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Draft Comparative Effectiveness Review
Number XX

Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis in Adults

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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 from 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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The information in this report is intended to help health care decision-makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis in Adults

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of rheumatoid arthritis and psoriatic arthritis in adults. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its comparative effectiveness reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.
The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Rheumatoid arthritis (RA), which affects 1.3 million individuals, is an autoimmune disease that involves inflammation of the synovium (a thin layer of tissue lining a joint space) with progressive erosion of bone leading in most cases to misalignment of the joint, loss of function, and disability. The disease tends to affect the small joints of the hands and feet in a symmetric pattern, but other joint patterns are often seen. The diagnosis is based primarily on the clinical history and physical examination with support from selected laboratory tests. Treatment of patients with RA aims to control pain and inflammation and, ultimately, to slow the progression of joint destruction and disability. Available therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs or DMARDs (hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine), and biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab). Five biologics (i.e., adalimumab, certolizumab, etanercept, golimumab, and infliximab) are also classified as anti-tumor necrosis factor (anti-TNF) drugs.

Experts have not arrived at consensus about the comparative effectiveness of corticosteroids, oral DMARDs, and biologic DMARDs. More importantly, it is unclear how the effectiveness and safety of different types of combination therapy compare—e.g., oral DMARDs with corticosteroids, oral DMARDs with biologic DMARDs, or triple combination of corticosteroids, oral DMARDs, and biologic DMARDs. In addition, there is debate about how early in the disease process combination therapy should be initiated and whether patients will respond to a biologic agent if they have previously failed a different biologic agent. Many questions remain about the risks of these agents across a spectrum of adverse events from relatively minor side effects such as injection site reactions to severe and possibly life-threatening problems such as severe infections or infusion reactions. Finally, very little is known about the benefits or risks of these drugs in different patient subgroups, including ethnic minorities, the elderly, pregnant women, and patients with other comorbidities.

This report summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with RA. The key questions (KQs) were developed through a public process in conjunction with the Scientific Resource Center at the Oregon Health and Science University. This report updates a previous version published in 2007. The KQs are as follows:

KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?

KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?

KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

We identified 3,487citations from our searches. Working from 1043 articles retrieved for full review, we included 219 for background and excluded 602 at this stage (Appendix D). We included 218 published articles reporting on 174 studies: 27 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 41 placebo-controlled trials, 11 meta-analyses or systematic reviews, and 94 observational studies. We identified 42 studies for quantitative syntheses. Our findings include studies rated good or fair for internal validity, unless a particular study rated poor provides some unique information that we judged to be of interest. Most studies were of fair quality.

Conclusions

We present our major findings in this section by type of drug comparison and important outcomes (both benefits and harms). Table ES-1 summarizes the information for RA. We have not presented findings from subpopulation analyses (KQ4) for RA in the table, but we describe them in the text because the evidence is very limited.

Table ES-1. Summary of findings

Key Comparisons	Efficacy Strength of evidence grade	Harms Strength of evidence grade
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses LOW Mixed results for functional capacity INSUFFICIENT Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide LOW	No consistent differences in tolerability and discontinuation rates LOW Mixed results for specific adverse events INSUFFICIENT
Leflunomide vs. sulfasalazine	Mixed ACR response rates INSUFFICIENT No differences in radiographic changes LOW Greater improvement in functional capacity for leflunomide LOW	No differences in tolerability and discontinuation rates LOW Mixed results for specific adverse events INSUFFICIENT
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and functional capacity MODERATE No differences in radiographic changes LOW	No differences in tolerability; more patients stayed on MTX long-term LOW Mixed results for specific adverse events INSUFFICIENT
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. SSZ or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes MODERATE No differences in functional capacity MODERATE	Withdrawal rates attributable to adverse events higher with combination LOW Insufficient evidence for specific adverse events INSUFFICIENT
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity INSUFFICIENT Less radiographic progression In patients on DMARD plus prednisone LOW In patients with early RA, significantly lower radiographic progression and fewer eroded joints LOW Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy MODERATE	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment MODERATE No differences in specific adverse events, except addition of corticosteroid may increase wound healing complications LOW

Table ES-1. Summary of findings (continued)

Key Comparisons	Efficacy Strength of evidence grade	Harms Strength of evidence grade
	No difference in quality of life LOW	
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity and quality of life for abatacept, but no difference in remission or functional capacity LOW	Discontinuation rates and severe adverse events higher with infliximab LOW
Biologic vs. Biologic *(indirect comparisons)*	Less improvement in disease activity (ACR 20/50) for anakinra compared to certolizumab and etanercept in Mixed Treatment Comparison (MTC) analyses. Comparisons with abatacept, adalimumab, golimumab, infliximab and tocilizumab did not reach statistical significance. LOW Greater improvement in disease activity (ACR 20/50) for certolizumab compared to abatacept, anakinra, infliximab in MTC analyses. No significant differences when compared with adalimumab, etanercept, golimumab and tocilizumab LOW Greater improvement in disease activity (ACR 20/50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab and tocilizumab in MTC analyses. No significant differences when compared with certolizumab (ACR 20/50) and golimumab (ACR 50) LOW No significant differences in disease activity for abatacept, adalimumab, golimumab, infliximab and tocilizumab in MTC analyses LOW	Risk for injection site reactions highest with anakinra LOW Indirect comparisons consistently showed better tolerability for certolizumab and etanercept. LOW Observational evidence suggests discontinuation rates and severe adverse events may be higher with infliximab than other biologic DMARDs LOW Risk of infusion reactions most common with infliximab LOW Mixed results for specific adverse events INSUFFICIENT
Biologic DMARDs vs. Oral DMARDs		
Anti-TNF drugs vs. MTX	In patients with early RA, no differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs MODERATE No difference in functional capacity between adalimumab and MTX for MTX naïve subjects with early RA; mixed results for ETN vs. MTX LOW; INSUFFICIENT Faster improvement in quality of life with ETN than MTX LOW	No differences in adverse events in efficacy studies LOW Insufficient evidence on differences in the risk for rare but severe adverse events INSUFFICIENT

Table ES-1. Summary of findings (continued)

Key Comparisons	Efficacy Strength of evidence grade	Harms Strength of evidence grade
	In patients who had failed initial RA treatment, greater functional independence and remission for anti-TNF drugs as a class than oral DMARDs as a class MODERATE	
Other Biologic DMARDs vs. Oral DMARDs	Greater improvement in disease activity and functional capacity with TCZ than MTX for patients with active RA and an inadequate response to MTX LOW	Insufficient evidence on differences in tolerability and in the risk for rare but severe adverse events INSUFFICIENT
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with ETN plus ABA vs. ETN LOW	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy MODERATE
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (ADA, ETN,INF,RTX) plus MTX than from monotherapy with biologics MODERATE In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group LOW In MTX naïve subjects or those not recently on MTX, greater improvement in functional capacity (MODERATE) and quality of life (LOW) with combination therapy In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life LOW	No differences in adverse events in efficacy studies LOW Insufficient evidence on differences in the risk for rare but severe adverse events INSUFFICIENT
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy LOW	No differences in adverse events in efficacy studies LOW Insufficient evidence on differences in the risk for rare but severe adverse events INSUFFICIENT

Table ES-1. Summary of findings (continued)

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy MODERATE, LOW for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis LOW Mixed evidence on differences in the risk for rare but severe adverse events INSUFFICIENT
Strategies in early RA		
2 oral DMARDs plus prednisone vs. oral DMARD	In patients on 3 oral DMARDs, improved ACR 50 response rates, disease activity scores, and less radiographic progression LOW In patients with early RA, significantly lower radiographic progression and fewer eroded joints LOW	No differences in discontinuation rates MODERATE
3 oral DMARDs plus prednisone vs. 1 oral DMARD	In patients on 3 oral DMARDs, improved ACR 50 response rates, disease activity scores, and less radiographic progression LOW In patients with early RA, significantly lower radiographic progression and fewer eroded joints LOW	No differences in discontinuation rates MODERATE
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high- dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 yrs LOW	No differences in serious adverse events between groups LOW

ABA, abatacept; ACR, American College of Rheumatology; DMARD, disease modifiying antirheumatic drug; ETN, etanercept; INF, infliximab; MTC, mixed treatment comparison; MTX, methotrexate; RA, Rheumatoid Arthritis; RTX, rituximab; TCZ, tocilizumab; TNF, tumor necrosis factor.

Oral DMARD vs. Oral DMARD

Leflunomide vs. MTX. The data show no differences in American College of Rheumatology (ACR) 20 or radiographic responses for leflunomide and MTX (low strength of evidence). Low strength of evidence exists for improvements in health related quality of life for patients on leflunomide. However, evidence remained mixed for functional capacity differences and specific adverse events. Overall tolerability and discontinuation rates appear similar (low strength of evidence).

Leflunomide vs. sulfasalazine. The evidence was insufficient to draw conclusions about disease activity for leflunomide and sulfasalazine but improvement in functional capacity was greater for patients on leflunomide (low strength of evidence). No differences were found for radiographic changes (low strength of evidence). Overall tolerability and discontinuation rates appeared similar (low strength of evidence), but evidence remains mixed for specific adverse events.

Sulfasalazine vs. MTX. No differences were found for ACR 20 response, disease activity scores and functional capacity or radiographic changes (moderate strength of evidence). No differences were found for radiographic changes (low strength of evidence). Overall tolerability appear similar, however, more patients stayed on MTX long term (low strength of evidence). Evidence remains mixed for specific adverse events.

Oral DMARD combination vs. oral DMARD

Sulfasalazine plus MTX vs. monotherapy. ACR response rates and radiographic changes did not differ in patients with early RA (moderate strength of evidence). Findings did not support a difference in functional capacity (low strength of evidence). Withdrawal rates attributable to adverse events were higher with combination therapy (low strength of evidence). Evidence was insufficient for specific adverse events.

Oral DMARD plus prednisone vs. oral DMARD. Studies of oral DMARD use with and without prednisolone found mixed results for disease activity (low strength of evidence). Patients on an oral DMARD plus prednisone had less radiographic progression (low strength of evidence). Moderate strength of evidence exist for greater improvement in functional capacity for oral DMARD plus prednisolone than oral DMARD monotherapy, but there were no differences found for quality of life (low strength of evidence). There were no differences in discontinuation rates; however the addition of a corticosteroid may increase the time to discontinuation of a treatment (moderate strength of evidence). There were no differences in specific adverse events, except that a corticosteroid may increase wound healing complications (low strength of evidence).

Biologic DMARD vs. Biologic DMARD

The evidence comparing biologic DMARDs was limited to one head-to-head RCT, several observational studies, indirect analyses, and our mixed treatment comparisons (MTC) meta-analyses.

Abatacept vs. infliximab. Based on one RCT, abatacept lessened disease activity more than infliximab, but remission rates were not significantly different at one year (low strength of evidence). Discontinuation rates and severe adverse events appeared higher with infliximab; these results were also supported by observational studies (low strength of evidence).

Biologic vs. biologic. Our mixed treatment comparisons of randomized-controlled trials of subjects with active RA despite MTX treatment found a higher odds of reaching the ACR 20/50 for etanercept compared to abatacept, adalimumab, anakinra, infliximab, or tocilizumab (low strength of evidence), but no statistically significant difference for etanercept compared to certolizumab (ACR 20/50) or golimumab (ACR 50). The same analyses found higher odds of reaching ACR 20/50 for certolizumab compared to abatacept, anakinra, and infliximab (low strength of evidence). Similarly, our indirect analyses from RCTs indicated that patients taking certolizumab or etanercept were less likely to withdraw treatment than patients taking other

biologic DMARDs (low strength of evidence). Our MTC meta-analysis indicated that anakinra was less efficacious than certolizumab and etanercept (low strength of evidence). Indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be verified, particularly the similarity of study populations.

