, 109	7.3	3.1	< 0.01
	SF-36 PCS	52	Infliximab (5 mg/kg every 8 wks), 107	Placebo, 109	6.1	2.5	< 0.05
	SF-36 PCS	52	Infliximab (10 mg/kg every 8 wks), 111	Placebo, 109	7.2	2.5	< 0.01
	SF-36 MCS	30	Infliximab (5 mg/kg every 8 wks), 107	Placebo, 109	4.6	2.9	NS
	SF-36 MCS	30	Infliximab (10 mg/kg every 8 wks), 111	Placebo, 109	4.9	2.9	NS
	SF-36 MCS	52	Infliximab (5 mg/kg every 8 wks), 107	Placebo, 109	5.1	2	NS
	SF-36 MCS	52	Infliximab (10 mg/kg every 8 wks), 111	Placebo, 109	5.8	2	< 0.05
Rutgeerts, 1999[128]	IBDQ	4	Infliximab (10 mg/kg every 8 wks), 37	Placebo, 36	14	-2	NR
	IBDQ	16	Infliximab (10 mg/kg every 8 wks), 37	Placebo, 36	14	-8	NR
	IBDQ	36*	Infliximab (10 mg/kg every 8 wks), 37	Placebo, 36	-8	-31	NR
Sands, 2004[137]	IBDQ	16	Infliximab (5 mg/kg every 8 wks), 96	Placebo, 99	14	4	0.002
	IBDQ	40	Infliximab (5 mg/kg every 8 wks), 96	Placebo, 99	10	5	0.003

IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = mental component score; mg/kg = milligrams per kilogram; NR = not reported; NS = not significant; PCS = physical component score; SF-36 = Short Form-36; wks = weeks

* Last dose of infliximab was at 24 weeks.

Quality Assessment

Out of the 46 trials included in this report that addressed KQ2, all were RCTs with a parallel arm design (Appendix D, Evidence Table 10). Among these 46 RCTs, 56% adequately generated their allocation sequence. Sixty- seven percent of these RCTs adequately concealed their allocation of participants into the different study arms. Sixty-three percent of studies were described as being double blind, while 37% were not double blinded or did not report on blinding. Sixty-three percent of these studies reported withdrawals and dropouts. Forty-eight percent of these RCTs had some form of threat to the validity of results that they reported. Fifty-seven percent and 33% of these RCTs received pharmaceutical support and company involvement in the design, conduct or reporting of the study, respectively. Among these 46 trials, 24% were rated as good quality, 52% as fair quality, and 24% as poor quality.

One systematic issue that came up in the TNF-alpha inhibitor trials dealt with blinding. According to study protocol, patients assigned to the placebo group could after a prespecified time period cross over to receive study drug (in some cases blinding was maintained). For most efficacy analyses, patients who crossed over to receive drug were deemed failures. However, for other outcomes (e.g., hospitalization, surgery, or patient-reported outcomes), patients may not have been censored from the analysis.

In one study,[99] data on inactive Crohn's disease could only be extracted as a subgroup analysis. These results should be interpreted with caution.

Of note, many studies reported on maintenance of patients who took part in induction studies. However, they did not re-randomize the responders, and instead just followed patients over time during maintenance therapy. These patients were not included here. Instead, they were included as part of KQ1 because they were originally randomized when they had active disease.

Applicability

Populations

- Determination of original disease severity sometimes was not possible. Unless patients took part in an induction trial for KQ1, it was difficult to ascertain whether they had had moderate-to-severe disease in the past, or more mild disease. Calculation of a retrospective CDAI was not possible.
- The vast majority of studies enrolled only Caucasians; African Americans, Hispanics, and Asians were not well represented.
- The median age at enrollment in most studies ranged between 25 and 40 years of age. Older populations were not well represented.
- Smoking was not consistently reported, even though smoking can affect drug efficacy. Additionally, smoking has been shown to impact on surgical rates (one of our endpoints).[123]
- Mean duration of disease, with the exception of a few studies,[83 86] was long (often greater than 10 years). Evidence is growing that patients with a shorter duration of disease are more responsive to medications.[124] Also, patients with a long duration of disease frequently have complications of stricturing or fistulization,[125] which can affect hospitalization and surgical rates.

- Most studies used the CDAI. The CDAI takes into account frequency of diarrhea, abdominal pain, rating of general well-being, extraintestinal manifestation, use of anti-diarrheals, abdominal mass, and hematocrit. Many of the mentioned symptoms are not unique to Crohn's, and could be seen with other common concurrent conditions such as irritable bowel syndrome. Most studies did not document the presence of mucosal disease prior to randomization. The effect size in those with mucosal disease is probably different from that reported for all patients (with or without mucosal disease).

Intervention

- The studies had significant heterogeneity in terms of the interventions.
  - Different doses of the same medications were used. Often the medications were under-dosed, particularly with regard to thiopurines.
  - Different delivery systems were used, including oral and intramuscular methotrexate, making comparisons difficult. In some cases, as for intravenous certolizumab pegol and intravenous azathioprine, routes that are not used in practice were evaluated in the studies. Even among oral aminosalicylate agents, different formulations were characterized by different delivery systems (pH dependent, microgranule, or other).
  - For studies where patients were started on corticosteroids at randomization, protocols for corticosteroid tapering were variable between studies.

Comparisons

- In patients who were corticosteroid dependent at the time of randomization, corticosteroids were not counted as an active intervention, in an effort to differentiate them from studies where corticosteroids were explicitly designated as an active intervention.

Outcomes

- Definitions for relapse were considerably more variable than those for response or remission, thus making comparisons between studies more difficult.
- Some older studies used rank outcome (where other clinical variables including x-ray results and clinical signs such as fever were accounted for) which are not used in more modern designs.[93 99] Other studies used indexes such as VHAI[111] that are not commonly used in research or clinical practice.
- Improvement in CDAI is non-specific for Crohn's disease; it can go down as a result of improvement in irritable bowel-type symptoms. This helps to explain the overall high placebo response, often exceeding 30%.
- Some studies looked at steroid-free remission, while others did not. This is often complicated by studies where steroids are part of the active intervention. Steroid-free remission is a different endpoint from remission still on steroids.
- Overall, there was inconsistent reporting of many of our predetermined outcomes, including: mucosal healing, hospitalizations, surgery, reduction of steroids, and fistula response.

Timing

- There were very few studies evaluating endpoints beyond one year. Thus, long term maintenance data is not available. Crohn's disease is a chronic disease of decades, not of one year. Clearly, long-term randomized trials are very expensive to conduct. They also may be impractical because of the large proportion of patients who drop out (frequently greater than 50%).

Key Question 3: What is the comparative safety of therapies alone or in combination used in adults with moderate-to-severe Crohn's disease in terms of minimizing short- and long-term adverse effects?

Data on one or more adverse effects of treatment were reported in 44 RCTs involving a total of 9,139 Crohn's disease patients, and in 46 observational studies including 121,649 inflammatory bowel disease patients. As noted for KQ 1 and 2, the main drug classes of interest were biologics, thiopurines, methotrexate, corticosteroids, and aminosalicylates. Because some observational studies combined thiopurines and methotrexate as immunomodulators, the additional classification of immunomodulators appears in this section.

Key Points

The key points are summarized below with the corresponding evidence grades. Additional details about the evidence grades are provided in Table 24 and Appendix D, Evidence Table 11.

Mortality

- Mortality rates were less than 1% in most of the observed comparisons.
- The only comparison for which mortality differed between groups was treatment with corticosteroids compared with treatment without corticosteroids. The RRs in observational studies ranged from 1.0 to 2.5, favoring no corticosteroids, with followup ranging from 6 weeks to 7 years, and low strength of evidence.
- In other comparisons, mortality did not differ between groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, aminosalicylates, or combinations of these drugs. The RRs in observational studies compared with no treatment or another treatment ranged from 0.8 to 1.0 for TNF-alpha inhibitors, 0.7 to 1.3 for immunomodulators, and 0.7 for aminosalicylates, with followup ranging from 4 weeks to 12 years, and low strength of evidence.
- The evidence was insufficient on the effects of ustekinumab on mortality.

Hepatosplenic T-cell Lymphoma

- We identified 37 unique cases of hepatosplenic T-cell lymphoma associated with treatment of Crohn's disease from research reports, case series, and the Adverse Events Reporting System.
- A thiopurine had been used in 95% of the cases, and at least one biologic had been used in 76% of the cases, but a causal relationship could not be established because of limitations in the available information.

Lymphoma

- Lymphoma occurred in less than 1% of patients in most observed comparisons.
- The risk of lymphoma did not differ between groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, corticosteroids, aminosalicylates, or combinations of these drugs. The observational RRs compared with no treatment or another treatment ranged from 0.6 to 1.7 for TNF-alpha inhibitors, 0.3 to 5.3 for immunomodulators, 1.0 for corticosteroids, and 1.0 for aminosalicylates, with followup ranging from 4 weeks to 12 years, and low strength of evidence.
- Lymphoma was not reported as an outcome in RCTs of ustekinumab, immunomodulators, corticosteroids, or aminosalicylates.

Cervical Cancer

- Very few cervical cancer cases were reported in the studies.
- The risk of cervical cancer did not differ between groups that received TNF-alpha inhibitors, immunomodulators, corticosteroids, or aminosalicylates, or combinations of these drugs, with followup ranging from 26 weeks to 3 years, and low strength of evidence.
- Cervical cancer was not reported as an outcome in most of the RCTs, and none of the studies of natalizumab or ustekinumab reported on cervical cancer.

All Cancers

- The risk of non-melanoma skin cancer was higher with TNF-alpha inhibitors alone or with immunomodulators used recently (within 90 days) or persistently (within 90 days and greater than 365 days) than with no TNF-alpha inhibitors or no immunomodulators. The odds ratios (ORs) in observational studies ranged from 2.1 to 6.8, with low strength of evidence.
- The risk of non-melanoma skin cancer was higher with thiopurines used recently (within 90 days) or persistently (within 90 days and greater than 365 days) than with no thiopurines. The ORs in observational studies ranged from 3.8 to 4.3, with low strength of evidence.
- The risk of adenocarcinoma of the small bowel was higher with 6-mercaptopurine than with no 6-mercaptopurine. The OR in an observational study was 10.8, with an unreported length of followup, and low strength of evidence.

- For all other comparisons, the risk of specific cancers or all cancers did not differ between treatment groups. The RRs compared with no treatment or another treatment from observational studies ranged from 0 to 10.8, with followup ranging from 4 weeks to 12 years, and low strength of evidence.

Infections

- Serious infections were frequently reported and occurred in less than 5% of patients in most trials.
- Opportunistic infections were occasionally reported and occurred less than five out of every 100 person-years.
- Infections (including serious and opportunistic) were frequently reported with a maximum incidence of 83% of patients in one trial. Most trials reported far fewer infections (5 to 20% of patients).
- The risk of infection did not differ between groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, or aminosalicylates. The RRs, hazard ratios (HRs), or ORs from RCTs and observational studies compared with no treatment or another treatment were 0.6 for ustekinumab, 0.3 to 1.3 for natalizumab, 0.3 to 11.1 for TNF-alpha inhibitors, 0.3 to 5.4 for immunomodulators, 0.4 to 3.4 for corticosteroids, and 0.9 to 1.8 for aminosalicylates, with followup ranging from 4 weeks to 9 years, and low strength of evidence.
- The risk of infection was lower with prednisone and sulfasalazine than with prednisone alone. The RR from one RCT was 0.3, with 8 weeks of followup, and moderate strength of evidence.

Tuberculosis

- Only six cases of tuberculosis were reported in the studies, most likely because many RCTs screened patients for tuberculosis or treated them before enrollment.
- The risk of developing tuberculosis did not differ between treatment groups in five RCTs comparing TNF-alpha inhibitors with placebo, one RCT comparing a combination of infliximab and immunomodulators with infliximab, and one RCT comparing a combination of infliximab and immunomodulators with immunomodulators. The followup ranged from 4 to 52 weeks, with low strength of evidence.

Infusion- and Injection-Site Reactions

- Infusion and injection-site reactions were frequently reported in the trials of biologics, with infusion reactions occurring in 0% to 40% of patients. Most trials reported that fewer than 20% of patients experienced reactions.
- The rate of infusion reactions did not differ between treatment groups in most comparisons with low strength of evidence. Reactions were reported in one ustekinumab trial, with 2% of ustekinumab versus 0% placebo patients experiencing a reaction. For the other medications the RRs, HRs, or ORs from RCTs and observational studies were: natalizumab versus placebo, RR ranged from 0.8 to 1.5; certolizumab pegol versus

placebo, RR ranged from 0.2 to 1.7; combinations with infliximab versus infliximab alone, RR ranged from 0.3 to 1.5; infliximab combined with thiopurine versus infliximab combined with methotrexate, RR ranged from 0.8 to 1.4.

- The rate of infusion reactions was higher with infliximab and adalimumab than with placebo. The RRs from RCTs ranged from 1.1 to 3.2, with low strength of evidence.
- The rate of infusion reactions was higher with infliximab than with azathioprine. The RR from one RCT was 3.0, with 1 year of followup, and high strength of evidence.
- The rate of infusion reactions after a single infusion was higher with intravenous azathioprine than with placebo. The RR from one RCT was 5.8, with high strength of evidence.
- We did not find any trials that administered corticosteroids or aminosalicylates intravenously.

Bone Fractures

- None of the studies of biologics, immunomodulators, or aminosalicylates reported on bone fractures.
- The risk of bone fracture did not differ between treatment groups that received budesonide or prednisolone. The RR from one RCT with 2 years of followup was 1.0, with moderate strength of evidence.
- The risk of bone fracture did not differ between corticosteroid users and corticosteroid non-users. The RR from observational studies ranged from 0 to 2.5, with 2 years of followup, and low strength of evidence.

Table 24. Key findings and strength of the available evidence comparing pharmacologic therapies for the management of Crohn's disease in terms of safety-related outcomes

Comparison	Mortality	Lymphoma	Cervical cancer	All cancers	Infections	Tuberculosis	Infusion- and injection-site reactions	Bone fractures
Natalizumab vs. placebo	NF; Low SOE	NF; Low SOE		NF; Low SOE	NF; Low SOE		NF; Low SOE	
Natalizumab + infliximab vs. infliximab		NF; Low SOE		NF; Low SOE	NF; Low SOE		NF; Low SOE	
Ustekinumab vs. placebo				NF; Low SOE	NF; Low SOE		NF; Low SOE	
TNF vs. no TNF			NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE		
Infliximab vs. placebo	NF; Low SOE	NF; Low SOE					Placebo favored; Low SOE	
Adalimumab vs. placebo	NF; Low SOE	NF; Low SOE					Placebo favored; Low SOE	
CP vs. placebo	NF; Low SOE	NF; Low SOE					NF; Low SOE	
Infliximab vs. azathioprine	NF; Low SOE			NF; Low SOE	NF; Low SOE		Azathioprine favored; Low SOE	
TNF + IMM vs. no therapy		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Infliximab + IMM vs. infliximab	NF; Low SOE	NF; Low SOE		NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	
Infliximab + IMM vs IMM	NF; Low SOE			NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	
Infliximab + IMM vs. steroids	NF; Low SOE	NF; Low SOE			NF; Low SOE			
Infliximab + thiopurine vs. infliximab + methotrexate							NF; Low SOE	
TNF + IMM + steroids vs. no therapy		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Infliximab + steroids vs. no therapy		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Infliximab + steroids vs. infliximab				NF; Low SOE			NF; Low SOE	

Table 24. Key findings and strength of the available evidence comparing pharmacologic therapies for the management of Crohn's disease in terms of safety-related outcomes (continued)

Comparison	Mortality	Lymphoma	Cervical cancer	All cancers	Infections	Tuberculosis	Infusion- and injection-site reactions	Bone fractures
IMM vs. placebo	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE		Placebo favored; High SOE	
Azathioprine vs. steroids	NF; Low SOE			NF; Low SOE	NF; Low SOE			
Azathioprine vs. sulfasalazine	NF; Low SOE			NF; Low SOE	NF; Low SOE			
Thiopurine + prednisone vs. placebo		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Azathioprine + prednisone vs. azathioprine	NF; Low SOE							
IMM + steroids vs. steroids					NF; Low SOE			
Thiopurine + ASA vs. thiopurine		NF; Low SOE		NF; Low SOE	NF; Low SOE			
Steroids vs. placebo	Placebo favored; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE			NF; Low SOE
Budesonide vs. prednisone								NF; Moderate SOE
Prednisone vs. ASA	NF; Low SOE			NF; Low SOE	NF; Low SOE			
Steroids + ASA vs. other	NF; Low SOE				NF; Low SOE			
ASA vs. placebo	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE	NF; Low SOE			

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable. Blank cells indicate insufficient evidence.
ASA = aminosalicylates; IMM = immunomodulator; NF = neither favored; SOE = strength of evidence; steroids = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor

Study Design and Population Characteristics

Forty-five RCTs and 46 observational studies reported on one or more safety-related outcomes. The study design and population characteristics of those RCTs and observational studies are reported in Tables 12 and 13 in Appendix D.

Forty-five of 87 (52%) RCTs that reported efficacy also reported a safety outcome of interest by treatment group. The 45 RCTs reporting safety included 9,139 Crohn's disease patients. The majority of RCTs reported that safety was assessed at study visits without further details as to how safety was ascertained (e.g., study-specific form or open-ended question) or if there were specific safety concerns of interest. The method of ascertainment was assumed to be active in all RCTs where active ascertainment was used for the efficacy outcome. However, the only information on safety assessment for nearly all RCTs was that unspecified safety outcomes were ascertained at study visits. Similarly, blinded assessment of safety was assumed in all RCTs where blinded assessment was used for the efficacy outcomes.

The observational studies on KQ3 included seven prospective studies (n = 26,973), 26 retrospective studies (n = 53,856), 11 case-control studies (n = 40,040), one cross-sectional study (n = 207)[32] and one observational study of unclear study design (n = 573).[33] A specific safety outcome of interest was a stated outcome of interest in all of the case-control and prospective studies. Eight case-control studies reported cancer outcomes, two reported on infections, and one reported on bone fractures. All of the retrospective studies aimed to assess safety, but only specified the exact safety outcomes of interest in about half of the studies. No observational study mentioned active ascertainment or blinded assessment of safety outcomes. Two of the prospective studies relied upon the patients' personal gastroenterologists to complete study-specific forms related to safety.[173 174]

Multiple publications were reported from several cohorts. These included 21 studies reporting on studies from a general practice database, a single health center with care delivered at multiple sites or a single inflammatory bowel disease clinic.[33 35 175-193] Although most cohorts with multiple publications reported different outcomes in each publication, potential duplication of outcomes from the same study center have been noted when relevant. Some of the centers also served as sites for clinical trials. Unless the authors of the observational study reported that the patients' outcomes were also reported in clinical trials, duplication of reporting in clinical trials and observational studies has not been noted.

Study design of observational studies. Most observational studies occurred at single study centers. Twenty-two observational studies occurred at multiple centers. Six multi-center studies occurred in the United States, one occurred in the United States and Europe, and the remainder occurred in Canada, Australia, or a single country in Europe. Of the single center studies, 11 occurred in the United States, one in Canada, nine in Europe, one in Australia, and one in Africa. No single or multi-center study included a site in Asia. The starting year of enrollment ranged from 1946 to 2005 among the 32 studies that reported year of enrollment (5 studies did not report). Median followup ranged from 16.4 weeks to 9 years (mean 34 weeks to 3.7 years; 13 studies did not report average followup). The majority of case-control studies used information from electronic records collected for routine care unrelated to the study from multiple study centers.

Population characteristics of observational studies. Twenty-eight studies reported results for inflammatory bowel disease patients without reporting results for Crohn's disease patients separately. Twenty studies reported results separately for Crohn's disease patients or included these patients exclusively. The age and gender distribution was very inclusive with some studies including patients of all ages (0 to 90 years) and studies of cervical cancer including exclusively female patients.

All activity levels and severities of Crohn's disease were included in the majority of observational studies reporting safety. One study explicitly included patients by disease behavior and activity. One study included patients without abscess or stricture with either fistulizing disease or luminal refractory Crohn's disease with CDAI of 220 to 400.[33] A study that aimed to study maintenance of remission required six months of remission with azathioprine therapy to be eligible.[35] Another prospective azathioprine study required patients to have well-controlled inflammatory bowel disease to be eligible.[194]

Most of the observational studies had no restrictions for previous medication use. Sixteen studies included only patients who had used infliximab. These 16 studies compared safety of infliximab alone or in combination with other medications. Two retrospective studies required azathioprine use as they aimed to compare effectiveness of azathioprine with or without concomitant aminosalicylates.[34 35]

Mortality

Twenty-seven RCTs including 6,867 Crohn's disease patients reported mortality by comparison group. No RCTs of ustekinumab or methotrexate reported on mortality. Mortality was reported as an outcome by comparison group in two prospective, nine retrospective, and one observational study of unclear study design,[33] including a total of 38,774 patients (Appendix D, Evidence Table 14).

Biologics

Tables 25 and 26 summarize the RCTs and Figure 12 summarizes the observational studies evaluating biologics in terms of mortality. Additional details about these studies are given below.

Table 25. Summary of reported mortality results in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Biologic	Comparison	# of deaths in biologic group	# of patients in biologic group	# of deaths in comparison group	# of patients in comparison group
Rutgeerts, 1999[128]	36	Infliximab	Placebo	0	37	1	36
Hanauer, 2002[126]	52	Infliximab	Placebo	3	193	0	188
Sandborn, 2005[76]	48	Natalizumab	Placebo	2	723	0	181
Colombel, 2010[83]	54	Infliximab + placebo	Azathioprine + placebo	0	163	1	161
Van Assche, 2008[133]	104	Infliximab + immunomodulators	Infliximab	0	40	1	40
Colombel, 2010[83]	54	Infliximab + azathioprine	Azathioprine + placebo	0	179	1	161

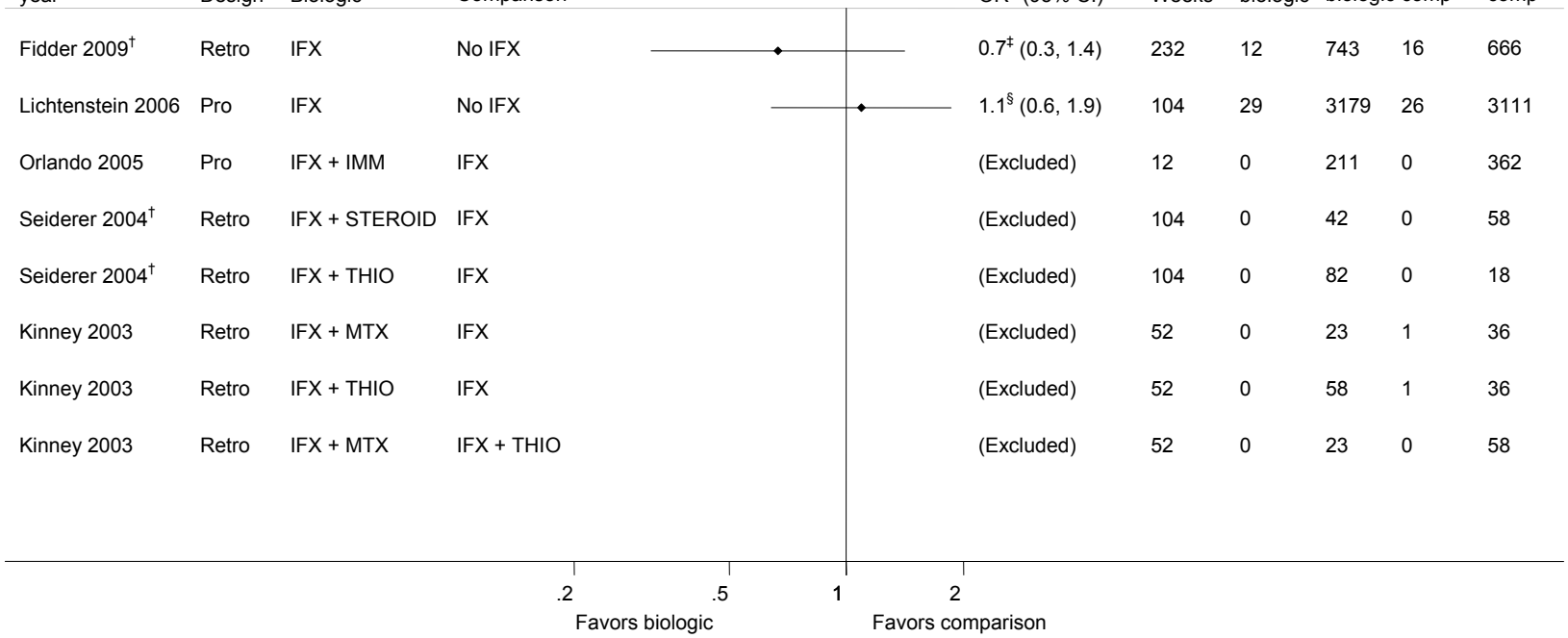
Table 26. Summary of randomized controlled trials that did not report on mortality when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*

Biologic	Comparison	# of trials reporting no deaths	Range of followup (weeks)	# of participants (estimated person-years) in biologic group	# of participants (estimated person-years) in comparison group
Natalizumab	Placebo	2[26 170]	12	474 (109)	464 (107)
Infliximab	Placebo	3[24 126 137]	18-52	363 (310)	362 (309)
Adalimumab	Placebo	4[78 79 129 130]	4-52	938 (584)	519 (297)
Certolizumab pegol	Placebo	4[80-82 131]	12-26	833 (284)	638 (243)
Infliximab + azathioprine	Infliximab + placebo	1[83]	54	179 (186)	163 (169)
Infliximab+ azathioprine	Infliximab + hydrocortisone	1[132]	104	23 (46)	23 (46)
Infliximab + thiopurine	Thiopurine + placebo	1[84]	52	57 (57)	56 (56)

*7 RCTs compared a biologic to another medication and did not report on mortality.[25 27 75-77 85 86]

Figure 12. Summary of Peto odds ratios of mortality among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease

Author year	Design	Biologic	Comparison	OR* (95% CI)	Weeks	# events biologic	N biologic	# events comp	N comp
Fidder 2009†	Retro	IFX	No IFX	0.7‡ (0.3, 1.4)	232	12	743	16	666
Lichtenstein 2006	Pro	IFX	No IFX	1.1§ (0.6, 1.9)	104	29	3179	26	3111
Orlando 2005	Pro	IFX + IMM	IFX	(Excluded)	12	0	211	0	362
Seiderer 2004†	Retro	IFX + STEROID	IFX	(Excluded)	104	0	42	0	58
Seiderer 2004†	Retro	IFX + THIO	IFX	(Excluded)	104	0	82	0	18
Kinney 2003	Retro	IFX + MTX	IFX	(Excluded)	52	0	23	1	36
Kinney 2003	Retro	IFX + THIO	IFX	(Excluded)	52	0	58	1	36
Kinney 2003	Retro	IFX + MTX	IFX + THIO	(Excluded)	52	0	23	0	58



Peto Odds Ratio and 95% Confidence Intervals of Mortality

BIO = biologics; CI = confidence interval; Comp = comparison; IFX = infliximab; IMM = immunomodulator; MTX = methotrexate; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Inflammatory bowel disease population

‡ Adjusted OR, 0.8 (95% CI, 0.3 to 1.8)

§ Adjusted OR, 1.0 (95% CI, 0.5 to 1.9)

Natalizumab versus placebo. Three RCTS reported in two articles reported mortality for natalizumab versus placebo in 1,414 patients.[26 76] The trials reported in the same publication included an induction trial of 904 patients followed for 8 weeks followed by a maintenance trial of 428 responders from the first trial.[76] One death occurred during the induction trial study period in the natalizumab group (<1%) and an additional death from progressive multifocal leukoencephalopathy occurred in the natalizumab group after the study ended during open-label extension (<1%).[76] No deaths were reported in the placebo groups. A 12-week trial of 510 patients reported no deaths in the induction or study periods.[26]

Infliximab versus placebo. Four RCTs including 1,022 patients compared infliximab with placebo and reported mortality.[24 126 128 137] An 18-week induction trial of 94 fistulizing Crohn's disease patients compared infliximab infusion with placebo.[24] They reported that no deaths occurred during the study period.

A 36-week maintenance trial[128] compared retreatment with infliximab or placebo among 73 responders to a single induction dose in a previous 12-week trial.[77] No deaths were reported in the infliximab group and one death was reported in the placebo group. The deceased patient received infliximab during the induction period.[128] The trial corresponding to the induction period did not report on mortality and did not report this death.[77]

A 40-week maintenance trial of 282 responders and non-responders to a 14-week induction period with infliximab compared infliximab with placebo.[137] They reported no deaths during the study period, but did report two deaths (1% of 306 given an induction dose prior to randomization) after the completion of the study.

A 52-week maintenance trial of 573 responders and non-responders to a 2-week induction period of a single infliximab dose compared 5 mg/kg and 10 mg/kg intravenous every eight weeks of infliximab with placebo.[126] They reported three deaths in the 5 mg/kg infliximab group (2%) and no deaths in the 10 mg/kg infliximab and placebo groups.[126]

Infliximab versus no infliximab. One prospective study of 6,290 Crohn's disease patients compared infliximab use with no infliximab use.[174] The study compared infliximab use within 12 weeks of enrollment, scheduled for 30 days after enrollment or at any other time during the observation period, with never use of infliximab during the observation period.[174] Mortality was followed through June 30, 2004 instead of August 2004 because there was incomplete information on medication usage after June 30, 2004. There was no statistically significant increase in mortality comparing infliximab with no infliximab during the study period in the relative rate (IRR, 1.2; 95% CI, 0.7 to 2.1), unadjusted odds ratio (OR, 1.1; 95% CI, 0.6 to 1.9) or OR adjusted for demographic factors and ever use of prednisone, immunomodulators, or narcotic analgesics (1.0; 95% CI, 0.5 to 1.9). Two deaths were excluded from the OR analysis because they occurred after June 30, 2004. These deaths appear to have been included in the relative rate.

Adalimumab versus placebo. Four RCTs compared adalimumab with placebo in 1,457 patients and reported mortality.[78 79 130 135] The 4- or 52-week trials reported no deaths during the study periods. However, one person died during an induction period prior to randomization after receiving adalimumab.[135]

Certolizumab pegol versus placebo. Four RCTs compared certolizumab pegol to placebo in 1,472 patients and reported mortality.[80-82 131] Three studies were induction trials of 12- or 26-weeks duration.[80-82] No deaths were reported during the study periods. One trial (26-weeks duration) reported one death after the study period in the certolizumab pegol group.[80]

An 18-week trial of 428 responders from an 8-week induction phase compared certolizumab pegol with placebo among patients without obstruction, stricture or abscess.[131] One patient died of an accidental fentanyl overdose during the induction phase (1%), but no deaths were observed during the randomization period.[131]

Infliximab versus immunomodulators. One RCT including 324 patients compared infliximab with immunomodulators and reported mortality. A 50-week induction trial compared infliximab with azathioprine among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[83] Safety information was collected through week 54. None of the 163 infliximab patients died compared with one of 161 azathioprine patients.

Combination of infliximab and immunomodulators versus infliximab. Three RCTs and two observational studies including 1,225 patients compared a combination of infliximab and immunomodulators with infliximab alone and reported mortality.[33 83 84 133 195] Three RCTs including 535 patients compared a combination of infliximab and immunomodulators with infliximab. A 50-week induction trial compared infliximab with concomitant azathioprine with infliximab among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[83] Safety information was collected through week 54. One patient died prior to randomization of the 817 patients assessed for eligibility (<1%). There were no deaths reported in the 179 combination infliximab and azathioprine or 161 infliximab patients during the study period. An open-label 104-week RCT of 80 patients compared retreatment with infliximab with or without continuation of the current immunomodulators.[133] One patient who discontinued immunomodulators died during the study period (1%). A 52-week induction trial of 113 steroid-dependent patients with luminal Crohn's disease reported no deaths in the combination infliximab and thiopurines or infliximab alone treatment groups.[84]

Two retrospective studies including 690 Crohn's disease patients compared a combination of infliximab and immunomodulators with infliximab alone and reported mortality. A single center retrospective study reported on 122 patients with a mean of three infliximab infusions per patient followed an average of 40 to 65 weeks.[195] No deaths were recorded in the charts of the 58 patients treated with infliximab with concomitant azathioprine or 6-mercaptopurine or 23 patients treated with concomitant methotrexate. One death was recorded in the medical records of 36 patients who received infliximab without concomitant thiopurines or methotrexate (3%).

One study reported no deaths among 362 patients treated with infliximab without immunomodulators and 211 patients who received infliximab and an immunomodulators during the 12-week treatment period.[33] The study is described as a large series that was likely retrospective in design because another study at the same centers reporting cancer outcomes was retrospective.[189] The study reporting cancer outcomes compared infliximab with no infliximab and reported that three patients treated with infliximab died from their cancer through September 2004. Because the deaths were not reported for the study reporting on 12 weeks of followup for mortality, these deaths likely did not occur during the first 12 weeks of followup or occurred after December 2003.[33]

Combination of infliximab and immunomodulators versus immunomodulators. One 50-week trial including 340 patients naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate compared infliximab with concomitant azathioprine with azathioprine alone and reported mortality.[83] There were no deaths reported in the 169 combination infliximab and azathioprine patients. One of 170 azathioprine patients died during the study period (<1%).

Combination of infliximab and immunomodulators versus other treatment. One 2-year trial of 46 corticosteroid-dependent patients with luminal Crohn's disease compared infliximab with concomitant azathioprine daily with infliximab with hydrocortisone given at the time of the infusion among those who achieved remission during the 8-week induction period.[132] No deaths were reported during the study period.

Other combinations with infliximab. Two retrospective cohorts including 657 patients aimed to describe the safety profile of infliximab use at their study centers.[179 186] Both studies reported concomitant medications at the time of the first infliximab infusion at the center for all Crohn's disease patients, but they reported concomitant medications used between infusion and the time of death only for those who died. Patients with unavailable information were classified as infliximab without concomitant medication. Because of the potential misclassification, we did not include these studies in the tables or the strength of evidence grading, but they are reported here because they met our inclusion criteria.

When patients who had received infliximab but were taking no concomitant medications through the time of death were categorized as infliximab with no concomitant medications at infliximab initiation, they had the greatest mortality in both studies (11% and 32%) compared with infliximab with corticosteroids (9% and 3%) or compared with infliximab with an immunomodulator with or without corticosteroids (less than 5%). A previous report from one of the study centers reported on the infliximab outcomes among the first 100 patients which included one death from chronic pancreatitis 16 weeks after last infliximab infusion.[180] Based on the age at death, this patient is likely the same as the patient who died of organ failure 8 weeks after the last infusion as reported in the first 500 infliximab patients.[179]

One of these studies also reported mortality among 30 of the 157 patients who used adalimumab after infliximab.[186] No deaths were observed among the 30 adalimumab patients compared with seven deaths among 127 infliximab users who did not subsequently use adalimumab (6%). The Peto OR comparing adalimumab after infliximab with infliximab without subsequent adalimumab with risk of mortality was 0.3 (95% CI, 0 to 3.5).[186]

Immunomodulators

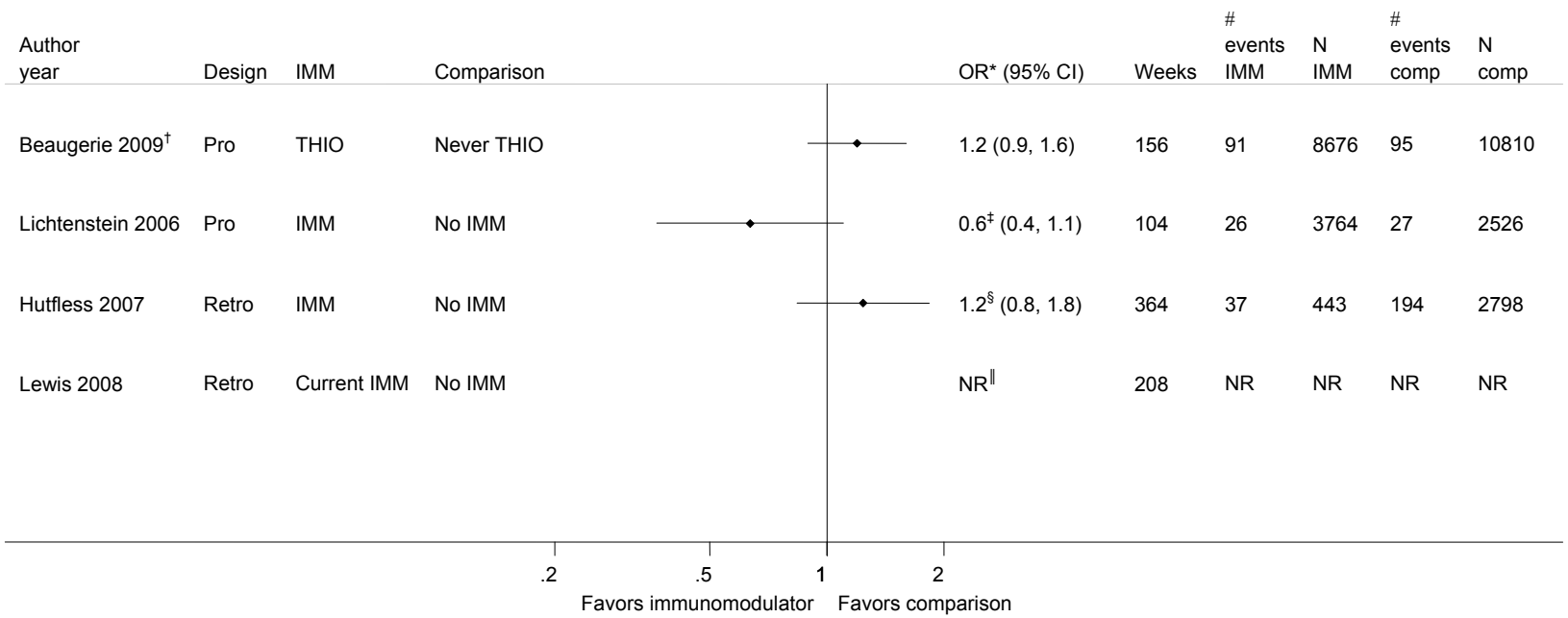
The effects of immunomodulators on mortality in patients with Crohn's disease are summarized in Table 27 (for RCTs) and Figure 13 (for observational studies). Additional details about the studies are given below.