Injection site reactions were highest with anakinra and infusion reactions were most common with infliximab (low strength of evidence). Results were mixed for specific adverse events.

Biologic DMARD vs. Oral DMARD

Anti-TNF drugs vs. MTX. The evidence comparing monotherapy using a biologic DMARD with monotherapy using an oral DMARD was mixed. Monotherapy of adalimumab in early RA did not reveal a benefit relative to MTX monotherapy for response rates (moderate strength of evidence) or functional capacity (low strength of evidence). Monotherapies of etanercept found no differences in clinical response rates (moderate strength of evidence) and mixed results for functional capacity. There was faster improvement in quality of life for etanercept (low strength of evidence). Radiographic outcomes were also significantly better in patients on adalimumab or etanercept than on MTX (moderate strength of evidence). Whether such differences are clinically relevant and can alter the long-term progression of the disease remains unclear.

Tocilizumab vs. MTX. Tocilizumab showed greater improvement in both disease activity and functional capacity in patients with active RA and an inadequate response to MTX (low strength of evidence). There was insufficient evidence on differences in tolerability and risk for rare but severe adverse events.

Biologic vs. oral DMARD. Population-based, observational evidence suggest that biologic DMARDs as a class resulted in better functional capacity than oral DMARDs as a class in patients who had failed initial treatment (moderate strength of evidence). No studies were available comparing biologics with oral DMARDs other than MTX.

Other biologic DMARDs have not been directly compared with MTX. In general, adverse events did not differ significantly between biologic and oral DMARDs. Studies were too small to reliably assess differences in rare but severe adverse events.

Biologic DMARD combinations

Biologic DMARD plus biologic DMARD vs. biologic DMARD. A combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy (moderate strength of evidence). There was no additional benefit in disease activity or functional capacity (low strength of evidence). The evidence, however, was limited to combinations of anakinra plus etanercept and abatacept plus anakinra, adalimumab, etanercept, or infliximab.

Biologic combination with MTX vs. biologic DMARDs alone. Overall, combination therapy of biologic DMARDs and MTX achieved better clinical response rates than monotherapy (moderate strength of evidence). Evidence included combination of adalimumab, etanercept, infliximab, or rituximab with MTX. In MTX-naive patients with early aggressive RA, biologic combination with MTX found better ACR 50 response, significantly greater clinical remission, and less radiographic progression (low strength of evidence). Patients not recently on MTX also had greater improvement in functional capacity (moderate strength of evidence) and quality of life (low strength of evidence). However patients with activity RA despite MTX found no differences in functional capacity of quality of life (low strength of

evidence). Overall, there were no differences in adverse events in efficacy studies (low strength of evidence). The evidence was insufficient for differences in the risk of rare but severe adverse events.

Biologic DMARD combinations with other orals vs. biologic DMARDs. A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy (low strength of evidence). No differences in adverse events were found between combinations of biologic and oral DMARDs and biologic DMARD monotherapy. The evidence was insufficient for differences in the risk of rare but severe adverse events.

Biologic DMARD combinations with MTX vs. MTX alone. A combination of adalimumab plus MTX or infliximab plus MTX or etanercept plus MTX in patients with early, aggressive RA who were MTX-naive led to better clinical and radiographic outcomes than MTX monotherapy (moderate strength of evidence). Additionally, improvements in functional capacity and quality of life were found with combination therapies (adalimumab, infliximab, or etanercept plus MTX) than with MTX alone (low strength of evidence).

In general, there was a better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept and rituximab than MTX alone (low strength of evidence). Studies, however, were too small to assess reliably differences in rare but severe adverse events.

Strategies in early RA

There were a few strategy studies in early RA, which allowed clinicians to vary their choice of medications and treatment regimens according to the patient's response. The evidence was limited to draw firm conclusions about whether one combination strategy was better than another in early RA.

Oral DMARDs plus prednisone vs. oral DMARD. Current evidence suggested improved functional capacity and less radiographic progression for combination strategies with corticosteroids and two oral DMARDs compared with oral DMARD monotherapy. For most of these comparisons, the evidence was limited to a single study (low strength of evidence).

Evidence of moderate strength suggested that combination studies of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs improved response rates, with less radiographic progression. There were similar withdrawal rates attributable to adverse events. Combination studies including prednisone with one or more DMARDs had similar discontinuation rates between groups.

Strategy comparisons. One effectiveness trial for patients with early RA reported less radiographic progression over 12 months with either (1) MTX, sulfasalazine, and high-dose tapered prednisone or (2) MTX and infliximab versus (3) sequential DMARD therapy or (4) step-up combination therapy (low strength of evidene). At two years patients on initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with MTX and infliximab had less radiographic progression. They also had more rapid improvement in disease activity, functional capacity, and quality of life, although the differences between groups were no longer present by two years. By four years, there was no difference in remission among the groups. Similarly, patients on combinations of biologic and oral DMARDs were less likely than patients on oral DMARD monotherapy to withdraw from trials because of lack of efficacy (low strength of evidence).

Subpopulations

Limited good or fair evidence for benefits or harms of subpopulations exist, the strength of evidence was therefore low and results should be interpreted cautiously. Patients with moderate RA had significant improvements and better overall functional status than those with severe RA, but those with severe RA had the greatest improvements from baseline in disease activity. For MTX, the odds for major clinical improvement dropped slightly as age increased in all clinical trial patients; age did not affect MTX efficacy or the rate of side effects. Biologics neither decreased nor increased cardiovascular risks in the elderly. Those taking anakinra and concomitant antidiabetic, antihypertensives, or statin medications did not have higher adverse events rates. Toxicity was more likely with MTX in patients with greater renal impairment. Those with high risk comorbidities and taking anakinra did not experience an increase in serious adverse events or overall infectious events.

Remaining Issues

Common problems for RA studies include the lack of effectiveness information—i.e., studies and findings with a high level of applicability to community populations. Future investigations need to take into account factors such as varying adherence because of administration schedules, costs, and adverse events. Information about the performance of these drugs in subgroups of patients defined by health status, sociodemographics, or other variables is also needed.

To address problems with current literature, future studies should include using designs of longer duration and followup, enrolling patients representing key subgroups (or reporting on them when they are enrolled), and ensuring that quality of life (or other patient-centered outcomes) is measured, in addition to clinician-centered measures such as joint erosion.

Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) applicability of combination strategies and biologic DMARD therapy in community practice, and (3) timing of initiation of therapies. The results of our MTC meta-analyses found greater improvement in disease activity for etanercept and CTZ than for some other biologic DMARDs. However, the strength of evidence was low, and head-to-head studies are needed to confirm or refute these results. Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases.

With respect to study design, studies of longer duration and followup will be beneficial, given that RA is a progressive, chronic condition. Such studies will also help to clarify whether early initiation of any regimen can improve the long-term prognosis of RA and, particularly, whether early use of biologic DMARDs is beneficial.

Evidence Report

Chapter 1. Introduction

Arthritis and other rheumatic conditions constitute the leading cause of disability among U.S. adults,[1] with more than 46 million Americans reporting doctor diagnosed arthritis.[2] Noninflammatory arthritic conditions (e.g., osteoarthritis) are most common, but inflammatory arthritides such as spondyloarthropathies (e.g., ankylosing spondylitis, psoriatic arthritis [PsA]), and reactive arthritis) and rheumatoid arthritis (RA) can be equally or more disabling.

Among patients with RA, the burden of disease is evidenced by decreased quality of life,[3-6] decreased employment rates,[7,8] and increased direct and indirect costs[9-12] In 2003, arthritis and other rheumatic conditions (AORC) cost the United States $127.8 billion ($80.8 billion in medical care expenditures and $47.0 billion in lost earnings).[13] Annually, approximately 9 million physician office visits and more than 250,000 hospitalizations occur as the result of RA. The mean total annual direct cost to patients with RA is estimated to be $9,519 per person,[9] and most studies have reported indirect costs to be roughly twofold greater than direct costs.[14]

Causes and Diagnosis

RA is an autoimmune disease that affects 1.3 million adults in the United States.[2] Disease onset generally occurs between ages 30 and 50 years, and incidence is higher in women and older adults. RA presentations range from mild to severe. Some people are affected for as little as a few months, whereas others are affected for a lifetime and suffer severe joint damage and disability.

The hallmarks of the disease are inflammation of the synovium (a membrane that lines the joint capsule and produces lubricating fluid in the joint) with progressive erosion of bone leading to malalignment of the joint. As the inflamed synovium destroys the joint, the surrounding muscles and tendons become weak, leading to disability in most cases. Unlike osteoarthritis, RA can affect other areas in addition to joints. Most patients develop anemia. Some patients have dry eyes and mouth (sicca syndrome). Rarely, patients develop inflammation in the lining of the lung (pulmonary fibrosis), various layers of the eye wall (episcleritis and scleritis), small vessels (vasculitis), and the outer covering of the heart (pericarditis).

The exact etiology of RA is not completely understood, but genetic susceptibility has been described in certain populations.[15,16] Studies have shown the importance of T cells, B cells, and cytokines in the pathogenesis of RA.[17,18] Cytokines of particular interest are tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6.

TNF plays a central role in the pathobiology of RA. It is an important regulator of other proinflammatory molecules and stimulates the secretion of matrix metalloproteinases. It also exerts a direct effect on the multiple tissues inside the joint including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. Together, its action leads to inflammation and the formation of pannus, a mass of tissue that causes localized joint destruction.[18]

The diagnosis of RA is primarily a clinical one, based on multiple patient symptoms. No single laboratory test confirms RA. Constitutional symptoms including low-grade fever, fatigue, or malaise are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. A serum rheumatoid factor is present in up to 75 percent of patients with RA but

is frequently negative in early disease. A more specific marker, anticyclic citrullinated peptide (CCP) antibody, has recently been described and may be a useful marker in patients with early disease.[19,20] Table 1 presents the diagnostic criteria for RA proposed by the American College of Rheumatology (ACR).[21] Patients are said to have RA if they meet four of the seven criteria in the table.[21] It should be noted that these criteria are relatively insensitive for early disease and efforts are underway to revise the criteria to address this issue.

Table 1. ACR criteria for the diagnosis of rheumatoid arthritis

Criteria
1. Morning stiffness lasting greater than 1 hour
2. Arthritis in 3 or more joint areas
3. Arthritis of the hand joints (metacarpophalangeal [MCP], proximal interphalangeal [PIP], wrists)
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes: erosions or unequivocal periarticular osteopenia

Source: Arnett et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar; 31(3):315-24.[21]

Treatment of Rheumatoid Arthritis

Treatment of patients with RA is aimed primarily at controlling pain and inflammation and, ultimately, at slowing or arresting the progression of joint destruction.

Corticosteroids. Corticosteroids—sometimes referred to as glucocorticoids or steroids—are used for many inflammatory and autoimmune conditions. As a class, corticosteroids have been used since the discovery of cortisone in the 1940s. Commonly used oral corticosteroids include methylprednisolone, prednisone, and prednisolone.

Corticosteroids are a synthetic form of cortisol, a hormone produced by the adrenal glands. They produce their anti-inflammatory and immunosuppressive response by interacting with steroid-specific receptors in the cytoplasm of cells, thereby inhibiting the movement of inflammatory cells into the site of inflammation, inhibiting neutrophil function, and inhibiting prostaglandin production. They are widely prescribed as an oral treatment for RA because of their ability to reduce inflammation and subsequent joint pain and swelling.