Table 27. Summary of reported mortality results in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Immunomodulator	Comparison	# deaths in IMM group	# of patients in IMM group	# of deaths in comparison group	# of patients in comparison group
O'Donoghue, 1978[29]	52	Azathioprine	Placebo	1	24	0	27
Lemann, 2005[138]	48	Azathioprine	Placebo	1	40	0	43
Summers, 1979[93]	104	Azathioprine	Placebo	0	113	0	178
Mantzaris, 2009[141]	52	Azathioprine	Budesonide	0	112	0	83
Summers, 1979[93]	104	Azathioprine	Prednisolone	0	113	0	146
Summers, 1979[93]	104	Azathioprine	Sulfasalazine	0	113	0	132
Reinisch, 2008[89]	28	Azathioprine + prednisone	Prednisone	0	52	0	28

IMM = immunomodulator

Figure 13. Summary of Peto odds ratios of mortality among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease



CI = confidence interval; Comp = comparison; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; THIO = thiopurine

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Inflammatory bowel disease population

‡ Adjusted OR, 0.7 (95% CI, 0.4 to 1.3)

§ Adjusted OR, 1.3 (95% CI, 0.9 to 1.9)

‖ Adjusted hazards ratio, 0.8 (95% CI, 0.4 to 1.9); the total number of mortality events for all treatment groups combined is 264 out of 5537 patients. The number of events was not reported by treatment group.

Azathioprine versus placebo. Three RCTs compared azathioprine with placebo in 425 patients and reported on mortality. An RCT published in 1971 reported no deaths due to Crohn's disease in either group.[93] Two RCTs compared continuation of azathioprine with placebo among 134 prevalent users of azathioprine. In one RCT conducted at multiple centers and powered as a non-inferiority trial to assess recurrent Crohn's disease among those who had used azathioprine and been in remission for at least 42 months, one death was observed in the 40 azathioprine patients (3%) compared with zero deaths in the 43 placebo patients.[138] An RCT published in 1978 required at least 6 months of azathioprine-induced remission before randomizing patients to azathioprine or placebo.[29] One patient who had been randomized to continue azathioprine after 10 years of azathioprine use died during the study period. No deaths were observed in the placebo group.

Immunomodulators versus no immunomodulators. For this comparison, mortality was reported in one prospective study and two retrospective studies including a total of 11,829 Crohn's disease patients. One prospective and one retrospective study reported mortality with immunomodulators compared with no immunomodulators.[174 190] The prospective study reported 1% mortality among 3,764 persons ever treated with immunomodulators during the study period compared with 1% mortality among 2,526 never users of immunomodulators during the study period.[174] The OR was 0.7 (95% CI, 0.4 to 1.3) comparing immunomodulators with no immunomodulators, after adjusting for age, sex, race, disease location, duration of disease, severity and ever use of infliximab, prednisone, and narcotic analgesics.[174] A retrospective study compared current thiopurine with no use during the study period. Death occurred in 264 of the 5,539 Crohn's disease patients, but the percent of thiopurine users by mortality status was not provided by current (within 91 days) thiopurine use. The HR was 0.8 (95% CI, 0.4 to 1.9) comparing current thiopurine use versus no use (no recorded use or use more than 182 days prior to death), after adjusting for age, sex, comorbidity, and time from registration.[176] In contrast, another retrospective study reported an OR of 1.3 (95% CI, 0.9 to 1.0) comparing immunomodulators with no immunomodulators, after adjusting for age, sex, and smoking.[190] The retrospective studies did not adjust for use of other Crohn's disease medications or disease characteristics.

Azathioprine versus corticosteroids. Two RCTs reported on mortality when comparing azathioprine with prednisone in a total of 336 patients.[93 141] One RCT published in 1971 compared 113 azathioprine patients and 146 prednisone patients over 2 years. The RCTs reported no deaths due to Crohn's disease during the study period.[93] Another RCT compared 112 azathioprine with 83 budesonide patients, and reported no deaths during the study period.[141]

Azathioprine versus aminosalicylates. One 2-year RCT including 245 patients compared azathioprine with sulfasalazine. No deaths due to Crohn's disease were reported during the study period.[93]

Combination of azathioprine and prednisone versus prednisone. One RCT including 81 patients compared: (a) 2.5 mg/kg per day azathioprine with concomitant 1 mg/kg per day of prednisone or at least 40 mg per day of prednisone (n = 52); (b) the same dose of prednisone and a placebo (n = 29); and (c) a medication not of interest for this report, everolimus (n = 63).[89] The

study was stopped early due to lack of efficacy with everolimus, and no deaths were reported within 7 months of followup.

Corticosteroids

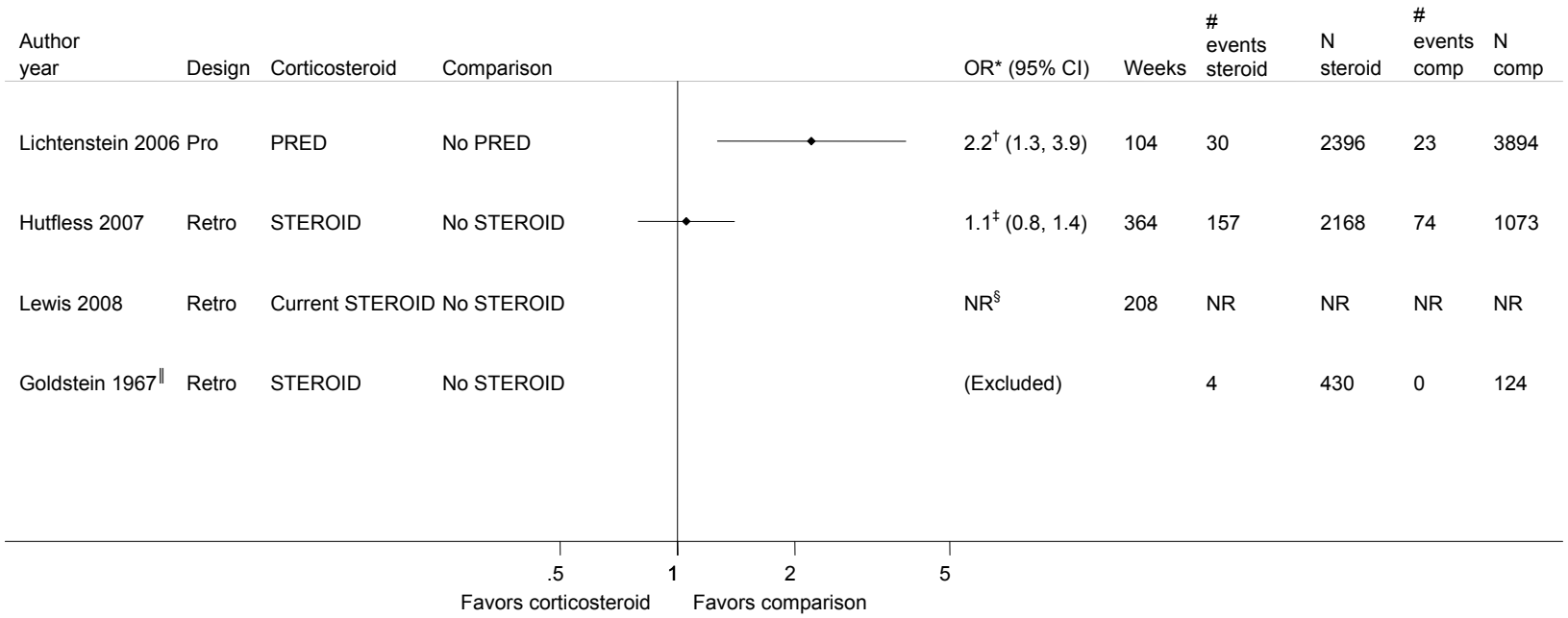
The effects of corticosteroids on mortality in patients with Crohn's disease are summarized in Table 28 (for RCTs) and Figure 14 (for observational studies).

Table 28. Summary of reported mortality results in randomized controlled trials comparing prednisone alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Corticosteroid	Comparison	# of deaths in steroid group	# of patients in steroid group	# of deaths in comparison group	# of patients in comparison group
Summers, 1979[93]	104	Prednisone	Placebo	0	146	0	178
Malchow, 1984[99]	104	Prednisone	Placebo	3	113	0	110
Summers, 1979[93]	104	Prednisone	Sulfasalazine	0	146	0	132
Malchow, 1984[99]	104	Prednisone	Sulfasalazine	3	113	0	117
Malchow, 1984[99]	104	Prednisone + sulfasalazine	Placebo	1	112	0	110
Malchow, 1984[99]	104	Prednisone + sulfasalazine	Sulfasalazine	1	112	0	117
Malchow, 1984[99]	104	Prednisone + sulfasalazine	Prednisone	1	112	3	113

Steroid = corticosteroid

Figure 14. Summary of Peto odds ratios of mortality among observational studies comparing a corticosteroid alone or in combination with another treatment in patients with Crohn's disease



CI = confidence interval; Comp = comparison; NR = not reported; OR = odds ratio; PRED = prednisone; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroid

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Adjusted OR, 2.1 (95% CI, 1.1 to 3.8)

‡ Adjusted OR, 1.0 (95% CI, 0.7 to 1.4)

§Adjusted hazards ratio, 2.5 (95% CI, 1.9 to 3.3); the total number of mortality events for all treatment groups combined is 264 out of 5537 patients. The number of events was not reported by treatment group.

‖Inflammatory bowel disease population

Corticosteroids versus placebo. Two RCTs including 547 patients compared corticosteroids with placebo and reported on mortality.[93 99] A 2-year RCT compared prednisone with placebo and reported no deaths due to Crohn's disease during the study period.[93] An RCT that included a 6-week corticosteroid taper for patients with active disease and a 2-year maintenance phase for inactive disease reported three deaths in the prednisolone group during the 2-year period.[99] An additional prednisolone patient died after the study period.

Corticosteroids versus no corticosteroids. Three observational studies including 15,070 Crohn's disease patients compared corticosteroids with no corticosteroids and reported mortality.[174 176 190] One prospective study of 6,290 Crohn's disease patients reported mortality by use of prednisone compared with no prednisone use during the study period.[174] Patients who used prednisone had a 2-fold increased odds of mortality compared with those who did not use prednisone during the study period (OR, 2.1; 95% CI, 1.1 to 3.8) after adjustment for demographics, disease characteristics, and use of other Crohn's disease medications and narcotic analgesics during the study period.

A retrospective study with a median of 7 years of observation among 3,241 Crohn's disease patients reported no difference in mortality comparing steroid users with non-users during the study period (age, sex, and smoking adjusted OR, 1.0; 95% CI, 0.7 to 1.4).[190] A retrospective study with a mean of 4 years of observation compared current and recent corticosteroids use versus no use during the study period. The HR was 2.5 (95% CI, 1.9 to 3.3) comparing current (within 91 days) corticosteroid use versus no use (no recorded use or use more than 182 days prior to death), after adjusting for age, sex, comorbidity, and time from registration.[176] The adjusted HR comparing recent use (92 to 182 days prior to death) with no use (no recorded use or use more than 182 days prior to death) was 1.2 (95% CI, 0.6 to 2.4).[176] The retrospective studies did not adjust for use of other Crohn's disease medications or disease characteristics.

Corticosteroids versus aminosalicylates. Two RCTs including 508 Crohn's disease patients compared corticosteroids with sulfasalazine and reported mortality.[93 99] One RCT compared prednisone with sulfasalazine and reported no deaths due to Crohn's disease during the study period.[93] The other RCT reported three deaths in the prednisolone group during the study period and an additional death after the study period in both the prednisolone and sulfasalazine groups.[99]

Combination of corticosteroids and aminosalicylates versus other treatment. One RCT including 452 Crohn's disease patients compared a combination of prednisolone and sulfasalazine with placebo, prednisolone, or sulfasalazine. During the study period, there was one death on prednisolone and sulfasalazine, three deaths on prednisolone, and no deaths on sulfasalazine or placebo. After the study period, an additional death was reported in each group except the placebo group.[99]

Aminosalicylates

The effects of aminosalicylates on mortality in patients with Crohn's disease are reported in Table 29.

Table 29. Summary of reported mortality results in randomized controlled trials and observational studies comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Study design	ASA	Comparison	# deaths in ASA group	# of patients in ASA group	# of deaths in comparison group	# of patients in comparison group	Unadjusted OR* (95% CI)
Lennard-Jones, 1977[196]	52	RCT	Sulfasalazine	Placebo	0	6	0	2	NA
Summers, 1979[93]	104	RCT	Sulfasalazine	Placebo	0	132	0	178	NA
Malchow, 1984[99]	104	RCT	Sulfasalazine	Placebo	0	117	0	110	NA
Modigliani, 1996[157]	48	RCT	Mesalamine	Placebo	0	65	1	64	NA
Hutfless, 2007[190]	364	Retrospective cohort	ASA	No ASA	175	2566	56	675	0.8 (0.6 to 1.1)**

ASA = aminosalicylates; CI = confidence interval; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.
**Adjusted OR, 0.7 (95% CI, 0.5 to 1.1)

Aminosalicylates versus placebo. Four RCTs including 674 patients compared aminosalicylates with placebo and reported mortality.[93 99 157 196] One RCT treated 150 patients with prednisolone for 3 to 7 weeks and randomized 129 who entered clinical remission to either mesalamine or placebo until the patient was weaned from prednisolone plus an additional year of followup.[157] One of 37 placebo patients died in the year after prednisolone discontinuation.

Three RCTs compared sulfasalazine with placebo. An RCT published in the 1970s compared sulfasalazine with placebo and included eight patients who had not undergone intestinal resection within the preceding 6 months.[196] No patients died. The other RCTs reported no deaths due to Crohn's disease during the study period[93] and no deaths during the study period.[99] After the study period, one sulfasalazine patient died.[99]

Aminosalicylates versus no aminosalicylates. One retrospective study including 3,241 Crohn's disease patients reported 1% fewer deaths in the aminosalicylates treated group compared with those who did not fill a prescription for aminosalicylates during the study period (age, sex, and smoking adjusted OR, 0.7; 95% CI, 0.5 to 1.1).[190]

Studies Evaluating Patients with Inflammatory Bowel Disease

Four studies reported on mortality in the treatment of inflammatory bowel disease without separating Crohn's disease from ulcerative colitis or indeterminate colitis. In general, the results were consistent between the studies. Details about those studies are given in Appendix F.

Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease

One study that used administrative data reported results for both Crohn's disease and inflammatory bowel disease.[190] There was not a meaningful difference in the relationship between medications and mortality when examining Crohn's disease separately from inflammatory bowel disease. The age, sex, and smoking adjusted mortality ORs were similar in Crohn's disease and inflammatory bowel disease for corticosteroid use during the study period versus no corticosteroid use (Crohn's disease OR, 1.0; inflammatory bowel disease OR, 0.9), and aminosalicylate use versus no aminosalicylate use (Crohn's disease OR, 0.7; inflammatory bowel disease OR, 0.8). Compared with non-users of immunomodulators, the OR for mortality was greater than 1 for immunomodulator use in Crohn's disease (OR, 1.3; 95% CI, 0.9 to 1.9) and below 1 for immunomodulator use in inflammatory bowel disease (OR, 0.9; 95% CI, 0.7 to 1.2) although neither finding was statistically significant. The ORs were not adjusted for use of the other medications compared.

Progressive Multifocal Leukoencephalopathy (PML)

We identified one case of PML associated with treatment of Crohn's disease.[197] A 60-year-old man with a 28-year history of Crohn's disease presented with confusion and disorientation in July 2003 during which PML was suspected. The patient expired three months later from PML. Subsequent immunohistochemical analysis of the brain tissue demonstrated positive staining for polyomavirus JC genotype 2, confirming the diagnosis of PML. The patient had received five doses of natalizumab over a 16-month interval. The last natalizumab dose was in May or June

2003, within two months of symptom presentation. The patient had also previously received infliximab starting in September 1998, prior to European approval of infliximab in August 1999. The last infliximab infusion was administered in September 2001, 20 months prior to PML diagnosis. The patient had also used azathioprine (discontinued eight months prior to suspected PML due to refractory anemia with low platelet counts and lymphopenia), corticosteroids, and antibiotics. The authors of the study linked the timing of PML to the use of natalizumab in this patient because JC virus appeared in serum samples (available from the inflammatory bowel disease center's serum bank from March 1999) only after administration of natalizumab. This case was also reported in the RCTs during which the patient first received natalizumab and an observational study examining the safety of infliximab at the study center.[76 192] A search of the Adverse Events Reporting System did not identify additional cases.

Lymphoma

Thirteen RCTs including 4,956 Crohn's disease patients reported on lymphoma risk by comparison group (Appendix D, Evidence Table 14). One prospective study (n = 19,486), ten retrospective studies (n = 31,641), and one case-control study (n = 15,471) reported lymphoma as an outcome. Lymphoproliferative disorder, including lymphoma, was a primary interest of outcome in one prospective study.[173] No trials of ustekinumab, immunomodulators, corticosteroids, or aminosalicylates reported on lymphoma risk. The total number of patients included was 71,554.

Biologics

The risk of lymphoma associated with use of biologics in Crohn's disease is summarized in Table 30 (for RCTs) and Figure 15 (for observational studies). Additional details are given below.

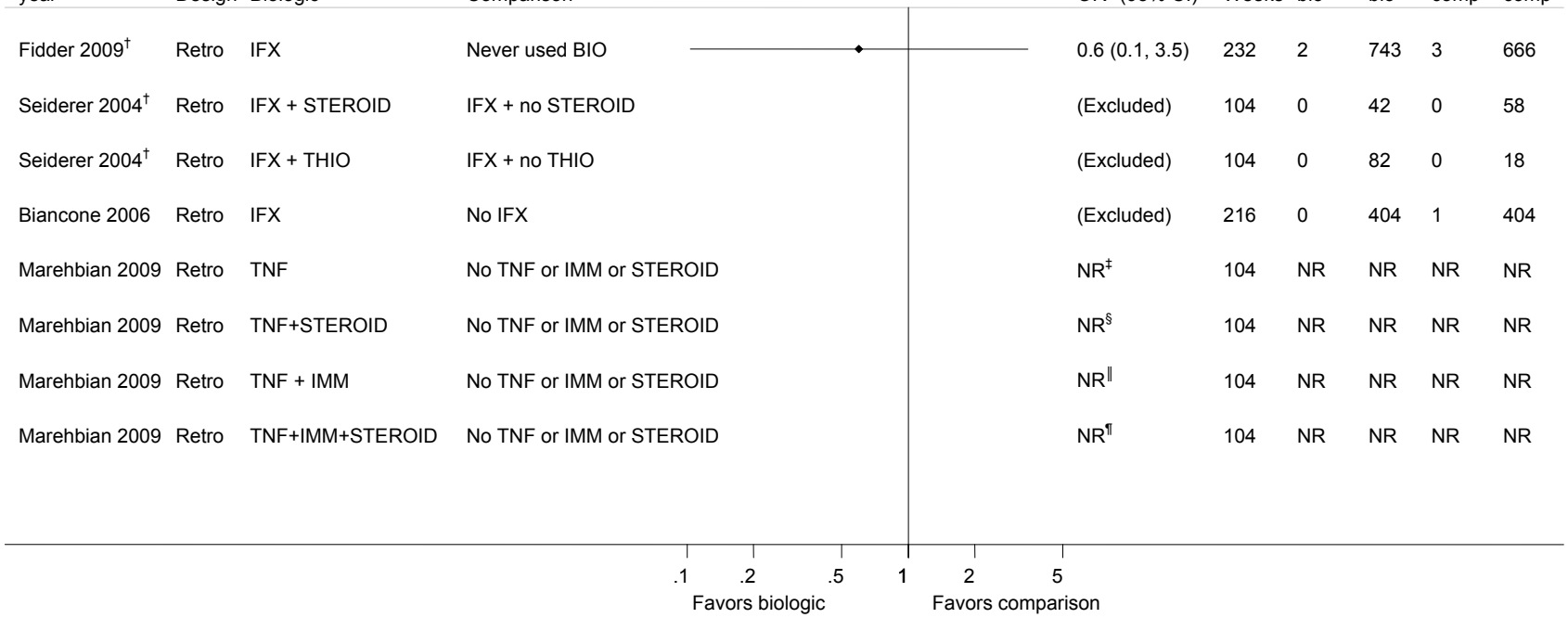
Table 30. Summary of lymphoma risk in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*

Author, year	Followup (weeks)	Biologic	Comparison	# of lymphoma cases in biologic group	# of patients in biologic group	# of lymphoma cases in comparison group	# of patients in comparison group
Rutgeerts, 1999[128]	36	Infliximab	Placebo	0	37	1	36
Hanauer, 2002[126]	52	Infliximab	Placebo	0	385	1	188
Schreiber, 2005[81]	20	Certolizumab pegol	Placebo	0	218	0	73
Schreiber, 2007[131]	18	Certolizumab pegol	Placebo	0	216	0	212
Sandborn, 2007[80]	26	Certolizumab pegol	Placebo	0	331	1	329
Sandborn, 2007[79]	4	Adalimumab	Placebo	0	159	0	166
Hanauer, 2006[78]	4	Adalimumab	Placebo	0	225	0	74
Sandborn, 2007[130]	52	Adalimumab	Placebo	0	37	0	18
Sandborn, 2005[76]	48	Natalizumab	Placebo	0	723	0	181
Targan, 2007[26]	8	Natalizumab	Placebo	0	260	0	250
Sands, 2007[27]	20	Natalizumab + infliximab	Infliximab	0	52	0	27

*Two RCTs compared a biologic to another medication and did not report on lymphomas.[83 133]

Figure 15. Summary of Peto odds ratios of lymphoma among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease

Author year	Design	Biologic	Comparison	OR* (95% CI)	Weeks	# events bio	N bio	# events comp	N comp
Fidder 2009†	Retro	IFX	Never used BIO	0.6 (0.1, 3.5)	232	2	743	3	666
Seiderer 2004†	Retro	IFX + STEROID	IFX + no STEROID	(Excluded)	104	0	42	0	58
Seiderer 2004†	Retro	IFX + THIO	IFX + no THIO	(Excluded)	104	0	82	0	18
Biancone 2006	Retro	IFX	No IFX	(Excluded)	216	0	404	1	404
Marehbian 2009	Retro	TNF	No TNF or IMM or STEROID	NR‡	104	NR	NR	NR	NR
Marehbian 2009	Retro	TNF+STEROID	No TNF or IMM or STEROID	NR§	104	NR	NR	NR	NR
Marehbian 2009	Retro	TNF + IMM	No TNF or IMM or STEROID	NR‖	104	NR	NR	NR	NR
Marehbian 2009	Retro	TNF+IMM+STEROID	No TNF or IMM or STEROID	NR¶	104	NR	NR	NR	NR



Peto Odds Ratio and 95% Confidence Intervals for Lymphoma

BIO = biologics; CI = confidence interval; Comp = comparison; IFX = infliximab; IMM = immunomodulator; Main = main intervention; NR = not reported; OR = odds ratio; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Inflammatory bowel disease population

‡ Incidence rate ratio, 1.7 events per person-year (95% CI, 0.2 to 6.3)

§ Incidence rate ratio, 0 events per person-year (95% CI, 0 to 6.5)

‖ Incidence rate ratio, 1.5 events per person-year (95% CI, 0.04 to 8.7)

¶ Incidence rate ratio, 0 events per person-year (95% CI, 0 to 30.0)

Natalizumab versus placebo. In three RCTs reported in two articles, including 1,414 patients, no case of lymphoma was reported in any natalizumab or control group during the study periods.[26 76] One lymphoma case was reported after the study in a patient who received natalizumab induction, placebo maintenance, and natalizumab during the open-label extension period.[26]

Combination of natalizumab and infliximab versus infliximab. One 20-week RCT including 79 infliximab non-responders randomized patients to additional treatments with natalizumab or placebo.[27] Patients were followed up to six months. No lymphoma cases were reported.

Infliximab versus placebo. Two RCTs including 646 patients compared infliximab with placebo and reported on lymphoma risk.[126 128] One study randomized infliximab responders and non-responders after a single infusion of infliximab or placebo.[126] The other study[128] compared retreatment with infliximab with placebo among responders to a single infusion from a previous RCT.[77] No lymphoma cases were reported in the infliximab groups (0% of 385 and 37 patients). In the placebo groups, one lymphoma was observed among 188 patients in one study (<1%),[126] and one lymphoma was seen in 36 patients in the other study (4%).[128] One lymphoma patient had received infliximab in the induction period and later died from sepsis, although neither the lymphoma nor death was reported in the induction study.[77]

Adalimumab versus placebo. Three RCTs including 679 patients compared adalimumab with placebo and reported no cases of lymphoma.[78 79 130]

Certolizumab pegol versus placebo. Three RCTs including 1,379 patients compared certolizumab pegol with placebo and reported on lymphoma risk.[80 81 131] One lymphoma case was reported in a placebo group (<1%).[80] The other two RCTs reported no cases of lymphoma.[81 131]

TNF-alpha inhibitor versus no TNF-alpha inhibitor. Two retrospective studies including 9,389 Crohn's disease patients compared a TNF-alpha inhibitor with no TNF-alpha inhibitor and reported on lymphoma risk.[189 192 198] One study reported no lymphoma cases among 404 Crohn's disease patients with a record of infliximab in their charts compared with one case of lymphoma among 404 Crohn's disease patients with no infliximab reported who had been matched to the infliximab users on age, sex, followup, immunomodulator use, Crohn's disease location and duration, and study center.[189] Because the non-Hodgkin's lymphoma patient did not use infliximab, the patient did not meet the inclusion criteria for another infliximab study at the center.[33] A claims-based study of health plan members with one or more encounters for Crohn's disease reported two lymphoma cases in TNF-alpha inhibitor users (1 per 100 person-years) and 64 lymphoma cases in patients who received no TNF-alpha inhibitor, immunomodulator, or corticosteroid (less than one per 100 person-years).[198] Although the authors did not report a rate ratio, the unadjusted rate ratio comparing TNF-alpha inhibitor use with no therapy based on the provided information is 1.7 (95% CI, 0.2 to 6.3).[198]

Combination of TNF-alpha inhibitors, immunomodulators, and corticosteroids versus no therapy. The same claims-based study that included 8,581 Crohn's disease patients, but did not report the number of patients in each medication category, reported no lymphoma cases among

31 person-years of exposure to combination therapy with TNF-alpha inhibitors, immunomodulators and corticosteroids compared with 64 cases among 15,673 person-years of no therapy.[198]

Combination of TNF-alpha inhibitors and immunomodulators versus no therapy. The claims-based study that included 8,581 Crohn's disease patients reported one lymphoma case among 162 person-years of exposure to combination therapy with TNF-alpha inhibitors and immunomodulators (with or without corticosteroids) compared with 64 cases among 15,673 person-years of no therapy (less than one per 100 person-years in both groups).[198] The corresponding unadjusted rate ratio was 1.5 (95% CI, 0 to 8.7).

Combination of TNF-alpha inhibitor and corticosteroids versus no therapy. The claims-based study that included 8,581 Crohn's disease patients reported no lymphoma cases among 142 person-years of exposure to combination therapy with TNF-alpha inhibitor and corticosteroids (with or without immunomodulators) compared with 64 cases among 15,673 person-years of no therapy.[198]

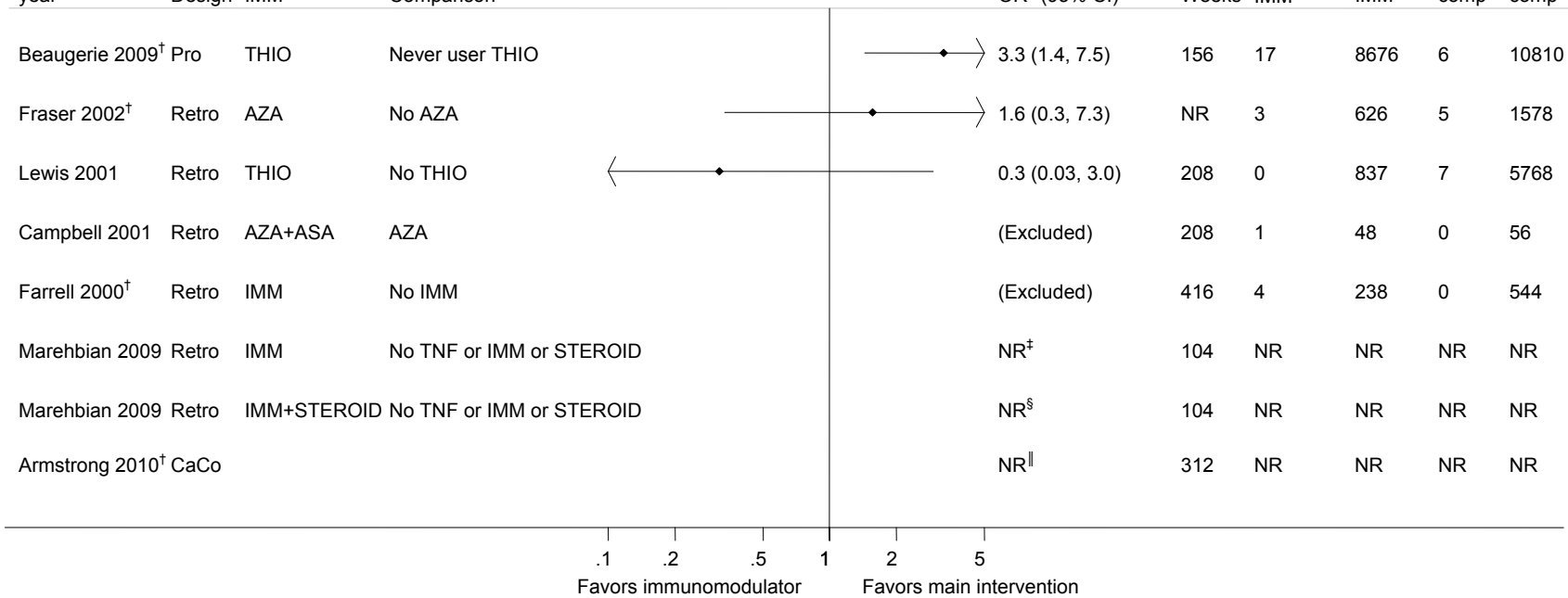
Other combinations with infliximab. Two retrospective cohorts including 657 patients aimed to describe the safety profile of infliximab use at their study centers.[179 186] As described in the mortality section, it is unclear if we have correctly classified patients by medication exposures accurately. When patients who had received infliximab and immunomodulators at the time of lymphoma diagnosis were categorized as infliximab with immunomodulators at infliximab initiation, there was one lymphoma among 51 combination infliximab and immunomodulator patients in one study[186] and two lymphomas among 307 combination infliximab and immunomodulator patients in the other study.[179] No lymphomas were reported in patients who received the other treatment combinations (combination of infliximab, immunomodulators, and corticosteroids, combination of infliximab and corticosteroids, or infliximab alone).

Immunomodulators

Figure 16 summarizes the risk of lymphoma in observational studies evaluating immunomodulators in patients with Crohn's disease. Additional details are given below.

Figure 16. Summary of Peto odds ratios of lymphoma among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease

Author year	Design	IMM	Comparison	OR* (95% CI)	Weeks	# events IMM	N IMM	# events comp	N comp
Beaugerie 2009†	Pro	THIO	Never user THIO	3.3 (1.4, 7.5)	156	17	8676	6	10810
Fraser 2002†	Retro	AZA	No AZA	1.6 (0.3, 7.3)	NR	3	626	5	1578
Lewis 2001	Retro	THIO	No THIO	0.3 (0.03, 3.0)	208	0	837	7	5768
Campbell 2001	Retro	AZA+ASA	AZA	(Excluded)	208	1	48	0	56
Farrell 2000†	Retro	IMM	No IMM	(Excluded)	416	4	238	0	544
Marehbian 2009	Retro	IMM	No TNF or IMM or STEROID	NR‡	104	NR	NR	NR	NR
Marehbian 2009	Retro	IMM+STEROID	No TNF or IMM or STEROID	NR§	104	NR	NR	NR	NR
Armstrong 2010†	CaCo			NR‖	312	NR	NR	NR	NR



Peto Odds Ratio and 95% Confidence Intervals for Lymphoma

ASA = aminosalicylates; AZA = azathioprine; CaCo = case-control study; CI = confidence interval; Comp = comparison; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitors

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Inflammatory bowel disease population

‡ Incidence rate ratio, 0.8 events per person-year (95% CI, 0.2 to 2.5)

§ Incidence rate ratio, 0 events per person-year (95% CI, 0 to 48.9)

‖ Adjusted OR, 3.2 (95% CI, 1.0 to 10.2)

Immunomodulators versus no immunomodulators. Two retrospective studies including 15,186 Crohn's disease patients reported lymphoma risk by immunomodulator use.[178 198] The claims-based study that included 8,581 Crohn's disease patients reported less than one lymphoma case per 100 person-years in the immunomodulator group (with or without corticosteroids or TNF-alpha inhibitors) and no therapy group (unadjusted relative rate, 0.8; 95% CI, 0.2 to 2.5).[198] In one study comparing at least one prescription for a thiopurine with no thiopurine prescription, none of the 837 thiopurine users developed lymphoma compared with seven of 5,768 (< 1%) non-users. The corresponding Peto OR was 0.3 (95% CI, 0 to 2.9).[178]

Combination of immunomodulators and corticosteroids versus no therapy. The claims-based study reported no lymphoma cases among patients receiving a combination of immunomodulators and corticosteroids (with or without TNF-alpha inhibitors) compared with less than one lymphoma per 100 person-years among patients receiving no therapy.[198]

Combination of azathioprine and aminosalicylates versus azathioprine. One retrospective study of 104 Crohn's disease patients reported a case of Waldenstrom's macroglobulinemia in the azathioprine and aminosalicylate group compared with no lymphoma in the azathioprine alone group.[35]

Corticosteroids

Table 31 summarizes the risk of lymphoma in observational studies evaluating corticosteroids in patients with Crohn's disease. See below for details about the studies.

Table 31. Summary of risk of lymphoma in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Study design	Corticosteroid	Comparison	# of lymphoma casesin steroid group	# of patients in steroid group	# of lymphoma cases in comparison group	# of patients in comparison group	Unadjusted relative measure (95% CI)	Adjusted relative measure (95% CI)
Lewis, 2001[178]*	208	Retrospective cohort	Steroid	No steroid	4	4064	11	11100	OR, 1.0 (0.3 to 3.1)	NR
Marehbian, 2009[198]	104	Retrospective cohort	Steroid	No TNF or IMM or Steroid	NR†	NR	NR‡	NR	IRR, 0 (0 to 2.5)	HR, 1.0 (0.4 to 2.4)

CI = confidence interval; HR = hazards ratio; IMM = immunomodulator; IRR = incidence rate ratio; NR = not reported; OR = odds ratio; Steroid = corticosteroid; TNF = tumor necrosis factor-alpha inhibitor

* Inflammatory bowel disease population

† There were 0 events during 379 person-years.

‡ There were 64 events during 15673 person-years.

Corticosteroids versus no therapy. The claims-based study reported no lymphoma cases among the corticosteroid users (with or without immunomodulators or TNF-alpha inhibitors) compared with the no therapy group.[198] The study reported a HR comparing use of corticosteroids alone with no therapy of 1.0 (95% CI, 0.4 to 2.4) after adjustment for age, gender, geographic region, health plan, and comorbidity.

Studies Evaluating Patients with Inflammatory Bowel Disease

Seven studies reported on lymphoma risk in inflammatory bowel disease patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. In general, the results were consistent between the studies. See Appendix F for more information about these studies.

Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease

One retrospective study reported similar results for inflammatory bowel disease patients as Crohn's disease patients (1 lymphoma (<1%) among 1,465 thiopurine users compared with 14 lymphomas (<1%) among 15,531 non-users).[178] The incidence density ratio comparing thiopurine to no thiopurine use was 0.8 for inflammatory bowel disease compared with the Peto OR of 0.3 for Crohn's disease. Neither was statistically significant. A lymphoma case with diagnosis codes for both Crohn's disease and ulcerative colitis was excluded from the study according to the exclusion criteria. The patient had also received a liver transplant four months before the lymphoma diagnosis.

Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) was first identified as a diagnosis distinct from other T-cell lymphomas in 1996.[199] HSTCL is a very rare type of lymphoma that is generally fatal.[199] To assess the risk of HSTCL associated with treatment for Crohn's disease, the primary search strategy was supplemented by searching for case reports or case series published in the literature or cases reported to the Food and Drug Administration's (FDA) Adverse Event Reporting System. A search of the publicly available Adverse Event Reporting System data files through March 2011 yielded 132 patient identification numbers representing 48 unique FDA-ascribed case numbers. From the literature and Adverse Event Reporting System search results, 37 HSTCL cases were considered unique based on age, sex, medications, country of origin, and length of survival. Two cases were considered duplicative. The remaining nine cases were considered possibly unique. Two of the 37 unique cases and none of the nine possibly unique cases were reported to survive (4% of 46 cases).

Tables 32 and 33 summarize the demographic and medication characteristics of the unique and possibly unique cases of HSTCL in patients with Crohn's disease. Of the 37 unique cases with Crohn's disease-associated HSTCL, most were young (86% younger than 40 years of age) and male (86%). Most cases (70%) had reported exposure to both a TNF-alpha inhibitor and thiopurines. Almost all cases (95%) had reported exposure to thiopurines compared with 75% who had exposure to at least one TNF-alpha inhibitor. Two cases (4%) were reported to have taken a TNF-alpha inhibitor without thiopurines.

Table 32. Demographic and survival characteristics of patients with Crohn's disease who developed hepatosplenic T-cell lymphoma

Patient Characteristic	Unique cases (n = 37)	Possibly unique additional cases (n = 9)
Age at HSTCL diagnosis (in years)	N = 36*	N = 0
Mean	30	--
Median	26	--
Range	12 to 79	--
Crohn's disease duration (in years)	N = 16	N = 0
Mean	10	--
Median	6	--
Range	4 to 35	--
Sex, number of cases (%)	N = 36	N = 6
Female	5 (14%)	1 (17%)
Survival, number of cases (%)	N = 37	N = 9
Died	24 (65%)	4 (44%)
Survived	2 (5%)	0 (0%)
Outcome unclear or not reported	11 (30%)	5 (56%)

HSTCL = hepatosplenic T-cell lymphoma
*Number with report of characteristic. Mean and percentages based on this denominator.

Table 33. Medications used prior to diagnosis of hepatosplenic T-cell lymphoma in 37 unique patients with Crohn's disease

Medication	Number of cases with exposure (%)	Mean cumulative dose in mg* (range)	Mean duration of drug use in years (range)	Mean number of infusions (range)
Biologics	28 (76%)	--	--	--
Adalimumab	8 (22%)	920 (800-1040)	1.5 (120 days-2.6 years)	11.5 (10-13)
Infliximab	27 (73%)	41 (10-120) mg/kg	1.8 (1 day-6 years)	9 (1-24)
Natalizumab	1 (3%)	NR	NR	3 (n=1)
Ustekinumab	1 (3%)	NR	NR	NR
Certolizumab pegol	0	NR	NR	NR
Thiopurines	35 (95%)	--	--	--
6-mercaptopurine	19 (51%)	55,290 (3900-93530)	4.5 (39 days-8 years)	NA
Azathioprine	23 (62%)	151,288 (1450-301,125)	5.8 (39 days-13.5 years)	NA
Aminosalicylates	15 (41%)	--	--	--
Balsalazide	1 (3%)	NR	NR	NA
Mesalamine	13 (35%)	NR	5 (n=1)	NA
Salazopyrine	2 (5%)	NR	10 (n=1)	NA
Corticosteroids	21 (57%)	--	--	--
Budesonide	2 (5%)	NR	NR	NA
Hydrocortisone	1 (3%)	NR	NR	NA
Prednisone	14 (38%)	NR	NR	NA
Prednisolone	4 (11%)	NR	13 (n=1)	NA
Corticosteroid, unspecified	6 (16%)	NR	10 (n=1)	NA
Antibiotics†	7 (19%)	NR	NR	NA
Cyclosporine	1 (3%)	NR	NR	NA

kg = kilograms; mg = milligrams; NA = not applicable; NR = not reported
* Reported as mg/kg for infliximab only
† The antibiotics used include ciprofloxacin, doxycycline, metronidazole, nitrofurantoin, and piperacillin/tazobactam.

Cervical Cancer

One trial (n = 660) reported on cervical cancer risk associated with medications for treatment of Crohn's disease. No trials of infliximab, adalimumab, natalizumab, ustekinumab, immunomodulators, corticosteroids, or aminosalicylates reported on cervical cancer.

Certolizumab pegol versus placebo. One RCT reported one carcinoma in situ of the cervix (grade 0) in a placebo patient (<1% of 197 females) and no cervical cancer in the 174 female certolizumab pegol patients during followup.[80]

Studies Evaluating Patients with Inflammatory Bowel Disease

Four observational studies reported on cervical cancer risk in inflammatory bowel disease patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. A summary of these studies is given in Appendix F.

Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease

We did not indentify any studies that reported on the comparative safety in terms of cervical cancer for patients with Crohn's disease and inflammatory bowel disease.

Other Cancers

Twenty RCTs including 6,711 Crohn's disease patients reported on other cancers by comparison group (Appendix D, Evidence Table 14). No methotrexate trial reported on cancer. One prospective (n = 19,486), 12 retrospective (n = 15,015), and one observational study of unclear study design (n = 573)[33] reported cancer as an outcome by comparison group.

Biologics

The risk of other cancers associated with treatment of Crohn's disease is summarized in Table 34 (for RCTs) and Figure 17 (for observational studies). Additional details are given below.

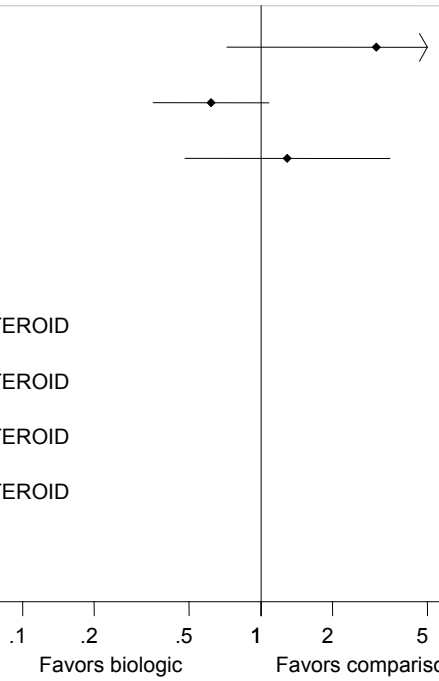
Table 34. Summary of the risk of other cancers in randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease*

Author, year	Followup (weeks)	Biologic	Comparison	# of cancer cases in biologic group	# of patients in biologic group	# of cancer events in comparison group	# of patients in comparison group
Sands, 2004[137]	40	Infliximab	Placebo	0	139	0	143
Hanauer, 2002[126]	52	Infliximab	Placebo	4	385	2	188
Schreiber, 2007[131]	18	Certolizumab pegol	Placebo	0	216	0	212
Sandborn, 2007[80]	26	Certolizumab pegol	Placebo	2	331	2	329
Schreiber, 2005[81]	12	Certolizumab pegol	Placebo	0	219	0	73
Sandborn, 2007[79]	4	Adalimumab	Placebo	0	159	0	166
Sandborn, 2007[130]	52	Adalimumab	Placebo	0	37	1	18
Colombel, 2007[129]	52	Adalimumab	Placebo	0	517	1	261
Targan, 2007[26]	12	Natalizumab	Placebo	1	260	0	250
Sandborn, 2005[76]	48	Natalizumab	Placebo	1	723	7	181
Sandborn, 2008[75]	28	Ustekinumab	Placebo	0	52	1	52
Colombel, 2010[83]	54	Infliximab	Azathioprine	0	163	2	161
Lemann, 2006[84]	24	Infliximab + thiopurine	Thiopurine	0	57	0	56
Colombel, 2010[83]	54	Infliximab + azathioprine	Infliximab	0	179	0	163
Colombel, 2010[83]	54	Infliximab + azathioprine	Azathioprine	0	179	2	161
Van Assche, 2008[133]	104	Infliximab + immunomodulator	Infliximab	0	40	2	40
Schroder, 2006[85]	48	Infliximab + methotrexate	Infliximab	0	11	0	8
Sands, 2007[27]	20	Natalizumab + infliximab	Infliximab	0	52	0	27

* Seven randomized controlled trials evaluating biologics did not report on any cancer outcomes.[24 25 77 82 86 132 170]

Figure 17. Summary of Peto odds ratios of cancer risk among observational studies comparing a biologic alone or in combination with another treatment in patients with Crohn's disease

Author year	Design	Biologic	Comparison	OR* (95% CI)	Weeks	# events biologic	N biologic	# events comp	N comp
Orlando 2005	Pro	IFX+IMM	IFX	3.06 (0.72, 12.97)	NR	5	211	3	362
Fidder 2009	Retro	IFX	Never user BIO	0.62 (0.35, 1.08)	232	21	743	30	666
Biancone 2006	Retro	IFX	No IFX	1.29 (0.48, 3.47)	216	9	404	7	404
Seiderer 2004	Retro	IFX+STEROID	IFX+no STEROID	(Excluded)	104	0	42	0	58
Seiderer 2004	Retro	IFX+THIO	IFX+no THIO	(Excluded)	104	0	82	0	18
Marehbian 2009	Retro	TNF	No TNF or IMM or STEROID	NR†	NR	NR	NR	NR	NR
Marehbian 2009	Retro	TNF+IMM	No TNF or IMM or STEROID	NR‡	NR	NR	NR	NR	NR
Marehbian 2009	Retro	TNF+IMM+STEROID	No TNF or IMM or STEROID	NR§	NR	NR	NR	NR	NR
Marehbian 2009	Retro	TNF+STEROID	No TNF or IMM or STEROID	NR‖	NR	NR	NR	NR	NR



Peto Odds Ratio and 95% Confidence Intervals for Cancer

BIO = biologics; CI = confidence interval; Comp = comparison; IFX = infliximab; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Incidence rate ratio, 0.1 events per person-year (95% CI, 0.01 to 0.2)

‡Incidence rate ratio, 0.9 events per person-year (95% CI, 0.6 to 1.4)

§Incidence rate ratio, 0.7 events per person-year (95% CI, 0.1 to 2.1)

‖Incidence rate ratio, 0.6 events per person-year (95% CI, 0.3 to 1.0)

Ustekinumab versus placebo. One crossover trial including 104 patients reported on cancer risk comparing ustekinumab with placebo.[75] One cancer was reported in the placebo group during the 8-week initial study period. Two additional cancers were reported through week 28 after crossover when all patients had been exposed to both ustekinumab and placebo.[75]

Natalizumab versus placebo. Three RCTs reported in two publications including 1,414 Crohn's disease patients compared natalizumab with placebo and reported on cancer risk.[26 76] A 12-week induction trial reported one basal cell carcinoma in the natalizumab group (1 out of 260) and no cancers in the 250 placebo patients.[26] In a 12-week induction trial followed by randomization of the responders to a 48-week maintenance trial, no cancers were reported during the induction trial.[76] In the maintenance trial, cancer occurred in a natalizumab (1 out of 214) and a placebo patient (1 out of 214).[76]

Combination of natalizumab with infliximab versus infliximab. One RCT including 79 Crohn's disease patients compared natalizumab with infliximab with infliximab alone and reported on cancer. The 20-week trial reported that no cancers occurred.[27]

Infliximab versus placebo. Two trials including 855 Crohn's disease patients reported on cancer risk.[126 137] A maintenance trial reported one case of cancer in the 10 mg/kg intravenous every eight weeks infliximab group, three in the 5 mg/kg intravenous every eight weeks infliximab group, and two in the placebo group over 52 weeks of followup.[126] A maintenance trial of fistulizing Crohn's disease reported no cancers during the 40-week trial period.[137] Two cancers occurred after the trial ended. Both patients had received infliximab.

Infliximab versus no infliximab. One retrospective study including 808 Crohn's disease patients reported on cancer by infliximab use versus no use.[189] Nine cancers were reported among 404 infliximab users followed for 48 months compared with seven cancers among 404 matched no infliximab users over 60 months of followup (2% in both groups).[189] The OR was 1.3 (95% CI, 0.5 to 3.8) comparing infliximab users with infliximab non-users accounting for the matching factors age, sex, followup, immunomodulator use, Crohn's disease site, Crohn's disease duration, and study center.[189] Another study reporting results from the same infliximab patients,[33] but comparing a combination of infliximab and immunomodulators with infliximab alone, reported one additional case of cancer among infliximab users. This study is reported below.

Adalimumab versus placebo. Three RCTs including 1,158 Crohn's disease patients compared adalimumab with placebo and reported on cancer.[78 79 129] A 4-week induction trial including 325 patients randomized to adalimumab or placebo among patients who had lost response or were intolerant to infliximab reported no cancers during the study period.[79] A 52-week maintenance trial reported one cancer case in 261 placebo patients (<1%) and no cancer cases in 517 adalimumab patients.[129] A 52-week maintenance trial of 276 responders to induction in a previous trial[78] reported one cancer in 18 placebo patients compared with no cancers in the 37 adalimumab patients who remained on randomized treatment during the entire study period.[130]

Certolizumab pegol versus placebo. Three RCTs including 1,380 Crohn's disease patients compared certolizumab pegol with placebo and reported on cancer.[80 81 131] A 12-week induction

trial (followed an additional 8 weeks for safety) reported no cancers in the 292 included patients.[81] A 26-week induction trial reported two cancers in placebo (1% of 329) and two cancers in certolizumab pegol (1% of 331) patients during the study period.[80] An 18-week maintenance trial reported no cancers during the study period.[131] One benign, malignant, or unspecified neoplasm (including cyst or polyp) was reported during the 8-week induction phase which included 668 patients, but specifics of the event were not provided.[131]

TNF-alpha inhibitors versus no therapy. A claims-based study that included 8,581 Crohn's disease patients reported two solid tumor cancer cases among 92 person-years of exposure to TNF-alpha inhibitors (with or without immunomodulators or steroids) compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR for TNF-alpha inhibitors (with or without immunomodulators or steroids) compared with no therapy of 1.0 (95% CI, 0.7 to 1.3) and HR 1.0 (95% CI, 0.8 to 1.3) when TNF-alpha inhibitors alone were compared with no therapy. The HRs were adjusted for age, gender, geographic region, health plan, and comorbidity. An unadjusted rate ratio comparing TNF-alpha inhibitors (with or without immunomodulators or steroids) with no therapy using the cancer cases and person-time provided favored TNF-alpha inhibitors over no therapy (unadjusted rate ratio, 0.2; 95% CI, 0 to 0.6).

Combination of TNF-alpha inhibitors, immunomodulators, and corticosteroids versus no therapy. The claims-based study reported three cancer cases among 31 person-years of exposure to TNF-alpha inhibitors with immunomodulators and corticosteroids compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR of 0.9 (95% CI, 0.3 to 2.4) comparing the 10 cancers per 100 person-years in the combination TNF-alpha inhibitor, immunomodulators, and corticosteroids exposed group with 13 cancers per 100 person-years in the no therapy group. These estimates are consistent with an unadjusted rate ratio of 0.7 (95% CI, 0.1 to 2.1).

Combination of TNF-alpha inhibitors and immunomodulators versus no therapy. The claims-based study reported 20 cancer cases among 162 person-years of exposure to TNF-alpha inhibitor with immunomodulators (with or without corticosteroids) compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR of 1.1 (95% CI, 0.7 to 1.8). The corresponding unadjusted rate ratio was 0.9 (95% CI, 0.6 to 1.4).

Combination of TNF-alpha inhibitors and corticosteroids versus no therapy. The claims-based study reported 11 cancer cases among 142 person-years of exposure to TNF-alpha inhibitors with corticosteroids (with or without immunomodulators) compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR of 0.3 (95% CI, 0 to 2.3). The corresponding unadjusted rate ratio was 0.6 (95% CI, 0.3 to 1.0).

Infliximab versus immunomodulators. One induction trial of 324 Crohn's disease patients naïve to TNF-alpha inhibitors and immunomodulators compared infliximab with azathioprine and reported mortality.[83] No cancers were reported in the 163 infliximab patients. Two cancers were reported in the 161 azathioprine patients during the 50-week study period.

Combination of infliximab and immunomodulators versus infliximab. Three RCTs[83 85 133] and one retrospective study[33] including 1,014 Crohn's disease patients compared a combination of infliximab and immunomodulators versus infliximab alone and reported on cancer risk. The

RCTs included 441 patients. One induction trial of 342 patients naïve to TNF-alpha inhibitors and immunomodulators reported no cancers during the 50-week study period in the combination infliximab and azathioprine and infliximab alone groups.[83] An open-label trial of 19 azathioprine intolerant or resistant patients compared a combination of infliximab and methotrexate with infliximab alone and reported no malignancies during the 48-week study period.[85] An 104-week open-label RCT of 80 non-fistulizing Crohn's disease patients retreated with infliximab while continuing or discontinuing immunomodulators reported two cancers in the infliximab group and no cancers in the combination infliximab and immunomodulators group.[133]

One retrospective study of 573 Crohn's disease patients followed for 12 weeks or 6 months reported five cancers among 211 combination infliximab and immunomodulator patients and three cancers in 362 patients using infliximab without immunomodulators.[33] The corresponding Peto OR was 2.9 (95% CI, 0.6 to 18.9).

Combination of infliximab and immunomodulators versus immunomodulators. Two RCTs including 453 Crohn's disease patients compared a combination of infliximab and immunomodulators with immunomodulators alone and reported on cancer.[83 84] One induction trial of Crohn's disease patients naïve to TNF-alpha inhibitors and immunomodulators reported no cancers in the 179 patients taking infliximab and azathioprine and two cancers in the 161 patients taking azathioprine during the 50-week study period.[83] A 52-week induction trial of 113 steroid-dependent Crohn's disease patients with luminal disease reported no cancers during the study period comparing combination infliximab and thiopurines with thiopurines.[84]

Other combinations with infliximab. Three retrospective studies including 772 Crohn's disease patients met the inclusion criteria but the cancer cases' concomitant medications may be misclassified as described in the mortality section. The three retrospective studies aimed to evaluate the safety profile of infliximab use at their centers.[179 186 187] Cancers were not observed in patients receiving a triple combination of infliximab, immunomodulators, and corticosteroids or a combination of infliximab and corticosteroids. In one study, cancers were reported in three of 51 (6%) patients taking infliximab and an immunomodulator and one of 19 (5%) patients taking infliximab.[186] One cancer was reported among 30 patients who used adalimumab after infliximab compared with four cancers among 127 who did not subsequently use adalimumab.[186] In another study, cancers were reported in six of 307 (2%) patients taking infliximab and an immunomodulator and three of 37 (8%) infliximab patients.[179] In another study, cancer was reported in one of 62 (2%) patients taking infliximab and a thiopurine and zero of 53 patients taking infliximab without a thiopurine.[187]

Immunomodulators

The risk of other cancers associated with use of immunomodulators for Crohn's disease is summarized in Table 35 (for RCTs) and Figure 18 (for observational studies). Additional details are given below.

Table 35. Summary of the risk of other cancers in randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease*

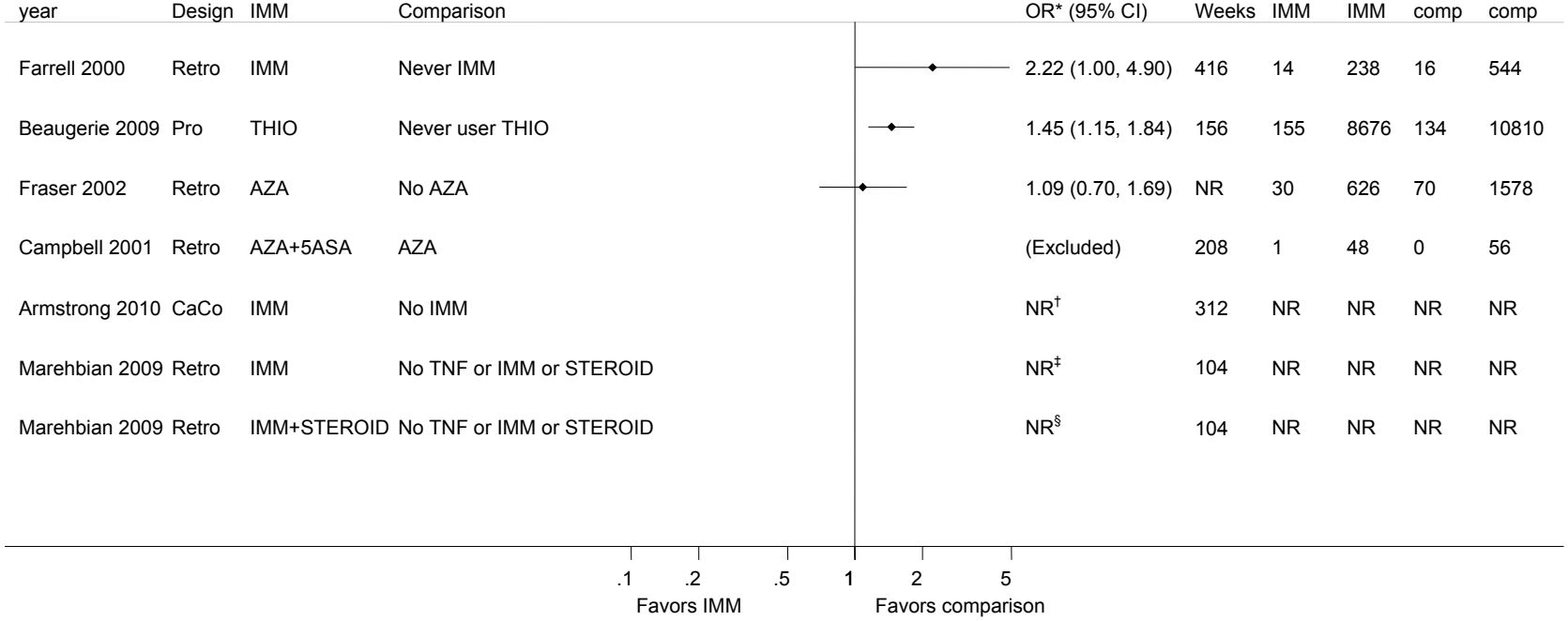
Author, year	Followup (weeks)	Immunomodulator	Comparison	# of cancer cases in IMM group	# of patients in IMM group	# of cancer cases in comparison group	# of patients in comparison group
Summers, 1979[93]	104	Azathioprine	Placebo	0	113	0	178
Summers, 1979[93]	104	Azathioprine	Prednisone	0	113	1	146
Summers, 1979[93]	104	Azathioprine	Sulfasalazine	0	113	0	132

IMM = immunomodulator

* We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 18. Summary of Peto odds ratios of cancer among observational studies comparing an immunomodulator alone or in combination with another treatment in patients with Crohn's disease

Author year	Design	IMM	Comparison	OR* (95% CI)	Weeks	# events IMM	N IMM	# events comp	N comp
Farrell 2000	Retro	IMM	Never IMM	2.22 (1.00, 4.90)	416	14	238	16	544
Beaugerie 2009	Pro	THIO	Never user THIO	1.45 (1.15, 1.84)	156	155	8676	134	10810
Fraser 2002	Retro	AZA	No AZA	1.09 (0.70, 1.69)	NR	30	626	70	1578
Campbell 2001	Retro	AZA+5ASA	AZA	(Excluded)	208	1	48	0	56
Armstrong 2010	CaCo	IMM	No IMM	NR†	312	NR	NR	NR	NR
Marehbian 2009	Retro	IMM	No TNF or IMM or STEROID	NR‡	104	NR	NR	NR	NR
Marehbian 2009	Retro	IMM+STEROID	No TNF or IMM or STEROID	NR§	104	NR	NR	NR	NR



Peto Odds Ratio and 95% Confidence Intervals for Cancer

5ASA = aminosalicylates; AZA = azathioprine; CaCo = case-control study; CI = confidence interval; Comp = comparison; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitors

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Adjusted OR, 2.1 (95% CI, 1.3 to 3.3)

‡ Incidence rate ratio, 0.02 events per person-year (95% CI, 0.005 to 0.07)

§ Incidence rate ratio, 0 events per person-year (95% CI, 0 to 1.4)

Azathioprine versus placebo. One RCT including 291 Crohn's disease patients compared azathioprine with placebo and reported on cancer risk.[93] No cancers were reported during the 2-year period.

Immunomodulators versus no therapy. The claims-based study reported three cancer cases among 911 person-years of exposure to immunomodulators (with or without corticosteroids or TNF-alpha inhibitors) compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR of 1.2 (95% CI, 1.0 to 1.4). The corresponding unadjusted rate ratio is 0 (95% CI, 0 to 0.1). The study also reported a HR comparing immunomodulators (with no corticosteroids and no TNF-alpha inhibitor) with no therapy (adjusted HR 1.2; 95% CI, 1.0 to 1.4).[198]

Combination of immunomodulators and corticosteroids versus no therapy. The claims-based study reported no cancer cases among 19 person-years of exposure to immunomodulators with corticosteroids (with or without TNF-alpha inhibitors) compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR of 1.0 (95% CI, 0.7 to 1.4).The corresponding unadjusted rate ratio is not estimable because of the absence of events in the group receiving a combination of immunomodulators and corticosteroids.

Azathioprine versus prednisone. One 2-year RCT including 259 Crohn's disease patients reported no cancers in 113 azathioprine and one cancer in 146 prednisone patients.[93]

Azathioprine versus sulfasalazine. The same 2-year RCT included 245 patients in the azathioprine versus sulfasalazine comparison. No cancers were reported in either group.[93]

Combination azathioprine and aminosalicylates versus azathioprine. A retrospective chart review in 104 Crohn's disease patients compared a combination of azathioprine and aminosalicylates with azathioprine and reported on cancer risk.[35] All patients were required to have at least six months of azathioprine use, no side effects to azathioprine, and be in remission to be eligible. One Waldenstrom's macroglobulinemia was reported among 48 patients on a combination of azathioprine and aminosalicylates compared with zero cancers among 56 patients receiving azathioprine without aminosalicylates. This cancer is also reported in the lymphoma section of the report.

Corticosteroids

Table 36 summarizes the risk of other cancers in RCTs and observational studies evaluating corticosteroids in patients with Crohn's disease.

Table 36. Summary of the risk of other cancers in randomized controlled trials and observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Study design	Corticosteroid	Comparison	# of cancer cases in steroid group	# of patients in steroid group	# of cancer cases in comparison group	# of patients in comparison group	Unadjusted relative measure* (95% CI)	Adjusted relative measure (95% CI)
Summers, 1979[93]	104	RCT	Prednisone	Placebo	1	146	0	178	(Excluded)	NR
Summers, 1979[93]	104	RCT	Prednisone	Sulfasalazine	1	146	0	132	(Excluded)	NR
Marehbian, 2009[198]	104	Retrospective cohort	Steroid	No TNF or IMM or Steroid	NR[†]	NR	NR[‡]	NR	IRR, 0 (0 to 0.7)	HR, 1.1 (0.9 to 1.3)

CI = confidence interval; HR = hazards ratio; IMM = immunomodulator; IRR = incidence rate ratio; NR = not reported; RCT = randomized controlled trial; Steroid = corticosteroid; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate relative measures when there were fewer than five events total in the main intervention and comparison arms.

[†] There were 0 events during 379 person-years.

[‡] There were 2115 events during 15673 person-years.

Prednisone versus placebo. One 2-year RCT including 324 Crohn's disease patients reported one cancer in 146 patients on prednisone and no cancers in 178 patients taking placebo.[93]

Prednisone versus sulfasalazine. The same 2-year RCT including 278 Crohn's disease patients reported one cancer in 146 patients on prednisone and no cancers in 132 patients taking sulfasalazine.[93]

Corticosteroids versus no therapy. The claims-based study reported no cancer cases among 379 person-years of exposure to corticosteroids (with or without immunomodulators or TNF-alpha inhibitors) compared with 2,115 cases among 15,673 person-years of no therapy.[198] The study reported an adjusted HR of 1.1 (95% CI, 0.9 to 1.3).The corresponding unadjusted rate ratio is not estimable because of no events in the corticosteroids group. The study also reported a HR comparing corticosteroids (with no immunomodulators and no TNF-alpha inhibitors) to no therapy (adjusted HR, 1.0; 95% CI, 0.8 to 1.3).[198]

Aminosalicylates

Table 37 summarizes the risk of other cancers in the one RCT reporting on cancer risk associated with use of aminosalicylates in patients with Crohn's disease.

Table 37. Summary of the risk of other cancers in a randomized controlled trial comparing an aminosalicylate with placebo in patients with Crohn's disease

Author, year	Followup (weeks)	Aminosalicylate	Comparison	# of cancer cases in ASA group	# of patients in ASA group	# of cancer cases in comparison group	# of patients in comparison group
Summers, 1979[93]	104	Sulfasalazine	Placebo	0	132	0	178

ASA = aminosalicylates

Sulfasalazine versus placebo. A 2-year RCT including 310 Crohn's disease patients reported no cancers in the sulfasalazine and placebo groups.[93]

Studies Evaluating Patients with Inflammatory Bowel Disease

Seven studies reported other cancers in inflammatory bowel disease patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. Information about these studies is given in Appendix F.

Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease

The retrospective chart review that reported a Waldenstrom's macroglobulinemia in a Crohn's disease patient reported no additional cancers among the 82 ulcerative colitis patients who received azathioprine with or without aminosalicylates.[35]

Case-Control Studies Designed to Examine Specific Cancers

Four case-control studies including 3,554 patients were designed to examine specific cancers. Two studies included only Crohn's disease patients.[184 200] Two studies used claims database to perform nested-case control studies.[200 201] A study of small bowel cancer risk included only patients with small bowel Crohn's disease.[184] A study of colon cancer risk included only patients with colonic inflammatory bowel disease.[202]

Comparisons including TNF-alpha inhibitor. A claims database study including 1,935 Crohn's disease patients followed a median of 484 days reported the relationship between recency (pharmacy claim within 90 days of diagnosis) and persistence (recency plus a pharmacy claim > 365 days prior to diagnosis) of medications with risk of non-melanoma skin cancer.[200] TNF-alpha inhibitors included infliximab and adalimumab. Immunomodulators included thiopurines, methotrexate, calcineurin inhibitor, and mycophenolate mofetil. Sixty-five percent of non-melanoma skin cancer cases and 86% of controls did not have a TNF-alpha inhibitor or immunomodulator claim within 90 days of the index date. Six percent of 387 cases and 1% of 1,548 controls were recent users of both TNF-alpha inhibitors and immunomodulators (Medicaid insurance adjusted OR compared with no use of TNF-alpha inhibitors or immunomodulators, 5.9; 95% CI, 3.2 to 10.8). Five percent of 228 cases and 1% of 913 controls had persistent use of a TNF-alpha inhibitor and immunomodulator (Medicaid insurance adjusted OR, 6.8; 95% CI, 2.7 to 16.7). Comparing TNF-alpha inhibitor use with no TNF-alpha inhibitor and no immunomodulator use, 4% of 387 cases and 2% of 1,548 controls were recent users of a TNF-alpha inhibitor (Medicaid insurance adjusted OR, 2.5; 95% CI, 1.3 to 4.7) and 3% of 228 cases and 1% of 913 controls were persistent users of a TNF-alpha inhibitor (Medicaid insurance adjusted OR, 3.2; 95% CI, 1.2 to 8.5). Comparing TNF-alpha inhibitor use versus no use, cases were more likely to be recent (immunomodulators and Medicaid insurance adjusted OR, 2.1; 95% CI, 1.3 to 3.3) and persistent (immunomodulators and Medicaid insurance adjusted OR, 2.2; 95% CI, 1.1 to 4.5) users of TNF-alpha inhibitor.

Comparisons including immunomodulators. All four case-control studies including 3,554 patients reported a comparison including an immunomodulator.[184 200-202] The claims database study including 1,935 Crohn's disease patients also evaluated the relationship between thiopurine use and non-melanoma skin cancer risk.[200] Cases were more likely to be recent (OR adjusted for Medicaid insurance, and use of other immunomodulators and TNF-alpha inhibitors, 3.8; 95% CI, 2.9 to 5.2) and persistent (OR adjusted for Medicaid insurance, and other immunomodulators and TNF-alpha inhibitors, 4.3; 95% CI, 2.8 to 6.4) users of thiopurines compared with controls. This study also compared methotrexate with no methotrexate use. Cases were more likely to be recent (OR adjusted for Medicaid insurance, and other immunomodulators and TNF-alpha inhibitors, 1.6; 95% CI, 0.6 to 4.3) and persistent (OR adjusted for Medicaid insurance, and other immunomodulators and TNF-alpha inhibitors, 2.7; 95% CI, 0.6 to 11.6) users of methotrexate compared with controls, although these associations were not statistically significant.

A case-control study of 35 Crohn's disease patients compared seven small bowel adenocarcinoma cases with controls matched on age, sex, and small bowel Crohn's disease.[184] Two of seven (29%) cases had a record of 6-mercaptopurine use for at least six months recorded in their chart compared with one of 28 controls (4%; OR, 10.8; 95% CI, 1.1 to 108.7).

A case-control study of 48 patients with colonic inflammatory bowel disease compared thiopurines users with non-users.[202] One of 18 colorectal cancer cases and four of 30 controls had thiopurine use recorded in their paper or electronic medical record. The corresponding Peto OR is 0.4 (95% CI, 0 to 4.4). The study collected information on TNF-alpha inhibitor and methotrexate use but observed no cases or controls with a record of use.

A case-control study using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) claim codes and outpatient pharmacy claims identified 364 colorectal cancer cases and 1,172 controls without a record of colorectal cancer or bowel surgery.[201] In the 12 months prior to or on the date of the colorectal cancer diagnosis, 41 of 364 (11%) cases and 101 of 1,172 (9%) controls had a pharmacy claim for immunomodulators. The study reported a crude OR comparing immunomodulators use with no immunomodulators use of 1.4 (95% CI, 0.9 to 2.0).

Comparisons including corticosteroids. Three of the case-control studies including 1,619 patients reported a comparison including a corticosteroid.[184 201 202] The case-control study of 35 Crohn's disease patients compared prednisone with no prednisone.[184] Five of seven (71%) cases had a record of prednisone use for at least six months prior to small bowel adenocarcinoma diagnosis recorded in their chart compared with 17 of 28 (61%) controls. The corresponding Peto OR was 1.6 (95% CI, 0.2 to 19.6). The case-control study of 48 inflammatory bowel disease patients reported 15 of 18 (83%) colorectal cancer cases and 25 of 30 (83%) controls had a record of corticosteroids use.[202] The corresponding Peto OR was 1.0 (95% CI, 0.2 to 7.4). The claims-based study of colorectal cancer in inflammatory bowel disease reported 28% of 364 colorectal cancer cases and 21% of 1,172 controls had a pharmacy claim for corticosteroids in the 12 months prior to or on the date of the colorectal cancer diagnosis.[201] The study reported a crude OR of 1.4 (95% CI, 1.1 to 1.9).

Comparisons including aminosalicylates. Three case-control studies including 1,619 patients reported a comparison including an aminosalicylate.[184 201 202] The case-control study of 35 Crohn's disease patients reported four of seven (57%) cases had a record of sulfasalazine use for at least six months prior to small bowel adenocarcinoma diagnosis recorded in their chart compared with 19 of 28 (68%) controls.[184] The corresponding Peto OR was 0.6 (95% CI, 0.1 to 5.3). The case-control study of 48 inflammatory bowel disease patients reported 15 of 18 (83%) colorectal cancer cases and 29 of 30 (97%) controls had a record of mesalamine use.[202] The corresponding Peto OR was 0.2 (95% CI, 0 to 2.4).

The claims-based case-control study of colorectal cancer in inflammatory bowel disease reported 43% of 364 colorectal cancer cases and 44% of 1,172 controls had a pharmacy claim for aminosalicylates in the 12 months prior to or on the date of the colorectal cancer diagnosis (crude OR, 1.0; 95% CI, 0.8 to 1.2).[201] The comparison of aminosalicylates with colorectal cancer risk was the primary aim of the study. They also reported relationships with colorectal cancer risk for the different aminosalicylate formulations (mesalamine OR, 0.9; 95% CI, 0.7 to 1.2; sulfasalazine OR, 1.2; 95% CI, 0.8 to 1.7; and balsalazide OR, 1.3; 95% CI, 0.7 to 2.4). When they performed a test for trend to examine a relationship between number of aminosalicylate prescription claims in the 12 months prior to diagnosis and odds of colorectal cancer, they observed a p-value for trend of borderline statistical significance for any aminosalicylate (P = 0.11) and mesalamine (P = 0.08) but not sulfasalazine (P = 0.27). They did not report a test of trend p-value for balsaladize.