Oral disease-modifying antirheumatic drugs (DMARDs). Oral DMARDs such as methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide modify the course of inflammatory conditions, presumably through their effects on the immune system. Most of the oral DMARDs have been used in clinical practice for more than 20 years. MTX was developed in the 1940s as a treatment for leukemia but was not approved for the treatment of arthritis until 1988. Sulfasalazine also has been available since the 1940s; it is a combination salicylate (acetylsalicylic acid) and antibiotic (sulfapyearidine) that originally was used to treat patients with inflammatory bowel disease. Hydroxychloroquine, approved in the 1950s for the treatment of malaria, is believed to work in arthritis by interfering with antigen presentation and the activation of immune response by increasing the pH within macrophage phagolysosomes. Additionally, hydroxychloroquine possibly inhibits toll-like receptors that mediate proinflammatory cytokine production. Only leflunomide, an isoxazole immunomodulatory agent, was specifically developed for treating inflammatory arthritis; the U.S. Food and Drug Administration (FDA) approved its use in 1998.

Oral DMARDs are not members of a single drug family. They are classified together, however, because they all are slow acting with the aim of improving symptoms, reducing or

preventing joint damage, and preserving structure and function in patients with inflammatory disease. All the oral DMARDs covered in this review can be given orally, although methotrexate can also be injected (SQ or IM).

Biologic DMARDs. Biologic DMARDs—commonly referred to as biological response modifiers or simply biologics—are a relatively new injectable category of DMARDs that differ from oral DMARDs in that they target specific components of the immune system. The FDA approved the first of the biologics (infliximab) in 1998; this report covers eight additional agents approved since that time: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), rituximab (2006), certolizumab pegol (2008), golimumab (2009), and tocilizumab (2010). Of the nine agents, all are currently FDA approved for treating RA.

The biologic DMARDs work by selectively blocking mechanisms involved in the inflammatory and immune response. Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are known as TNF inhibitors (i.e., drugs that block specific proinflammatory mediators known as cytokines). They produce their primary effect by blocking TNF from interacting with cell surface TNF receptors. Adalimumab, infliximab, and golimumab are monoclonal antibodies. Adalimumab is a fully human monoclonal antibody that binds specifically to TNF, blocking its interaction with both the p55 and p75 cell surface TNF receptor. Golimumab is also a human monoclonal antibody that binds to TNF alpha with high affinity. Infliximab is a chimeric (i.e., made from human and mouse proteins) monoclonal antibody that binds specifically to human TNF. Etanercept is not a monoclonal antibody, but rather a TNF-soluble receptor protein. More specifically, it is a soluble dimeric form of the p75 TNF receptor linked to the Fc portion of human immunoglobulin G1 (IgG1). Etanercept exerts its action by binding circulating TNF and preventing it from interacting with a cell surface receptor. Certolizumab pegol is a pegylated humanized antibody fragment of tumor necrosis factor monoclonal antibody. The drug binds to the TNF alpha-receptor and blocks TNF alpha actvity. It only possesses the Fab fragment and lacks the Fc region. Hence, it does not induce antibody-dependant cell mediated apoptosis or toxicity.

IL-1, another naturally occurring cytokine, has both immune and proinflammatory actions. Anakinra is a human recombinant protein that competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agent abatacept produces its immune response by interfering with T lymphocyte activation. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of IgG1.

Rituximab, a chimeric murine/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes. Thus, it removes circulating B cells from the pre-B cell stage through the activated B cells. B cells are believed to play a role in autoimmune and inflammatory processes, such as those involved in RA.

IL-6 is a naturally occurring cytokine involved in the regulation of immune responses and inflammation. Tocilizumab is a monoclonal antibody that inhibits interleukin-6 (IL-6) receptors, blocking the action of IL-6, and leading to a reduction in cytokine and inflammatory response. Table 2 provides detailed information (names, manufacturers, and available dosage forms) on agents used in the treatment of RA that we have included in this review.

Table 2. Pharmaceutical treatments for rheumatoid arthritis

Class	Generic Name	U.S. Trade Name(s)*	Manufacturer	How Supplied
Corticosteroids				
	Methylprednisolone	Medrol®, Depo-Medrol®, Solu-Medrol®	Multiple	Injectable (acetate)—20, 40, and 80 mg/ml Injectable (sodium succinate)—40, 125, and 500 mg, 1 and 2 g vials Tabs—2, 4, 8, 16, and 32 mg
	Prednisone	Deltasone®, Sterapred®, LiquiPred	Multiple	Solution—1 and 5 mg/ml Tabs—1, 2.5, 5, 10, 20, and 50 mg
	Prednisolone	Orapred®, Pediapred®, Prelone®, Delta-Cortef®, Econopred®	Multiple	Solution/Syrup—5, 15, and 20 mg/5 ml Tabs—5 and 15 mg
Oral DMARDs				
	Hydroxychloroquine	Plaquenil®	Multiple	Tabs—200 mg
	Leflunomide	Arava®	Multiple	Tabs—10 and 20 mg
	Methotrexate	Trexall®, Folex®, Rheumatrex®	Multiple	Injectable—25 mg/ml, 20 mg and 1 g vials Tabs—2.5, 5, 7.5, 10, and 15 mg
	Sulfasalazine	Azulfidine®, EN-tabs®, Sulfazine®	Multiple	Suspension—250 mg/5 ml Tabs—500 mg
Biologic DMARDs				
	Abatacept	Orencia®	Bristol Myers Squibb	Injectable—250 mg vial
	Adalimumab	Humira®	Abbott	Injectable—40 mg/0.8 ml, 20mg/0.4ml prefilled syringe
	Anakinra	Kineret®	Amgen	Injectable—100 mg/0.67 ml syringe
	Certolizumab Pegol	Cimzia®	UCB	Injectable – 200 mg powder for reconstitution, 200mg/ml solution
	Golimumab	Simponi®	Centocor Ortho Biotech	Injectable – 50 mg/0.5 ml syringe
	Etanercept	Enbrel®	Amgen Wyeth Immunex	Injectable—50 mg/ml in 25 mg or 50 mg single use prefilled syringe
	Infliximab	Remicade®	Centocor	Injectable—100 mg in a 20 ml vial
	Rituximab	Rituxan®	Biogen Idec / Genentech	Injectable—100 mg/10 ml and 500 mg/50 ml vial
	Tocilizumab	Actemra®, RoActemra®	Genentech / Roche	Injectable—80mg/4ml, 200mg/10ml, 400mg/20ml vial

DMARD, disease-modifying antirheumatic drug.
*Listed trade names are limited to commonly prescribed U.S. products when multiple are available.

Table 3 shows routes of administration, labeled uses, and usual (recommended) adult doses and frequency for RA.

Table 3. Route and usual dose of treatments for rheumatoid arthritis

Class	Generic Name	Route	Usual Adult Dose
Corticosteroids			
	Methylprednisolone	Injectable / Oral	IM (acetate)—10 to 80 mg every 1 to 2 weeks IM (sodium succinate)—10 to 80 mg daily Intra-articular, intralesional (acetate)—4 to 80 mg every 1 to 5 weeks IV (sodium succinate)—10 to 40 mg every 4 to 6 hours; up to 30 mg/kg every 4 to 6 hours Oral—2 to 60 mg in 1 to 4 divided doses to start, followed by gradual reduction
	Prednisone	Oral	Oral—Use lowest effective dose (5-60 mg/day)
	Prednisolone	Oral	Oral—Use lowest effective dose (5 to 7.5 mg/day)
Oral DMARDs			
	Hydroxychloroquine	Oral	Oral—200 to 400† mg/day in 1 or 2 divided doses
	Leflunomide	Oral	Oral—10 to 20 mg/day in a single dose
	Methotrexate	Oral	IM, SQ, oral—7.5 to 20 mg/week in a single dose
	Sulfasalazine	Oral	Oral—500 to 3,000 mg/day in 2 to 4 divided doses
Biologic DMARDs			
	Abatacept	Injectable	IV—Dosed according to body weight (< 60 kg = 500 mg; 60-100 kg = 750 mg; > 100 kg = 1,000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter
	Adalimumab	Injectable	SQ—40 mg every other week; may increase to 40 mg per week in patients not taking concomitant MTX
	Anakinra	Injectable	SQ—100 mg/day; dose should be decreased to 100 mg every other day in renal insufficiency
	Certolizumab Pegol	Injectable	Initial dose of 400 mg, repeat dose 2 and 4 weeks after initial dose; Maintenance dose is 200 mg every other week (May consider maintenance dose of 400 every 4 weeks)
	Golimumab	Injectable	SQ - 50 mg once per month
	Etanercept	Injectable	SQ—25 mg twice weekly or 50 mg once weekly
	Infliximab	Injectable	IV—3 mg/kg in combination with MTX at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treat as often as every 4 weeks
	Rituximab	Injectable	IV—1,000 mg on days 1 and 15 in combination with MTX
	Tocilizumab	Injectable	IV—4mg/kg followed by an increase to 8mg/kg based on clinical response; given every 4 weeks with or without MTX

DMARD, disease-modifying antirheumatic drug; IM, intramuscular; IV, intravenous; NSA, nonspecific anti-inflammatory (or immunosuppressant) indication; SQ, subcutaneous; RA, rheumatoid arthritis.

Treatment Strategies

In RA, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in early or mild disease, but they do not have any disease-modifying properties. The oral DMARD MTX is the cornerstone of treatment, as it has demonstrated good disease control. However, MTX toxicity may limit its use, and many patients do not adequately respond to MTX monotherapy. Leflunomide, hydroxychloroquine, and sulfasalazine are alternative oral DMARDs that can be given as monotherapy or in combination; recommendations for their use are largely based on disease duration, degree of disease activity, and prognostic features.[22]

Combination therapies serve an important role because treatment with a single DMARD often does not adequately control symptoms. Low-dose systemic corticosteroids (prednisone 7.5-10 mg/day) or intra-articular corticosteroids are used as an adjunct to DMARDs. In patients with persistent disease despite aggressive management with standard agents, biologic agents, often in

combination with MTX, are now considered the standard of care. Although combination therapies improve response rates in patients initially receiving monotherapy, available evidence does not predict which combination strategy will provide the best outcome.[23]

There is debate about which types of combination therapy are preferred and how early in the disease process to initiate this intervention. No settled opinion exists as to whether treatment should proceed in a sequential "step-up" approach (progressing from single therapy to combination therapy) or in a "step-down" approach (beginning with combination therapy and stepping down treatment when symptoms are under control). Additional uncertainty remains regarding risks and benefits of therapies in patient subgroups.

Recent reports have examined treatment of RA, supporting the overall efficacy of treatments.[24-27] However, additional agents have since been introduced on the market, necessitating an update of the evidence. A further examination of the comparative efficacy and effectiveness of various treatments and treatment strategies, as well as long-term outcomes and subpopulations, is warranted.

Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and harms of corticosteroids, oral DMARDS, and biologic DMARDs in the treatment of patients with RA. We address the following four key questions (KQs):

- KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?
- KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
- KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?
- KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Organization of the Report

The remainder of this comparative effectiveness review describes our methods to review and synthesize this literature, presents our results by key question and discusses the implications of those results for clinical applications and future research. Appendix A lists our peer reviewers and technical expert panel; Appendix B describes our search strategy; Appendix C contains studies included in meta-analyses; Appendix D lists excluded studies; Appendix E presents evidence tables; Appendix F contains abstract-only studies; Appendix G presents the criteria for assessing the quality of individual studies; Appendix H provides characteristics of studies with poor internal validity; and Appendix I describes clinical assessment scales commonly used in arthritis trials.

Chapter 2. Methods

In this chapter, we document the procedures that the RTI International–University of North Carolina Evidence-based Practice Center (RTI–UNC EPC) used to develop this comparative effectiveness review (CER) on pharmacologic treatments for rheumatoid arthritis. We briefly describe the topic development process below. We then document our literature search and retrieval process and describe methods of abstracting relevant information from the eligible articles to generate evidence tables. We also document our criteria for rating the quality of individual studies and for grading the strength of the evidence as a whole.

Topic Development

This report is an update of a CER completed in 2007.[25] The topic of the original report and the preliminary key questions arose through a public process involving the public, the Scientific Resource Center (SRC, at www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#RC) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov), and various stakeholder groups (www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#SG). Investigators from the RTI-UNC EPC then refined the original questions into the key questions used for the original report, in consultation with AHRQ, the SRC, and the Technical Expert Panel (TEP) during multiple conference calls. For this update, the original key questions were again refined into the final set of key questions cited in the introduction. No substantive changes to the key questions were made for this update other than adding new medications that have been approved since the previous report. The protocol for the project was posted on the AHRQ website (http://www.effectivehealthcare.ahrq.gov/). The original report included both rheumatoid arthritis (RA) and psoriatic arthritis (PsA). When updating the material, the decision was made to divide into the material into two separate reports, one for RA and one for PsA. This report includes only the information related to patients with RA. This report is intended to replace the original report; it includes the information from the original report as well as the new information we identified.

Literature Search

To identify articles relevant to each key question we searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix B. This review was conducted at the same time as a review on psoriatic arthritis; the literature searches and review processes were conducted in parallel, shown in Appendix B. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (rheumatoid arthritis [RA], psoriatic arthritis [PsA]), drug interactions, and adverse events with a list of included medications. The following medications were included: corticosteroids (methylprednisolone, prednisone, and prednisolone), four oral disease-modifying antirheumatic drugs (DMARDs) (methotrexate [MTX], leflunomide, sulfasalazine, and hydroxychloroquine), and nine biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab). We limited the electronic searches to

"human" and "English language." For the original report, sources were searched from 1990 to September 2006. For this update, sources were searched from June 2006 to March 2010. We overlapped the update search with the original search to account for delays in indexing. We used the National Library of Medicine (NLM) publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We manually searched reference lists of pertinent review articles and letters to the editor to supplement searches for the original report. We used Scopus™ abstract and citation database to supplement searches for this update. We imported all citations into an electronic database (EndNote X.0.2). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the U.S. Food and Drug Administration (FDA). The SRC contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from five pharmaceutical companies (Abbott, Amgen, Bristol-Myers Squibb, Centocor, and Genetech). The SRC also searched the following for potentially relevant unpublished and ongoing literature: FDA website, Health Canada, Authorized Medicines for EU, ClinicalTrial.gov, Current Controlled Trials, Clinical Study Results, WHO Clinical Trials, Conference Papers Index, Scopus, NIH RePORTER, HSRPROJ, Hayes, Inc. Health Technology Assessment, and the New York Academy of Medicine's Grey Literature Index.

Study Selection

We developed eligibility (inclusion and exclusion) criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons for each key question, as described in Table 4 below. For efficacy and effectiveness, we focused on head-to-head trials and prospective cohort studies comparing one drug to another. For biologic DMARDs, we also included placebo-controlled, double-blinded randomized controlled trials (RCTs). For harms and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and observational studies.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and harms. We defined head-to-head trials as those comparing one drug of interest with another. RCTs or prospective cohort studies of at least 3 months' duration were eligible for inclusion. Because multiple large RCTs had been conducted on this topic, we adopted a minimum sample size requirement ($N \geq 100$) to focus on the best available evidence. However, we did not use a sample size cutoff for our meta-analyses (RCTs of any sample size were eligible for our mixed treatment comparisons). For harms (i.e., evidence pertaining to tolerability, adverse effects, and adverse events), we examined data from both experimental and observational studies. We included RCTs and observational studies with sample sizes of at least 100 patients, lasting at least 3 months, and that reported an outcome of interest.

As equipotency among the reviewed drugs is not well established, we assume that comparisons made within the recommended dosing ranges in Chapter 1 are appropriate. Dose comparisons made outside the recommended daily dosing range are not in our report.

Table 4. Outcome measures and study eligibility criteria

Key Questions, Outcomes of Interest, and Specific Measures	Study Eligibility Criteria
KQ 1 /KQ 2: **Efficacy/effectiveness** **KQ 1:** • Disease activity • Radiographic joint damage • Remission **KQ 2:** • Functional capacity • Quality of life	**Study Design** • Head-to-head double-blind RCTs • Systematic reviews • Prospective, controlled cohort studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100
KQ 3: **Harms, tolerability, adherence, adverse effects**	**Study Design** • Head-to-head double-blind RCTs • Systematic reviews • Observational studies, prospective and retrospective **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100
KQ 4 **Benefits and harms in subgroups based on stage, history of prior therapy, demographics, concomitant therapies, comorbidities**	**Study Design** • Head-to-head double-blind RCTs • Systematic reviews • Observational studies **Minimum Study Duration** • RCT—3 months • Observational—3 months **Study Population** • Age 19 and older • Patients with RA **Sample Size** • RCT N ≥ 100 • Observational N ≥ 100

KQ, key question; N, number of subjects enrolled (i.e. sample size); RA, rheumatoid arthritis; RCT, randomized controlled trial.

Two individuals independently reviewed abstracts (Appendix C contains review criteria for title/abstract stage). If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility criteria (Appendix C) to determine which, if any, to exclude at this stage. Appendix D lists our full bibliography and their source database. Appendix E summarizes reasons for exclusion of studies that were reviewed as full text articles but did not meet eligibility criteria. We did not include studies that met eligibility criteria but were reported as an abstract only.

We reviewed studies that reported health outcomes for efficacy or effectiveness. For example, these included clinical response to treatment, remission, functional capacity, and quality of life. In addition, we included radiographic outcomes as intermediate outcome measures. For harms, we looked for both overall and specific outcomes ranging in severity (e.g.,

serious infections, malignancies, hepatotoxicity, hematological adverse events, infusion and injection reactions, and nausea), withdrawals attributable to adverse events, and drug interactions.

We included systematic reviews and meta-analyses in our evidence report if we found them to be relevant for a key question and of good or fair methodological quality. We did not abstract individual studies if they had been used in an included systematic review or meta-analysis of good quality; studies in this group that met eligibility criteria are cited in Appendix F. However, we reviewed them to determine whether any other outcomes of interest were reported.

Data Extraction

We designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Trained reviewers abstracted data from each study. A senior reviewer read each abstracted article and evaluated the completeness of the data abstraction.

We abstracted the following data from included articles: study design, eligibility criteria, intervention (drugs, dose, and duration), additional medications allowed, methods of outcome assessment, population characteristics (such as age, sex, race or ethnicity, or mean disease duration), sample size, loss to followup, withdrawals because of adverse events, results, and adverse events reported. We recorded intention-to-treat (ITT) results if available. All data abstraction employed SRS 4.0, Mobius Analytics™. Evidence tables containing all abstracted data of included studies are presented in Appendix G.

Quality Assessment

To assess the quality (internal validity) of trials, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)[28] and the National Health Service Centre for Reviews and Dissemination.[29] Elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis (i.e., all patients were analyzed as randomized with missing values imputed), adequacy of blinding, and overall and differential loss to followup.

In general terms, a "good" study has a low risk of bias and results are considered to be valid. A "fair" study is susceptible to some risk of bias, but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant risk of bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results.

To assess the quality of observational studies, we used criteria outlined by Deeks et al.[30] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis. To assess the quality of systematic reviews and meta-analyses, we assessed the following: whether the review was based on a clear question, clear reporting of inclusion criteria, methods used for identifying literature (the search strategy), whether two reviewers independently reviewed publications to determine eligibility, whether authors used a standard method of critical appraisal (or quality rating or validity assessment), assessment of heterogeneity, assessment of publication bias, and statistical analysis. Systematic reviews were categorized as good when all criteria were met.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. Appendix H details the predefined criteria used for evaluating the quality of all included studies. We gave a good quality rating to studies that met all criteria. The majority of studies received a quality rating of fair. This category includes studies that presumably fulfilled all quality criteria but did not report their methods sufficiently to answer all of our questions. Thus, the fair-quality category includes studies with quite different strengths and weaknesses. We gave a poor quality rating to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. Poor-quality studies and reasons for that rating are presented in Appendix I.

Applicability Assessment

We used the parameters for evaluation on guidance provided by AHRQ's Methods Guide for Comparative Effectiveness Reviews,[31] to evaluate the applicability of the included studies. Applicability is similar to generalizability or external validity of the studies included in the evidence base. We evaluated applicability using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of follow-up, and setting. We specifically considered whether populations enrolled in these trials or studies differed from target populations as laid out in Chapter 1, whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings.

Grading Strength of Evidence

We evaluated the strength of evidence based on methods guidance for the EPC program.[31,32] Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains (Table 5): risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships).

Table 5. Strength of evidence grades and their definitions

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of 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 effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

As described in Owens et al., the evaluation of risk of bias includes assessment of study design and aggregate quality of studies.[32] We judged good quality studies to result in evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same direction. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. We graded evidence as being precise when results had a low

degree of uncertainty. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions.[32]

We dually evaluated the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain and reconciled all disagreements. The levels of strength of evidence are shown in Table 5.

Data Synthesis

Throughout this CER, we generally synthesized the literature qualitatively. The exceptions are the mixed treatment comparison (MTC) meta-analysis of biologic DMARDS described below and the meta-analyses of withdrawals from placebo-controlled trials (overall withdrawals, withdrawals due to lack of efficacy, and withdrawals due to adverse events). Comparisons of the drugs that had not yet been quantitatively analyzed in any of the included meta-analyses were either limited to fewer than three good or fair RCTs or had heterogenous/noncomparable study populations. Therefore, we did not attempt any quantitative analyses of such comparisons.

Because only limited head-to-head evidence on biologic DMARDs was available, we conducted MTC meta-analysis using Bayesian methods when data were sufficient and trials were of similar design and conducted in similar settings with a comparable patient population. To do this, we included all placebo- and active-controlled studies of good or fair quality of biologic DMARDS that were fairly homogenous in study populations and outcome assessments. For this analysis, we excluded studies of subjects that were methotrexate or oral DMARD naïve and studies of subjects that had failed treatment with biologic DMARDS. All included studies in the MTC meta-analysis enrolled patients with active RA despite oral DMARD therapy. Our outcome measures of choice were American College of Rheumatology (ACR) 20/50/70 response rates and withdrawals (overall, due to lack of efficacy, and due to adverse events).[33] Evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials.[34-36] Nevertheless, findings must be interpreted cautiously.