Studies reporting for Crohn's disease and inflammatory bowel disease. The claims-based study of non-melanoma skin cancer reported results for all inflammatory bowel disease patients in addition to Crohn's disease patients exclusively.[200] The results for thiopurine use versus no thiopurine use in inflammatory bowel disease patients were similar in direction for the Crohn's disease patients (inflammatory bowel disease OR, 3.1; 95% CI, 2.1 to 4.5; Crohn's disease OR, 3.9; 95% CI, 2.9 to 5.2) when adjusted for other classes of medications and Medicaid insurance status. The authors stated that because infliximab was approved for ulcerative colitis after the study period ended in June 2005, the TNF-alpha inhibitor and combination TNF-alpha inhibitor and immunomodulators versus no immunomodulators ORs were not calculated for all inflammatory bowel disease patients. The authors stated that the methotrexate relationship was not reported because methotrexate use is not indicated for the treatment of ulcerative colitis in the United States.[200]

Infections

The risk of infection may be increased by immune suppression caused by medications to treat Crohn's disease or by the disease itself. These infections can range from life-threatening to relatively mild. Because serious infections that may be life-threatening or associated with hospitalization have different implications for clinical care and patient quality of life, we have indicated when studies reported serious infections compared with any infection, regardless of severity. We have also indicated when the study considered an infection opportunistic.

Fifty-three studies including 39,499 patients reported on infections (Appendix D, Evidence Table 14). Thirty-six RCTs including 7,690 patients reported infections as an outcome by comparison of interest. Two prospective studies (n = 6,520), 13 retrospective studies (n = 22,751), and two case-control studies (n = 2,538) reported infections by a comparison of interest. Infections were a primary outcome of interest in twelve studies.

Ustekinumab and Natalizumab

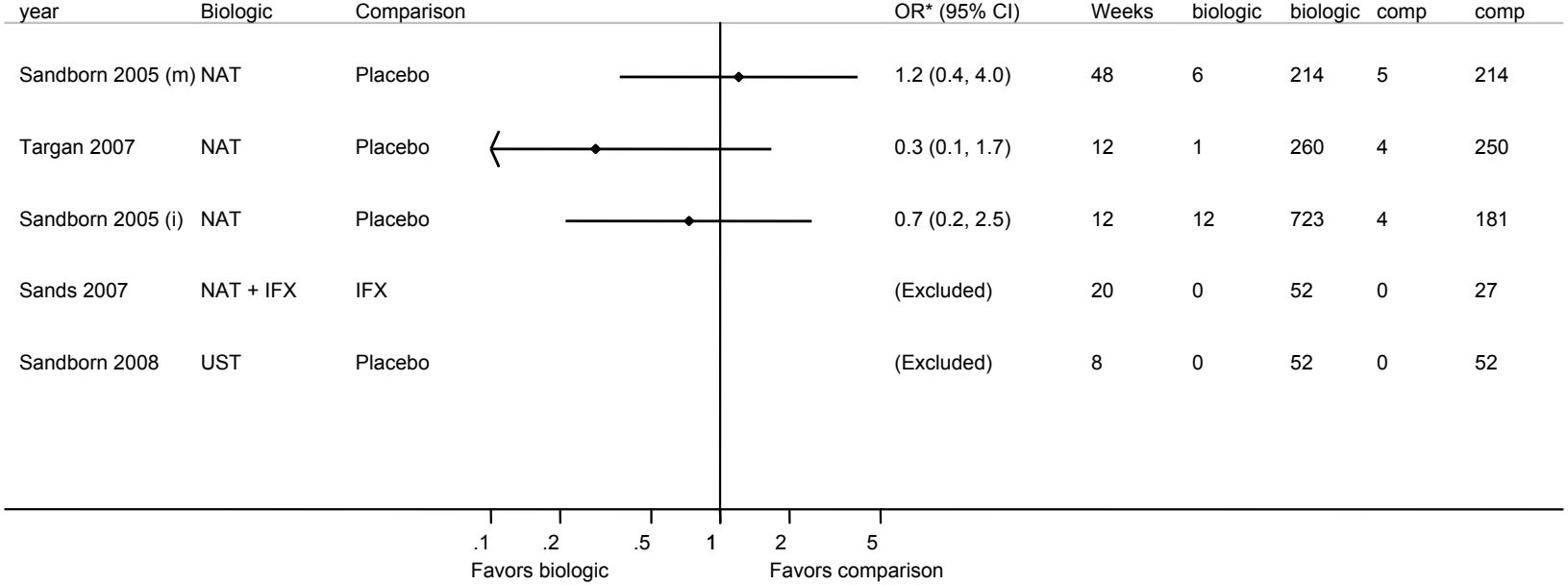
Figures 19 and 20 summarize the serious infections and any infections reported in RCTs evaluating either ustekinumab or natalizumab. Table 38 lists the RCTs evaluating either ustekinumab or natalizumab that reported no opportunistic infections. Additional details are given below.

Table 38. Summary of the randomized controlled trials reporting no opportunistic infections when comparing the effectiveness of a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease

Biologic	Comparison	# of trials reporting no events	Range of followup (weeks)	# participants in biologic group	# participants in comparison group
Natalizumab	Placebo	1[26]	8	260	250
Ustekinumab	Placebo	1[75]	8	52	52
Natalizumab + infliximab	Infliximab	1[27]	NR	52	27

NR = not reported

Figure 19. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease

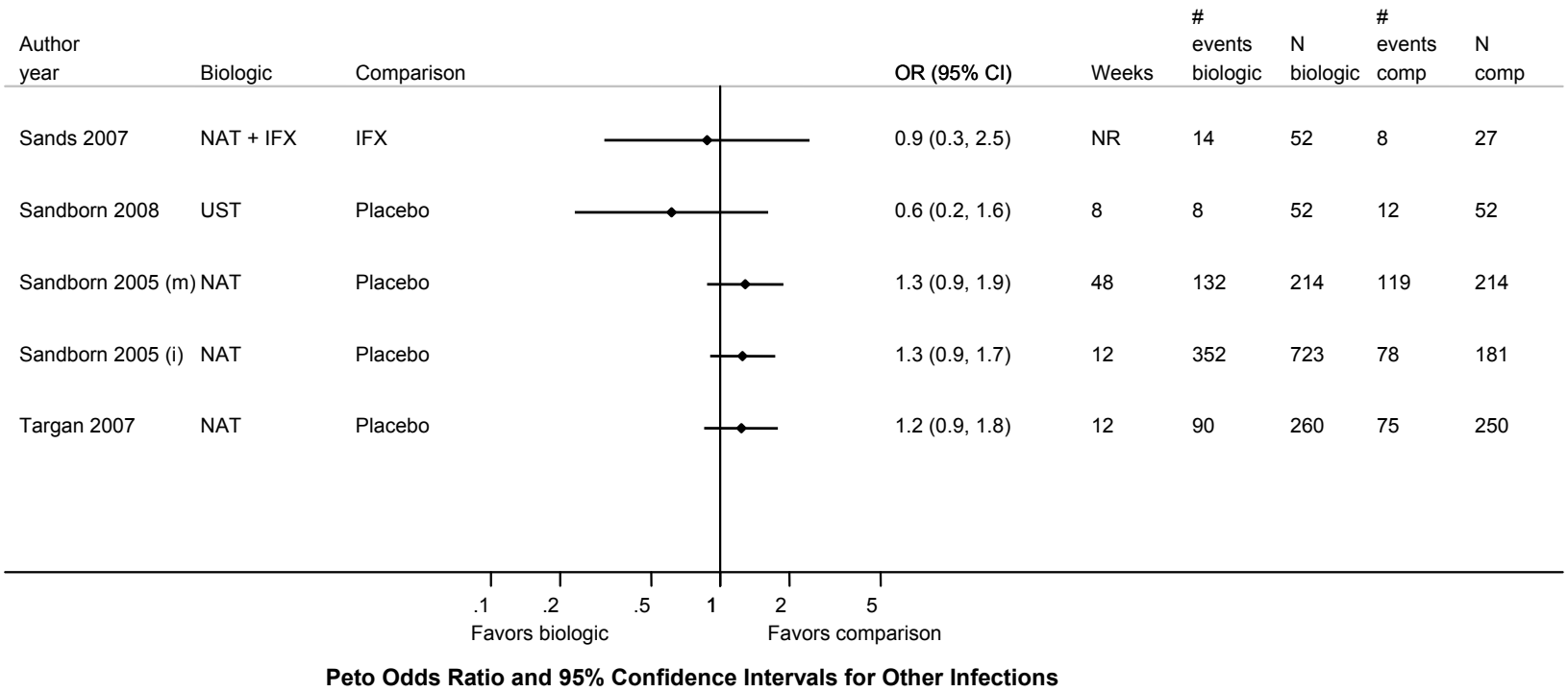


Peto Odds Ratio and 95% Confidence Intervals for Serious Infections

CI = confidence interval; Comp = comparison; i = induction trial; IFX = infliximab; m = maintenance trial; Main = main intervention; NAT = natalizumab; OR = odds ratio; UST = ustekinumab

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 20. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a biologic alone or in combination with placebo or another treatment in patients with Crohn's disease



Peto Odds Ratio and 95% Confidence Intervals for Other Infections

CI = confidence interval; Comp = comparison; i = induction trial; IFX = infliximab; m = maintenance trial; Main = main intervention; NAT = natalizumab; NR = not reported; OR = odds ratio; UST = ustekinumab

Ustekinumab versus placebo. One RCT including 104 Crohn's disease patients compared ustekinumab versus placebo and reported infections.[75] Patients were assigned to intravenous or subcutaneous ustekinumab or intravenous or subcutaneous placebo for 8 weeks then crossed over to the other treatment. Safety was reported during the 8-week initial period and then for the period after 8 weeks to 28 weeks. In an open-label trial reported in the same publication comparing intravenous with subcutaneous ustekinumab in 27 patients, two serious, two opportunistic, and 21 non-serious infections were reported through week 28.

Serious infections. None were reported through 28 weeks.[75]

Opportunistic infections. None were reported through 28 weeks.[75]

Any infection. Eight of 52 (15%) ustekinumab patients and 12 of 52 (23%) placebo patients had infections though week 8. After week 8 through week 28 (after all patients had been exposed to ustekinumab), an additional 12 patients originally exposed to ustekinumab and one fewer placebo patient than reported through week 8 had infections.[75]

Natalizumab versus placebo. Three natalizumab versus placebo RCTs (reported in two publications) including 1,414 Crohn's disease patients reported infections.[26 76]

Serious infections. All three trials included 1,414 patients.[26 76] A 12-week induction trial reported serious infections in less than 1% (1 out of 260) of patients on natalizumab and 2% (4 out of 250) of patients taking placebo.[26] The corresponding Peto OR was 0.3 (95% CI, 0.1 to 1.7). Another 12-week induction trial of patients without fistula, abscess or stricture reported serious infections in 2% (12 out of 723) of patients on natalizumab and 2% (4 out of 181) of patients taking placebo.[76] The corresponding Peto OR was 0.7 (95% CI, 0.2 to 2.5). Responders to induction were re-randomized and followed in a 48-week maintenance trial that reported serious infections in 3% (6 out of 214) of patients on natalizumab and 2% (5 out of 214) of patients taking placebo.[76] The corresponding Peto OR was 1.2 (95% CI, 0.4 to 4.0).

Opportunistic infections. One RCT including 510 patients reported no opportunistic infections (including PML) during the study period.[26]

Any infection. Three trials including 1,414 patients reported on any infection.[26 76] The 12-week induction trial (without maintenance trial) reported infections (including serious) in 35% (90 out of 260) of patients on natalizumab and 30% (75 out of 250) of patients on placebo.[26] The other 12-week induction trial reported infections (including serious) in 49% (352 out of 723) of patients on natalizumab versus 43% (78 out of 181) of patients on placebo.[76] The corresponding Peto OR was 1.3 (95% CI, 0.9 to 1.7). The maintenance trial reported infections (including serious) in 62% of patients on natalizumab compared with 56% of patients on placebo.[76] The corresponding Peto OR was 1.3 (95% CI, 0.9 to 1.9).

Combination of natalizumab and infliximab versus infliximab. One RCT including 79 Crohn's disease patients reported infections comparing a combination of natalizumab and infliximab with infliximab alone in initial non-responders to infliximab.[27] They randomized 79

patients to infliximab 5 mg/kg every 8 weeks with natalizumab 300 mg every 4 weeks or infliximab 5 mg/kg every 8 weeks.[27]

Serious infections. No serious infections were reported during the study period.[27]

Opportunistic infections. No opportunistic infections were reported during the study period.[27]

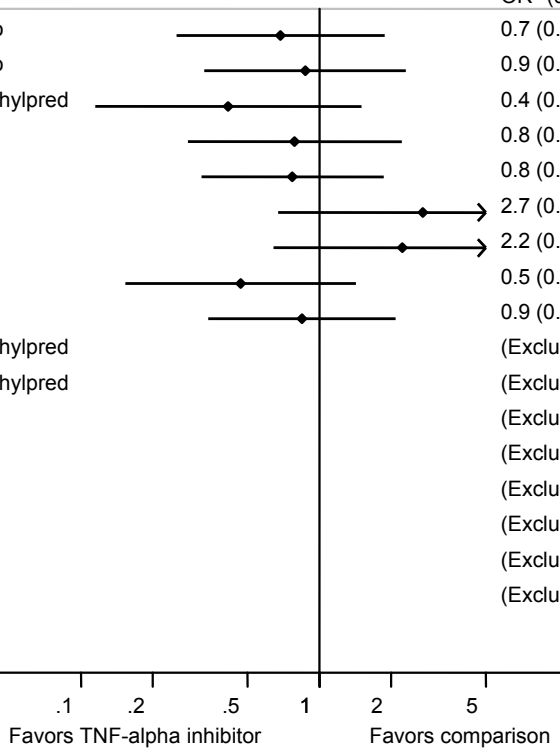
Any infection. Infections were reported in 27% (14 out of 52) of patients taking natalizumab and infliximab and 30% (8 out of 27) of patients taking infliximab.[27] The corresponding Peto OR was 0.9 (95% CI, 0.3 to 2.5).

TNF-Alpha Inhibitors

We planned to conduct a meta-analysis of the RCTs comparing TNF-alpha inhibitors with placebo that were combined in KQ1 in terms of serious infections, but we chose not to include the meta-analysis figure because four out of the five trials had fewer than five events. Figures 21 and 22 summarize the RCTs and observational studies, respectively, evaluating TNF-alpha inhibitors in terms of serious infections. Figure 23 summarizes the opportunistic infections reported in RCTs evaluating TNF-alpha inhibitors. Figure 24 and Table 39 summarize any infections reported in RCTs and observational studies evaluating TNF-alpha inhibitors. Additional details about the studies are given below.

Figure 21. Summary of Peto odds ratios of serious infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	TNF-alpha inhibitor	Comparison	OR* (95% CI)	Weeks	# events TNF	N TNF	# events comp	N comp
Colombel 2010	AZA + IFX	AZA + Placebo	0.7 (0.3, 1.9)	54	7	179	9	161
Colombel 2010	IFX + Placebo	AZA + Placebo	0.9 (0.3, 2.3)	54	8	163	9	161
D'Haens 2008	IFX + AZA	BUDE + 6-Methylpred	0.4 (0.1, 1.5)	104	3†	65	7†	64
Colombel 2010	AZA + IFX	IFX + Placebo	0.8 (0.3, 2.2)	54	7	179	8	163
Colombel 2007	ADA	Placebo	0.8 (0.3, 1.9)	52	14	517	9	261
Schreiber 2007	CP	Placebo	2.7 (0.7, 11.0)	18	6	216	2	212
Sandborn 2007	CP	Placebo	2.2 (0.6, 7.8)	26	7	331	3	329
Sands 2004	IFX	Placebo	0.5 (0.2, 1.4)	40	4	138	9	144
Hanauer 2002	IFX	Placebo	0.9 (0.3, 2.1)	52	14	385	8	188
D'Haens 2008	IFX + AZA	BUDE + 6-Methylpred	(Excluded)	104	1‡	65	0‡	64
D'Haens 2008	IFX + AZA	BUDE + 6-Methylpred	(Excluded)	104	0§	65	1§	64
Schroder 2006	IFX+MTX	IFX	(Excluded)	48	0	11	0	8
Sandborn 2007	ADA	Placebo	(Excluded)	4	0	159	4	166
Sandborn 2007	ADA	Placebo	(Excluded)	52	0	37	0	18
Hanauer 2006	ADA	Placebo	(Excluded)	4	2	223	0	74
Winter 2004	CP	Placebo	(Excluded)	12	1	68	0	24
Schreiber 2005	CP	Placebo	(Excluded)	20	1	219	1	73



Peto Odds Ratio and 95% Confidence Intervals for Serious Infections

6-Methylpred = 6-methylprednisolone; ADA = adalimumab; AZA = azathioprine; BUDE = budesonide; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; IFX = infliximab; MTX = methotrexate; OR = odds ratio; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

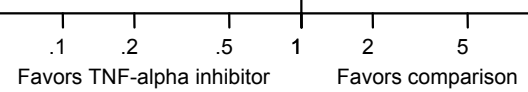
†The number of events is for serious cases of perianal abscess or fistula.

‡The number of events is for serious cases of pneumonia.

§The number of events is for serious cases of hepatitis C.

Figure 22. Summary of Peto odds ratios of serious infections among observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	Design	TNF-alpha inhibitor	Comparison	OR* (95% CI)	Weeks	# events TNF	N TNF	# events comp	N comp
Ricart 2001	Retro	IFX + IMM	IFX + Never IMM	0.1 (0.0, 3.3)	NR	5	95	1	5
Ricart 2001	Retro	IFX + Steroid	IFX + Never Steroid	0.6 (0.1, 3.3)	NR	2	44	4	56
Ricart 2001	Retro	IFX + IMM	IFX + Steroid	1.2 (0.2, 5.9)	NR	5	95	2	44
Fidder 2009	Retro	IFX	Never user BIO	0.7 (0.5, 1.0)	NR	48	743	62	666
Lichtenstein 2006	Pro	IFX	Never user IFX	2.1† (1.4, 3.1)	99	69	2933	37	3320
Mortimore 2001	Retro	IFX + No IMM	IFX	(Excluded)	NR	1	15	0	42



Peto Odds Ratio and 95% Confidence Intervals for Serious Infections

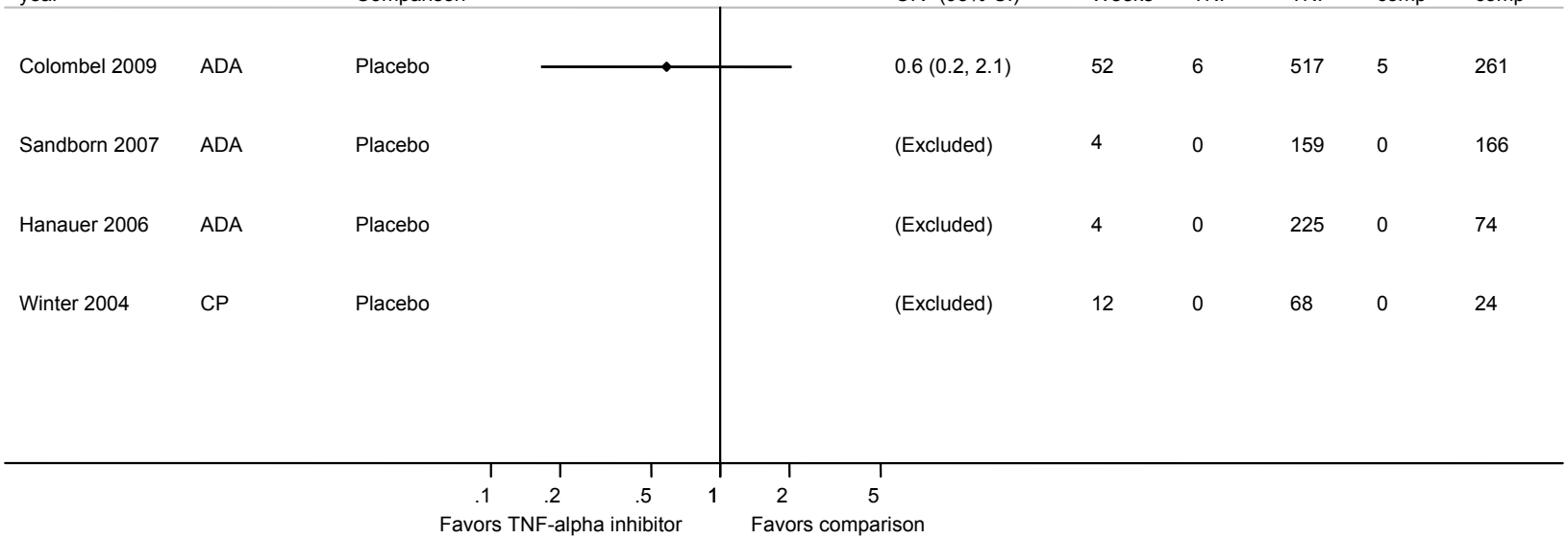
BIO = biologics; CI = confidence interval; Comp = comparison; IFX = infliximab; IMM = immunomodulator; NR = not reported; OR = odds ratio; Pro = prospective cohort; Retro = retrospective cohort; STEROID = corticosteroids; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† Adjusted relative risk, 2.2 (95% CI, 1.4 to 3.2)

Figure 23. Summary of Peto odds ratios of opportunistic infections among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	TNF-alpha inhibitor	Comparison	OR* (95% CI)	Weeks	# events TNF	N TNF	# events comp	N comp
Colombel 2009	ADA	Placebo	0.6 (0.2, 2.1)	52	6	517	5	261
Sandborn 2007	ADA	Placebo	(Excluded)	4	0	159	0	166
Hanauer 2006	ADA	Placebo	(Excluded)	4	0	225	0	74
Winter 2004	CP	Placebo	(Excluded)	12	0	68	0	24

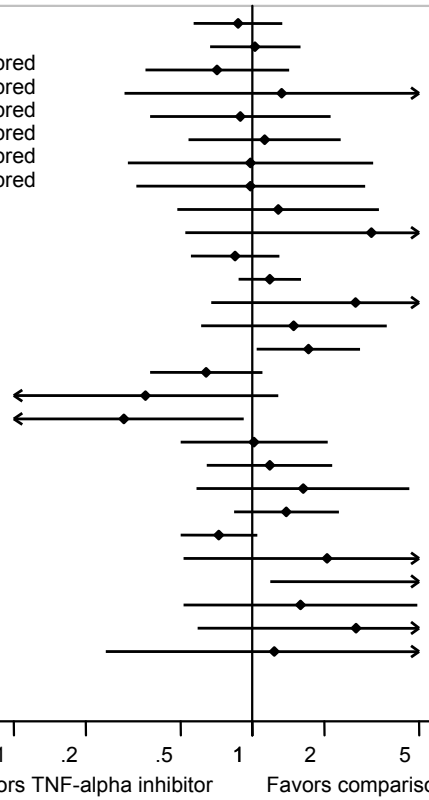


Peto Odds Ratio and 95% Confidence Intervals for Opportunistic Infections

ADA = adalimumab; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; OR = odds ratio; TNF = tumor necrosis factor-alpha inhibitor
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 24. Summary of Peto odds ratios of other infections among randomized controlled trial comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	Outcome definition	TNF-alpha inhibitor	Comparison	OR (95% CI)	Weeks	# events TNF	N TNF	# events comp	N comp
Colombel 2010	Any infections	AZA + IFX	AZA + Placebo	0.9 (0.6, 1.3)	54	75	179	73	161
Colombel 2010	Any infection	IFX + Placebo	AZA + Placebo	1.0 (0.7, 1.6)	54	75	163	73	161
D'Haens 2008	Common cold	IFX + AZA	BUDE + 6-methylpred	0.7 (0.4, 1.4)	104	26	65	31	64
D'Haens 2008	Eye infections	IFX + AZA	BUDE + 6-methylpred	1.3 (0.3, 6.1)	104	4	65	3	64
D'Haens 2008	GI infection	IFX + AZA	BUDE + 6-methylpred	0.9 (0.4, 2.1)	104	12	65	13	64
D'Haens 2008	URI	IFX + AZA	BUDE + 6-methylpred	1.1 (0.5, 2.3)	104	22	65	20	64
D'Haens 2008	UTI	IFX + AZA	BUDE + 6-methylpred	1.0 (0.3, 3.2)	104	6	65	6	64
D'Haens 2008	Vaginal infection	IFX + AZA	BUDE + 6-methylpred	1.0 (0.3, 3.0)	104	7	65	7	64
Van Assche 2008	Any infection	IFX + IMM	IFX	1.3 (0.5, 3.4)	104	12	40	10	40
Schroder 2006	Any infection	IFX+MTX	IFX	3.2 (0.5, 19.0)	48	6	11	2	8
Colombel 2010	Any infection	AZA + IFX	IFX + Placebo	0.8 (0.6, 1.3)	54	75	179	75	163
Colombel 2009	Any infection	ADA	Placebo	1.2 (0.9, 1.6)	52	314	517	148	261
Schreiber 2007	Any infection	CP	Placebo	2.7 (0. 7, 11.0)	18	6	216	2	212
Schreiber 2007	Nasopharyngitis	CP	Placebo	1.5 (0.6, 3.7)	18	12	216	8	212
Sandborn 2007	Nasopharyngitis	CP	Placebo	1.7 (1.0, 2.8)	26	43	331	26	329
Sandborn 2007	Any infection	ADA	Placebo	0.6 (0.4, 1.1)	8	26	159	39	166
Sandborn 2007	Nasopharyngitis	ADA	Placebo	0.4 (0.1, 1.3)	52	7	37	7	18
Sandborn 2007	TEI	ADA	Placebo	0.3 (0.1, 0.9)	8	20	37	15	18
Hanauer 2006	Any infection	ADA	Placebo	1.0 (0.5, 2.1)	4	37	225	12	74
Schreiber 2005	Any infection	CP	Placebo	1.2 (0.4, 2.2)	12	58	219	17	73
Winter 2004	Any infection	CP	Placebo	1.6 (0.6, 4.6)	12	21	68	5	24
Sands 2004	Any infection	IFX	Placebo	1.4 (0.8, 2.3)	40	47	138	39	144
Hanauer 2002	Any infection	IFX	Placebo	0.7 (0.5, 1.1)	52	116	385	70	188
Rutgeerts 1999	Bronchitis	IFX	Placebo	2.1 (0.5, 8.2)	36	6	37	3	36
Rutgeerts 1999	Pharyngitis	IFX	Placebo	5.1 (1.2, 22.0)	36	7	37	1	36
Rutgeerts 1999	URI	IFX	Placebo	1.6 (0.5, 4.9)	36	9	37	6	36
Present DH 1999	Abscess	IFX	Placebo	2.7 (0.6, 12.6)	18	7	63	1	31
Present DH 1999	URI	IFX	Placebo	1.2 (0.2, 6.3)	18	5	63	2	31
Lemann 2006	Any infection	IFX + THIO	Placebo + THIO	(Excluded)	52	NR*	57	NR*	56



Peto Odds Ratio and 95% Confidence Intervals for Other Infections

6-methylpred = 6-methylprednisolone; ADA = adalimumab; AZA = azathioprine; BUDE = budesonide; CI = confidence interval; Comp = comparison; CP = certolizumab pegol; GI = gastrointestinal; IFX = infliximab; IMM = immunomodulator; MTX = methotrexate; NR = not reported; OR = odds ratio; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor; URI = upper respiratory infection; UTI = urinary tract infection

*There were 18 events in the combination infliximab and thiopurine arm and 16 events in the thiopurine arm.

Table 39. Summary of other infections reported in observational studies comparing a TNF-alpha inhibitor alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	TNF-alpha inhibitor	Comparison	# of other infections in TNF group	# of patients in TNF group	# of other infections in comparison group	# of patients in comparison group
Seiderer, 2004[203]	NR	Infliximab + thiopurine	Infliximab + no thiopurine	4	82	0	18
Seiderer, 2004[203]	NR	Infliximab + corticosteroids	Infliximab + no corticosteroids	0	42	3	58

TNF = tumor necrosis factor-alpha inhibitor

Infliximab versus placebo. Five RCTs including 1,130 Crohn's disease patients compared infliximab with placebo and reported infections.[24 77 126 128 137]

Serious infections. Three RCTS including 963 patients reported on serious infections.[77 126 137] A 40-week maintenance trial of 282 fistulizing patients compared infliximab with placebo infusion.[137] Serious infections were reported in 3% (4 out of 138) of infliximab patients and 6% (9 out of 144) of placebo patients (Peto OR, 0.5; 95% CI, 0.2 to 1.4). A 52-week maintenance trial reported serious infections (undefined) in 4% (14 out of 385) of infliximab patients and 4% (8 out of 188) of placebo patients (Peto OR, 0.9; 95% CI, 0.3 to 2.1).[126] A 12-week trial of a single infusion reported one salmonella colitis requiring hospitalization among 83 infliximab patients and one abdominal abscess requiring hospitalization among 25 placebo patients.[77]

Opportunistic infections. No study reported on opportunistic infections.

Any infection. Four RCTs including 1,022 patients reported on infections.[24 126 128 137] The 40-week maintenance trial of fistulizing patients reported any infection (including serious) that required antimicrobial treatment in 34% (47 out of 138) of infliximab patients versus 27% (39 out of 144) of placebo patients (Peto OR, 1.4; 95% CI, 0.8 to 2.3).[137] The 52-week maintenance trial reported any infection (including serious) that required antimicrobial treatment in 30% (116 out of 385) of infliximab patients and 37% (70 out of 188) of placebo patients (Peto OR, 0.7; 95% CI, 0.5 to 1.1).[126] An 18-week induction trial including a single infusion reported adverse events occurring in at least 10% of the population including 63 infliximab and 31 placebo patients with fistulizing disease.[24] Infectious adverse events included gastrointestinal abscess (7 infliximab patients versus one placebo patient; Peto OR, 2.7; 95% CI, 0.6 to 12.6) and upper respiratory infection (5 infliximab patients versus two placebo patients; Peto OR, 1.6; 95% CI, 0.5 to 8.2).[24] A 36-week retreatment trial subsequent to another trial[77] reported adverse events occurring in at least 10% of any group including 37 infliximab patients and 36 placebo patients.[128] Infectious adverse events included bronchitis (six infliximab patients versus three placebo patients; Peto OR, 2.1; 95% CI, 0.5 to 8.2), pharyngitis (seven infliximab patients versus one placebo patient; Peto OR, 5.1; 95% CI, 1.2 to 22.0), and upper respiratory infection (which may or may not have included bronchitis and pharyngitis; 9 infliximab patients versus six placebo patients; Peto OR, 1.6; 95% CI, 0.5 to 8.2).[128]

TNF-alpha inhibitor versus no TNF-alpha inhibitor. One prospective study and one retrospective observational study including 14,871 Crohn's disease patients compared TNF-alpha inhibitor with no TNF-alpha inhibitor and reported infections.[174 198]

Serious infections. One observational study including 6,290 patients reported on serious infections.[174] An observational study with 2 mean years of followup reported serious infections (undefined) in 2% of 3,179 infliximab users compared with 1% of non-users during the study period. The OR was 1.0 (95% CI, 0.6 to 1.5) when comparing infliximab with no infliximab excluding infliximab used in the 6-month period during which the infection occurred, adjusted for age, sex, race, disease location, severity of Crohn's disease, and duration of followup and possibly adjusted for other medications. The relative rate comparing number of infections by person-years of exposure unadjusted for potential confounders was 2.2 (95% CI, 1.4 to 3.2).

Opportunistic infections. A claims-based study that included 8,581 Crohn's disease patients reported opportunistic infections, candidiasis, and tuberculosis together.[198] Eleven of these infections were reported in 292 infliximab person-years compared with 305 in 15,673 person-years with no associated Crohn's disease pharmacy claims. The study reported a HR of 2.0 (95% CI, 1.1 to 3.7) comparing infliximab (with or without corticosteroids or immunomodulators) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. They also reported an adjusted HR comparing infliximab alone (without corticosteroids or immunomodulators) with no therapy of 2.1 (95% CI, 1.1 to 3.8).

Any infection. The claims-based study also reported on four additional infections that were not specifically identified by the authors as serious.[198] For herpes simplex, herpes zoster, and encephalopathy, encephalitis, or meningitis, the unadjusted rate ratios and adjusted hazard ratios ranged from 0.9 to 1.7 without statistical significance. There was an increased risk of sepsis among infliximab users compared with those without therapy. There were 48 sepsis events reported in 292 person-years of infliximab use compared with 1833 events among 15673 person-years of no therapy (adjusted HR comparing infliximab [with or without corticosteroids and immunomodulators] with no therapy, 1.5; 95% CI, 1.1 to 2.0; HR for infliximab alone versus no therapy, 1.5; 95% CI, 1.1 to 2.0).

Adalimumab versus placebo. Four RCT's (reported in five publications) including 1,457 Crohn's disease patients compared adalimumab with placebo and reported infections.[78 79 129 130 135]

Serious infections. Four RCTs including 1,457 patients reported on serious infection. A 4-week induction trial of adalimumab after infliximab failure reported infections in zero of 159 adalimumab patients and four of 166 placebo patients.[79] A 4-week induction trial reported serious infections in two of 225 (1%) adalimumab patients and zero of 74 placebo patients.[78] A maintenance trial of those who achieved remission in a previous trial[78] reported no infections in 37 adalimumab patients and 18 placebo patients who stayed on their randomized treatment for the duration of the 52-week period.[130] Nine of 221 (4%) patients who elected to switch to adalimumab from placebo, increased the adalimumab dose, or discontinued at week 4 experienced a serious infection. A 52-week maintenance trial reported 3% of adalimumab and placebo patients experienced serious infections during the study period.[129] Another publication of

the same trial reported serious infections in 4% of adalimumab patients and 5% of placebo patients.[135] The corresponding Peto OR was 0.8 (95% CI, 0.3 to 1.9). During the adalimumab induction period prior to randomization, serious infections occurred in 1% of 854 patients.[129]

Opportunistic infections. Three RCTs including 1,402 patients reported on opportunistic infections.[78 79 129] The two induction trials reported that no opportunistic infections occurred.[78 79] A 52-week maintenance trial reported six (1%) opportunistic infections in the adalimumab patients compared with five (2%) opportunistic infections in placebo.[129] The corresponding Peto OR was 0.6 (95% CI, 0.2 to 2.1).

Any infection. Three RCTs including 679 patients reported on any infections.[78 79 130] The 4-week induction trial after infliximab failure reported infections in 16% of adalimumab patients compared with 23% of placebo patients.[79] The corresponding Peto OR was 0.6 (95% CI, 0.4, 1.1). The other 4-week induction trial reported infections (including serious) in 16% of adalimumab and placebo patients.[78] The corresponding Peto OR was 1.0 (95% CI, 0.5 to 2.1). The maintenance trial of patients who achieved remission from a previous trial reported infections requiring treatment in 54% of adalimumab and 83% of placebo patients (Peto OR, 0.3; 95% CI, 0.1 to 0.9) and nasopharyngitis in 19% of adalimumab and 39% of placebo patients (Peto OR, 0.4; 95% CI, 0.1 to 1.3).[130] After week 4 when patients could switch therapy, 127 of 221 (57%) who elected to switch therapy experienced an infection requiring treatment. Nasopharyngitis was reported in 37 of 221 (17%) of these patients.[130]

Certolizumab pegol versus placebo. Four RCTs including 1,472 Crohn's disease patients compared certolizumab pegol with placebo and reported infections.[80-82 131]

Serious infections. Four RCTs including 1,472 patients reported on serious infections.[80-82 131] A 12-week induction trial of patients without fistula or abscess reported the serious infection of perianal abscess in one of 68 certolizumab pegol patients compared with no serious infections in placebo patients.[82] Another 12-week induction trial of patients without abscess or obstruction reported serious infections of gastrointestinal abscess in one certolizumab pegol patient and genital warts in a placebo patient.[81] A 26-week induction trial of patients without abscess, obstruction, or stricture reported serious infections in seven of 331 (2%) and three of 329 (1%) of placebo patients.[80] The corresponding Peto OR was 2.2 (95% CI, 0.6 to 7.8). Responders from this trial were re-randomized and followed for 18 additional weeks in a maintenance phase.[131] During maintenance, serious infections were reported in six of 216 (3%) certolizumab pegol and two of 212 (1%) placebo patients.[131] The corresponding Peto OR was 2.7 (95% CI, 0.7 to 11.0).

Opportunistic infections. Two RCTs including 384 patients reported on opportunistic infections.[81 82] No opportunistic infections were reported in one 12-week induction trial.[82] Another reported "no increase" in opportunistic infections but did not specify the infections considered.[81]

Any infection. Four RCTs including 1,472 patients reported on any infections.[80-82 131] The 12-week induction trial of patients without fistula or abscess reported infections (including serious) in 21 of 68 (31%) certolizumab pegol patients and five of 24 (21%) placebo patients.[82] The corresponding Peto OR is 1.6 (95% CI, 0.6 to 4.6). The other 12-week induction trial reported

infections in 26% of 219 certolizumab pegol patients and 23% of 73 placebo patients.[81] The corresponding Peto OR was 1.2 (95% CI, 0.4 to 2.2). During the 8-week safety followup after the trial, additional infections occurred in 31 certolizumab pegol patients and 10 placebo patients.[81] The induction trial followed by maintenance trial reported specific infections. Nasopharyngitis was reported in both trials. In the induction trial, 13% of certolizumab pegol patients and 8% of placebo patients (Peto OR, 1.7; 95% CI, 1.0 to 2.8) were reported to have nasopharyngitis.[80] Some of these patients may have been randomized in the maintenance trial where 12 of 216 (6%) certolizumab pegol patients and eight of 212 (4%) placebo patients had nasopharyngitis (Peto OR, 1.5; 95% CI, 0.6 to 3.7).[131]

Infliximab versus azathioprine. One RCT including 324 Crohn's disease patients compared infliximab with azathioprine and reported infections.[83] The induction trial included patients who were treatment naïve to TNF-alpha inhibitors and immunomodulators.