The treatments in each study were considered to have binary outcome measures. These data provided information on the probability, $p_{j;k}$, of the response of drug k in study j. A logistic regression model was considered. Each study has a reference ‘‘placebo’’ arm or another common control arm, b_j, with study-specific ‘‘baseline’’ log-odds of response, l_j, for this placebo arm or common control arm b_j. The log-odds ratio, $d_{j;k}$, of outcome for drug k, relative to baseline, b_j, is assumed to come from a random effects model with mean log-odds ratio, $(d_k - d_b)$, and between-study standard deviation, ζ, where d_k is the mean log-odds ratio of the outcome for a drug relative to a first drug (so that $d_1 = 0$). This model can be written as follows:[37]

$$\text{Log odds } (pj, k) = \begin{Bmatrix} \mu_j \\ \mu_j + \delta_{j,k} \end{Bmatrix}$$

where $\delta_{j,k} \sim \text{Normal}((d_k - d_{b,j}), \zeta^2)$

The main hypothesis of the model was: $d_k = d$ (log odds ratio of all drugs are same)

All models were fitted by using Bayesian inference computed with Monte Carlo Markov Chain (MCMC) simulation in WinBUGS version 1.4.1. All drug effect parameters were given flat Normal(0,1000) priors and the between-study standard deviation flat uniform distributions with a large range. In all cases a burn-in of 20,000 simulations was discarded. All results presented are based on a further sample of 40,000 simulations. We calculated the odds ratio and 95% credible intervals of outcomes of interest for all possible comparisons among our drugs of interest.

Peer Review

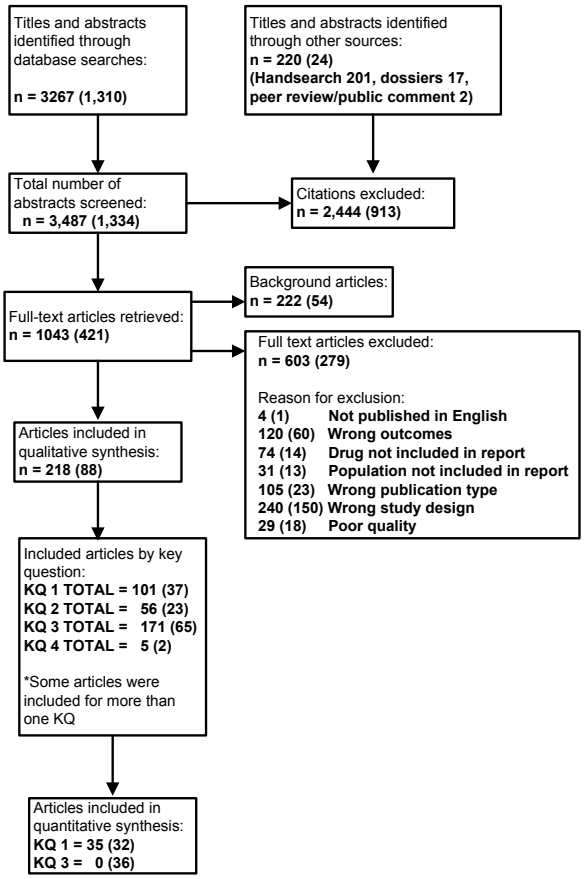
Individuals who were experts in rheumatology and various stakeholder and user communities (listed in Appendix A [to be completed for final report]) performed an external peer review on this CER. The SRC oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we had conceptualized and defined the topic and key questions. Our peer reviewers (Appendix A) gave us permission to acknowledge their review of the draft. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. In addition, the SRC placed the draft report on the AHRQ website (http://effectivehealthcare.ahrq.gov/) and compiled the comments for our review.

Chapter 3. Results

Results

We identified 3,487citations from our searches (Appendix B). Figure 1 documents the results of the literature search. Working from 1,043 articles retrieved for full review, we retrieved 222 for background and excluded 603 at this stage (Appendix D). We included 218 published articles reporting on 174 studies: 27 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 41 placebo-controlled trials, 11 meta-analyses or systematic reviews, and 94 observational studies. We identified 42 studies for quantitative syntheses. Our findings include studies rated good or fair for internal validity, unless a particular study rated poor provides some unique information that we judged to be of interest. Most studies were of fair quality; we designate in the text only those of good or poor quality. Evidence tables for included studies, by key question (KQ), can be found in Appendix G.

Figure 1. Disposition of articles (PRISMA figure)



*The first number listed includes all references identified in both the original and update reports.
The number in parentheses indicates references identified in the update report only.

*Number of included articles differs from number of included studies because some studies have multiple publications.

*The first number listed includes all references identified in both the original and update reports. The number in parentheses indicates references identified in the update report only.

Appendixes are cited in this report and provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/___/___.pdf

Of the 175 included studies, 78 (45 percent) were supported by pharmaceutical companies; 30(17 percent) were funded by governmental or independent funds; and 14 (8 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 53 (30 percent) studies.

This chapter is organized by key question. We then present findings in order by class of drugs and combinations of drugs as appropriate to the particular key question. Generally, the chapter is organized using the following categories: individual oral disease-modifying antirheumatic drug (DMARD) vs. oral DMARD, oral DMARD combinations (with or without corticosteroids) vs. oral DMARD combinations, biologic vs. biologic, biologic vs. oral DMARD, biologics plus oral DMARD vs. biologic, biologic plus oral DMARD vs. oral DMARD, and early RA strategies (see Table 2 in Chapter 1). For purposes of this review, we defined strategies as studies where drug regimens were not fixed, but rather when a clinician made dose adjustments or drug changes according to patient response.

Across all key questions, we included head-to-head studies, observational studies, and systematic reviews. When comparative evidence is available, we discuss it before presenting indirect analyses of placebo-controlled trials.

Table 6 below gives the numbers of trials or studies for drug class comparisons reported only from *head-to-head studies;* when some groupings have important subcomparisons, we note these as well.

Table 6. Number of head-to-head studies (observational and RCT) by drug comparison for rheumatoid arthritis

Drug Comparison	Number of Studies; Quality Rating
Oral DMARDs vs. oral DMARDs	8 fair
Oral DMARD combinations	6 fair; 3 good
Biologic DMARDs vs. biologic DMARDs	25 fair; 2 good
Biologic DMARDs vs. oral DMARDs	8 fair; 2 good
Biologic DMARD + oral DMARD combinations	13 fair; 2 good
Early RA Strategies	1 fair; 2 good
*Other	6 fair

DMARD, disease modifying anti-rheumatic drug.

*The other comparison category includes studies that do not fit into one category due to multiple arms or multiple types of comparisons made

Table 7 lists abbreviations and full names of key outcome measurement instruments encountered in these studies. For further details about such instruments and scales, see Appendix I.

Table 7. Disease activity, radiographic progression, functional capacity, and quality of life measures

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by
ACR-N	American College of Rheumatology percent improvement from baseline to endpoint	0 to 100 percent	Increase
ACR 20/50/70*	American College of Rheumatology response scores based on 20, 50, or 70 percent criteria for improvement	0 to 100 percent	Increase
ASHI	Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific Health Index)	0 to 100	Increase
DAS*	Disease Activity Score	0 to 10	Decrease
DAS 28	Disease Activity Score Short Form	0 to10	Decrease
EULAR response*	European League Against Rheumatism response	N/A	N/A
EQ-5D*	EuroQol EQ-5D Quality of Life Questionnaire	0 to 1	Increase
HAQ* (D-HAQ)	Health Assessment Questionnaire (Dutch Version)	0 to 3	Decrease
HAQ-DI	Disability Index of the Heath Assessment Questionnaire	0 to 3	Decrease
Larsen Scale*	Larsen Scale for Grading Radiographs in Rheumatoid Arthritis	0 to 250	Decrease
SF-36*	Medical Outcomes Study Short Form 36 Health Survey	0 to 100	Increase
Sharp Scale	Sharp Scoring System for Radiographic Rheumatoid Arthritis	Erosion: 0 to 170 Narrowing: 0 to 144	Decrease
SHS*	Sharp/van der Heijde Method (SHS) for Scoring Radiographs (SHS is frequently modified by individual authors to meet study requirements and needs; there is no standard modified SHS)	Erosion: 0 to 160 for hands; 0 to 120 for feet Joint space narrowing: 0 to 168 Total: 0 to 448	Decrease
SOFI	Signals of Functional Impairment Scale	0 to 44	Decrease

* These key scales are defined in Appendix I.

Key Question 1: Reductions in Disease Activity, Limitations of Disease Progression, and Maintenance of Remission

This key question concerned three main topics. Specifically, "for patients with rheumatoid arthritis, do drug therapies differ in their ability to reduce disease activity, to slow or limit progression of radiographic joint damage, or to maintain remission?" Evidence Tables 1 (for head-to-head studies) and 2 (for systematic reviews and meta-analyses) in Appendix G document details about all these studies.

Overview

A total of 56 RCTs, 1 nonrandomized controlled trial, 11 observational studies, and 6 systematic reviews or meta-analyses compared symptom response, radiographic joint damage, and remission. Details are found in Evidence Tables 1 and 2, Appendix G. The main drug classes that we compared include oral DMARDs, biologic DMARDs (also referred to simply as biologics), and various combined strategies.

Rheumatoid Arthritis: Key Points

Overall strength of evidence by disease activity and radiographic changes, when available is listed in Table 8. Table 9 provides information on comparisons made, symptom response, and quality ratings. Table 10 provides information on radiographic joint damage, indicating whether the study populations included patients with early RA.

Table 8. Strength of evidence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD						
Corticosteroid vs. Corticosteroid 1 study N =143	Low 1 RCT/ fair	Unknown, single study	Direct	Precise	No difference in ACR 20 and DAS for prednisolone and budesonide	Low
LEF vs. MTX 1 meta-analysis, 2 RCTs; N = 3213	Low 1 Meta-analysis/ Good 2 RCTs/Fair	Consistent	Direct	Imprecise	No difference in ACR 20 at 1 to 2 years	Low
1 meta-analysis, 2 RCTs; N = 3213	Low 1 Meta-analysis, Good 2 RCTs/Fair	Consistent	Indirect	Precise	No difference in radiographic changes at 2 years	Low
LEF vs. SSZ 1 meta-analysis, 1 RCT; N =2090	Low 1 Meta-analysis/ Good 1 RCT/Fair	Inconsistent	Direct	Imprecise	Mixed results for ACR response at 2 yrs	Insufficient
	Low 1 RCT/Fair	Unknown, single study	Indirect	Imprecise	Similar Radiographic changes at 2 years	Low
SSZ vs. MTX 3 RCTs; N = 1001	Low 3RCTs/Fair	Consistent	Direct	Precise	No difference in disease activity	Moderate
	Low 2RCTs/Fair	Consistent	Indirect	Imprecise	No difference in radiographic changes	Low
Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticosteroids						
SSZ + MTX vs. SSZ 3 RCTs: N = 479	Low 1 RCT/Fair	Unknown, single study	Direct	Imprecise	Sulfasalazine + MTX improves disease activity	Low
	Low 2RCTs/Fair	Consistent	Direct	Precise	No differences in disease activity in patients with early RA	Low
	Low 2RCTs/Fair	Consistent	Indirect	Precise	No difference in radiographic changes	Low

ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; MTC, mixed treatment comparison; N, number; RA, rheumatoid arthritis rituximab, RIT; RCT, randomized controlled trial; SSZ, sulfasalzine; TCZ, tocilizumab; TNF, tumor necrosis factor; vs., versus.

Table 8. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
MTX + HCQ + SSZ vs. 1 or 2 oral DMARDs 2 RCTs; N = 273	Low 2RCTs/Good	Consistent	Direct	Imprecise	Improvement in disease activity in 3 versus 2 oral DMARDs	Moderate
Oral DMARD + corticosteroid vs. Oral DMARD 1 meta-analysis, 1 RCT, 1 open label trial; N = 2131	Low 1 RCT/Good 1 open label trial/fair	Inconsistent	Direct	Imprecise	Mixed results for disease activity	Insufficient
	Low 1 Meta-analysis/ Good 1 Open label trial/ Fair	Consistent	Indirect	Imprecise	Less radiographic changes with oral DMARD plus prednisone	Low
Biologic DMARDs vs. Biologic DMARDs						
Biologic DMARDs vs. Biologic DMARDs (MTC) 30 RCTs; N = 1073*	Medium, 1 MTC	Consistent	Indirect	Imprecise	No significant differences in disease activity (ACR 50) in MTC analyses for abatacept, adalimumab, infliximab and tocilizumab	Low
ABA vs. INF 1 RCT; N = 431; Mixed treatment comparisons (MTC) 30 RCTs; N = 1073*	Low 1 RCT/Fair, 1 MTC	Inconsistent	Direct and Indirect	Imprecise	Abatacept improves disease activity over 1 year more than infliximab No differences in MTC analyses	Low
ADA vs. INF 1 prospective cohort; N = 707 Mixed treatment comparisons (MTC) 30 RCTs; N = 1073*	Medium 1 Prospective cohort/Fair, 1 MTC	Consistent	Direct and Indirect	Imprecise	Adalimumab improves disease activity over 1 year more than infliximab No differences in MTC analyses	Low
ANA vs. Biologics Mixed treatment comparisons (MTC) 30 RCTs; N = 1073*	Medium, 1 MTC	Consistent	Indirect	Imprecise	Less improvement in disease activity (ACR 20/50) for anakinra compared to certolizumab and etanercept. Comparisons with abatacept, adalimumab, golimumab, infliximab, and tocilizumab did not reach statistical significance.	Low

Table 8. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
CTZ vs. Biologics Mixed treatment comparisons (MTC) 30 RCTs; N = 1073*	Medium, 1 MTC	Consistent	Indirect	Precise	In MTC analyses, greater improvement in disease activity (ACR 20/50) for certolizumab compared to abatacept, anakinra, infliximab. No significant differences when compared with adalimumab, etanercept, golimumab and tocilizumab	Low
ETN vs. Biologics Mixed treatment comparisons (MTC) 30 RCTs; N = 1073*	Medium, 1 MTC	Consistent	Indirect	Precise	In MTC analyses, greater improvement in disease activity (ACR 20/50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab, tocilizumab. No significant differences when compared with certolizumab and golimumab.	Low
ETN vs. INF 1 open label trial, 4 prospective cohorts; N = 3557 MTC analyses not significant, ACR 20: OR 1.02 (0.52-1.01)	Medium 1 Open label trial, 4 prospective cohort/Fair, 1 MTC	Consistent	Direct and indirect	Imprecise	Faster onset of efficacy for ETN but no differences at 1 year or later MTC analyses (ACR 20: OR 4.68, 95% CI, 2.01-9.33, ACR 50: OR 5.82, 95% CI 2.19-13.08)	Low
RTX vs. anti TNF 1 prospective cohort; N = 116	Medium 1 Prospective cohort/Fair	Unknown, single study	Direct	Precise	RTX reduces DAS 28 at 6 months more than anti-TNF	Low
Biologic DMARDs vs. Oral DMARDs						
Biologic DMARDs vs. Oral DMARDs 4RCTs/2Cohorts; N = 4381	Low 4RCTs/2 Cohorts	Consistent	Direct	Imprecise	Higher response rates for biologic DMARDs (ADA, ANA, ENT, INF, TCZ) vs. oral DMARDs (MTX, LEF)	Moderate
ADA vs. MTX 1 RCT; N = 799	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Lower response rates for ADA vs. MTX	Low
	Low 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic progression for ADA vs. oral DMARD	Low
ETN vs. Oral DMARDs 2RCT, 1nonrandomized trial, 1 prospective cohort ; N =3455	Medium 1 RCT, 1 nonrandomized trial, 1prospective cohort/Fair	Consistent	Direct	Imprecise	Greater improvement in disease activity in ETN vs. oral DMARD	Low

Table 8. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
	Low 2RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic changes for ETN vs. oral DMARD	Low
TCZ vs. MTX 1 RCT; N = 125	Low 1 RCT/Fair	Unknown	Direct	Precise	Great improvement in disease activity for Tocilizumab than MTX at 24wks	Low
Biologic DMARDs + Biologic DMARDs vs. Biologic DMARDs						
1. ETN + AKA vs. ETN 2. ETN + ABA vs. ETN 2 RCTs; N = 363	Low 2 RCTs/Fair	Consistent	Direct	Imprecise	No difference in disease activity	Low
Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs						
ADA+ MTX vs. ADA 1 RCT; N = 799	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Higher ACR50 response for ADA + MTX	Low
	Low 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ADA + MTX	Low
ETN + DMARD vs. ETN 3RCTs, 3 cohorts; N =8529	Medium 3RCTs/Fair, 3 cohorts/ Good, Fair	Consistent	Direct	Imprecise	Trend toward improved disease activity for ETN+ MTX vs. ETN	Low
	Low 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ETN + MTX vs. ETN	Low
INF + MTX vs. MTX 1 Prospective cohort; N = 2711	Medium 1 Prospective cohort/Good	Unknown, single study	Direct	Precise	Improved disease activity for INF + MTX vs. INF	Low
RTX +MTX vs. RTX 1 RCT; N = 161	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for RTX + MTX vs. RTX	Low
Biologic DMARDs + Oral DMARDs vs. Oral DMARDs						
ADA + MTX vs. MTX 1 RCT; N = 799	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for ADA + MTX vs. MTX	Low
	Low RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ADA + MTX	Low
ETN + oral DMARD vs. oral DMRD (MTX or SSZ) 3 RCTs; N = 1488	Low 3RCTs/Fair	Consistent	Direct	Imprecise	Improved disease activity for ETN + oral DMARD vs. oral DMARD	Low
	1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic change for ETN + MTX vs. MTX	Low
INF + MTX vs. MTX 1 RCT; N = 1049	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for INF + MTX vs. MTX	Low

Table 8. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs + Oral DMARDs						
ANK + MTX vs. ANT + LEF; ETN + DMARD vs. INF + DMARD; Anti-TNF + MTX vs. anti-TNF vs. LEF 3 prospective cohorts; N = 4225	Medium 3 Prospective cohort/Fair	Consistent	Direct	Imprecise	No significant difference between Biologic DMARD + Oral DMARD vs. Biologic DMARD + oral DMARD. (ANK, INF, ETN, ADA with MTX or LEF	Low
Strategies in Early RA						
Two oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT; N = 155	Low 1 RCT/Good	Unknown, single study	Direct	Precise	Improved disease activity in combination group at 28 weeks, but no difference by 52 weeks	Low
	Low 1 RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic progression in combination group up to 5 years	Low
Three oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT; N = 199	Medium 1 RCT/Fair	Unknown, single study	Direct	Precise	Higher remission in combination group at 2 years but not significant at 5 yrs	Low
	Medium 1 RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic progression in combination group up to 5 years	Low
(1)Sequential monotherapy vs. (2)Step-up combination therapy vs. (3) initial combination therapy with prednisone vs. (4) initial combination therapy with infliximab RCT; N = 508	Low 1 RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity in groups 3 and 4 than in groups 1 and 2 at 1 year; no difference in remission by four years.	Low
	Low 1 RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic progression in groups 3 and 4 by four years	Low

Table 9. Disease activity and remission for oral DMARD vs. oral DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Corticosteroid vs. Corticosteroid					
Kirwan et al., 2004[38]	RCT 143 12 weeks	Population-based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	No significant difference between 9 mg BUD and PNL for ACR 20, DAS (ACR 20: 42% vs. 56%; *P* = 0.11) at 12 weeks	Fair
Leflunomide vs. MTX					
Osiri et al., 2003[39]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week)	Lower ACR 20 responses for LEF vs. MTX at 12 months (OR, 1.43; 95% CI, 1.15-1.77; *P* = 0.001); no significant differences in ACR response rates at 2 years	Good
Emery et al., 2000[40]	RCT 999 1 year with optional 2nd year	Mean disease duration 3.5 to 3.8 years	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Lower ACR 20 responses at 12 months (50.5% vs. 64.8%; *P*<0.001); no significant differences in ACR at 2 years (64.3% vs. 71.7%; *P* = NS, NR)	Fair
Strand, et al., 1999[41,42]	RCT 482 12 months (1 year continuation)	Mean disease duration 6.5 to 7 years	LEF (20 mg/day) vs. MTX (7.5 to 15 mg/week)	At 1 year, ACR 20 numerically higher for LEF but not significant (52% vs. 46%; *P* = NR); at 2 years, ACR 20 difference not significant (79% vs. 67%; *P* = 0.049)	Fair
Leflunomide vs. Sulfasalazine					
Osiri et al., 2003[39]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	Higher ACR 20 and ACR 50 responses for LEF vs. SSZ at 24 months (ACR 20: OR, 0.35; 95% CI, 0.16-0.77; *P* = 0.009) (ACR 50: OR, 0.32; 95% CI, 0.15-0.67; *P* = 0.003); no significant differences in any ACR response rates at 6 and 12 months	Good
Smolen et al., 1999[43]; Larsen et al., 2001[44]	RCT 358 24 weeks (12 and 24 month followup)	Mean disease duration 5.7 to 7.6 years	LEF (20 mg/day) vs. SSZ (2 g/day)	Similar ACR 20 response rates (48% vs. 44%; *P* = NR)	Fair

ACR, American College of Rheumatology; BUD, budesonide; CI, confidence interval;; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; g, gram; LEF, leflunomide; ; MTX, methotrexate; mg, milligram;; NR, not reported;NS, not significant; ; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 9. Disease activity and remission for oral DMARD vs. oral DMARD studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Sulfasalazine vs. MTX					
Capell et al., 2006[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland; multicenter; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	At 18 months, no significant difference in DAS for SSZ vs. MTX (-0.30 vs. -0.26; *P* = 0.79); no significant difference in any ACR responses	Fair
Dougados et al., 1999[46]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in DAS between SSZ vs. MTX (-1.15 vs. -0.87; *P* = NS, NR); no significant difference in ACR 20 responses; *P* = NR	Fair
Haagsma et al., 1997[47]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week	No significant difference in DAS for SSZ vs. MTX (-1.6 vs. -1.7; *P* = NS, NR)	Fair

Table 10. Radiographic joint damage in Oral DMARD vs. Oral DMARD

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Leflunomide vs. MTX				
Osiri et al., 2003[39]	Systematic review and meta-analysis 1,732 2 years	No	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week)	No differences in total Sharp score change or Larsen score change
Emery et al., 2000[40]	RCT 999 1 year with optional 2nd year	No	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Larsen score change at 1 year: 0.3 vs. 0.3; *P* = NS Larsen score change at 2 years: 1.27 vs. 1.31; *P* = NS, NR
Strand et al., 1999[41]	RCT 482 12 months (1 year continuation)	No	LEF (20 mg/day) vs. MTX (7.5 to 10 mg/week)	Total Sharp score change at 1 year: 0.53 vs. 0.88 ;*P* = 0.05 Total Sharp score at 2 years: 1.6 vs. 1.2; *P* = 0.659

DMARD, disease-modifying antirheumatic drug; g, gram; LEF, leflunomide; mg, milligram; MTX, methotrexate; NR, not reported; NS, not significant; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 10. Radiographic joint damage in Oral DMARD vs. Oral DMARD (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Leflunomide vs. Sulfasalazine				
Smolen et al., 1999;[43] Larsen, et. al., 2001[44]	RCT 358 24 weeks (12 and 24 month followup)	No	LEF (20 mg/day) vs. SSZ (2 g/day)	Larsen score change at 24 weeks: 0.01 vs. 0.01; *P* = NS Larsen score change at 1 year: 0.02 vs. 0.02; *P* = NS Larsen score change at 2 years: -0.07 vs. -0.03; *P* = NR
Sulfasalazine vs. MTX				
Capell et al., 2006[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Yes (70% 1 year or less)	SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	No significant difference in total modified Sharp/van der Heijde score change (Data NR)
Dougados et al., 1999[46]	RCT 209 (146) 52 weeks (5 years)	Yes	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Total modified Sharp/van der Heijde score change: 4.64 vs. 4.50 vs. 3.36; *P* = NS,NR; change at 5 years: 8.5 vs. 7.5; *P* = 0.7

Oral DMARDs vs. oral DMARDs. One trial found no statistically significant difference between budesonide and prednisolone for disease activity outcomes.[38] The strength of evidence is low.