Serious infections. Eight serious infections were reported in 163 (5%) infliximab patients compared with nine serious infections in 161 (6%) azathioprine patients.[83] The corresponding Peto OR was 0.9 (95% CI, 0.3 to 2.3).

Opportunistic infections. This trial did not report on opportunistic infections.[83]

Any infection. A serious or non-serious infection was reported in 46% of infliximab patients and 45% of azathioprine patients. The corresponding Peto OR was 1.0 (95% CI, 0.7 to 1.6).[83]

Combination of infliximab and immunomodulators versus infliximab. Three RCTs including 607 Crohn's disease patients compared a combination of infliximab and immunomodulators with infliximab and reported infections.[83 85 133] One observational study including 57 Crohn's disease patients compared a combination of infliximab and thiopurines with infliximab and reported infections.[204]

Serious infections. Two RCTs including 527 patients reported on serious infections.[83 85] An open-label 48-week induction trial of azathioprine intolerant or resistant patients reported no serious infections in 11 patients on infliximab and methotrexate and eight patients on infliximab who had not received a Crohn's disease related surgery within the 6 months prior to the study.[85] A 50-week RCT followed to 54 weeks for safety compared a combination of infliximab and azathioprine with azathioprine alone among TNF-alpha inhibitor and immunomodulator-naïve patients.[83] Serious infections were reported in seven of 179 (4%) patients on infliximab and azathioprine and eight of 163 (5%) infliximab patients. The corresponding Peto OR was 0.8 (95% CI, 0.3 to 2.2).

One observational study including 57 Crohn's disease patients reported on serious infections. A study of the early experience with infliximab at several centers reported one case of pneumocystis carinii pneumonia among 42 patients on infliximab and immunomodulator (thiopurines, methotrexate, or mycophenolate mofetil) and one episode of sepsis among 15 users of infliximab without an immunomodulator.[204]

Opportunistic infections. None of the RCTs reported on opportunistic infections.

Any infection. All three RCTs including 607 patients reported and included serious and non-serious infections.[83 85 133] The open-label induction trial reported infections in six (55%) patients on infliximab and methotrexate and two (25%) infliximab patients.[85] The corresponding Peto OR was 3.2 (95% CI, 0.5, 19.0). The other induction trial reported infections in 42% of patients on infliximab and azathioprine and 46% of infliximab patients.[83] The corresponding Peto OR was 0.8 (95% CI, 0.6 to 1.3). An open-label trial of 80 non-fistulizing Crohn's disease patients retreated patients with infliximab and randomized them to continue or stop their immunomodulators.[133] Twelve infections were reported among 40 people in the infliximab and immunomodulators group and ten infections were reported in the infliximab group (Peto OR, 1.3; 95% CI, 0.5 to 3.4).

Combination of infliximab and immunomodulators versus immunomodulators. Two RCTs including 340 Crohn's disease patients compared the combination of infliximab and immunomodulators with immunomodulators alone and reported infections.[83 84]

Serious infections. A 52-week trial of steroid-dependent patients co-treated with thiopurines reported no infections among 57 patients on a combination of infliximab and thiopurines and one pneumonitis among 56 patients on thiopurines.[84] A 50-week RCT followed to 54 weeks for safety compared TNF-alpha inhibitors- and immunomodulators-naïve patients.[83] Serious infections were reported in seven of 179 (4%) patients on infliximab and azathioprine and seven of 161 (4%) azathioprine patients. The corresponding Peto OR was 0.7 (95% CI, 0.3 to 1.9).

Opportunistic infections. Neither of the RCTs reported on opportunistic infections.

Any infection. A 52-week trial of steroid-dependent patients co-treated with thiopurines reported 18 infectious events among 57 patients on the combination of infliximab and thiopurines and 16 infectious events among 56 patients on thiopurines.[84] The trial of TNF-alpha inhibitors- and immunomodulators-naïve patients reported infections in 42% of 179 patients on infliximab and azathioprine compared with 45% of 161 azathioprine patients.[83] The corresponding Peto OR was 0.7 (95% CI, 0.3 to 1.7).

Combination of infliximab and immunomodulators versus corticosteroids. One RCT including 129 Crohn's disease patients compared a combination of infliximab and immunomodulators with corticosteroids and reported infections.[86]

Serious infections. An 104-week open-label trial reported four infections in 65 patients on the combination of infliximab and azathioprine or methotrexate compared with eight infectious events in 64 patients on prednisone or budesonide.[86]

Opportunistic infections. This RCT did not report on opportunistic infections.

Any infection. The trial reported 77 infections in 65 patients on infliximab and azathioprine or methotrexate compared with 80 infectious events in 64 patients on prednisone or budesonide.[86]

Combination of TNF-alpha inhibitors, immunomodulators, and corticosteroids versus no therapy. One study including up to 8,581 Crohn's disease patients compared a triple

combination of TNF-alpha inhibitors, immunomodulators, and corticosteroids with no therapy and reported opportunistic and specific other infections.[198]

Opportunistic infections. The claims-based study that included 8,581 Crohn's disease patients reported two opportunistic infections among 31 person-years of exposure to combination therapy with TNF-alpha inhibitors, immunomodulators, and corticosteroids compared with 305 opportunistic infections among 15,673 person-years of no therapy.[198] The adjusted HR comparing triple combination therapy with no therapy was 3.6 (95% CI, 0.9 to 14.6).

Any infection. The claims-based study also reported on four additional infections that were not specifically identified by the authors as serious. In the 31 person-years of triple combination therapy of infliximab, immunomodulators, and corticosteroids and 15,673 person-years of no therapy over an average of two years per person, claims associated with herpes simplex were identified in none of the triple therapy patients compared with 134 in the no therapy patients.[198] One herpes zoster infection was reported in the triple therapy group compared with 123 infections in the no therapy group (unadjusted rate ratio, 4.1; 95% CI, 0.1 to 23.3). Nine claims for sepsis were reported in the triple therapy group compared with 1,833 claims in the no therapy group (adjusted HR, 2.4; 95% CI, 1.2 to 4.7). Four encephalopathy, encephalitis, or meningitis infections were reported in the triple therapy group compared with 499 infections in the no therapy group (unadjusted rate ratio, 4.1; 95% CI, 1.1 to 1.4).

Combination of TNF-alpha inhibitors and immunomodulators versus no therapy. One study including up to 8,581 Crohn's disease patients compared a combination of TNF-alpha inhibitors and immunomodulators with no therapy and reported opportunistic and specific other infections.[198]

Opportunistic infections. The claims-based study that included 8,581 Crohn's disease patients reported 15 opportunistic infections among 162 person-years of exposure to combination therapy with TNF-alpha inhibitors and immunomodulators (with or without corticosteroids) compared with 305 opportunistic infections among 15,673 person-years of no therapy.[198] The corresponding unadjusted rate ratio was 4.8 (95% CI, 2.6 to 8.0).

Any infection. The claims-based study reported three herpes simplex infections among the patients receiving a TNF-alpha inhibitor and immunomodulator and 134 infections among patients receiving no therapy. The corresponding rate ratio was 2.2 (95% CI, 0.4 to 6.5). Four herpes zoster infections were reported among patients receiving a TNF-alpha inhibitor and immunomodulator compared with 123 infections among patients receiving no therapy (unadjusted rate ratio, 3.1; 95% CI, 0.8 to 8.3). Sepsis claims were reported in 23 patients receiving the combination therapy and 1,833 patients receiving no therapy (adjusted HR, 1.9; 95% CI, 0.8 to 1.8). Encephalopathy, encephalitis, or meningitis claims were reported in 12 patients receiving the combination therapy and 499 patients receiving no therapy (unadjusted rate ratio, 2.3; 95% CI, 1.2 to 4.1).

Combination of TNF-alpha inhibitor and corticosteroids versus no therapy. One study including up to 8,581 Crohn's disease patients compared a combination of TNF-alpha inhibitors and corticosteroids with no therapy and reported opportunistic and specific other infections.[198]

Opportunistic infections. The claims-based study that included 8,581 Crohn's disease patients reported two opportunistic infections among 142 person-years of exposure to combination therapy with TNF-alpha inhibitors and corticosteroids (with or without immunomodulators) compared with 305 opportunistic infections among 15,673 person-years of no therapy.[198] The corresponding unadjusted rate ratio was 0.7 (95% CI, 0.1 to 2.6).

Any infection. The claims-based study reported one herpes simplex infection in the group receiving a TNF-alpha inhibitor and corticosteroids compared with 134 infections in the no therapy group (unadjusted rate ratio, 0.8; 95% CI, 0 to 4.7). Herpes zoster claims were reported in three patients receiving the combination therapy and 123 patients receiving no therapy (unadjusted rate ratio, 2.7; 95% CI, 0.5 to 8.1). Sepsis claims were reported in 27 patients receiving the combination therapy and 1,833 patients receiving no therapy. The study reported an adjusted HR for sepsis of 2.8 (95% CI, 1.2 to 6.5) that differed in magnitude from the unadjusted rate ratio of 1.6 (95% CI, 1.1 to 2.4). Encephalopathy, encephalitis, or meningitis was reported in six patients receiving the combination therapy and 499 patients receiving no therapy (unadjusted rate ratio 1.3; 95% CI, 0.5to 2.9).

Other combinations with infliximab. Four retrospective studies including 970 Crohn's disease patients met the inclusion criteria but the concomitant medications may be misclassified as described in the mortality section. Three studies aimed to evaluate the safety profile of infliximab use at their centers[179 186 205] and one study focused specifically on the role of concomitant immunomodulators on outcomes.[187]

Serious infections. Three studies (reported in four manuscripts) including 855 patients reported on serious infections.[179 180 186 205] The two retrospective studies including 157 and 500 Crohn's disease patients reported serious infections in patients with medications that could be classified as: a triple combination of infliximab, immunomodulators, and corticosteroids; a combination of infliximab and immunomodulators; a combination of infliximab and corticosteroids; or infliximab alone at baseline. Serious infections were reported in 7% (4 out of 55) and 0% (0 out of 111) of patients receiving the combination of infliximab, immunomodulator, and corticosteroid, 18% (9 out of 51) and 3% (9 out of 307) of patients receiving infliximab and an immunomodulator, 0% (0 out of 32) and 9% (4 out of 45) of patients receiving infliximab and corticosteroids; and 16% (3 out of 19) and 5% (2 out of 37) of patients receiving only infliximab.[179 186] A previous report on 500 patients from the center reported on the infliximab outcomes among the first 100 patients.[180] Six "significant" infections were reported, with concomitant immunomodulator use (with or without corticosteroids) in five of the six patients and concomitant corticosteroid use (with or without immunomodulators) in two of the six patients.[180] The study of 157 patients also reported on 30 patients who received adalimumab after infliximab.[186] Of the 30 adalimumab patients, two experienced sepsis-related complications.

A 29-month mean followup retrospective study reported no serious infections in 157 infliximab patients, including 127 patients that used a concomitant immunomodulator at baseline.[205]

Opportunistic infections. Two studies including 657 patients reported on opportunistic infections.[179 186] One study including 157 patients reported that no opportunistic infections

occurred.[186] In the study of 500 patients, three non-serious varicella-zoster infections were considered "probably" opportunistic.[179] Two of these patients were treated with a combination of infliximab, azathioprine, and corticosteroids and the other was treated with a combination of infliximab and azathioprine.

Any infection. Four studies (reported in five manuscripts) including 970 patients reported on any infection.[179 180 186 187 205] The two retrospective studies including 157 and 500 Crohn's disease patients reported infections (including serious) in 16% (9 out of 55) and 3% (3 out of 111) of patients receiving the combination of infliximab, immunomodulator, and corticosteroid, 33% (17 out of 51) and 9% (29 out of 307) of patients receiving infliximab and an immunomodulator, 6% (2 out of 32) and 13% (6 out of 45) of patients receiving infliximab and corticosteroids, and 26% (5 out of 19) and 14% (5 out of 37) of patients receiving only infliximab.[179 186] A previous report on 500 patients from the center reported on the infliximab outcomes among the first 100 patients and did not report other infections.[180] The study of 157 patients also reported on 30 patients who received adalimumab after infliximab.[186] Of the 30 adalimumab patients, seven (23%) patients had an infection.

A retrospective study with a mean followup of 29 months reported one pneumonia in 127 patients receiving infliximab and an immunomodulator compared with no infections in 71 patients receiving infliximab without concomitant immunomodulators, as recorded in a database that included most of the patients treated with infliximab at the center.[205] A followup study with a median followup of 9 years reported two "atypical" infections in 53 patients receiving infliximab with no concomitant thiopurine use compared with no infections among those with concomitant thiopurine use.[187] The infections reported were necrotizing pneumonia and methicillin-resistant Staphylococcus aureus (MRSA) skin abscess.

Immunomodulators

Table 40 summarizes the risk of serious infections in observational studies evaluating immunomodulators in patients with Crohn's disease. Figure 25 and Table 41 summarize the risk of any infection in RCTs and observational studies, respectively, evaluating immunomodulators in patients with Crohn's disease. Additional details are given below.

Table 40. Summary of the risk of serious infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Design	Immunomodulator	Comparison	# of serious infections in IMM group	# of patients in IMM group	# of serious infections in comparison group	# of patients in comparison group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lichtenstein, 2006[174]	99	Prospective cohort	Immunomodulator	No immunomodulator	58	3478	48	2775	1.0 (0.7 to 1.4)	0.8 (0.5 to 1.2)

IMM = immunomodulator

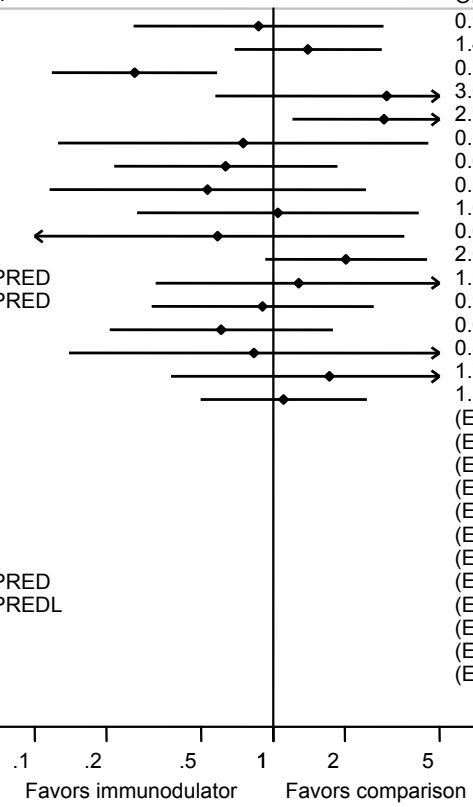
Table 41. Summary of the risk of other infections in observational studies comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Immunomodulator	Comparison	# of other infections in IMM group	# of patients in IMM group	# of other infections in comparison group	# of patients in comparison group
Maher, 2009[206]	NR	Azathioprine	Never azathioprine	NR*	12	NR*	60
Shah, 2008[34]	NR	Azathioprine + mesalamine	Azathioprine + never mesalamine	2	104	2	95

IMM = immunomodulator
* There were two events among 12 patients in the azathioprine group and seven events among 60 patients in the never azathioprine group.

Figure 25. Summary of Peto odds ratios of other infections among randomized controlled trials comparing an immunomodulator alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	Outcome definition	IMM	Comparison	OR* (95% CI)	Weeks	# events IMM	N IMM	# events comp	N comp
Sandborn 1999	Viral LRI	AZA (IV + oral)	AZA (oral)	0.9 (0.3, 2.9)	16	6	51	6	45
Mantzaris 2009	URI	AZA	BUDE	1.4 (0.7, 2.8)	78	25	112	14	83
Summers 1979	Any infections	AZA	PRED	0.3 (0.1, 0.6)	NR	5	59	27	85
Summers 1979	Total abscess	AZA	PRED	3.0 (0.6, 15.8)	104	4	59	2	85
Summers 1979	Any infections	AZA	PRED	2.9 (1.2, 7.1)	104	17	54	8	61
Summers 1979	Total abscess	AZA	PRED	0.7 (0.1, 4.5)	104	2	54	3	61
Summers 1979	Any infections	AZA	Placebo	0.6 (0.2, 1.9)	17	5	59	10	77
Summers 1979	Perianal abscess	AZA	Placebo	0.5 (0.1, 2.5)	104	2	59	5	77
Summers 1979	Total abscess	AZA	Placebo	1.0 (0.3, 4.1)	8	4	59	5	77
Feagan 2000	Any infections	MTX	Placebo	0.6 (0.1, 3.6)	40	2	40	3	36
Summers 1979	Any infections	AZA	Placebo	2.0 (0.9, 4.4)	104	17	54	19	101
Reinisch 2008	Nasopharyngitis	AZA + PRED	Placebo + PRED	1.3 (0.3, 5.1)	28	7	52	3	28
Feagan 1995	Influenza	MTX + PRED	Placebo + PRED	0.9 (0.3, 2.6)	16	11	94	6	47
Summers 1979	Any infections	AZA	SUL	0.6 (0.2, 1.8)	17	5	59	10	74
Summers 1979	Perianal abscess	AZA	SUL	0.8 (0.1, 5.0)	104	2	59	3	74
Summers 1979	Total abscess	AZA	SUL	1.7 (0.4, 7.9)	104	4	59	3	74
Summers 1979	Any infections	AZA	SUL	1.1 (0.5, 2.5)	104	17	54	17	58
Sandborn 1999	Pneumonia	AZA (IV + oral)	AZA (oral)	(Excluded)	16	0	51	2	45
Summers 1979	Other abscess	AZA	PRED	(Excluded)	104	2	59	1	85
Summers 1979	Perianal abscess	AZA	PRED	(Excluded)	104	2	59	1	85
Summers 1979	Other abscess	AZA	PRED	(Excluded)	104	1	54	2	61
Summers 1979	Other abscess	AZA	Placebo	(Excluded)	104	2	59	0	77
Summers 1979	Other abscess	AZA	Placebo	(Excluded)	104	1	54	1	101
Summers 1979	Total abscess	AZA	Placebo	(Excluded)	8	2	54	1	101
Reinisch 2008	Perianal abscess	AZA + PRED	Placebo + PRED	(Excluded)	28	0	52	3	28
Ewe 1993	Intra-abdominal abscess	AZA + PREDL	Placebo + PREDL	(Excluded)	16	1	21	0	21
Summers 1979	Other abscess	AZA	SUL	(Excluded)	104	2	59	0	74
Summers 1979	Other abscess	AZA	SUL	(Excluded)	104	1	54	0	58
Summers 1979	Total abscess	AZA	SUL	(Excluded)	104	2	54	2	58



Peto Odds Ratio and 95% Confidence Intervals for Other Infections

AZA = azathioprine; BUDE = budesonide; CI = confidence interval; Comp = comparison; IMM = immunomodulator; IV = intravenous; LRI = lower respiratory infection; MTX = methotrexate; NR = not reported; OR = odds ratio; PRED = prednisone; PREDL = prednisolone; SUL = sulfasalazine; URI = upper respiratory infection
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Immunomodulators versus placebo. Three RCTs including 463 Crohn's disease patients compared azathioprine with placebo and reported on infections.[93 96 144] A study published in 1971 included an induction and maintenance phase comparing oral azathioprine with placebo.[93] Some patients participated in induction and maintenance, whereas some patients in remission at enrollment only participated in the maintenance phase. Another study compared a single infusion of azathioprine or placebo followed by oral azathioprine in both groups.[96]

Serious infections. Two studies including 367 patients reported on serious infections. The 1971 study reported serious infections as those requiring hospitalization or causing disability of at least 3 months (a "disaster") or those that required withdrawal from the study or required treatment ("serious"). During induction, two of 59 (3%) patients taking azathioprine and three of 55 (4%) patients taking placebo experienced a serious infection.[207] The corresponding Peto OR was 0.6 (95% CI, 0.05 to 5.6). During the maintenance trial, four of 54 (7%) patients taking azathioprine and two of 101 (2%) patients taking placebo had a serious infection.[207] The corresponding Peto OR was 4.0 (95% CI, 0.5 to 44.7). Another trial included patients who were in steroid-free remission from a previous trial[98] or responded to methotrexate within 16 to 24 weeks.[144] The 40-week maintenance trial compared 40 patients on methotrexate with 36 patients on placebo.[144] One infection-related severe adverse event was reported in a placebo patient.[144]

Opportunistic infections. No study reported on opportunistic infections for this comparison.

Any infection. Three studies including 463 patients reported on any infection.[96 144 207] The 1971 study reported infections in 8% of the azathioprine patients and 13% of the placebo patients during the 17-week induction phase (Peto OR, 0.6; 95% CI, 0.1 to 2.5) compared with 31% of azathioprine patients and 19% of placebo patients in the 104-week maintenance phase (Peto OR, 2.0; 95% CI, 0.9 to 4.5).[207] The 16-week study that compared a single infusion of azathioprine with placebo to induce remission combined with oral azathioprine in both groups reported no pneumonia cases in the 51 azathioprine patients compared with two pneumonia cases in the 45 placebo patients.[96] Viral lower respiratory infections were reported in six (12%) azathioprine patients compared with two (4%) placebo patients. The corresponding Peto OR was 2.9 (95% CI, 0.5 to 30.2).[96] The methotrexate trial reported two flu-like illnesses in the methotrexate group (5%) and in the placebo (5%) group.[144]

Immunomodulators versus no immunomodulators. One prospective study including 6,290 Crohn's disease patients compared immunomodulators with no immunomodulators and reported on infections.[174]

Serious infections. One prospective study including 6,290 Crohn's disease patients reported on serious infections.[174] Two percent of 3478 patients using immunomodulators compared with 2% of 2,775 patients using no immunomodulators had a serious infection. The study reported an OR of 0.8 (95% CI, 0.5 to 1.2) comparing immunomodulators with no immunomodulators adjusted for age, sex, race, disease location, severity of Crohn's disease, and duration of followup and possibly other medications. The authors did not include in the analysis the medication exposure during the 6-month time period when the infection occurred.

Opportunistic infections. This prospective study did not report on opportunistic infections.

Any infection. This prospective study did not report on any other infections.

Immunomodulators versus no therapy. The claims-based study that included 8,581 Crohn's disease patients reported opportunistic infections, candidiasis, and tuberculosis together.[198] Seventeen of these infections were reported in 911 person-years associated with claims for immunomodulator use compared with 305 in 15,673 person-years with no claims for medical treatment of Crohn's disease. The study reported an HR of 1.1 (95% CI, 0.6 to 1.8) comparing immunomodulators (with or without infliximab or corticosteroids) with no therapy adjusted for age, gender, geographic region, health plan, and comorbidity. They also reported an adjusted HR comparing immunomodulators alone (without infliximab or corticosteroids) with no therapy of 1.1 (95% CI, 0.6 to 1.8).

Any infection. The claims-based study also reported on four additional infections that were not specifically identified by the authors as serious. Immunomodulator person-years numbered 911 compared with 15,673 person-years in the no therapy group.[198] No associations were statistically significant for herpes simplex; herpes zoster; sepsis; or encephalopathy, encephalitis, or meningitis comparing immunomodulators with no therapy. The HRs ranged from 0.6 to 1.0.

Azathioprine versus corticosteroids. Two RCTs including 454 Crohn's disease patients compared azathioprine with corticosteroids and reported on infections.[141 207]

Serious infections. One RCT including 259 patients reported on serious infections.[207] The 1971 study reported serious infections as those requiring hospitalization or causing disability of at least 3 months (a "disaster") or those that required withdrawal from the study or required treatment ("serious"). During induction, two of 59 (3%) patients on azathioprine and two of 85 (2%) patients on prednisone experienced a serious infection.[207] The corresponding Peto OR was 1.5 (95% CI, 0.1 to 20.6). During the maintenance trial, four of 54 (7%) patients on azathioprine and four of 61 (7%) patients on prednisone had a serious infection.[207] The corresponding Peto OR was 1.1 (95% CI, 0.2 to 6.5).

Opportunistic infections. Neither of the RCTs reported on opportunistic infections.

Any infection. Two RCTs including 454 patients reported on any infection. The 1971 study reported non-serious infections during induction in 8% of patients on azathioprine and 32% of patients on prednisone.[207] The corresponding Peto OR was 0.3 (95% CI, 0.1 to 0.6). During maintenance, infections were reported in 31% of patients on azathioprine and 13% of patients on prednisone. The corresponding Peto OR was 2.9 (95% CI, 1.2 to 7.1). A 1.5-year maintenance trial comparing azathioprine with budesonide reported infections in 66% of 112 patients on azathioprine and 36% of 83 patients on budesonide.[141] The majority of infections were upper respiratory or herpes infections. The corresponding Peto OR was 3.4 (95% CI, 1.8 to 6.5).

Azathioprine versus sulfasalazine. One RCT including 245 Crohn's disease patients compared azathioprine with sulfasalazine and reported on infections.[207]

Serious infections. The 1971 RCT reported serious infections during the induction period in two of 59 (3%) patients on azathioprine and zero of 74 patients on sulfasalazine.[207] During maintenance therapy, four of 54 (7%) patients on azathioprine and zero of 58 patients on sulfasalazine had a serious infection.

Opportunistic infections. This RCT did not report on opportunistic infections.

Any infection. The 1971 study reported non-serious infections during induction in 8% of patients on azathioprine and 14% of patients on sulfasalazine.[207] The corresponding Peto OR was 0.6 (95% CI, 0.2 to 1.8). During maintenance therapy, infections were reported in 31% of patients on azathioprine and 54% of patients on sulfasalazine. The corresponding Peto OR was 0.4 (95% CI, 0.2 to 0.9).

Combination of immunomodulators and corticosteroids versus corticosteroids. Three RCTs including 263 Crohn's disease patients compared a combination of immunomodulators and corticosteroids with corticosteroids alone and reported on infections.[89 92 98]

Serious infections. None of the RCTs reported on serious infections for this comparison.

Opportunistic infections. None of the RCTs reported on opportunistic infections for this comparison.

Any infections. Three RCTs including 263 patients reported on any infections.[89 92 98] A 4-month induction trial compared a combination of azathioprine and prednisolone with prednisolone alone and reported no infections in the 42 patients.[92] A 7-month induction trial reported adverse events that occurred in at least 10% of the study population.[89] Nasopharyngitis was reported in seven of 52 (13%) patients receiving azathioprine and prednisone and three of 28 (11%) patients receiving prednisone. The corresponding Peto OR was 1.3 (95% CI, 0.3 to 5.1). A 16-week induction trial reported influenza in 10 of 94 (11%) patients on methotrexate and prednisone compared with six of 47 (13%) patients on prednisone.[98] The corresponding Peto OR was 0.9 (95% CI, 0.3 to 2.6). Pneumonia was reported in one patient taking methotrexate and prednisone and no patients taking prednisone.[98]

Combination of immunomodulators with corticosteroids versus no therapy. The claims-based study that included 8,581 Crohn's disease patients reported opportunistic infections, candidiasis, and tuberculosis together.[198] Two of these infections were reported in 19 person-years of followup on a combination of immunomodulator and corticosteroid compared with 305 infections in 15,673 person-years of followup without any claims for medical treatment of Crohn's disease. The study reported a HR of 4.8 (95% CI, 2.7 to 8.3) comparing a combination of immunomodulators and corticosteroids (with or without infliximab) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. The corresponding unadjusted rate ratio was 5.4 (95% CI, 0.7 to 19.7).

Any infection. The claims-based study also reported on four additional infections that were not specifically identified by the authors as serious. The study had 19 person-years of followup on patients receiving an immunomodulator and corticosteroid compared with 15,673 person-years

of followup on patients receiving no therapy.[198] The reported infections included herpes simplex (0 in the combination group versus 134 in the no therapy group); herpes zoster (0 in the combination group versus 123 in the no therapy group); sepsis (6 in the combination group versus 1,833 in the no therapy group; adjusted HR comparing a combination of immunomodulators and corticosteroids [with or without infliximab] with no therapy, 1.2; 95% CI, 0.8 to 1.8; unadjusted rate ratio, 2.7; 95% CI, 1.0 to 5.9), and encephalopathy, encephalitis, or meningitis (3 in the combination group versus 499 in the no therapy group; corresponding unadjusted rate ratio, 5.0; 95% CI, 1.0 to 14.6).

Corticosteroids

Table 42 summarizes the risk of serious infections in studies evaluating corticosteroids in patients with Crohn's disease. Figure 26 and Table 43 summarize the risk of any infection in RCTs and observational studies, respectively, evaluating corticosteroids in patients with Crohn's disease. Additional details about the studies are given below. We did not identify any RCT or observational study that evaluated corticosteroids in patients with Crohn's disease and reported on opportunistic infections.

Table 42. Summary of the risk of serious infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Design	Corticosteroid	Comparison	# of serious infections in steroid group	# of patients in steroid group	# of serious infections in comparison group	# of patients in comparison group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lichtenstein, 2006[174]	99	Prospective cohort	Prednisone	No prednisone	61	2142	45	4111	2.9 (1.9 to 4.3)	2.2 (1.5 to 3.3)

Steroid = corticosteroid

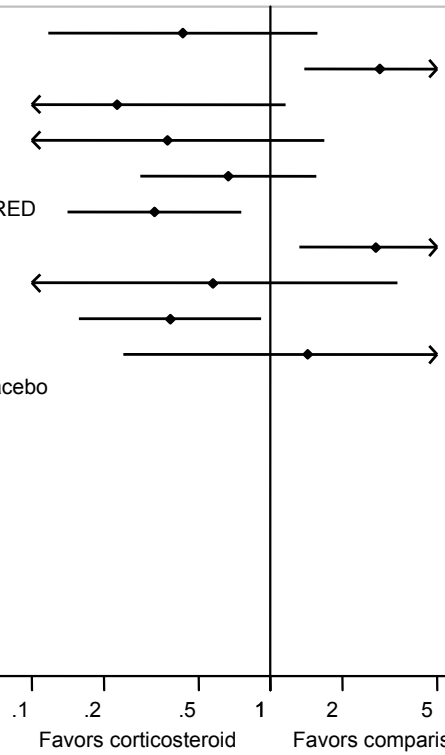
Table 43. Summary of the risk of other infections in observational studies comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author, year	Followup (weeks)	Design	Corticosteroid	Comparison	# of other infections in steroid group	# of patients in steroid group	# of other infections in comparison group	# of patiengs in comparison group	Unadjusted OR (95% CI)
Goldstein, 1967[183]	NR	Retrospective cohort	Corticosteroid	Never corticosteroid	95	430	17	124	1.7 (1.0 to 2.8)

CI = confidence interval; NR = not reported; OR = odds ratio; steroid = corticosteroid

Figure 26. Summary of Peto odds ratios of other infections among randomized controlled trials comparing a corticosteroid alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	Outcome definition	Corticosteroid	Comparison	OR* (95% CI)	Weeks	# events steroid	N steroid	# events comp	N comp
Tremaine 2002	Respiratory infection	BUDE	Placebo	0.43 (0.12, 1.57)	8	10	159	5	41
Summers 1979	Any infections	PRED	Placebo	2.88 (1.39, 6.00)	17	27	85	10	77
Summers 1979	Perianal abscess	PRED	Placebo	0.23 (0.04, 1.16)	NR	1	85	5	77
Summers 1979	Total abscess	PRED	Placebo	0.37 (0.08, 1.68)	104	2	85	5	77
Summers 1979	Any infections	PRED	Placebo	0.67 (0.28, 1.56)	104	8	61	19	101
Singleton 1979	Any infections	SUL + PRED	Placebo + PRED	0.33 (0.14, 0.75)	8	19	43	33	46
Summers 1979	Any infections	PRED	SUL	2.76 (1.32, 5.76)	17	27	85	10	74
Summers 1979	Total abscess	PRED	SUL	0.57 (0.10, 3.40)	104	2	85	3	74
Summers 1979	Any infections	PRED	SUL	0.38 (0.16, 0.91)	104	8	61	17	58
Summers 1979	Total abscess	PRED	SUL	1.44 (0.24, 8.55)	104	3	61	2	58
Campieri 1997	UTI	BUDE + Placebo	PREDL + Placebo	(Excluded)	12	NR†	119	NR†	58
Summers 1979	Other abscess	PRED	Placebo	(Excluded)	8	1	85	0	77
Summers 1979	Other abscess	PRED	Placebo	(Excluded)	104	2	61	1	101
Summers 1979	Total abscess	PRED	Placebo	(Excluded)	104	3	61	1	101
Summers 1979	Other abscess	PRED	SUL	(Excluded)	104	1	85	0	74
Summers 1979	Perianal abscess	PRED	SUL	(Excluded)	104	1	85	3	74
Summers 1979	Other abscess	PRED	SUL	(Excluded)	104	2	61	0	58



Peto Odds Ratio and 95% Confidence Intervals for Other Infections

BUDE = budesonide; CI = confidence interval; Comp = comparison; NR = not reported; OR = odds ratio; PRED = prednisone; steroid = corticosteroid; UTI = urinary tract infections

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

† The number of patients with urinary tract infections was reported to be higher in the budesonide twice daily group.

Corticosteroids versus placebo. Two RCTs including 362 Crohn's disease patients compared corticosteroids with placebo and reported on infections.[100 207]

Serious infections. One RCT including 302 patients reported on serious infections.[207] The 1971 study reported serious infections during the induction period in two of 85 (2%) patients on prednisone and three of 55 (4%) patients on placebo.[207] The corresponding Peto OR was 0.4 (95% CI, 0.03 to 3.8). During the maintenance trial, four of 61 (7%) patients on prednisone and two of 101 (2%) patients on placebo had a serious infection.[207] The corresponding Peto OR was 3.5 (95% CI, 0.5 to 39.2).

Any infection. Two trials including 362 patients reported on any infection.[100 207] The 1971 study reported non-serious infections during the induction period in 32% of patients on prednisone and 13% of patients on placebo.[207] The corresponding Peto OR was 2.9 (95% CI, 1.4 to 6.0). During the maintenance trial, 13% of patients on prednisone and 19% of patients on placebo had a non-serious infection.[207] The corresponding Peto OR was 0.7 (95% CI, 0.3 to 1.6). A trial comparing budesonide with placebo reported common adverse events. Respiratory infections were reported in 10 of 159 (6%) patients on budesonide and five of 41 (12%) patients on placebo (Peto OR, 0.4; 95% CI, 0.1 to 1.6).[100] Flu-like disorder was reported in 6% of budesonide patients and 6% of placebo patients.

Corticosteroids versus no corticosteroids. One prospective study including 6,253 Crohn's disease patients compared corticosteroids with no corticosteroids and reported on infections.[174]

Serious infections. Serious infections were reported in 3% of 2,142 patients on prednisone taken at least 6 months prior to the infection and 1% of 4,111 patients not taking prednisone.[174] The demographic and medication adjusted OR was 2.2 (95% CI, 1.5 to 3.3).

Any infection. This prospective study did not report on any other infections.[174]

Corticosteroids versus no therapy. The claims-based study that included 8,581 Crohn's disease patients reported opportunistic infections, candidiasis, and tuberculosis together.[198] Twenty-five of these infections were reported in 379 person-years of followup for corticosteroid use compared with 305 infections in 15,673 person-years of followup without therapy for Crohn's disease. The study reported a HR of 3.2 (95% CI, 2.1 to 4.8) comparing corticosteroids (with or without immunomodulators and infliximab) with no therapy, adjusted for age, gender, geographic region, health plan, and comorbidity. The HR for corticosteroids only was 3.2 (95% CI, 2.1 to 4.8).

Any infection. The claims-based study also reported on four additional infections that were not specifically identified by the authors as serious. The study reported 379 person-years of followup for corticosteroid users and 15,673 person-years of followup for the no therapy group.[198] The reported infections included herpes simplex (3 in the corticosteroid group versus 134 in the no therapy group; HR for corticosteroids only, 0.9; 95% CI, 0.2 to 2.8); herpes zoster (9 in the corticosteroid group versus 123 in the no therapy group; HR for corticosteroids only, 3.1; 95% CI, 1.6 to 6.2); sepsis (72 in the corticosteroid group versus 1,833 in the no therapy group; adjusted HR comparing corticosteroids [with or without immunomodulators and infliximab] with

no therapy, 1.6; 95% CI, 1.3 to 2.0; HR for corticosteroids only, 1.6; 95% CI, 1.3 to 2.0), and encephalopathy, encephalitis, or meningitis (34 in the corticosteroid group versus 499 in the no therapy group; unadjusted rate ratio for corticosteroids only, 2.6; 95% CI, 1.8 to 3.7).

Corticosteroids versus aminosalicylates. Two RCTs including 216 Crohn's disease patients compared corticosteroids with aminosalicylates and reported on infections.[152 207]

Serious infections. One trial including 159 patients reported on serious infections. The 1971 study reported serious infections during the induction period in two of 85 (2%) patients on prednisone and none of 74 patients on sulfasalazine.[207] During the maintenance trial, four of 61 (7%) patients on prednisone and none of 58 patients onsulfasalazine had a serious infection.[207]

Any infection. Two trials including 216 patients reported on any infection.[152 207] The 1971 study reported non-serious infections during the induction period in 32% of 85 patients on prednisone and 14% of patients on sulfasalazine patients (Peto OR, 2.8; 95% CI, 1.3 to 5.8).[207] During the maintenance trial, 13% of patients on prednisone and 29% of patients on sulfasalazine had a non-serious infection (Peto OR, 0.4; 95% CI, 0.2 to 0.9).[207] A RCT comparing 29 patients on budesonide with 28 patients on mesalamine reported 19 infections in budesonide patients and 16 in mesalamine patients.[152] The infections reported included upper respiratory tract infections and urinary tract infections.

Combination of prednisone and sulfasalazine versus sulfasalazine. One RCT including 89 Crohn's disease patients reported on infections for this comparison.[110]

Serious infections. Serious infections were not reported in this RCT.

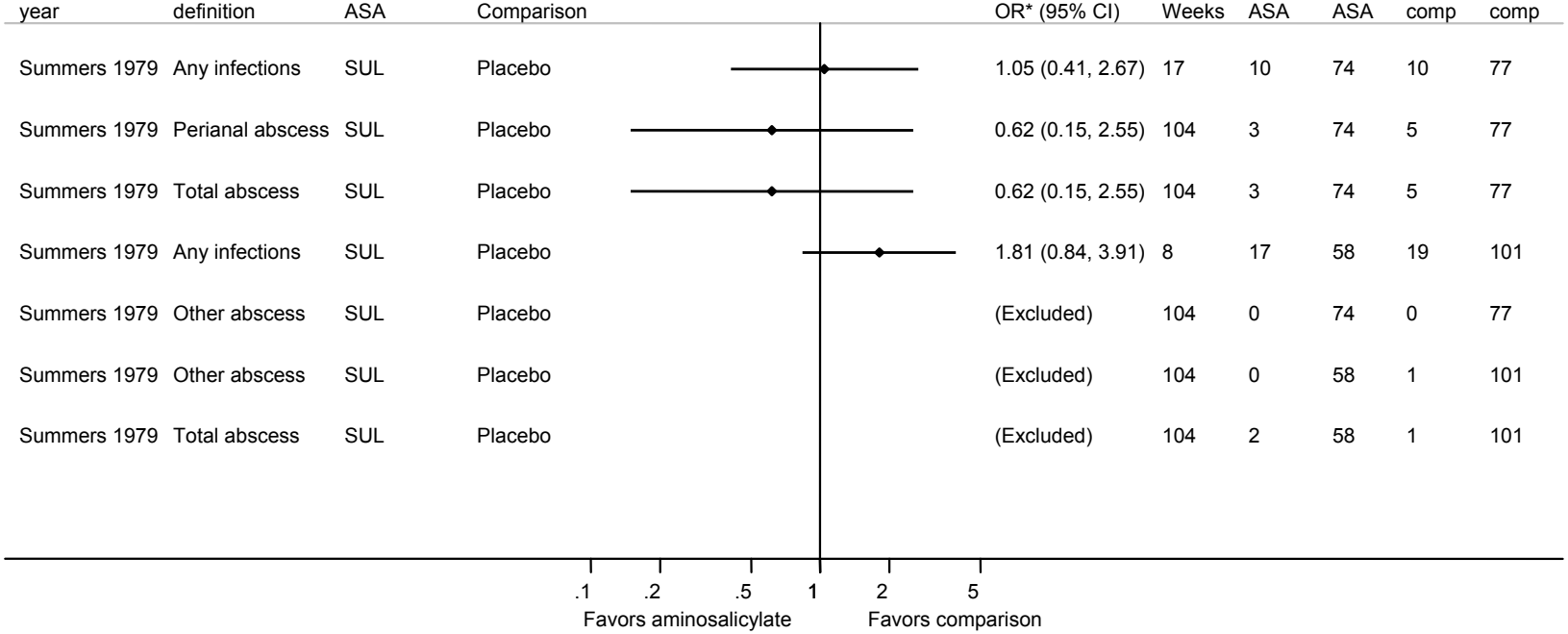
Any infection. During the 8-week induction trial, 44% of 43 patients on prednisone and 72% of 46 patients on sulfasalazine were reported to have an infection.[110] The corresponding Peto OR was 0.3 (95% CI, 0.1 to 0.8).

Aminosalicylates

Figure 27 summarizes the risk of infection in the one RCT evaluating infections associated with use of aminosalicylates in patients with Crohn's disease.

Figure 27. Summary of Peto odds ratios of other infections in a randomized controlled trial comparing an aminosalicylate alone or in combination with placebo or another treatment in patients with Crohn's disease

Author year	Outcome definition	ASA	Comparison	OR* (95% CI)	Weeks	# events ASA	N ASA	# events comp	N comp
Summers 1979	Any infections	SUL	Placebo	1.05 (0.41, 2.67)	17	10	74	10	77
Summers 1979	Perianal abscess	SUL	Placebo	0.62 (0.15, 2.55)	104	3	74	5	77
Summers 1979	Total abscess	SUL	Placebo	0.62 (0.15, 2.55)	104	3	74	5	77
Summers 1979	Any infections	SUL	Placebo	1.81 (0.84, 3.91)	8	17	58	19	101
Summers 1979	Other abscess	SUL	Placebo	(Excluded)	104	0	74	0	77
Summers 1979	Other abscess	SUL	Placebo	(Excluded)	104	0	58	1	101
Summers 1979	Total abscess	SUL	Placebo	(Excluded)	104	2	58	1	101



Peto Odds Ratio and 95% Confidence Intervals for Other Infections

ASA = aminosalicylate; CI = confidence interval; Comp = comparison; Main = main intervention; OR = odds ratio; SUL = sulfasalazine
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Sulfasalazine versus placebo. One RCT on this comparison included 159 Crohn's disease patients and reported on infections.[207]

Serious infections. The 1971 trial reported serious infections in zero of 74 patients on sulfasalazine and three of 55 patients on placebo.[207] During maintenance therapy, serious infections were reported in zero of 61 patients on sulfasalazine and two of 101 patients on placebo.

Opportunistic infections. This RCT did not report on opportunistic infections.

Any infection. The 1971 trial reported non-serious infections during the induction period in 14% of patients on sulfasalazine and 13% of patients on placebo.[207] The corresponding Peto OR was 1.1 (95% CI, 0.4 to 2.7). During the maintenance trial, 29% of patients on sulfasalazine and 19% of patients on placebo had an infection (Peto OR, 1.8; 95% CI, 0.8 to 3.9).

Studies Evaluating Patients with Inflammatory Bowel Disease

Eight studies reported infections in inflammatory bowel disease patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. Details about these studies are given in Appendix F.

Case-Control Studies Designed to Examine Specific Infections

Two case-control studies including 2,538 inflammatory bowel disease patients were designed to examine specific infections. One study reported on opportunistic infections[181] and the other on herpes zoster.[177] The case-control studies were nested within a large primary care database covering multiple centers[177] and a single center.[181] Both studies may have patients that contributed to other studies using these data sources.[175 176 178-180]

Combinations including infliximab. One study including 300 inflammatory bowel disease patients reported on specific infections associated with combination therapy including infliximab.[181]

Infliximab versus no inflammatory bowel disease medication. The single center case-control study cross-referenced the system's diagnostic index for inpatient and outpatient inflammatory bowel disease patients with a viral, fungal, or bacterial opportunistic infection.[181] Infections were confirmed by microbiologic, pathologic, or physician consensus. The first 100 consecutive infection cases diagnosed between 1998 and 2003 were analyzed and matched to two controls (who did not have an opportunistic infection) per case by type of inflammatory bowel disease, sex, geographic region, and duration of visits for inflammatory bowel disease at the center. Three of 100 (3%) opportunistic infection cases had used infliximab alone while a patient at the center compared with two of 200 (1%) controls. Compared with no use of mesalamine, corticosteroids, immunomodulators, and infliximab, the age and matching factor adjusted OR was 11.1 (95% CI, 0.8 to 148). The percent of cases and controls that did not use an inflammatory bowel disease medication was not provided. One case developed Epstein-Barr virus lymphoma, but the

medication history of this patient was not provided. The authors also reported that no patient died as a result of their opportunistic infection.

Combination of infliximab, thiopurines, and corticosteroids versus no inflammatory bowel disease medication. The single center case-control study reported five of 100 (5%) opportunistic infection cases compared with zero of 200 (0%) matched controls used a triple combination of infliximab, thiopurines, and corticosteroids.[181]

Combination of infliximab and thiopurines versus no inflammatory bowel disease medication. The single center case-control study reported one of 100 (1%) opportunistic infection cases compared with five of 200 (2%) matched controls used a combination of infliximab and thiopurines.[181] Compared with no inflammatory bowel disease medication use, the age and matching factor adjusted OR was 1.6 (95% CI, 0.1 to 19).

Combinations including immunomodulators. Two case-control studies including 2,538 inflammatory bowel disease patients reported on specific infections associated with combination therapy including immunomodulators.[177 181]

Thiopurines versus no inflammatory bowel disease medication. The single center case-control study reported that 20 of 100 (20%) opportunistic infection cases compared with 31 of 200 (15%) matched controls used thiopurines alone (compared with no inflammatory bowel disease medication, the age and matching factor adjusted OR was 3.4; 95% CI, 1.5 to 7.5).[181]

A case-control study of herpes zoster infections was reported in inflammatory bowel disease patients within a multi-center general practice database.[177] Controls were matched to cases on sex, year of birth, duration of followup (prior to the case's herpes zoster diagnosis date). Up to four controls that did not have herpes zoster during the followup were matched to each case. Herpes zoster cases had a four times increased odds of having a prescription for thiopurines alone versus no inflammatory bowel disease medication in the 30 days prior to the index date compared with controls (OR, 4.1; 95% CI, 1.9 to 8.7). When corticosteroids and mesalamine were adjusted in the model instead of excluded, the OR was 3.1 (95% CI, 1.7 to 5.6). When thiopurine use was considered 31 to 90 days before herpes zoster index date, the odds of infection with thiopurine use were no longer increased (OR, 0.6; 95% CI, 0.2 to 1.8).

Combination of thiopurines and corticosteroids versus no inflammatory bowel disease medication. The single-center case-control study reported 16 of 100 (16%) opportunistic infection cases compared with six of 200 (3%) matched controls used a combination of infliximab and thiopurines.[181] Compared with no inflammatory bowel disease medication use, the age and matching factor adjusted OR was 17.5 (95% CI, 4.5 to 68). The multi-center case-control study reported herpes zoster cases had a three times increased odds of having a prescription for thiopurines alone versus no inflammatory bowel disease medication in the 30 days prior to the index date compared with controls (OR, 3.0; 95% CI, 1.2 to 7.3).[177]

Combinations including corticosteroids. Two case-control studies including 2,538 inflammatory bowel disease patients reported on specific infections associated with combination therapy including corticosteroids.[177 181]

Corticosteroids versus no inflammatory bowel disease medication. The single center case-control study reported 16 of 100 (15%) opportunistic infection cases compared with 27 of 200 (14%) matched controls used corticosteroids alone (compared with no inflammatory bowel disease medication, the age and matching factor adjusted OR was 2.2, 95% CI, 1.0 to 4.9).[181] The multiple center case-control study reported herpes zoster cases had a 60% increased odds of prescription for thiopurines alone versus no inflammatory bowel disease medication in the 30 days prior to the index date compared with controls (OR, 1.6; 95% CI, 1.1 to 2.4).[177]

Combinations including aminosalicylates. One case-control study including 2,238 inflammatory bowel disease patients reported on specific infections associated with combination therapy including aminosalicylates.[177]

Mesalamine versus no mesalamine. The multiple center case-control study reported herpes zoster cases had no increased odds of having a prescription for mesalamine compared with controls in the 30 days prior to the index date (OR, 0.9; 95% CI, 0.7 to 1.2).[177]

Tuberculosis

Tuberculosis is of special concern in Crohn's disease because the treatments suppress the immune system. The FDA has mandated a warning on infliximab and adalimumab regarding the risk of tuberculosis.[208 209] Nine RCTs (n = 3,295) and four observational studies (n = 2,166) reported on the risk of tuberculosis in patients receiving treatment for Crohn's disease (Appendix D, Evidence Table 14). Four of the RCTs reported excluding patients with a prior history of tuberculosis. None of the RCTs described active assessment of tuberculosis specifically.

No RCTs of natalizumab, ustekinumab, immunomodulators, corticosteroids, or aminosalicylates reported tuberculosis as an outcome. A study published in 1970 randomized patients to sulfasalazine, prednisone, or azathioprine and included isoniazid as part of the treatment regimen in patients randomized to prednisone because of the known increased risk of tuberculosis associated with prednisone.[93]

Table 44 summarizes the reported rates of tuberculosis in studies of the treatment of Crohn's disease. Additional details of the studies are given below.

Table 44. Summary of reported rates of tuberculosis in randomized controlled trials* comparing the safety of therapies for the management of Crohn's disease

Author, year	Design, duration N with CD New users only (Y/N)	Comparison, dose	Specific aim (Y/N)	Ascertainment of tuberculosis during study Exclusion of tuberculosis before enrollment	Concomitant medications	Tuberculosis results
Hanauer, 2002[126]	RCT, 52 wk 573 N	Infliximab vs placebo	N	Not specified N	5-ASA Steroids IMM Antibiotics	1/385 (<1%) vs 0/188 (0%)
Colombel, 2010[83]	RCT, 52 wk 503 Y	Infliximab vs azathioprine vs infliximab + azathioprine	N	Not specified Y	5-ASA Steroids Antibiotics NR	0/161 (0%) vs 0/163 (0%) vs 1/179 (1%)
Colombel, 2009[135]	Unblinded RCT, 52 wk 778 N	Adalimumab vs placebo	N	Not specified Y	5-ASA Steroids IMM Antibiotics NR	2/517 (<1%) vs 0/261 (0%)
Sandborn, 2007[130]	RCT, 52 wk 55 N	Adalimumab vs placebo	N	Not specified Y	5-ASA Steroids IMM Antibiotics	0/37 (0%) vs 0/18 (0%)
Sandborn, 2007[79]	RCT, 4 wk 325 N	Adalimumab vs placebo	N	Not specified Y		0/159 vs 0/166
Hanauer, 2006[78]	RCT, 4 wk 299 Y	Adalimumab vs placebo	N	Not specified Y	5-ASA Steroids IMM Antibiotics	0/225 (0%) vs 0/74(0%)
Schreiber, 2007[131]	RCT, 18 wk 668 N	Certolizumab pegol vs placebo	N	Not specified Y	5-ASA Steroids IMM Antibiotics	1/216 (<1%) vs 0/212 (0%)
Schreiber, 2005[81]	RCT, 12 wk 292 N	Certolizumab pegol vs placebo	N	Not specified Y		0/219 vs 0/73
Winter, 2001[82]	RCT, 12 wk 92 N	Certolizumab pegol vs placebo	N	Not specified Y		0/68 vs 0/24

ASA = aminosalicylates; CD = Crohn's disease; IBD = inflammatory bowel disease; IMM = immunomodulators; N = no; NR = not reported; RCT = randomized controlled trial; Steroids = corticosteroids; vs = versus; wk = weeks; Y = yes

*Four observational studies reported on tuberculosis. Two cases among 743 infliximab users compared with no cases among 666 never users of biologic.[192] No cases among 757 patients treated with combinations of medications with infliximab or infliximab alone.[179 186 203]

Infliximab versus placebo. One RCT[126] including 573 patients evaluated infliximab compared with placebo. One incident case of tuberculosis was detected in an infliximab patient.

Adalimumab versus placebo. Four RCTs[78 79 129 130] including 1,447 patients compared adalimumab with placebo. One of those studies[129] reported two cases of tuberculosis (one patient receiving adalimumab 40 mg weekly and one patient receiving adalimumab 40 mg every other week compared with none receiving placebo). The other three studies reported no incident cases of tuberculosis. Patients with untreated tuberculosis within three months were excluded from one of the studies.[79]

Certolizumab pegol versus placebo. Three RCTs including 812 Crohn's disease patients compared certolizumab pegol with placebo and reported on tuberculosis.[81 82 131] A maintenance trial after induction response reported one tuberculosis case in the certolizumab pegol group (<1% of 216 patients) during 26 weeks of followup despite the exclusion of purified protein derivative (PPD) positive patients from the study.[131] Another trial also excluded patients with prior tuberculosis. They reported no incident cases of tuberculosis in the 68 patients receiving certolizumab pegol or 24 patients receiving placebo.[82] An induction trial reported no cases of tuberculosis in 219 patients receiving certolizumab pegol or 73 patients receiving placebo . All patients in this trial received a chest x-ray for tuberculosis screening within 12 weeks of enrollment and at the final visit.[81]

Other combinations with infliximab. An induction trial[83] including 503 Crohn's disease patients compared infliximab, azathioprine, and the combination of infliximab and azathioprine. One incident case of tuberculosis was reported in the group receiving infliximab and azathioprine.

Four retrospective studies including 2,166 patients reported on tuberculosis.[179 186 192 203] Three studies compared combinations of medications with infliximab and reported no tuberculosis cases.[179 186 203] One study reported two tuberculosis cases among 743 infliximab users compared with no cases among 666 non-users.[192]

Infusion- and Injection-Site Reactions

Infusion reactions can include a wide range of symptoms (from local irritation or pain to anaphylaxis) that occur during or shortly after an infusion. Within the studies below, this definition is generally consistent (when reported). Other types of reactions can occur a few days to a few weeks after medication administration including hypersensitivity-type reactions, delayed infusion reactions, and serum sickness. These longer-term reactions are not addressed in this review. In some cases, the study authors did not define the symptoms and timing of the infusion reactions, but such studies were included in this review.

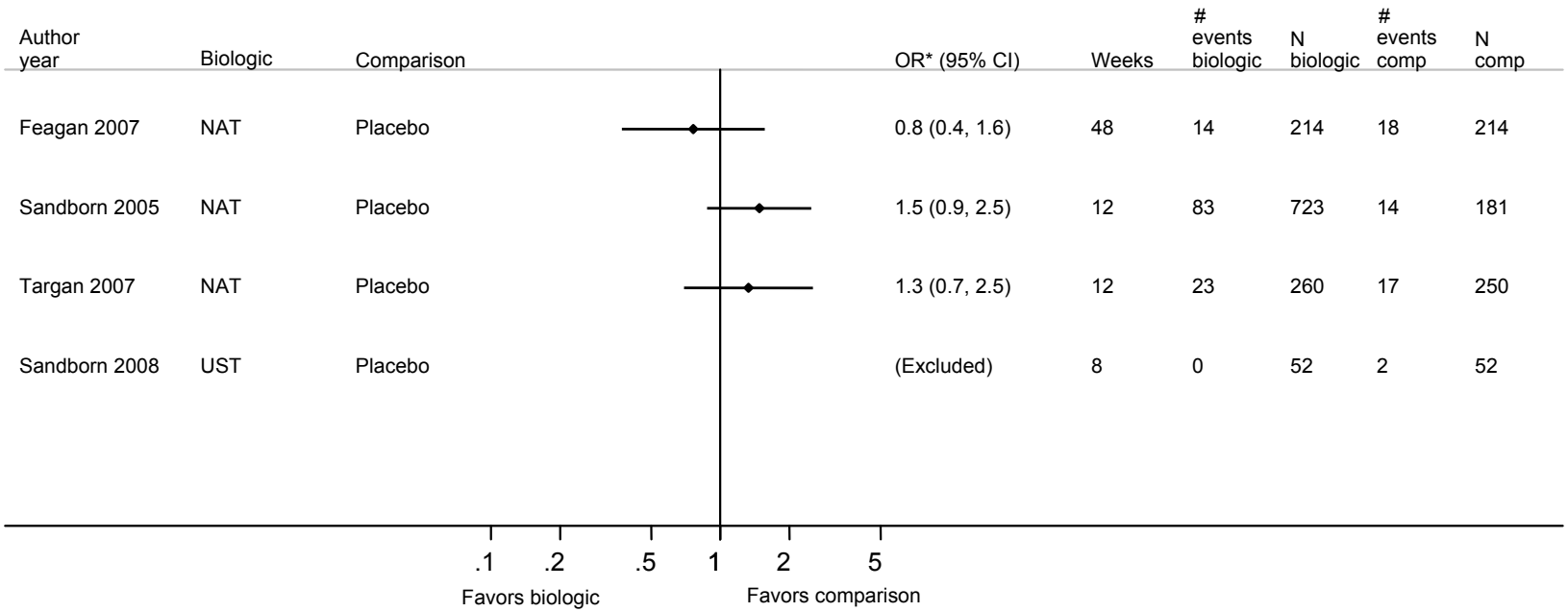
Twenty-one RCTs including 6,371 patients reported infusion reactions as an outcome by comparison group, one of which addressed infusion reactions as a primary outcome of interest (Appendix D, Evidence Table 14).[132] Three prospective studies (with 394 patients) and eight retrospective studies (with 2,457 patients) reported infusion reactions as an outcome. Two observational studies mentioned active ascertainment as a means of identifying infusion reactions.[180 210] All retrospective studies relied on chart review for identification of infusion

reactions. Many of the prospective and retrospective studies specifically stated or implied that patients were pre-treated with medications at the infusion center to prevent infusion reactions. Most RCTs did not report pre-treating patients with medications to prevent infusion reactions.

Ustekinumab and Natalizumab

Figure 28 summarizes the data on infusion- and injection-site reactions in RCTs evaluating either ustekinumab or natalizumab in patients with Crohn's disease. Additional details are given below.

Figure 28. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing a biologic alone or in combination with another treatment in patients with Crohn's disease



Peto Odds Ratio and 95% Confidence Intervals for Infusion- and Injection- Site Reactions

CI = confidence interval; comp = comparison; NAT = natalizumab; OR = odds ratio; UST = ustekinumab
*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Ustekinumab versus placebo. One crossover RCT, including 104 patients, compared ustekinumab with placebo and reported infusion reactions.[75] Two of 52 patients on ustekinumab and zero of 52 patients on placebo experienced any adverse event during or within 1 hour of infusion in the first 8 weeks of the induction trial. Four additional infusion reactions were reported after patients had been exposed to both ustekinumab and placebo after crossover or during the open-label period after the trial.

Natalizumab versus placebo. Three RCTs including 1,414 Crohn's disease patients reported in two publications reported infusion reactions for in patients receiving natalizumab compared with placebo.[26 76] A 12-week induction trial reported acute reactions within 2 hours of the start of infusion in 9% (23 out of 260) of new users of natalizumab and 7% (17 out of 250) of patients taking placebo.[26] The corresponding Peto OR was 1.3 (95% CI, 0.7 to 2.5). Another 12-week induction trial reported any adverse event occurring during or within 2 hours of the start of infusion in 11% (83 out of 723) of natalizumab users and 8% (14 out of 181) of placebo users.[76] The 228 responders from this trial were re-randomized for a 48-week maintenance trial.[76] Any adverse event occurring during or within 2 hours of infusion were reported in 7% (14 out of 214) of natalizumab users and 8% (18 out of 214) of placebo users. The corresponding Peto OR was 1.5 (95% CI, 0.9 to 2.5) for induction and 0.8 (95% CI, 0.4 to 1.6) for maintenance therapy.

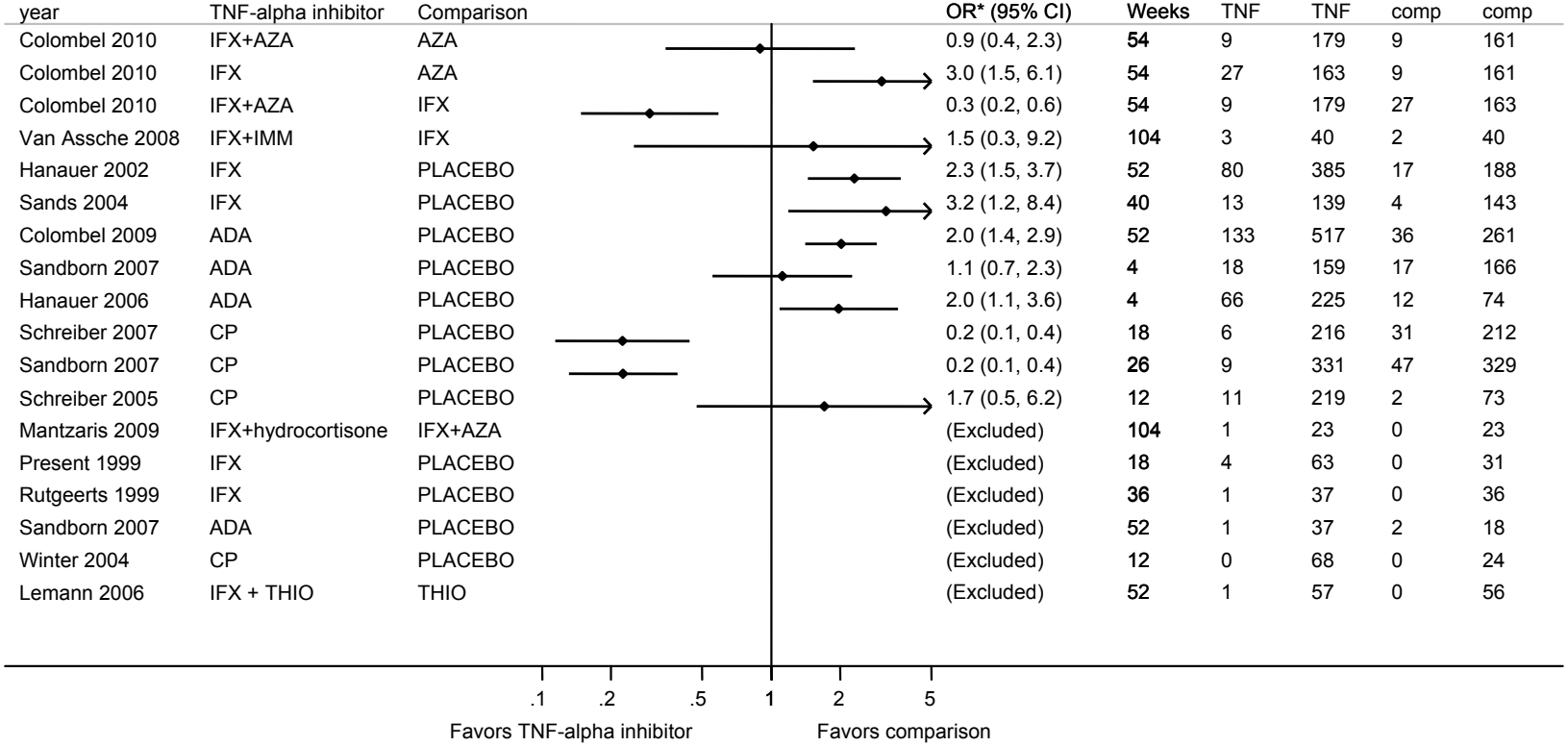
Combination of natalizumab and infliximab versus infliximab. One 20-week RCT including 79 non-responders to infliximab randomized patients to continued infliximab alone or natalizumab in addition to infliximab. Three of 52 patients taking natalizumab and infliximab had a non-serious hypersensitivity reaction during or within 120 minutes of infusion compared with zero of 27 patients taking only infliximab.[27]

TNF-Alpha Inhibitors

We tried to conduct meta-analyses separately for induction and maintenance RCTs comparing TNF-alpha inhibitors with placebo in terms of infusion- and injection-site reactions for those studies that were combined in KQs 1 and 2, but we were unable to do so because of statistical heterogeneity (I-squared, 82% for induction trials and 87% for maintenance trials). Figures 29 and 30 summarize the data on infusion- and injection-site reactions in RCTs and observational studies evaluating TNF-alpha inhibitors in patients with Crohn's disease. Additional details are given below.

Figure 29. Summary of Peto odds ratios of infusion- and injection-site reactions among randomized controlled trials comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease

Author year	TNF-alpha inhibitor	Comparison	OR* (95% CI)	Weeks	# events TNF	N TNF	# events comp	N comp
Colombel 2010	IFX+AZA	AZA	0.9 (0.4, 2.3)	54	9	179	9	161
Colombel 2010	IFX	AZA	3.0 (1.5, 6.1)	54	27	163	9	161
Colombel 2010	IFX+AZA	IFX	0.3 (0.2, 0.6)	54	9	179	27	163
Van Assche 2008	IFX+IMM	IFX	1.5 (0.3, 9.2)	104	3	40	2	40
Hanauer 2002	IFX	PLACEBO	2.3 (1.5, 3.7)	52	80	385	17	188
Sands 2004	IFX	PLACEBO	3.2 (1.2, 8.4)	40	13	139	4	143
Colombel 2009	ADA	PLACEBO	2.0 (1.4, 2.9)	52	133	517	36	261
Sandborn 2007	ADA	PLACEBO	1.1 (0.7, 2.3)	4	18	159	17	166
Hanauer 2006	ADA	PLACEBO	2.0 (1.1, 3.6)	4	66	225	12	74
Schreiber 2007	CP	PLACEBO	0.2 (0.1, 0.4)	18	6	216	31	212
Sandborn 2007	CP	PLACEBO	0.2 (0.1, 0.4)	26	9	331	47	329
Schreiber 2005	CP	PLACEBO	1.7 (0.5, 6.2)	12	11	219	2	73
Mantzaris 2009	IFX+hydrocortisone	IFX+AZA	(Excluded)	104	1	23	0	23
Present 1999	IFX	PLACEBO	(Excluded)	18	4	63	0	31
Rutgeerts 1999	IFX	PLACEBO	(Excluded)	36	1	37	0	36
Sandborn 2007	ADA	PLACEBO	(Excluded)	52	1	37	2	18
Winter 2004	CP	PLACEBO	(Excluded)	12	0	68	0	24
Lemann 2006	IFX + THIO	THIO	(Excluded)	52	1	57	0	56

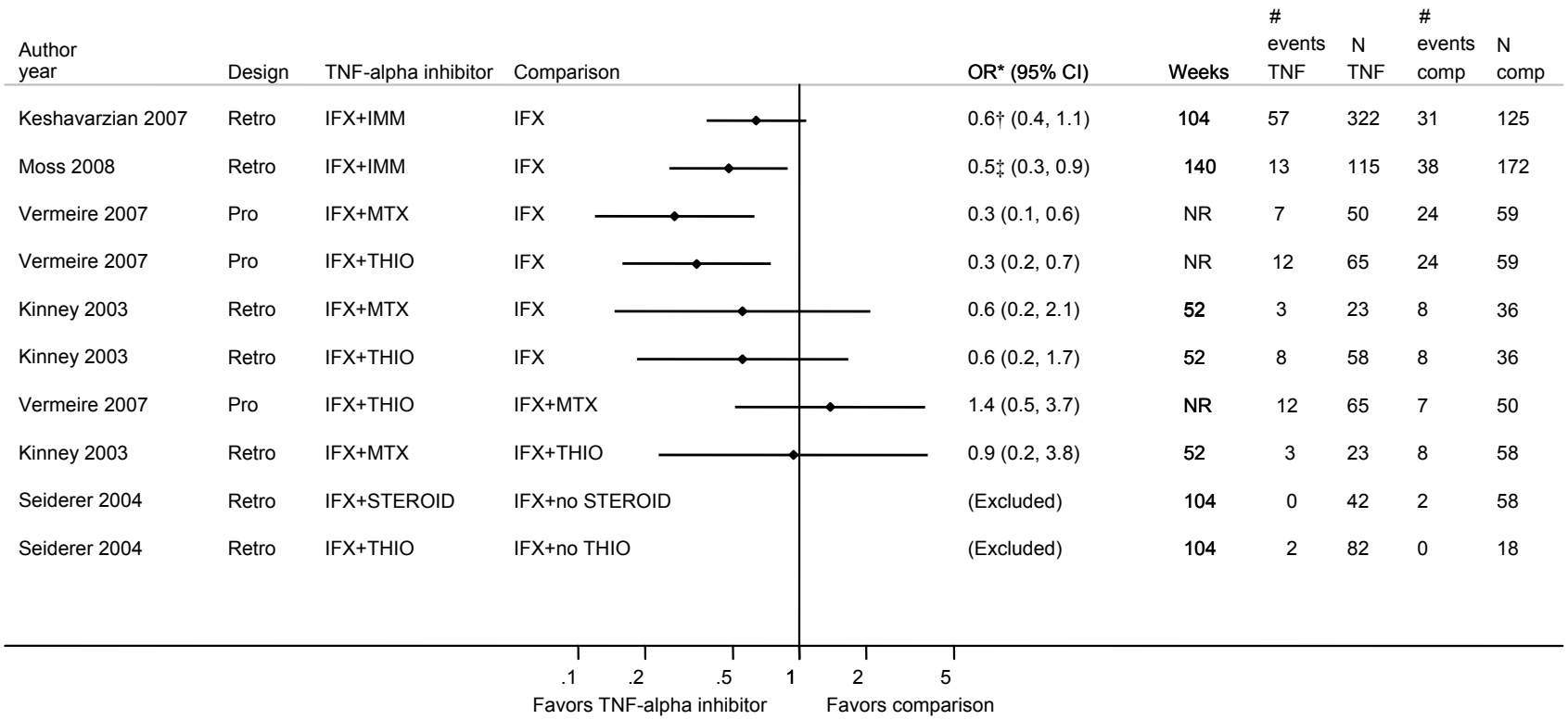


Peto Odds Ratio and 95% Confidence Intervals for Infusion- and Injection-Site Reactions

ADA = adalimumab; AZA = azathioprine; CI = confidence interval; comp = comparison; CP = certolizumab pegol; IFX = infliximab; OR = odds ratio; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

* We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

Figure 30. Summary of Peto odds ratios of infusion- and injection-site reactions among observational studies comparing a TNF-alpha inhibitor alone or in combination with another treatment in patients with Crohn's disease



Peto Odds Ratio and 95% Confidence Intervals for Infusion- and Injection-Site Reactions

ADA = adalimumab; AZA = azathioprine; CI = confidence interval; comp = comparison; CP = certolizumab pegol; IFX = infliximab; NR = not reported; OR = odds ratio; Pro = prospective study; Retro = retrospective study; STEROID = corticosteroids; THIO = thiopurine; TNF = tumor necrosis factor-alpha inhibitor

*We did not calculate odds ratios when there were fewer than five events total in the main intervention and comparison arms.

†Adjusted odds ratio, 0.7 (95% CI, 0.4 to 1.1).

‡Adjusted odds ratio, 0.3 (95% CI, 0.2 to 0.9)

Infliximab versus placebo. Four RCTs including 1,022 patients compared infliximab with placebo and reported infusion reactions.[24 126 128 137] An 18-week induction trial of 94 fistulizing Crohn's disease patients compared infliximab infusion with placebo.[24] They reported four of 63 (6%) patients on infliximab and zero of 31 patients on placebo experienced an adverse event during or within 2 hours of infusion. The adverse events were chest pain with flushing, dizziness, fever, and headache.

A 36-week trial[128] compared retreatment with infliximab or placebo among 73 responders to a single induction dose in a previous 12-week trial.[77] An acute infusion reaction with dyspnea was reported in one of 36 infliximab patients. No infusion reactions were reported in 36 patients on placebo, although it is unclear if infusion reactions were a possible safety outcome for placebo patients. The trial corresponding to the induction period reported infusion reactions only for those who received two doses of infliximab (the second after the randomized period) and infusion reactions occurring during the second infusion only (2 of 29 patients).[77]

A 40-week maintenance trial of 282 responders and non-responders to a 14-week induction period with infliximab for fistulizing Crohn's disease compared infliximab with placebo.[137] They reported infusion reactions during or within 1 hour of infusion in 13 of 139 (9%) patients on infliximab and four of 143 (3%) patients on placebo during the randomized period. The corresponding Peto OR was 3.2 (95% CI, 1.2 to 8.4). During induction, 7% of patients on infliximab and 8% of patients on placebo had an infusion reaction among those who were randomized for maintenance therapy (9 of 306 given induction were not randomized because of adverse events, but the adverse events were not reported). At 22 weeks, placebo patients were eligible to crossover to 5 mg/kg intravenous every eight weeks infliximab treatment and patients receiving 5 mg/kg of infliximab were eligible to have the dose increased to 10 mg/kg (blinding was maintained after crossover). During crossover, 9% of those who had a dose increase to 10 mg/kg experienced an infusion reaction compared with 23% of patients who crossed over to infliximab from placebo.

A 52-week maintenance trial of 573 responders and non-responders to a 2-week induction period of a single infliximab dose compared infliximab with placebo and reported adverse events during or within 1 hour of infusion.[126] Infusion reactions were reported in 21% of infliximab patients and 9% of placebo patients during the maintenance period (reactions during the initial infusion were excluded from reporting). The corresponding Peto OR was 2.3 (95% CI, 1.5 to 3.7).

Combination of infliximab and immunomodulators versus infliximab. Three RCTs including 468 Crohn's disease patients compared a combination of infliximab and immunomodulators with infliximab alone and reported infusion reactions.[83 132 133] A 50-week induction trial compared a combination of infliximab and azathioprine with infliximab among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[83] They reported adverse events during or within 1 hour of infusion in 5% of 179 patients taking infliximab and azathioprine and 17% of 163 patients taking infliximab.[83] The corresponding Peto OR was 0.3 (95% CI, 0.2 to 0.6).