Two trials found no statistically significant difference between methotrexate (MTX) and leflunomide for disease activity outcomes at 2 years or radiographic changes.[39,42] The strength of evidence is low.

Three trials did not find a significant difference between MTX and sulfasalazine for disease activity outcomes.[45-47] The strength of evidence is moderate.

One trial found that leflunomide lessens disease activity outcomes at 2 yrs compared to sulfasalazine but did not detect differences in radiographic changes.[44] The strength of evidence is insufficient for disease activity and low for radiographic changes.

No fair or good evidence exists for comparing hydroxychloroquine monotherapy with other oral DMARD monotherapy.

Oral DMARD combinations. Combination therapy with sulfasalazine and MTX compared to monotherapy provides different results depending on the population.[45-47] Two trials of DMARD naïve patients with early RA showed no difference between combination sulfasalazine and MTX vs. monotherapy.[46,47] The strength of evidence is low. The one trial in those without early RA (up to 10 years duration) supported combination therapy with sulfasalazine and MTX vs. monotherapy with either drug; the changes in DAS scores were greater for combination therapy than for monotherapy (-1.26 for combination, -1.15 for sulfasalazine, and -0.87 for MTX) ($P = 0.019$).[46] The strength of evidence is low

The strength of evidence is low for suggesting that sulfasalazine and MTX compared to monotherapy alone limits progression of radiographic joint damage.

The strength of evidence is moderate for suggesting that combinations of MTX, sulfasalazine, and hydroxychloroquine lessen disease activity compared to one or two drugs.[48,49]

Low doses of glucocorticoids taken with an oral DMARD (generally MTX or sulfasalazine) reduce x-ray progression over 1-2 years.[50-52] The strength of evidence is low. However, the evidence is conflicting for change in disease activity scores (DAS) over 2 years; one study found significant change and one did not.[51,52] The strength of evidence is insufficient.

Biologic DMARDs. We found one head-to-head RCT that compared one biologic DMARD with another[53]providing low strength of evidence that abatacept lessens disease activity at one year compared with infliximab. However remission did not reach significance at one year. Other existing direct head-to-head evidence is limited to a nonrandomized, open-label effectiveness trial[54] and five prospective cohort studies.[55-59] Because of the methodological limitations of observational studies, findings of these studies must be interpreted cautiously. The studies that compared etanercept with infliximab reported a faster onset of response for etanercept during the first months of therapy but no differences in efficacy thereafter.[54-58] The faster onset of etanercept might be attributable partly to necessary dose adjustments for patients treated with infliximab. The strength of evidence is low.

Adalimumab lessens disease activity over 1 year compared with infliximab.[58] Evidence is limited to a single cohort study. The strength of evidence is low.

A cohort of patients who had failed at least one anti-TNF drug were subsequently treated with rituximab, and their outcomes were compared to that of patients treated with other anti-TNF agents. The results indicated that the patients treated with rituximab had a greater reduction in disease activity at 6 months than the patients treated with the other anti-TNF agents.[59] The strength of evidence is low.

Mixed treatment comparisons in this report, suggest higher efficacy for improving disease activity (ACR 20/50) for etanercept compared to individual biologics including abatacept, adalimumab, anakinra, infliximab; nonsignificant differences with certolizumab and golimumab). The strength of evidence is low.

Higher ACR 20 and ACR 50 response rates were also noted for certolizumab compared with the other biologics, including abatacept, anakinra, and infliximab; nonsignificant differences for adalimumab, golimumab and tocilizumab). The strength of evidence is low.

Anakinra, appears to have lower efficacy based on our mixed treatment comparisons. Although not all results reached statistical significance, patients receiving anakinra consistently achieved lower response rates on ACR 20 and ACR 50 (for ACR 20 statistically significant for adalimumab, certolizumab and etanercept; for ACR 50 significant for certolizumab and etanercept).[60,61]The strength of evidence is low.

Mixed treatment comparisons found no significant differences disease activity with abatacept, adalimumab, infliximab, and tocilizumab. The strength of evidence is low. No evidence from adjusted indirect comparisons exists for rituximab.

Biologic DMARDs vs. oral DMARDs. Population-based, observational evidence from prospective cohort studies and RCTs of individual drugs indicated that biologic DMARDs as a class (adalimumab, anakinra, etanercept, infliximab, tocilizumab) were more efficacious than oral DMARDs as a class (MTX, leflunoamide).[54,55,62-65] The strength of evidence for available comparisons is moderate.

Radiographic outcomes were significantly better in patients treated with biologic DMARDs than patients treated with MTX. How such intermediate outcomes translate to the long-term

clinical progression of the disease remains unclear. The strength of the evidence for the available comparisons is low

Individual trials of adalimumab, etanercept, and tocilizumab favor biologic vs. MTX. The strength of evidence for these comparisons is low.

Biologic DMARD combinations. There are no synergistic effects of a combination treatment of etanercept and anakinra[66] or etanercept and abatacept[67] compared with etanercept monotherapy. The strength of evidence is low.

Overall, the evidence is limited for suggesting that there is some benefit to biologic DMARD combinations over monotherapy, at least in relation to combining MTX with adalimumab,, infliximab or rituximab. A combination of MTX with either adalimumab,[62] or infliximab,[55,68-70] or rituximab[71] led to statistically significantly greater improvements than with biologic DMARD monotherapy. A combination of etanercept with MTX trended toward greater improvements is disease activity and radiographic outcomes than with monotherapy but not all studies reached statistical significance.[55,68,72-75] A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy at one year.[72] All RCTs were funded by the makers of the biologic DMARDs. Except for the PREMIER study on adalimumab,[62] none of these trials was conducted in patients with early RA. The strength of evidence is low for the comparisons. No evidence is available on abatacept, anakinra, certolizumab pegol, golimumab, tocilizumab and combinations with oral DMARDs.

Overall, the evidence is low for combination of biologic DMARD with oral DMARD vs. oral DMARD. A combination of MTX with adalimumab,[62] etanercept[73,76] or infliximab[69]led to significantly greater improvements in disease activity than MTX alone.

Evidence from two prospective cohorts for anti-TNF drugs with MTX compared to anti-TNF with leflunomide note similar efficacy.[77,78] Anti-TNF drugs included anakinra, etanercept and adalimumab. The strength of evidence is low.

None of the RCTs can be considered an effectiveness study. Of four population-based prospective cohort studies, only one was conducted in the United States. The generalizability of results to the average population of community rheumatology patients, therefore, remains unclear. All RCTs were funded by the makers of the biologic DMARDs.

Strategies limited to early RA. Combination therapy, which included two oral DMARDs (MTX and sulfasalazine) plus a stepped-down prednisolone treatment, demonstrated less radiographic progression than sulfasalazine alone.[79,80] The strength of evidence is low.

Combination of three oral DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone led to less radiographic change than one oral DMARD (SSZ which could be changed to MTX).[81,82] The strength of evidence is low.

A strategy of either (1) MTX, sulfasalazine, and tapered high-dose prednisone or (2) MTX and infliximab resulted in less radiographic change over 12 months than (3) sequential DMARD therapy or (4) step-up combination therapy.[83] At four years, the remission among groups was similar.[84-86] The strength of evidence is low.

Rheumatoid Arthritis: Detailed Analysis

Oral DMARDs vs. oral DMARDs. Table 9 presents disease activity and remission and Table 10 radiographic joint damage results.

Corticosteroids vs. corticosteroids. We found one head-to-head RCT (N = 143) comparing two corticosteroids (Table 9).[38] It examined the efficacy of low-dose budesonide (3 mg/day), high-dose budesonide (9 mg/day), and prednisolone (7.5 mg/day) over 12 weeks. Mean disease

duration of RA was 9 years. When comparing drugs, the percentage achieving ACR 20 response criteria for high-dose budesonide (9 mg) was significantly greater than that for lower dose budesonide (3 mg) (42 percent vs. 22 percent; $P < 0.001$), but the percentages for high-dose budesonide and prednisolone did not differ significantly (42 percent vs. 56 percent; $P = 0.11$). Similarly, high-dose budesonide and prednisolone did not differ significantly for tender joint count, swollen joint count, and the DAS.

Leflunomide vs. MTX. We found two trials comparing leflunomide (20 mg/day) with MTX (studies ranging from 7.5 mg/week to 15 mg/week) and one systematic review with meta-analysis of leflunomide (Table 9).[39-41] Given that the systematic review included only two trials comparing these two agents, we describe these two studies in detail here first. One trial randomized 482 patients to leflunomide (n = 182) or MTX (n = 182) over 12 months.[41] Mean disease duration of RA across these groups was 6.5 years to 7 years. The proportion of patients meeting ACR 20 response criteria at 12 months was higher for leflunomide than MTX but not statistically significantly so (52 percent vs. 46 percent; *P* = NR). Proportions meeting ACR 50 and ACR 70 criteria also did not differ significantly. Leflunomide had less disease progression by Sharp score than MTX (respectively, 0.53 vs. 0.88; $P = 0.05$) (Table 10).

A continuation study followed the same cohort for 2 years (leflunomide, n = 98; MTX, n = 101).[42] At 2 years, leflunomide was associated with a higher proportion of patients meeting ACR 20 response criteria than MTX (79 percent vs. 67 percent; $P = 0.049$). The percentage of patients meeting either ACR 50 or ACR 70 criteria at 2 years did not differ significantly, and the change in total Sharp score also did not differ significantly at 2 years (1.6 vs. 1.2; $P = 0.659$).

These 2-year follow-up results are limited by the 45 percent attrition rate from the initial study.

The other trial comparing leflunomide to MTX examined 999 patients for 12 months with an optional second year (leflunomide, n = 501; MTX, n = 498).[40] Mean disease duration across the groups was 3.5 to 3.8 years. At 12 months, the proportion of patients meeting ACR 20 response criteria was lower for leflunomide than for MTX (50.5 percent vs. 64.8 percent; $P < 0.001$), but differences were not significant at 2 years (64.3 percent vs. 71.7 percent; *P* = NS, NR). Radiological outcomes at 12 months using Larsen Scale scores for joint narrowing were statistically equivalent (0.03 increase in both groups). After 2 years, no further increase in joint damage occurred in patients treated with leflunomide; patients taking MTX had a small improvement (data NR). The overall result was a small significant difference in Larsen Scale scores favoring MTX after 2 years (data NR).