A 104-week induction trial of blinded physicians and unblinded steroid-dependent luminal Crohn's disease patients reported severe infusion reactions in zero of 23 patients taking infliximab and azathioprine and one of 23 patients taking infliximab and hydrocortisone.[132] The group taking infliximab and azathioprine included only azathioprine-naïve patients whereas the infliximab group included both azathioprine-naïve patients as well as those who had previously

been exposed to azathioprine for less than a month (but treatment was stopped because of intolerance or severe adverse events). The infliximab group received a pre-infusion dose of hydrocortisone whereas the infliximab and azathioprine group did not.

A 104-week open-label retreatment trial of non-fistulizing Crohn's disease patients reported that three unspecified infusion reactions occurred in the 40 patients taking infliximab and an immunomodulator (it is possible that these reactions occurred in the same person) and two infusion reactions occurred in the 40 patients taking infliximab.[133]

Combination of infliximab and immunomodulators versus immunomodulators. Two RCTs (N = 452)[83 84] and four observational studies (N = 1025)[188 193 195 211] including 1,477 Crohn's disease patients reported infusion reactions in users of infliximab and an immunomodulator compared with users of an immunomodulator only.

A 52-week induction trial in steroid-dependent, luminal Crohn's disease patients reported a severe infusion reaction in one of 57 patients taking infliximab and a thiopurine and none of 56 patients taking a thiopurine.[84] A 50-week induction trial compared infliximab and azathioprine with azathioprine alone among patients who were naïve to TNF-alpha inhibitors, azathioprine, 6-mercaptopurine, and methotrexate.[83] The trial reported adverse events during or within 1 hour of infusion in 5% of 179 patients taking infliximab and azathioprine and 6% of 161 patients taking azathioprine.[83] The corresponding Peto OR was 0.9 (95% CI, 0.4 to 2.3).

One prospective and three retrospective observational studies including 1,025 patients reported on infusion reactions.[188 193 195 211] The prospective study[193] included patients given infliximab without concomitant immunomodulators during 2000 and 2001 before the authors reported that concomitant immunomodulators appeared to be associated with a decreased risk of infusion reactions.[127] During 2002 and 2003, patients were treated with infliximab and concomitant azathioprine, 6-mercaptopurine, or methotrexate.[193] Patients with luminal disease were given a single induction infusion compared with fistulizing disease patients who received a three-dose induction regimen (at 0, 2, and 6 weeks). If clinicians felt the patients lost response or had an acute flare, the patients were retreated with infliximab and considered at risk of infusion reaction. Infusion reactions in retreated patients occurred in 16% of 115 patients taking infliximab and an immunomodulator compared with 40% of 59 patients taking infliximab without an immunomodulator. The Peto OR was similar for both the combination of infliximab and a thiopurine (OR, 0.3; 95% CI, 0.2 to 0.7) and the combination of infliximab and methotrexate (OR, 0.3; 95% CI, 0.1 to 0.6) compared with infliximab.

A retrospective study of 1 year mean followup reported infusion reactions in 11 of 81 (14%) patients taking infliximab and an immunomodulator and eight of 36 (22%) patients taking infliximab.[195] The Peto OR for an infusion reaction was similar for both the combination of infliximab and a thiopurine (OR, 0.6; 95% CI, 0.2 to 1.7) and the combination of infliximab and methotrexate (OR, 0.6; 95% CI, 0.2 to 2.1) compared with infliximab.

A retrospective study with 35 months median followup reported adverse events occurring during or within 1 to 2 hours of infusion in 13 of 115 (11%) patients taking infliximab and a thiopurine and 38 of 172 (22%) patients taking infliximab without a thiopurine.[188] The study reported an OR of 0.3 (95% CI, 0.2 to 0.9) comparing concomitant immunomodulators at first infliximab infusion at the center versus no immunomodulators at first infusion, adjusted for gender, smoking, disease location, treatment regime (on-demand or maintenance infliximab), concomitant steroids, and disease phenotype (Vienna classification).[188] Another publication from

the same center included 123 of these patients receiving infliximab for maintenance only and reported a similar OR.[187]

A retrospective study with 2 years median followup reported adverse events occurring during or within 1 hour of infusion in 18% of 322 patients taking infliximab and an immunomodulator and 25% of 125 patients taking infliximab.[211] The study reported an unadjusted OR comparing combination infliximab and immunomodulators with infliximab alone of 0.7 (95% CI, 0.4 to 1.1).

Combination of infliximab and thiopurines versus combination of infliximab and methotrexate. Two observational studies including 291 Crohn's disease patients compared a combination of infliximab and azathioprine with a combination of infliximab and methotrexate and reported infusion reactions.[193 195] The prospective study of retreated patients reported infusion reactions by type of concomitant immunomodulators. Infusion reactions occurred in 18% of 65 patients taking infliximab and azathioprine compared with 14% of 50 patients taking infliximab and methotrexate.[193] The corresponding Peto OR was 1.4 (95% CI, 0.5 to 3.7). The retrospective study of 1 year mean followup reported infusion reactions in eight of 58 (14%) patients taking infliximab and a thiopurine and three of 23 (13%) patients taking infliximab and methotrexate.[195] The corresponding Peto OR was 0.9 (95% CI, 0.2 to 3.8).

Infliximab versus azathioprine. One RCT including 324 Crohn's disease patients compared infliximab with azathioprine and reported on infusion reactions.[83] Seventeen percent of 163 patients taking infliximab and 6% of 161 patients taking azathioprine experienced an adverse event during or within 1 hour of infusion. The corresponding Peto OR was 3.0 (95% CI, 1.5 to 6.1).

Other combinations with infliximab. Three retrospective studies including 855 Crohn's disease patients met the inclusion criteria but the concomitant medications may be misclassified as described in the mortality section. The three retrospective studies aimed to evaluate the safety profile of infliximab use at their centers.[179 186 205] A retrospective study reported infusion reactions requiring discontinuation in 5% of 127 patients taking infliximab and an immunomodulator compared with 13% of 71 patients receiving infliximab without concomitant immunomodulators as recorded in a database that included most of the patients treated with infliximab at the center.[205] Two retrospective studies of Crohn's disease patients reported infusion reactions in 5% (3 out of 55) and 2% (2 out of 111) of patients receiving a triple combination of infliximab, immunomodulators, and corticosteroids, 20% (10 out of 51) and 4% (12 out of 307) of patients receiving the combination of infliximab and immunomodulator, 0% (0 out of 32) and 7% (3 out of 45) of patients receiving the combination of infliximab and corticosteroid, and 21% (4 out of 19) and 5% (2 out of 37) of patients receiving only infliximab.[179 186] In a previous report from one of these centers, 19 infusion reactions occurred in the first 100 patients given infliximab.[180] . However, a discrepancy was noted in the reporting of concomitant medications among the first 100 patients reported in one article and the first 500 patients reported in another article from the same center. Concomitant medications were reported in 18 of 19 infusion reactions among the first 100 patients,[180] but in only 17 of 19 infusion reactions among the first 500 patients.[179]

Adalimumab versus placebo. Four RCTs including 1,457 Crohn's disease patients compared adalimumab with placebo and reported injection reactions. A 4-week induction trial included 325 patients who did not respond or lost response to infliximab.[79] Injection-site reactions were not defined. Eleven percent of 159 patients using adalimumab and 10% of 166 patients using placebo experienced at least one reaction. The corresponding Peto OR was 1.1 (95% CI, 0.7 to 2.3).

A 4-week induction trial reported unspecified injection-site reactions in 29% of 225 patients using adalimumab and 16% of 74 patients using placebo.[78] The corresponding Peto OR was 2.0 (95% CI, 1.1 to 3.6). The 52-week maintenance trial of the 55 who achieved remission during induction reported injection-site reactions (burning was reported as the most common reaction) in one of 37 patients on adalimumab and two of 18 patients on placebo.[130] Those who were not randomized for the maintenance study received adalimumab without blinding. Twenty-six of 221 (12%) patients who entered open-label adalimumab therapy or were not randomized for the maintenance trial were reported to have an infusion reaction.[130] The publications reporting maintenance and induction reported different numbers of patients randomized in the induction trial (n = 299 and n = 276).

A 52-week maintenance trial of responders from a 4-week induction period reported injection-site reactions in 26% of 517 patients on adalimumab and 14% of 261 patients on placebo who were allowed to re-initiate adalimumab after week 12 (blinding maintained).[135] The corresponding Peto OR was 2.0 (95% CI, 1.4 to 2.9). Another publication of this trial reported injection-site reactions in 5% of patients on adalimumab and less than 1% of the patients on placebo during the randomized followup.[129] Injection-site reactions were not defined in the publications.

Certolizumab pegol versus placebo. Four RCTs including 1,472 Crohn's disease patients compared certolizumab pegol with placebo and reported infusion reactions.[80-82 131] In a 12-week induction trial of a single infusion, no infusion reactions were reported in 68 patients on certolizumab pegol or 24 patients on placebo during the 30 minute infusion or 30 subsequent minutes.[82]

Another 12-week induction trial reported infusion reactions within 30 minutes of subcutaneous injection in 5% of patients on certolizumab pegol (11 out of 219) and 3% (2 out of 73) of patients on placebo.[81] The corresponding Peto OR was 1.7 (95% CI, 0.5 to 6.2).

A 26-week induction trial reported local reactions to infusions in 3% (9 out of 331) of patients on certolizumab pegol and 14% (47 out of 329) of patients on placebo.[80] The corresponding Peto OR was 0.2 (95% CI, 0.1 to 0.4). The maintenance trial of the 428 patients who responded to certolizumab pegol induction reported any local reaction to infusion in 3% (6 out of 216) of patients on certolizumab pegol and 15% (31 out of 212) of patients on placebo during the 18-week followup.[131] The corresponding Peto OR was the same as the induction OR (0.2; 95% CI, 0.1 to 0.4).

Immunomodulators

Azathioprine versus placebo. One RCT including 96 patients evaluated infusion reactions (not defined) following a single infusion of azathioprine 40 mg/kg compared with placebo.[96] Infusion reactions were reported in 11 of 51 (22%) patients receiving azathioprine and one of 45 patients receiving placebo. The corresponding Peto OR was 5.8 (95% CI, 1.7 to 19.2).

Studies Evaluating Patients with Inflammatory Bowel Disease

Four studies reported infusion- and injection-site reactions in inflammatory bowel disease patients without separating Crohn's disease from ulcerative colitis or indeterminate colitis patients. Details about these studies are given in Appendix F.

Bone Fractures

We did not identify any studies comparing biologics, immunomodulators, or aminosalicylates in terms of the risk of bone fracture. Three studies including 1,032 patients with at least one corticosteroids group reported bone fractures (Table 45; Appendix D, Evidence Table 14).[32 212 213] Two of these studies excluded patients who had used medications for preventing fractures or osteoporosis[214] such as bisphosphonates, hormone replacement therapy and certain doses of calcium, fluoride or Vitamin D supplements within 6 or 24 months of the study.[32 212] One of the studies that made these exclusions included patients with osteoporosis.[32]

Table 45. Summary of the risk of bone fracture in studies comparing the safety of therapies for the management of Crohn's disease

Author, year	Design, duration N CD/IBD New users only / Specific aim (Y/N)	Comparison, dose Source for non-RCTs	Assessment of bone fracture	Surveillance Blinded assessments (Y/N)	Concomitant medications	Bone fracture results
Schoon, 2005[212]	RCT, 2y 271 CD N / Y	Budesonide, 9 mg qd vs. Prednisolone, 40 mg qd	Vertebrae with a height reduction of >20% as measured by X-ray and traumatic fractures	Active Y	5ASA, IMM, vitamin D and calcium supplementation	2/137 (2%) vs. 3/134 (2%)
Siffledeen, 2007[32]	Cross-sectional 207 CD N / Y	Steroid use vs. No steroid use in past year Questionnaire	Vertebrae with a height reduction of >20% and a loss of surface area >10% in the presence of a biconcave, crush, or wedge deformity as measured by DXA scan	Active Y	NR	25/105 (24%) vs. 17/102 (17%)
Bernstein, 2003[213]	Case-control 116 CD N / Y	Steroid use in two years prior to fracture vs. No steroid use in two years prior to fracture Electronic pharmacy record	ICD-9 codes 805, 807.0, 807.1, 813 and 820 representing fractures at the hip, spine, ribs or wrist	NA	NR	7/13 (54%) vs. 23/103 (22%)
Goldstein, 1967[183]	Retrospective cohort, NR 554 IBD N / N	Steroid non-user vs. Steroid user Chart review	Pathologic fractures recorded in patient chart	Passive NR	NR*	0/124 (0%) vs. 6/430 (1%)

5ASA = aminosalicylates; CD = Crohn's disease; DXA = dual energy x-ray absorptiometry; IBD = inflammatory bowel disease; ICD-9 = International Classification of Diseases, Ninth Revision; IMM = immunomodulators; mg = milligrams; N = no; NA = not applicable, secondary database analysis; NR = not reported; qd = once daily; RCT = randomized controlled trial; vs = versus; y = year; Y = yes

* Concomitant medication use other than aminosalicylates was deemed unlikely because the last point of data collection was 1965.

Budesonide versus prednisolone. One 2-year RCT (n = 271) specifically aimed to compare the risk of vertebral fractures between budesonide and prednisolone in ileal or ileocolonic uncomplicated Crohn's disease.[212] The study found a similar percentage of vertebral or traumatic fractures in both study groups (2%). The authors also reported that 14% of patients had non-symptomatic vertebral fractures at baseline.

Corticosteroids versus no corticosteroids. A cross-sectional study of 207 Crohn's disease patients compared questionnaire-reported use of corticosteroids in the year prior to a dual-energy X-ray absorptiometry (DXA) scan with no reported use of corticosteroids in the prior year.[32] Seventeen of 102 (17%) non-users had a vertebral fracture compared with 24% of 105 corticosteroid users. The study reported a Pearson correlation coefficient *P*-value of 0.27 for this comparison. A case-control study of Crohn's disease patients reported seven corticosteroid users within two years of hip, spine, rib, or wrist fracture in the 13 (54%) cases compared with 23 corticosteroid users among 103 (22%) controls.[213]

Studies Evaluating Patients with Inflammatory Bowel Disease

One retrospective cohort reported on bone fractures in the treatment of inflammatory bowel disease without separating Crohn's disease from ulcerative colitis or indeterminate colitis (see Appendix F).

Studies Reporting Results for Crohn's Disease and Inflammatory Bowel Disease

The previously mentioned case-control study reported similar rates of bone fracture for all inflammatory bowel disease patients (30% of 40 cases of bone fracture were corticosteroid users compared with 22% of 276 controls; univariate OR, 1.8; 95% CI, 0.6 to 3.7).[213]

Study Quality

Many of the studies containing data relevant to KQ3 were rated as low quality for assessing the question of patient safety because they were not designed to report on the specific safety outcomes that we sought to assess in this review. In many cases, the studies did report their primary exposure-outcome relationship sufficiently and accounted for confounding and selection bias in those analyses. Another common reason for studies to be rated as poor quality was the inability to adjust for confounders because of the small number of events, even if all other reporting and bias adjustment categories were sufficient.

Of the prospective and retrospective observational studies, all were rated poor quality except eight. Seven studies were rated good quality and one study was rated fair quality. Of the nine included case-control studies, four were rated good quality and five were rated poor quality (see Appendix D, Tables 15 and 16).

Applicability

The non-randomized studies that reported safety outcomes of interest did not have as many eligibility criteria as the RCTs. Very few non-randomized studies had disease activity or disease location exclusions. Because there were fewer restrictions made on the patient populations, the observational studies likely apply to Crohn's disease patients of all disease severities. Despite the differences in eligibility criteria, the RCTs and observational studies did not have meaningful differences in safety signals. The studies that included all inflammatory bowel disease patients had similar safety findings as studies that included only Crohn's disease patients or those studies that reported results for both Crohn's disease and inflammatory bowel disease patients.

Key Question 4: What is the comparative effectiveness of agents used to prevent post-operative recurrence in Crohn's disease as pertains to patient-reported outcomes?

Studies Included

Two studies with 120 participants were included in KQ4, one a RCT and one a prospective cohort study (Appendix D, Evidence Tables 17-20).[215 216] These studies considered comparisons with azathioprine and mesalamine; thus no evidence is available for this KQ with regard to other agents.

Study Design and Population Characteristics

Randomized Controlled Trial

The RCT was a 1 year, double-blind, double-dummy, randomized trial which took place in 21 gastroenterology centers in Austria, the Czech Republic, Germany, and Israel.[215] The study participants were 78 adults with Crohn's disease who had undergone resection with ileocolonic anastomosis in the preceding 6 to 24 months without subsequent clinical recurrence and with a CDAI score less than 200, but with moderate or severe endoscopic recurrence. The study drugs were azathioprine 2.0-2.5 mg/kg/day (N = 41) or mesalamine 4 g/day (N = 37) over 1 year.

The mean age in the groups was 35.5 years for azathioprine and 36.0 for mesalamine. Fifty-nine percent of the azathioprine group was male, and 54% of the mesalamine group. Proportions of continuous, recurrent, and unknown course were similar in the two groups. Mean baseline IBDQ in the two groups was 191 and 175 for azathioprine and mesalamine, respectively.

Observational Study

The observational study[216] was a prospective cohort study with 42 participants which investigated the influence of azathioprine on postoperative recurrence in a subgroup of Crohn's disease patients considered to have aggressive disease. In a nested case-control study, controls were patients selected to treatment but intolerable to azathioprine or 6-mercaptopurine; their

postoperative course was compared with that of patients receiving and tolerating the drugs postoperatively.

Twenty-eight participants received azathioprine, compared to 14 controls. The participants receiving azathioprine had a median age of 34.5 years (range, 17 to 71 years), with controls 38.0 years (range, 19 to 64 years). Of patients receiving azathioprine, three (10%) were smokers, and none of the controls. The duration of disease among participants receiving azathioprine was a median of 13 years (range, 0 to 34 years) and, among controls, 12.5 years (range, 0 to 36 years). Among azathioprine recipients, perianal disease was present in 14 (50%) and among controls, six (43%). Median followup among azathioprine recipients and controls, respectively, was 85.1 months (range, 23 to 139 months) and 78.7 months (range, 25.4 to 140 months).

Study Results

Randomized Controlled Trial

The RCT used the IBDQ as its patient-reported outcome.[215] The change in mean IBDQ score from baseline (azathioprine, 191; mesalamine, 175) to last on-treatment visit (azathioprine, 200; mesalamine, 180) was similar in both treatment arms (change in the azathioprine group, 9; standard deviation, 17.7, change in the mesalamine group, 5; standard deviation, 27.4; P = 0.4565, two-sided Wilcoxon test).

Observational Study

The prospective cohort used as its patient-reported outcome the patients' assessment of general health according to a visual analogue scale (VAS) integrated over time.[216] The VAS used runs from 0 to 100, where 0 is the worst possible score and 100 corresponds to perfect health. The authors stated that "repeated observations on the VAS …were integrated over time as a way of describing the patients' condition during the study period."[216] No further detail was given.

No difference was found between the groups in perceived health over time as evaluated on the VAS. In the azathioprine group, the mean VAS integrated over time was 65.4 (range, 0 to 99.4); in the control group, 55.5 (range, 14.6 to 98.6). This difference was given as not statistically significant, though no measures of variation were given.

Study Quality and Limitations

Randomized Controlled Trial

The risk of bias for the RCT[215] is low. However, consideration should be given to the fact that the study was industry-funded and that industry investigators were among the co-authors; no information is given on what role was played by industry in design or analysis. Consistency is unclear given that this is a single study. With regard to directness, this study is direct. The study is precise. In summary, the quality of this study is high.

Observational Study

The risk of bias for this study is moderate to high,[216] given its small sample size and uncontrolled nature; in addition, it is unclear whether the participants were blinded to their treatment assignment, and whether the study authors, in "integrating" the VAS over time (about which no detail was given), were blinded to the participants' treatment group. Consistency is unclear given that this is a single study. With regard to directness, this study is direct. The precision cannot be determined given the lack of information. In summary, the quality of this study is low. Limitations of this study include the lack of information on variation and statistical procedures used in integrating the VAS, and in selecting a measure of patient outcome not used in other studies (e.g., the SF-36 or IBDQ).

Applicability

The studies here are of intermediate applicability to the key question. While the IBDQ is a validated scale often used for research purposes in the analysis of patient-reported outcomes in Crohn's disease, the clinical significance of the scale in everyday practice is not clear. Similar considerations apply to the VAS, with the additional caveat that it is not as widely used as the IBDQ.

Pediatric Results

Few studies aimed to compare the efficacy or safety of Crohn's disease treatments in the pediatric population (younger than 18 years old). Four RCTs compared the efficacy of therapies alone or in combination to induce or maintain remission in children with Crohn's disease. No other RCTs that included participants under 18 years of age reported results separately for the pediatric population.

Nine studies reported the comparative safety of therapies alone or in combination in children with Crohn's disease. Of these nine studies, the majority aimed to study height or weight change as their primary outcomes of interest. Five additional studies included both children and adults, but did not report results separately for the pediatric population.

Key Question 1: What is the comparative effectiveness of therapies alone or in combination used to induce remission in children with moderate-to-severe Crohn's disease?

Key Points

Disease activity scales.

- The strength of evidence was low to demonstrate the superiority of 6-mercaptopurine and prednisone combination therapy versus prednisone alone to induce remission after 1 month of treatment in children with moderate-to-severe Crohn's disease (RR, 1.18; 95% CI, 0.95 to 1.47).

- The strength of evidence was moderate to demonstrate no difference in the effectiveness of budesonide versus prednisolone to induce remission at week 8 in children with mild-to-moderate Crohn's disease (RR, 0.77; 95% CI, 0.49 to 1.22).
- The strength of evidence was low to demonstrate no difference in the effectiveness between combination therapy with prednisone and mesalamine versus combination therapy with budesonide and mesalamine to induce remission at week 12 in children with mild-to-moderate Crohn's disease (RR, 0.95; 95% CI 0.47 to 1.92).
- We did not find any studies addressing the comparative effectiveness of other therapies alone or in combination to induce remission in children with moderate-to-severe Crohn's disease.

Reduction of steroids.

- The strength of evidence was low to demonstrate the superiority of 6-mercaptopurine over placebo to reduce the need for corticosteroids in children with moderate-to-severe Crohn's disease (observed-to-expected ratio of days on prednisone of 0.73 for the 6-mercaptopurine group and 1.34 for the placebo group, $P < 0.001$).
- The evidence was insufficient to determine the comparative effectiveness of other therapies alone or in combination to reduce the need for corticosteroids in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the effects of the biologics, azathioprine, methotrexate, corticosteroids, or 5-aminosalicylate acids on the reduction of steroids in children.

Mucosal healing, hospitalization, surgery, fistula response, and patient-reported outcomes.

- The strength of evidence was insufficient to determine the comparative effectiveness of therapies alone or in combination with respect to mucosal healing, hospitalization, surgery, fistula response, and patient-reported outcomes in children with moderate-to-severe Crohn's disease. No studies evaluating those outcomes in children met our inclusion criteria.

Table 46 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 21.

Table 46. Key findings and strength of evidence comparing pharmacologic therapies for the management of Crohn's disease to induce remission in children

Comparison	Disease activity scale	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
6-Mercaptopurine and prednisone versus prednisone alone	Favors 6-mercaptopurine and prednisone; Low	Insufficient	Insufficient	Favors 6-mercaptopurine; Low	Insufficient	Insufficient	Insufficient
Prednisone and mesalamine versus budesonide and mesalamine	Neither drug combination favored; Low	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide versus prednisolone	Neither drug favored; Mod	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
All other comparisons and outcomes were graded as insufficient since there were no eligible studies.

Study Design and Population Characteristics

Three RCTs compared the effectiveness of therapies alone or in combination to induce remission in children with Crohn's disease (Appendix D, Evidence Tables 22 and 23).[36-38] None of these RCTs were crossover studies and none had a run-in period. All three RCTs were multi-centered studies (one in the United States, one in Europe, and one in Israel). The total length of followup for the three RCTs was 8 weeks, 12 weeks, and 18 months.

All three RCTs included pediatric patients exclusively, totaling 136 children. The mean age of the children was 13.3 years (range: 13.0 to 13.9 years), reported in all three studies. The mean disease duration was 0.7 year, reported in one study for 48 children.[38] Eighty-six of the 136 children were male (63 percent, range: 60 to 69 percent). Race was reported in one study; 51 of 55 children (93 percent) were white.[37]

Age, disease location, disease severity, and baseline disease activity were comparable in the RCTs. Disease location was reported in two of the three studies[37 38]: twenty-five of 103 children (24 percent, range: 9 to 42 percent) had ileal disease, 65 of 103 children (63 percent, range: 50 to 75 percent) had ileocolonic disease, 12 of 103 children (12 percent, range: 6 to 16 percent) had colonic disease, and zero of 103 children had perianal disease. Disease severity was reported in all three studies: forty percent (one study[37]), 60 percent (two studies[36 38]). The mean baseline pediatric Crohn's disease activity index (PCDAI) score was consistent with moderate to severe disease in all three studies range: 29.1 to 45.7]).[217] The CDAI and HBI were reported in one study of 48 children.[38] The mean CDAI score was 255 and mean baseline HBI score was 7.5. None of these studies reported on smoking status, age at diagnosis, disease behavior, baseline IBDQ score or C-reactive protein (CRP) level.

Other inclusion criteria were similar for the three studies. Individual studies further restricted their patients on disease location, disease duration, and medications allowed prior to and during the study. One study comparing budesonide with prednisolone[38] included children with disease of the ileum or ascending colon exclusively. One study comparing a combination of prednisone and mesalamine with a combination of budesonide and mesalamine[36] only included children with a disease duration of at least 2 months, while another study comparing a combination of 6-mercaptopurine and prednisone with prednisone alone included children with a disease duration of less than 8 weeks.[37] Two studies[36 37] did not allow children any additional treatment during the study. The third study[38] allowed children to continue taking additional 5-aminosalicylate acids or antibiotics as long as they were administered at a constant dose for the thirty days prior to randomization to budesonide or prednisolone.

Disease Activity Indexes

All three RCTs used disease activity scales to measure remission (Appendix D, Evidence Table 24).[36-38] The disease activity scales were the PCDAI, CDAI, and HBI. The absolute disease activity scores are summarized in Table 47. None of these studies provided a measure of variability, thereby limiting our ability to comment of the effectiveness of these therapies on affecting these indexes.

Combination of 6-mercaptopurine and prednisone versus prednisone alone. One RCT randomized 55 children to a combination of 1.5 mg/kg per day of 6-mercaptopurine and prednisone or prednisone alone with a scheduled taper and evaluated inactive disease (defined as

total HBI score less than three).[37] After one month of treatment, 93 percent of 27 children in the combination group and 79 percent of 28 children in the prednisone alone group had inactive disease.

Budesonide versus prednisolone. One RCT assessed remission (defined as CDAI less than or equal to 150) in 18 children with active Crohn's disease (CDAI greater than 150) randomized to 9 mg per day of budesonide taper or 1 mg/kg per day of prednisolone taper.[38] Remission was achieved at 8 weeks in 12 of 22 children (55 percent) in the budesonide treatment group and 17 of 24 children (71 percent) in the prednisolone treatment group. The remission rate difference between the two groups was 16 percent (95% CI, 13 to 45, $P = 0.25$).

Combination of budesonide and mesalamine versus combination of prednisone and mesalamine. One RCT examined remission within 12 weeks (defined as PCDAI of less than or equal to 10) in 33 pediatric patients with mild-to-moderate Crohn's disease (PCDAI 12.5 to 40).[36] The percent of children in remission did not differ between the two treatment groups at 4, 8, or 12 weeks. At 12 weeks, nine of 19 children (47 percent) receiving 9 mg per day budesonide taper with mesalamine and seven of 14 children (50 percent) receiving 40 mg per day prednisone taper with mesalamine were in remission.

Table 47. Summary of absolute disease activity scores in studies comparing the effectiveness of medications in inducing remission in children with Crohn's disease

Author, year	Length of followup	Main intervention (dose), n	Comparison (dose), n	Baseline activity score	Final activity score
Markowitz, 2000[37]	1 mo	6-Mercaptopurine (1.5 mg/kg daily) + prednisone taper, 27	Placebo + prednisone taper, 28	7.7 vs. 7.4 (mean HBI)	NR
Escher, 2004[38]	8 wks	Budesonide (9 mg daily x 8 wks, then 6 mg daily x 4 wks), 22	Prednisolone (1 mg/kg daily x 4 wks, then tapering for 8 wks), 24	39 vs. 45 (mean PCDAI)	149 vs. 97 (mean CDAI)
Levine, 2003[36]	12 wks	Budesonide (3 mg q 8 hours x 8 wks, then tapered wks 9-10, discontinued after wk 10) + mesalamine, (3-4 g daily wks 11-12), 19	Prednisone (40 mg daily x 2 wks, then tapered wks 3-10, discontinued after wk 10) + mesalamine (3-4 g daily wks 11-12), 14	29.3 vs. 28.9 (mean PCDAI)	-9.3 vs. -13.4 (change in PCDAI)

CDAI = Crohn's Disease Activity Index; HBI = Harvey-Bradshaw Index; mg = milligram; mg/kg = milligrams per kilogram; mo = month; NR = not reported; PCDAI = Pediatric Crohn's Disease Activity Index; wk = weeks

Mucosal Healing

We did not find any studies conducted among children with active Crohn's disease that evaluated mucosal healing.

Hospitalizations

We did not find any studies conducted among children with active Crohn's disease that evaluated hospitalization rates.

Surgeries

No study of children with Crohn's disease reported surgeries as an outcome of interest. One study of children with moderate-to-severe Crohn's disease did comment that four children who were withdrawn from the study (one patient from the 6-mercaptopurine and prednisone group and three children from the placebo and prednisone group) did require surgery after their withdrawal.[37]

Reduction of Steroids

6-Mercaptopurine versus placebo. One RCT of pediatric patients with moderate-to-severe Crohn's disease[37] looked at the reduction of corticosteroids as an outcome of interest among children randomized to a combination of 6-mercaptopurine and prednisone or prednisone alone (Appendix D, Evidence Table 24). Prednisone dosage was increased, decreased, or held the same based on the patient's change in partial HBI score. Children in the 1.5 mg/kg per day 6-mercaptopurine group required fewer days of prednisone treatment than the children in the placebo group, with an observed-to-expected ratio of days on prednisone of 0.73 for the 6-mercaptopurine group and 1.34 for the placebo group ($P < 0.001$). Both groups required comparable time to initially wean off prednisone, with the children in the 6-mercaptopurine group requiring a median of 121 days (95% CI, 117 to 143) and the children in the placebo group requiring a median of 131 days (95% CI, 120 to 178, $P > 0.05$).

Fistula Response

None of the studies looked at fistula response as an outcome of interest among children with active Crohn's disease.

Patient-Reported Outcomes

We did not find any studies evaluating patient-reported outcomes as an outcome of interest among children with active Crohn's disease.

Study Quality

Of the studies on treatment of children with Crohn's disease, two studies[37 38] had good quality and one study[36] had poor quality (Appendix D, Evidence Table 25). The two good-quality studies had an adequate allocation sequence and concealment, adequate blinding, and complete outcome data. The other study was unclear about the allocation sequence and concealment, blinding technique, and completeness of outcome data. Only one of the studies reported pharmaceutical support and company involvement in the design, conduct, or reporting of the trial.[38]

Applicability

The applicability of these studies was limited because few children were included (136 among three studies), the longest study was only 12 weeks, and very few medications were compared.

Key Question 2: What is the comparative effectiveness of therapies alone or in combination used to maintain remission in children with moderate-to-severe Crohn's disease?

Key Points

Disease activity scales.

- The strength of evidence was low to demonstrate no difference in the effectiveness of mesalamine versus placebo to maintain remission at 1year in children with mild-to-moderate Crohn's disease (RR, 0.90; 95% CI, 0.67 to 1.21).
- The strength of evidence was insufficient to determine the comparative effectiveness of other therapies alone or in combination to maintain remission in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the effectiveness of the biologics, thiopurines, methotrexate, corticosteroids, or sulfasalazine in children with Crohn's disease.

Surgeries.

- The strength of evidence was low to demonstrate no difference in the effectiveness of mesalamine versus placebo to maintain remission and avoid surgeries at year 1 in children with mild-to-moderate Crohn's disease (no events observed in either arm).
- The strength of evidence was insufficient to determine the comparative effectiveness of other therapies alone or in combination to maintain remission and avoid surgeries in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the effectiveness of the biologics, thiopurines, methotrexate, corticosteroids, or sulfasalazine in children with Crohn's disease.

Mucosal healing, hospitalization, reduction of steroids, fistula response, and patient-reported outcomes.

- The strength of evidence was insufficient to determine the comparative effectiveness of therapies alone or in combination to maintain remission with respect to mucosal healing, hospitalizations, reduction of steroids, fistula response and patient-reported outcomes in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the effectiveness of the biologics, thiopurines, methotrexate, corticosteroids, or 5-aminosalicylate acids in children with Crohn's disease.

Table 48 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 21.

Table 48. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease to maintain remission

Comparison	Disease activity scale	Mucosal healing	Hospitalizations	Surgeries	Reduction of steroids	Fistula response	Patient-reported outcomes
Mesalamine versus placebo	Neither drug favored; Low	Insufficient	Insufficient	Neither drug favored; Low	Insufficient	Insufficient	Insufficient

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
All other comparisons and outcomes were graded as insufficient since there were no eligible studies.

Study Design and Population Characteristics

One RCT compared the effectiveness of therapies alone or in combination to maintain remission in children with Crohn's disease (Appendix D, Evidence Tables 22 and 23).[39] This study took place in Europe at multiple centers. The length of followup was 1 year.

This RCT included 122 pediatric patients 18 years and younger, diagnosed with Crohn's disease before the age of 16 years. The mean age was 11.8 years. Seventy-three of 122 children (58 percent) were male. The mean disease duration was 0.8 years.

Only children with active Crohn's disease were eligible (defined as HBI score greater than or equal to five or erythrocyte sedimentation rate (ESR) greater than or equal to 25 mm at 1 hour). The mean baseline HBI was 0.8 indicating that the majority of children were included based on ESR value. No restriction was made for disease activity of moderate-to-severe disease; all disease activity levels were included in this study. However, children were excluded if they had documented previous use of thiopurines or methotrexate. Disease location included 12% ileal, 69% ileocolonic, and19% colonic. Combining all disease locations, 32% of children also had perianal involvement. Smoking status, age at diagnosis, race, disease behavior, baseline IBDQ score and CRP level were not reported.

Disease Activity Indexes

Mesalamine versus placebo. One RCT[39] examined clinical relapse at 1 year (defined as HBI score of greater than or equal to five) in 122 pediatric patients with active Crohn's disease, randomized after induction treatment (Appendix D, Evidence Table 24). The difference in relapse was not meaningfully different between children receiving 50 mg/kg per day of mesalamine and children receiving placebo. The 1-year relapse rate was 34 of 60 children (57 percent) receiving mesalamine and 39 of 62 children (63 percent) receiving placebo. The average time without relapse was 8.6 months in the mesalamine group and 7.9 months in the placebo group and was not clinically or statistically different between the two groups.

Mucosal Healing

This study did not look at mucosal healing as an outcome of interest.

Hospitalizations

This study did not look at hospitalizations as an outcome of interest.

Surgeries

Mesalamine versus placebo. The same RCT[39] examined surgery for acute complications as an outcome of interest. By 1 year, no surgeries were reported for children in either the 1 mg/kg per day mesalamine treatment group or the placebo group.

Reduction of Steroids

This study did not look at reduction of steroids as an outcome of interest.

Fistula Response

This study did not look at fistula response as an outcome of interest.

Patient-Reported Outcomes

This study did not look at patient-reported outcomes as an outcome of interest.

Study Quality

The overall quality of this one RCT[39] was fair (Appendix D, Evidence Table 25). The study had adequate allocation sequence and concealment and adequate blinding, but the completeness of outcome data was unclear. The authors reported no conflict of interest.

Applicability

The applicability of this one study[39] was limited because few children were included (122 total) and only one drug was studied.

Key Question 3: What is the comparative safety of therapies alone or in combination used in children with moderate-to-severe Crohn's disease in terms of minimizing short- and long-term adverse effects?

Key Points

Mortality, lymphoma, other cancers, tuberculosis, infusion- and injection-site reactions, and bone fractures.

- The strength of evidence was insufficient to determine the comparative safety of therapies alone or in combination in children with moderate-to-severe Crohn's disease. We did not find any studies reporting on mortality, lymphoma or other cancers, tuberculosis, infusion- and injection-site reactions, and bone fractures.

Serious infections.

- The strength of evidence was low to demonstrate the superior safety of placebo over 6-mercaptopurine to minimize serious infections at 18 months in children with Crohn's disease (RR, 3.1; 95% CI, 0.1 to 73.1).

- The strength of evidence was insufficient to determine the comparative safety of other therapies alone or in combination to minimize serious infections in children with moderate-to-severe Crohn's disease. We found no studies evaluating the biologics, azathioprine, methotrexate, corticosteroids, or 5-aminosalicylate acids in terms of serious infections among children with Crohn's disease.

Other infections.

- The strength of evidence was low to demonstrate the superior safety of budesonide versus prednisone to minimize other infections at week 8 in children with Crohn's disease (RR, 0.2; 95% CI 0.01 to 3.8).
- The strength of evidence was low to demonstrate the superior safety of budesonide and mesalamine combination therapy versus prednisone and mesalamine combination therapy to minimize other infections at week 12 in children with Crohn's disease (RR, 0.3; 95% CI, 0.01 to 5.7).
- The strength of evidence was moderate to demonstrate the superior safety of prednisolone versus budesonide to minimize other infections in children with Crohn's disease (RR, 2.4; 95% CI 0.2 to 24.4).
- The strength of evidence was insufficient to determine the comparative safety of other therapies alone or in combination to minimize other infections in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the biologics, thiopurines, methotrexate, or 5-aminosalicylate acids in children with Crohn's disease.

Height change.

- The strength of evidence was low to demonstrate no difference in the effectiveness of 6-mercaptopurine versus placebo at 6 months, 12 months, and 18 months to allow growth in children with Crohn's disease (6.8 cm versus 5.3 cm after 18 months, respectively, $P = 0.3$).
- The strength of evidence was low to demonstrate the effect of prednisone versus placebo to allow growth in children with Crohn's disease.
- The strength of evidence was low to demonstrate no difference in the effectiveness of prednisone versus budesonide to allow growth at 6 months in children with Crohn's disease (change in height percentile, 0.25 versus -2.35 for budesonide and prednisone, respectively; $P = 0.1$).
- The strength of evidence was insufficient to determine the comparative safety of other therapies alone or in combination to allow growth in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the effects of biologics, azathioprine, methotrexate, and 5-aminosalicylate acids in children with Crohn's disease.

Weight change.

- The strength of evidence was low to demonstrate the superior effect of infliximab over placebo to allow weight gain in children with Crohn's disease (fat mass to height Z score beta-coefficient, 0.29; 95% CI, 0.06 to 0.52).

- The strength of evidence was low to demonstrate the superior effect of methotrexate over placebo to allow weight gain in children with Crohn's disease (fat mass to height Z score beta-coefficient, 0.30; 95% CI, 0.04 to 0.56).
- The strength of evidence was low to demonstrate the superior effect of prednisone over placebo to allow weight gain in children with Crohn's disease (fat mass to height Z score beta-coefficient, 0.69; 95% CI, 0.12 to 1.26).
- The strength of evidence was low to demonstrate the superior effect of prednisone over budesonide to allow weight gain after 8 weeks in children with Crohn's disease (weight gain, 4.6 kg versus 2.5 kg for prednisone and budesonide, respectively; $P < 0.05$).
- The strength of evidence was insufficient to determine the comparative safety of other therapies alone or in combination to allow weight gain in children with moderate-to-severe Crohn's disease. We did not find any studies evaluating the effects of natalizumab, ustekinumab, adalimumab, certolizumab pegol, thiopurines, and 5-aminosalicyate acids on weight in children with Crohn's disease.

Table 49 summarizes the evidence grades and specific conclusions for each comparison. Details of the evidence grades are in Appendix D, Table 21.

Table 49. Key findings and strength of evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of safety

Comparison	Mortality	Lymphoma, cervical cancer, and other cancers	Serious infections	Tuberculosis	Other infections	Infusion- and injection-site reactions	Bone fractures	Height change	Weight change
Infliximab versus placebo	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors infliximab; Low
6-Mercaptopurine and prednisone versus prednisone alone	Insufficient	Insufficient	Neither drug combination favored; Low	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug combination favored; Low	Insufficient
Methotrexate versus placebo	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Favors methotrexate; Low
Prednisone versus placebo	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Conflicting evidence; Low	Favors prednisone; Low
Budesonide versus prednisone	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug favored; Low	Insufficient	Insufficient	Neither drug favored; Low	Favors prednisone; Low
Budesonide and mesalamine versus prednisone and mesalamine	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug combination favored; Low	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide versus prednisolone	Insufficient	Insufficient	Insufficient	Insufficient	Neither drug favored; Mod	Insufficient	Insufficient	Insufficient	Insufficient

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Mod = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.
All other comparisons and outcomes were graded as insufficient since there were no eligible studies.

Study Design and Population Characteristics

Eight studies compared the safety of therapies alone or in combination in children with Crohn's disease (Appendix D, Evidence Tables 22 and 23). Three studies were RCTs,[36-38] two studies were prospective cohort studies,[40 41] and three studies were retrospective cohort studies.[42-44] None of the RCTs were crossover studies and none had a run-in period. Studies were conducted in various countries (two in the United States, one in Canada, three in Europe, and two in Israel), and four studies were multi-centered trials.[36-38 42] The length of followup ranged from 8 weeks to 43 months.

The eight studies included pediatric patients exclusively, totaling 533 children. The mean age of children ranged from 12.7 to 13.9 years as reported in six studies for 351 children.[36-38 40 42 43] The mean disease duration ranged from 0.6 to 0.7 year as reported in two studies for 126 children.[38 43] All eight studies reported the percent of male patients which ranged from 33 to 100 percent. Race was reported in two studies - 51 of 55 children (93 percent) were white in one study[37] and eight of 78 children (10 percent) were black in another study.[43] The mean age at diagnosis ranged from 7.0 to 13.9 years as reported in two studies for 72 children.[40 41]

Crohn's disease characteristics were reported as disease location, severity, and baseline disease activity. Disease location was reported in five studies[37 38 41 43 44] for 333 children: fourteen percent (range: 3 to 42 percent) of children had ileal disease, 71 percent (range: 21 to 84 percent) of children had ileocolonic disease, 12 percent (range: 6 to 16 percent) of children had colonic disease, and eight percent (range: 0 to 36 percent) of children had perianal disease. Disease severity was reported in six studies[36-38 41-43] for 297 children: twelve percent (range: 0 to 83 percent) of children had mild disease, 57 percent (range: 0 to 100 percent) of children had mild-to-moderate disease, less than one percent (range: 0 to 6 percent) of children had moderate disease, 28 percent (range: 0 to 100 percent) of children had moderate-to-severe disease, and less than one percent (range: 0 to 12 percent) of children had severe disease. The mean baseline PCDAI score ranged from 27.6 to 45.7 as reported in five studies[36-38 42 43] for 334 children. The mean baseline CDAI was 255, reported in one study[38] for 48 children. The mean baseline HBI score was 7.5, reported in one study for 55 children. None of these studies reported on smoking status, disease behavior, baseline IBDQ score, or CRP level.

Inclusion criteria were mostly the same among the studies except for disease severity. All studies included mostly children, with a maximum age of 22 years. Crohn's disease severity was used for inclusion in four studies[37 38 42 218] and determined using physician assessment, PCDAI, and CDAI. Seven studies included only children with Crohn's disease; one study included children with inflammatory bowel disease.[41] One study excluded girls;[40] all others included both sexes.

Three studies examining 6-mercaptopurine and prednisone[37] and corticosteroids[36 38] excluded children who had previously used thiopurines. Two studies measuring growth[43 44] excluded children who had an illness or were taking any other medications that could affect growth or development.

Mortality

No studies meeting our inclusion criteria reported on the outcome of mortality in children with Crohn's disease.

Cancer

No studies meeting our inclusion criteria reported on cancer rates in children with Crohn's disease.

Serious Infections

Combination of 6-mercaptopurine and prednisone versus prednisone alone. One RCT of 55 children reported on serious infections (Table 50; Appendix D, Evidence Table 24).[37] Over the course of the 18-month study, one of 27 children receiving 1.5 mg/kg per day of 6-mercaptopurine and prednisone taper developed an intra-abdominal abscess. None of 28 children receiving a prednisone taper alone developed a serious infection.

Table 50. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of serious infections

Comparison	Type of infection	Type of studies	Number of studies	Results	Conclusions	Strength of evidence
6-Mercaptopurine and prednisone versus prednisone alone	Intra-abdominal abscess	Randomized controlled trial	1	1/27 6-mercaptopurine 0/28 placebo	Neither favored	Low

Tuberculosis

No studies meeting our inclusion criteria reported on tuberculosis rates in children with Crohn's disease.

Other Infections

Three studies of 201 children with Crohn's disease[36 38 42] reported other infections during the course of their study (Table 51; Appendix D, Evidence Table 24). All three studies were comparing some combination of corticosteroids. Two studies[36 42] of 153 patients reported herpetic infections, all three of which occurred only in patients taking prednisone, none of which occurred in patients taking budesonide. One study[38] of 48 patients reported on pharyngitis, reporting that two of 22 patients developed pharyngitis in the budesonide treatment group and one of 26 patients developed pharyngitis in the prednisone treatment group.

Budesonide versus prednisolone. One RCT[38] of 48 pediatric patients with mild-to-moderate Crohn's disease treated children with either budesonide or prednisolone. Over the 8-week course of the study, one of the 26 children in the 1 mg/kg per day prednisolone taper treatment group developed pharyngitis compared with two of the 22 children in the 9 mg per day budesonide taper treatment group.

Budesonide versus prednisone. One retrospective cohort study[42] of 120 pediatric patients with mild-to-moderate Crohn's disease looked at children who were treated with either prednisone or budesonide. Among the records reviewed, two of the 58 children in the prednisone treatment

group developed herpetic infections compared with zero of the 62 children in the budesonide treatment group. There was no difference in herpetic infection rates between the two groups.

Combination of budesonide and mesalamine versus the combination of prednisone and mesalamine. One RCT[36] of 33 pediatric patients with mild-to-moderate Crohn's disease treated children with either prednisone and mesalamine or budesonide and mesalamine. Over the 12-week course of the study, one of 14 children in the 40 mg per day prednisone taper and 3 to 4 g per day mesalamine treatment group developed a herpetic infection compared with zero of 19 children in the 9 mg per day budesonide taper and 3 to 4 g per day mesalamine treatment group. There was no difference in herpetic infection rates between the two groups.

Table 51. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of other infections

Comparison	Type of infection	Type of studies	Number of studies	Results	Conclusions	Strength of evidence
Budesonide versus prednisolone	Pharyngitis	Randomized controlled trial	1[38]	2/22 budesonide 1/26 prednisone	Not statistically significant	Moderate
Budesonide versus prednisone	Herpetic infection	Retrospective cohort study	1[42]	0/62 budesonide 2/58 prednisone	Neither favored	Low
Combination budesonide and mesalamine versus combination prednisone and mesalamine	Herpetic infection	Randomized controlled trial	1[36]	0/19 budesonide and mesalamine 1/14 prednisone and mesalamine	Neither favored	Low

Infusion- and Injection-site Reactions

No studies meeting our inclusion criteria reported infusion- or injection-site reactions in children with Crohn's disease.

Bone Fractures

No studies meeting our inclusion criteria reported bone fractures in children with Crohn's disease.

Height Change

Six studies of 452 children reported on the effects on height (Table 52; Appendix D, Evidence Table 24).

Combination of 6-mercaptopurine and prednisone versus prednisone alone. One RCT of 55 children[37] compared the linear growth of children treated with 1.5 mg/kg per day of 6-mercaptopurine and prednisone taper versus those who were treated with a prednisone taper alone. This study found no significant difference in linear growth between the two groups at 6

months, 12 months, or 18 months. From 0 to 6 months, the 6-mercaptopurine group (n = 26) grew an average of 3.4 cm and the placebo group (n = 25) grew an average of 1.9 cm ($P = 0.06$). From 6 to 12 months, the 6-mercaptopurine group (n = 23) grew an average of 0.7 cm and the placebo group (n = 24) grew an average of 1.3 cm ($P = 0.4$). From 12 to 18 months, the 6-mercaptopurine group (n = 23) grew an average of 2.8 cm and the placebo group (n = 24) grew an average of 2.3 cm ($P = 0.5$). Overall, from 0 to 18 months, the 6-mercaptopurine group (n = 23) grew an average of 6.8 cm and the placebo group (n = 24) grew an average of 5.3 cm ($P = 0.3$).

Prednisone versus placebo. Four studies[40 41 43 44] of 277 children found mixed results when comparing the effect of prednisone versus placebo on linear growth in children: one study found children who had taken prednisone were shorter than those who had not taken prednisone, one study found that children who had taken prednisone were taller than those who had not taken prednisone, and two studies found no difference in height between children who had taken prednisone and those who had not.

One prospective cohort study of 17 children[40] compared the linear growth of nine boys with Crohn's disease who were treated with alternate day prednisone (0.3 mg per kg) for longer than 3 months with eight boys with Crohn's disease who had not been treated with alternate day prednisone for longer than 3 months. At the end of 2 years, both groups showed similar linear growth.

One retrospective cohort study[44] looked at 135 children with an early onset of Crohn's disease. This study asked adults about their growth and medication use for men with onset of symptoms before age 22 years and for women with onset of symptoms before age 18 years. Eight children had received corticosteroids before puberty and nineteen children had received corticosteroids during puberty. Children who had received corticosteroids during puberty were significantly shorter than those who had not ($P = 0.005$). This study also found that children with disease onset during puberty who had received corticosteroids were significantly shorter than those with disease onset during puberty who had not received corticosteroids ($P = 0.03$).

One prospective cohort study[41] looked at 47 pediatric patients with either Crohn's disease (n = 18) or ulcerative colitis (n = 29). This study found no significant difference in height standard deviation score (HSDS) or the height velocity standard deviation score (HVSDS) between those children who had received prednisone compared with those children who had not received prednisone. The HSDS for children treated with prednisone was -0.50 at diagnosis, -0.47 after 1 year, -0.24 after 2 years, -0.10 after 3 years, and +0.00 after 4 years. The HSDS for children not treated with prednisone was -0.20 at diagnosis, -0.31 after 1 year, -0.13 after 2 years, -0.09 after 3 years, and +0.13 after 4 years. The HVSDS for children treated with prednisone was -1.20 at diagnosis, +0.29 after 1 year, +0.87 after 2 years, +1.47 after 3 years, and +0.78 after 4 years. The HVSDS for children not treated with prednisone was -0.01 at diagnosis, -0.26 after 1 year, +0.63 after 2 years, +0.16 after 3 years, and +1.25 after 4 years.

One prospective cohort study[43] looked at 78 patients (ages 5 to 21 years) with Crohn's disease of varied severity and reported on the height of their patients. This study performed a subgroup analysis on the 46 children who had completed four study visits, and found that children who had taken corticosteroids had a significantly lower height Z score than children who had not taken corticosteroids.

Budesonide versus prednisone. One retrospective cohort study[42] compared the post-remission linear growth of 41 of 120 children whose records included height measures. The children had mild-to-moderate Crohn's disease and had received either prednisone or budesonide for at least two weeks. This study found no significant difference in the change of height percentile at 6 months between those children who had taken prednisone compared with those children who had taken budesonide.

Table 52. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of height change

Comparison	Height measure	Type of studies	Number of studies	Results	Conclusions	Strength of evidence
6-Mercaptopurine versus placebo	Linear growth (cm)	Randomized controlled trial	1[37]	6.8 6-mercaptopurine 5.3 placebo	*P* = 0.3	Low
Prednisone versus placebo	Linear growth over 2 years (cm)	Prospective cohort study	1[40]	9.1 prednisone 10.3 placebo	NR	Low
Prednisone versus placebo	Height (cm)	Retrospective cohort study	1[44]	NR	*P* = 0.005	Low
Prednisone versus placebo	HSDS	Prospective cohort study	1[41]	+0.00 prednisone +0.13 placebo	No difference	Low
Prednisone versus placebo	HVSDS	Prospective cohort study	1[41]	+0.78 prednisone +1.25 placebo	No difference	Low
Corticosteroids versus placebo	Height Z-score	Retrospective cohort study	1[43]	Beta-coefficient = -0.63; 95% CI, -1.00 to -0.28	*P* = 0.0005	Low
Budesonide versus prednisone	Change in height percentile	Retrospective cohort study	1[42]	+0.25 budesonide -2.35 prednisone	*P* = 0.1	Low

cm = centimeter; HSDS = height standard deviation score; HVSDS = height velocity standard deviation score; NR = not reported

Weight Change

Two studies[42 43] of 198 children reported on the outcome of weight (Table 53; Appendix D, Evidence Table 24).

Infliximab versus placebo. One prospective cohort study of 78 children with Crohn's disease of varied severity[43] reported on the interaction of body mass and height. This study performed a subgroup analysis on the 46 children who had completed four study visits, and found that children who had taken infliximab had a significantly higher lean mass – height Z score than children who had not taken infliximab. This study also found that children who had taken infliximab had a significantly higher fat mass – height Z score than children who had not taken infliximab.

Methotrexate versus placebo. The above cohort study[43] also reported that children who had taken methotrexate had a significantly higher fat mass – height Z score than children who had not taken methotrexate.

Corticosteroids versus placebo. The above cohort study[43] also reported that children who had taken corticosteroids had a significantly higher fat mass – height Z score than those who had not taken corticosteroids.

Budesonide versus prednisone. One retrospective cohort study of 120 children[42] looked at pediatric patients with mild-to-moderate Crohn's disease. This study looked at weight loss or gain in children who had received treatment with either prednisone or budesonide. After reviewing patient records, they found that those children who had been treated with prednisone gained significantly more weight than those children who had been treated with budesonide after eight weeks.

Table 53. Summary of the evidence comparing pharmacologic therapies for the management of children with Crohn's disease in terms of weight change

Comparison	Weight measure	Type of studies	Number of studies	Results	Conclusions	Strength of evidence
Infliximab versus placebo	Lean mass – height Z score	Case-control study	1[43]	Beta-coefficient, 0.30; 95% CI, 0.02 to 0.58	$P < 0.05$	Low
Infliximab versus placebo	Fat mass – height Z score	Case-control study	1[43]	Beta-coefficient, 0.29; 95% CI, 0.06 to 0.52	$P < 0.05$	Low
Methotrexate versus placebo	Fat mass – height Z score	Case-control study	1[43]	Beta-coefficient, 0.30; 95% CI, 0.04 to 0.56	$P < 0.05$	Low
Corticosteroids versus placebo	Fat mass – height Z score	Case-control study	1[43]	Beta-coefficient, 0.69; 95% CI, 0.12 to 1.26	$P < 0.05$	Low
Budesonide versus prednisone	Weight gain (kg)	Retrospective cohort study	1[42]	+2.54 kg budesonide +4.6 kg prednisone	$P < 0.05$	Low

CI = confidence interval; kg = kilogram

Study Quality

For serious infections (intra-abdominal abscess): the quality of the one RCT[37] was good due to adequate allocation sequence and concealment, adequate blinding, and complete outcome data (Appendix D, Evidence Table 25). This study[37] was supported by a pharmaceutical company.

For other infections (herpetic infections): the quality of one RCT[36] was poor because the allocation sequence and concealment, blinding technique, and completeness of outcome data of the poor quality study were unclear. The quality of the retrospective cohort study[42] was fair due to good descriptions of outcomes, interventions, and patient characteristics.

For other infections (pharyngitis): the quality of one study[219] was good due to adequate allocation sequence and concealment, adequate blinding, and complete outcome data.

For height change: the six studies[37 40-44] had variable quality. The quality of one RCT[37] was good due to adequate allocation sequence and concealment, adequate blinding, and complete outcome data. Two cohort studies[42 43] had fair quality due to good descriptions of outcomes and

patient characteristics. Two other cohort studies[40 44] had poor quality due to study population selection bias. One study[37] was supported by a pharmaceutical company.

For weight change: the two studies[42 43] had fair quality with good descriptions of outcomes and patient characteristics.

Applicability

The applicability of these studies was limited because few children were included (553 among eight studies), the longest prospective study was 43 months, and very few medications were compared.

Comparative Effectiveness of Therapies in Subgroups

Key Points

- No consistent relationship was seen for the interaction of a medication and disease characteristic on remission rates in adults with Crohn's disease.
- No study reported on a medication by disease characteristic interaction for safety or for post-operative quality of life in adults with Crohn's disease.
- No pediatric Crohn's disease study reported on a medication by disease characteristic interaction.

A total of 18 studies performed at least one subgroup analysis on the characteristics of interest. Fifty-five subgroup analyses were performed in these studies (Appendix G).

Our ability to assess the effectiveness and safety of therapies in subgroups is limited. Because no study stated that it was powered for an endpoint other than efficacy at a single time point, it is likely that the studies were underpowered to conduct subgroup analyses. Although three studies (17%) reported a *P*-value for a test of heterogeneity using an interaction term between treatment and subgroup, the majority of studies did not. None of the studies assessed how the effects of therapies differed among subgroups in terms of safety or patient-reported outcomes after intestinal resection in adults. No pediatric study reported on subgroups.

Only studies that performed a statistical test for interaction are described below.

KQ1 – Induction of Remission

Baseline CRP

Four studies reported how results related to high versus low CRP at baseline.[75 78 79 83] Only one study,[79] which evaluated remission at 4 weeks for adalimumab versus placebo, reported a *P*-value for an interaction term. Remission rates for high versus low CRP (cutoff at 10 mg/L) did not differ between groups ($P = 0.67$).

Baseline Corticosteroid Use

Four studies reported a subgroup analysis by baseline corticosteroid use.[24 79 80 83] Only one study,[79] which evaluated remission at 4 weeks for adalimumab versus placebo, reported a *P*-value for an interaction term. Remission rates were higher for patients who were on baseline corticosteroids at the time of randomization ($P = 0.01$).

Baseline Immunomodulator Use

Four studies reported a subgroup analysis by baseline immunomodulator use.[76 78-80] Two of the studies[76 79] reported a *P*-value for an interaction term. One study[79] evaluating 4 week remission for adalimumab versus placebo found no effect of baseline immunomodulator use ($P = 0.88$). Another study evaluating natalizumab versus placebo at 10 weeks found higher response and remission rates for patients on baseline immunomodulators at randomization ($P < 0.05$).

Prior TNF-Alpha Inhibitor Exposure

Three studies reported a subgroup analysis by prior TNF-alpha inhibitor use.[75 76 80] Only one study,[76] which evaluated natalizumab versus placebo at 10 weeks, reported a *P*-value for an interaction term. Response rates were higher for patient with prior TNF-alpha inhibitor exposure ($P < 0.05$). No effect was seen for remission ($P > 0.05$).

The following subgroup analyses were performed, but did not contain any studies that reported a *P*-value for an interaction term: baseline mucosal lesions, baseline aminosalicylates, baseline antibiotic use, prior immunomodulator exposure, prior aminosalicylates exposure, prior corticosteroids exposure, disease duration, disease location, and prior Crohn's disease-related surgery.

KQ2 – Maintenance of Remission

The following subgroup analyses were performed, but did not contain any studies that reported a *P*-value for an interaction term: baseline CRP, baseline immunomodulator use, baseline antibiotic use, prior TNF-alpha inhibitor exposure, disease location, and prior Crohn's disease-related surgery.

Discussion

Key Findings and Implications

Summary of Key Findings for Adults

We did not identify a single medication or class of medications that was most effective at inducing and maintaining remission, while producing the highest quality of life and the best safety profile. We were able to identify medications that were efficacious at inducing or maintaining short-term (less than 1 year) remission according to the disease activity scales with high strength of evidence for KQ1 and KQ2. Using a disease activity scale, we found high strength of evidence for the clinical effectiveness of particular medications at specific time points. Statistical significance was not required for an effect to be considered in the clinically significant range, although comparisons with high strength of evidence tended to be statistically significant. For induction of remission, the strength of evidence was high that natalizumab was more effective than placebo at 2-4 weeks, adalimumab was more effective than placebo at 2-4 weeks, and certolizumab pegol was more effective than placebo at 22-30 weeks. For maintenance of remission, the strength of evidence was high that, among those who achieved response or remission during an open-label run-in period, infliximab and adalimumab were more effective than placebo at maintaining remission at 22-30 and 48-54 weeks, and adalimumab and certolizumab pegol were more effective than placebo at 15-19 weeks. No measure of remission other than the disease activity scale had high strength of evidence, although several had moderate strength of evidence, including infliximab and adalimumab compared with placebo, and azathioprine compared with placebo or budesonide.

We found that no medication or combination of medications was consistently associated with adverse effects across the safety outcomes of interest for KQ3. The strength of evidence for nearly every comparison was insufficient or low. Frequently, no medication was favored among those comparisons with low evidence. We found high strength of evidence for two safety comparisons, each from a single RCT and in both cases for an outcome of infusion and injection-site reactions. Oral azathioprine with placebo infusion was favored over intravenous infliximab with oral placebo, and placebo was favored over intravenous azathioprine. Moderate strength of evidence was found for two safety comparisons, each from a single RCT. A combination of prednisone and sulfasalazine was favored compared with prednisone alone for infections, and neither budesonide nor prednisolone was favored in terms of bone fractures.

Only one RCT was identified that measured a patient-reported outcome after intestinal resection for KQ4 and no difference was found between the medications compared.

Summary of Key Findings for Pediatrics

Only eight studies were identified that reported on pediatric outcomes. The strength of evidence was low or insufficient to support any medication to induce or maintain remission in pediatric Crohn's disease for KQ1 and KQ2. No pediatric study reported on a serious adverse event such as mortality, progressive multifocal leukoencephalopathy, lymphoma, or other cancers. No pediatric study reported on a patient-reported outcome for KQ1, KQ2 and KQ4.

Comparison to Other Systematic Reviews

Other systematic reviews have reported on the efficacy and safety of treatments to induce or maintain remission in Crohn's disease.[67 73 220-228]

The most recent systematic review was performed by the American College of Gastroenterology (ACG) Task Force.[53] Although the ACG Task Force review was similar to our review in that we both applied similar inclusion criteria across medication classes, there were also differences. The major differences between our inclusion criteria and the criteria of that review were that (a) we required that all studies have a comparison group, allowed head-to-head trials, and allowed observational studies for safety outcomes, while the ACG Task Force did not require studies to have a comparison group or placebo controlled group, excluded head-to-head trials, and did not include observational studies for safety outcomes; (b) we abstracted information at multiple clinically relevant time points, and the ACG Task Force focused on the last time point of assessment; (c) we did not restrict the analysis to a minimum duration of treatment, and the ACG Task Force focused on a minimum treatment duration of 14 days for induction of remission and 6 months for relapse prevention; (d) we included multiple outcomes associated with treatment aimed at achieving remission, and the ACG Task Force focused on one outcome reported in the study according to a hierarchy starting with CDAI followed by endoscopic healing and other definitions; (e) we specifically included mortality, PML, HSTCL, other lymphomas and cancers, serious infections and infusion reactions, and the ACG Task Force considered overall adverse events, serious adverse events, infections and a list of specific common but less serious adverse events including abdominal pain, nausea or vomiting, joint conditions, fever, rash, headache and fatigue; and (f) we reviewed and graded the strength of evidence separately for safety and efficacy, and the ACG Task Force considered the balance between safety and efficacy in a single grade of the strength of evidence.

The strength of evidence and direction of the association were consistent between our review and the ACG Task Force review, Cochrane reviews, and other reviews across the classes of medications. However, we stratified the strength of evidence and the direction of relationship if these factors differed by medication doses or time points within the medication class. The assessment of risk of bias differed between our review and the ACG Task Force, especially for the studies of biologic agents. The ACG Task Force review graded very few biologic studies as having low risk of bias, compared with our grading of almost all studies as having a low risk of bias. The strength of evidence tended to be graded as moderate for the biologics in the ACG Task Force review, but low in our report, possibly because they pooled all comparisons regardless of study or statistical heterogeneity, whereas we only pooled studies when we felt studies were comparable and statistical heterogeneity was low, frequently leading to inconsistent and imprecise evidence.[5]

Limitations

The major limitations in our review were: (a) the inability to perform meta-analyses of all comparisons, (b) potential measurement error, and (c) no established standard for a clinically meaningful difference in remission or safety related outcomes.

[5] For induction: 3 out of 29 were high SOE among those that were not insufficient; 10 moderate. For remission: 9 out of 16 were high SOE among those that were not insufficient; 0 moderate.

Heterogeneity in study design prohibited meta-analyses. One common source of heterogeneity was the variation in study designs, especially for the maintenance trials of biologics. For example, the studies of maintenance therapy varied in how they identified patients as being eligible for randomization to the study arms. Some of the maintenance trials had a run-in period to identify patients having a response to the study medication of interest. Other maintenance trials enrolled patients that had a response to the study medication of interest in a previous remission trial. Another source of heterogeneity was the use of varied definitions of remission and response using different disease activity scales, different disease activity scale thresholds for remission or response, and inconsistency in combining disease activity scales with serum markers, changes in corticosteroid use, or other clinical outcomes. Variable study durations contributed to heterogeneity, especially for the observational studies.

Potential for measurement error for time points other than the primary outcome of interest. Because we included clinically meaningful time points of interest that may not have corresponded to the primary outcome of interest, we frequently abstracted data for these time points from figures. These figures did not consistently display time points of assessment as reported in the study design and rarely included measures of variation for each time point. The lack of information on the variation of an outcome was especially pronounced for reporting of the IBDQ scores and prevented us from performing statistical analyses of the difference in IBDQ scores between treatment groups.

No standard exists for a clinically meaningful difference in remission or safety. When we assessed the effectiveness and safety of the medications, we sought to consider whether any differences were clinically meaningful and statistically significant. Because there is no standard for a clinically meaningful absolute difference in remission for Crohn's disease or in general, we chose a conservative threshold of 10%. Many of the trials that reported on power calculations in the methods sections of their papers stated that they used a 20% difference for this calculation. If we used a 20% difference as the clinically meaningful difference in remission rates, fewer differences would have been considered clinically meaningful. Because many of the adverse events are very rare, we did not assign a threshold for a clinically meaningful difference. We relied on a statistically significant difference instead, which resulted in only two comparisons with high strength of evidence, both with a greater than 10% absolute difference between the treatment groups for the outcome of infusion and injection site reactions.

Other limitations included: (a) many of the observational studies were not designed to examine the medication-outcome relationships that we abstracted from them, resulting in low study quality due to poor reporting and bias control for our comparison of interest; (b) the majority of trials were sponsored by the manufacturer of the medications, which has been associated with the reporting of results that are more favorable than studies not supported by industry;[56] (c) our analyses indicated the presence of publication bias, especially for corticosteroids and aminosalicylates; (d) we excluded 223 non-English articles; and (e) we only included information from peer-reviewed journals, excluding information reported in abstract-only form which has been documented to differ from the subsequent peer-reviewed article.[58 229]

Future Research Needs

The major future research needs include: (a) evidence to induce and maintain remission in patients with complicated and severe Crohn's disease (defined later); (b) evidence that supports the most effective treatment strategy over a number of years, instead of one to two years; (c) reporting on efficacy outcomes other than the CDAI, especially mucosal healing outcomes as recommended by the FDA in 1995;[59] (d) ensuring that observational studies for safety are sufficiently long to observe outcomes; (e) performing trials and safety studies in pediatric populations; (f) incorporating patient-reported outcomes into post-surgical relapse studies; (g) comparing medications and medication classes head-to-head to provide evidence on the step-up versus top-down treatment approach; and (h) studies of newly diagnosed patients are needed. Other reviews have identified similar gaps in the research on treatment of Crohn's disease.[53 73 221]

Few studies included patients with complicated and severe disease. Many modern RCTs apply only to patients with uncomplicated, luminal Crohn's disease without stricture or abscess. Additionally, many RCTs excluded patients with severe disease (CDAI > 450). Only two RCTs aimed to examine patients with fistula exclusively. The observational studies tended to include patients with all patterns of disease activity or behavior. Although the observational study findings are applicable to a wider range of patients, the majority of evidence was graded as low or insufficient. Because the risk-benefit ratio of medication use may depend on severity of disease, both effectiveness and safety should be assessed by disease severity.

Evidence is lacking on the optimal treatment of Crohn's disease over a number of years. The short duration of the RCTs and observational studies limits the ability to assess one or more medications over a sizeable portion of a person's lifetime with disease. The duration of time that a treatment works, particularly for maintaining remission, is especially relevant for children who may not be fully developed and have a lifetime of disease and its treatment ahead of them.

RCTs did not routinely report on outcomes other than disease activity scales. Few studies reported on other indications of clinical remission such as hospitalizations, surgeries or mucosal healing. Controversy exists over the clinical relevance of the widely used disease activity scale CDAI as a measure of clinical disease activity[31] and the CDAI is not considered an accurate measure of disease activity in stricturing or fistulizing disease.[230] The CDAI also does not correlate well with mucosal healing.[31] Additionally, disease activity indices are difficult to calculate and are not practical in the clinical setting,[230] limiting the applicability of the remission findings to clinical practice. Even though a representative from the FDA reported in 1995 that induction and maintenance of remission in Crohn's disease should include both absence of symptoms and endoscopic evidence of healing, few studies reported on mucosal healing.[59] There was information on the patient-reported IBDQ outcome measure and occasionally the SF-36, but not days of work or school missed, which may be more meaningful and easier to communicate to Crohn's disease patients.

Observational studies may be too short in duration to observe some safety outcomes. The rare safety outcomes may take years to develop after exposure to the medication or may take years of medication use to develop. The majority of observational studies were shorter than five

years, which may not be sufficient to observe cases caused by the use of medication recorded during the study time period.

Few pediatric studies were identified. Nine studies were identified that included exclusively pediatric patients. None of the adult studies that allowed participants under age 18 reported the results for children separately. Given the paucity of trials or observational studies that reported on safety, there is little evidence to guide the most effective and safe treatment for children. There is no existing evidence of quality of life or other patient-reported outcomes for these medications as reported by children or their parents.

One study reported on a patient-reported outcome after surgical resection. Given that patient-reported outcomes may be even more relevant to patients who are not currently experiencing active clinical or endoscopic disease, these outcomes may be most relevant for treatment choice in these patients.

Comparative effectiveness studies of the step-up versus top-down approach are needed. The step-up versus top-down approach for treatment was one of the controversies that prompted this report. We also chose to organize our report according to the top-down approach to provide relevance to this controversy. However, only one small open-label study directly tested step-up versus top-down treatment. Because patients were allowed to step-up throughout the study, by week 52, 20% of all patients were receiving infliximab, regardless of which group they were originally randomized, and by week 78 fewer than 10% of all patients were receiving prednisolone.[86] We had hoped to perform indirect comparisons in the absence of direct comparisons of step-up versus top-down treatment. However, we were not able to perform these indirect comparisons due to the heterogeneity of the study designs as described in the limitations.

Studies of recently diagnosed patients are needed. Most RCTs included patients with a long disease duration, often greater than ten years. Only a few studies randomized patients within three years of diagnosis. There is preliminary subgroup data that patients with a short duration of disease have better response and remission rates.[124]

Additional future research needs include: (a) the inclusion of non-white patients in RCTs and safety studies; (b) performing head to head comparisons, especially for the biologics where no head-to-head study was identified; (c) performing head-to-head trials of biologics and immunomodulators that allow all thiopurine methyl transferase (TPMT) phenotypes, because the rate of TPMT metabolism rarely prohibits treatment in the clinical setting; (d) identifying treatments to induce and maintain remission in patients who do not respond to biologics, as these patients were excluded from many of the biologic maintenance trials; (e) specifying safety outcomes in advance and including them as primary or secondary outcomes in RCTs; (f) clarify whether safety outcomes associated with medication efficacy (such as disease flare and abscess) are safety outcomes or efficacy outcomes; (g) clearly accounting for the use of other medications in both RCTs and observational studies so that the independent effect of the medication of interest is more clear; (h) accounting for other confounders in observational studies and examining the reasons for the imbalance of potential confounders in the setting of RCTs; (i) conducting and reporting subgroup analyses appropriately in pre-specified groups and using interaction terms; (j) consistent reporting of outcomes in text and figures, especially for clinically relevant time points other than the primary outcome time point; and (k) for extremely rare safety

outcomes that are likely to be reported in case reports, such as PML or HSTCL, synthesizing the data on a potential causal relationship would be more efficient if case reports emphasized criteria used to estimate these causal relationships such as the McMaster Quality Assessment Scale of Harms.[60]

Opportunities for the Crohn's disease community to address the limitations and future research needs. The Crohn's disease community could address the limitations by: (a) creating registries that include both adult and pediatric patients to measure safety outcomes that are unlikely to occur in RCTs, such as lymphoma and other cancers; (b) work collaboratively to create evidence-based treatment algorithms and guidelines based on the best available evidence and update the guidelines regularly as new evidence becomes available; (c) identify the most important measures of remission and most important safety outcomes that should be measured in all RCTs; and (d) determine the need for RCTs of medications that are not approved for the treatment of Crohn's disease such as immunomodulators, corticosteroids, and aminosalicylates, possibly comparing these medications head-to-head and in combinations to inform the top-down versus step-up treatment strategy. Ideally, the registries, guidelines, and RCTs should be performed independent of industry support and with minimal conflicts of interest to prevent the biases that sometimes result from industry-sponsored research.

Abbreviations

ACG = American College of Gastroenterology
AERS = Adverse Events Reporting System
AHRQ = Agency for Healthcare Research and Quality
CDAI = Crohn's disease activity index
CDEIS = Crohn's disease endoscopic index of severity
CI = confidence interval
DXA = dual X-ray absorptometry
EPC = Evidence-based Practice Center
FDA = Food and Drug Administration
HBI = Harvey-Bradshaw index
HR = hazards ratio
HSTCL = hepatosplenic T-cell lymphoma
IBDQ = Inflammatory bowel disease questionnaire
KQ = Key Question
OR = odds ratio
PCDAI = Pediatric Crohn's disease activity index
PML = progressive multifocal leukoencephalopathy
RCT = randomized controlled trial
RD = risk difference
RR = relative risk
TNF = tumor necrosis factor
TPMT = thiopurine methyltransferase

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