In the systematic review that included two trials comparing leflumonide with MTX (n = 1,481), significantly more patients treated with MTX achieved an ACR 20 response than patients treated with leflunomide at 12 months (OR, 1.43; 95% CI, 1.15-1.77; $P = 0.001$); however, by 2 years, the statistically significant difference favoring MTX disappears (OR, 1.28; 95% CI, 0.98-1.67; $P = 0.07$). Patients receiving leflunomide and MTX did not differ in ACR 50 and ACR 70 responses, and the two drugs also did not differ in delaying bone erosions or joint damage assessed by total Sharp score.[39] This systematic review was limited by the small number of studies that the authors could use for the meta-analysis.

Leflunomide vs. sulfasalazine. One study[43] with a 2-year followup[44] compared leflunomide with sulfasalazine. In addition, one systematic review did a meta-analysis of leflunomide against sulfasalazine (Table 9).[39] Given that the systematic review included only one trial with this comparison, we describe it in detail first.[43] This study was a 24-week, double-blind, multinational RCT of 358 patients on 20 mg/day leflunomide (n = 133) or 2 g/day sulfasalazine

(n = 133).[43] Mean disease duration across groups was 5.7 to 7.6 years. ACR 20 response at 24 weeks was similar for leflunomide and sulfasalazine (48 percent vs. 44 percent; *P* = NR). The percentage achieving ACR 50 response criteria was also similar in the two groups (33 percent leflunomide, 30 percent sulfasalazine). Larsen Scale scores were also similar for leflunomide and sulfasalazine, and the Larsen Scale change score at endpoint was 0.01 for both drugs (Table 10). In the follow-up study, patients who completed the first study could opt to continue on the 12- and 24-month double-blind extension.[44] At 12 months (leflunomide, n = 80; sulfasalazine, n = 76), ACR 20 response was similar for leflunomide and sulfasalazine (77 percent vs. 73 percent; *P* = NR). At 24 months (leflunomide, n = 28; sulfasalazine, n = 27), ACR 20 response was significantly greater for leflunomide than for sulfasalazine (82 percent vs. 60 percent; *P* = 0.0085). Changes in Larsen Scale scores were also similar for leflunomide and sulfasalazine (mean change: 0.02 vs. 0.02 at 12 months, -0.07 vs. -0.03 at 24 months; *P* = NR). Changes in Sharp scores were also not significantly different (mean change: 0.97 vs. 1.38; *P* = 0.685). However, these long-term results are significantly limited by the attrition rates of 65 percent to 70 percent.

The systematic review with a meta-analysis compared leflunomide (10 to 20 mg/day) with sulfasalazine (2 g/day).[39] The analysis included the study described above.[43,44,87] Response to the two drugs did not differ as measured by either ACR 20 or ACR 50 criteria at 6 months and 12 months. However, leflunomide was more efficacious at 24 months (ACR 20: OR, 0.35; 95% CI, 0.16-0.77; *P* = 0.009; ACR 50: OR, 0.32; 95% CI, 0.15-0.67; *P* = 0.003). The groups did not differ in the ACR 70 at 6, 12, or 24 months. Leflunomide and SSZ also did not differ in delaying bone erosions or joint damage by Sharp score or Larsen Scale score at 6, 12, or 24 months. Again, these results are significantly limited because they include only the one study.[43]

Sulfasalazine vs. MTX. Three RCTs examined the efficacy of sulfasalazine and MTX (Tables 9 and 10.[45-47] Overall, findings from these studies showed similar improvement rates between sulfasalazine and MTX for any ACR, DAS, and radiological outcomes. Two of the trials included patients with disease burden of less than 1 year and used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States.[46,47] These trials also included a combination therapy arm, which we describe below (in the section on *Oral DMARD combinations vs. oral DMARD combinations or oral DMARD monotherapy)*.

One trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine (n = 68), 7.5 mg/week to 15 mg/week MTX (n = 69), or a combination of sulfasalazine and MTX (n = 68) for 52 weeks.[46] Mean disease duration for the groups ranged from 2.3 months to 3.4 months. The trial did not detect any differences between the MTX and sulfasalazine groups in improvement as measured on the ACR 20 (59 percent sulfasalazine; 59 percent MTX; *P* = NR). The DAS change score favored sulfasalazine therapy (-1.15, sulfasalazine; -0.87, MTX; *P* = NR), but the statistical analysis examined only the comparison with combination therapy (reported under "*Oral DMARD combinations vs. oral DMARD combinations or oral DMARD monotherapy*"). The mean total modified Sharp/van der Heijde scores of 8.5 for sulfasalazine and 7.5 for MTX indicated that the radiological scores at 5 years did not differ significantly (*P* = 0.7).

Another RCT, lasting 52 weeks (N = 105), also demonstrated similar ACR 20 and DAS results for sulfasalazine and MTX.[47] This trial compared 1 g/day to 3 g/day sulfasalazine (n = 34) with 7.5 mg/week to 15 mg/week MTX (n = 35) and with a combination (discussed later in this chapter); mean disease duration was 2.6 to 3.1 months. The mean change in DAS over 52 weeks was -1.6 in the sulfasalazine group and -1.7 in the MTX group (*P* = NS). The percentage of

patients achieving improvement on the ACR 20 was 25 percent for sulfasalazine and 25 percent for MTX.

Finally, one trial included a population with disease duration of up to 10 years.[45] The investigators gave 687 patients sulfasalazine (up to 4 g/day) for 6 months. Those with DAS ≥ 2.4 were offered inclusion into a Phase II study and randomized to (1) sulfasalazine (n = 55), (2) MTX (n = 54) (maximum dose, 25 mg/week), and (3) sulfasalazine plus MTX (n = 56). At 18 months, the DAS change was similar for sulfasalazine and MTX alone (-0.30 vs. -0.26; *P* = 0.79). The ACR 20, 50, and 70 responses were also similar (ACR 20, 18 percent vs. 15 percent; ACR 50, 6 percent vs. 7 percent; ACR 70, 2 percent vs. 2 percent; *P* = NR). The groups also did not differ in modified Sharp/van der Heijde score, total erosions, and joint space narrowing (data NR) (Table 9). However, 18 months is a short period for observing radiological outcomes, and this study was not powered to detect radiological progression.

Oral DMARD combinations vs. oral DMARD combinations or oral DMARD monotherapy, with or without Corticosteroids. Table 11 presents disease activity and remission and Table 12 provides radiographic joint damage results.

Table 11. Disease activity and remission for oral DMARD combinations vs. monotherapy or combinations with without corticosteroid studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Sulfasalazine + MTX vs. Sulfasalazine or MTX					
Capell et al., 2006[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland, 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) + MTX (≤ 25 mg/week) vs. SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	Combination therapy better than monotherapy MTX or SSZ for DAS (-0.67, -0.30, -0.26; *P* = 0.039 for SSZ + MTX vs. SSZ; *P*= 0.023 for SSZ + MTX vs. MTX) No significant difference in ACR responses	Fair
Dougados et al., 1999[46] Maillefert et al., 2003[88]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR responses (65 vs. 59 vs. 59; *P* = NS, NR) DAS change (-1.26 vs. -1.15 vs. -0.87; *P* = 0.019) DAS change NS at year 5	Fair
Haagsma et al., 1997[47]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week) vs. SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR or DAS responses	Fair

*New studies since last review

ACR, American College of Rheumatology; DAS, disease activity score, DMARD, disease-modifying antirheumatic drug; g, gram; HQC, hydroxychloroquineMTX, methotrexate; mg, milligram; NHS, National Health Service; NR, not reported; NS, not significant; PNL, prednisolone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 11. Disease activity and remission for oral DMARD combinations vs. monotherapy or combinations with without corticosteroid studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
MTX +Hydroxychloroquine + Sulfasalazine vs. one or two oral DMARDs					
O'Dell et al., 2002[48]	RCT 171 2 years	Mean disease duration 5.8 to 7.9 years	1: MTX (7.5 titrated to 17.5 mg/week) + SSZ (2 g/day) + HCQ (400 mg/day) vs. 2: MTX + HCQ vs. 3: MTX + SSZ	ACR 20: 78%, 60%, 49% 1 vs. 2: *P* = 0.05 1 vs. 3: *P* = 0.002	Good
O'Dell et al., 1996[49]	RCT 102 2 years	Poor response to at least 1 DMARD; mean disease duration 6 to 10 years	1: MTX (7.5 to 17.5 mg/week) + SSZ (1 g/day) + HCQ (400 mg/day) vs. 2: MTX vs. 3: SSZ (+ HCQ	50% improvement (defined by authors): 77%, 40%, 33% 1 vs. 3: *P* < 0.001 1 vs. 2: *P* = 0.003	Good
Oral DMARD + Corticosteroid vs. Oral DMaRD					
* Choy, et al., 2008[51]	RCT 467 2 years	England/Wales, Multicenter: early RA; mean disease duration 2.7-5.1 months	MTX (≤ 15mg/week) + PNL (60mg/day stepped down and stopped at 34 weeks) vs. MTX	No significant differences for DAS (-1.37 vs. -1.42; *P* = 0.19); DAS 28 remission 20% vs. 18%; *P* = NR	Good
Svensson et al., 2005[52]	Open-label trial 250 2 years	Population-based; active RA; early RA	DMARD (SSZ or MTX, dosages NR) + PNL (7.5 mg/day) vs. DMARD	More patients in DMARD + PNL combination group achieve remission (DAS < 2.6) than DMARD-only group (55.5% vs. 43.8%; *P* = 0.0005)	Fair

Table 12. Radiographic joint damage in oral DMARD combinations with our without corticosteroid studies

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Sulfasalazine + MTX vs. Sulfasalazine or MTX				
Capell et al., 2006[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Yes (70% 1 year or less)	SSZ (≤ 4 g/day) + MTX (≤ 25 mg/week) vs. SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	No significant difference in total Sharp score (Data NR)
Dougados et al., 1999;[46] Maillefert et al., 2003[88]	RCT 209 (146) 52 weeks (5 year followup)	Yes	SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	5-year mean modified Sharp/van der Heijde score change: 8.5 vs. 7.5; *P* = 0.7

ACR, American College of Rheumatology; DAS, disease activity score, DMARD, disease-modifying antirheumatic drug; g, gram; HQC, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; mg, milligram; NR, not reported; NS, not significant; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 12. Radiographic joint damage in oral DMARD combinations with our without corticosteroid studies (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Oral DMARD + Corticosteroid vs. Oral DMaRD				
*Kirwan, et al., 2009[50]	Systematic review and meta-analysis 1414 2 yrs	Yes, 15 trials, majority studied early RA	DMARD (NR) + PRED (low dose, mean cumulative dose 2300 mg/year + vs. DMARD treatment	Less progression of erosion scores [(0.40 in favor of glucocorticoids (95% CI, 0.27, 0.54)]
* Choy, et al., 2008[51]	RCT 467 2yrs	Yes	MTX (≤ 15 mg/week) + PNL (60 mg/day stepped down and stopped at 34 weeks) vs. MTX	Larsen score change 7.41 vs. 4.70; *P* = 0.008
Svensson et al., 2005[52]	Open-label RCT trial 250 2 years	Yes	DMARD (SSZ or MTX, dosages NR) + PNL (7.5 mg/day) vs. DMARD	Median modified Sharp/van der Heijde score change: 1.8 vs. 3.5; *P* = 0.019 Erosion score median change: 0.5 vs. 1.25; *P* = 0.007 Joint space narrowing score median change: 1.0 vs. 2.0; *P* = 0.08

Sulfasalazine plus MTX vs. sulfasalazine or MTX. Three RCTs compared the efficacy of sulfasalazine and MTX vs. that of either sulfasalazine or MTX alone (Table 11).[45-47] Findings from two of these randomized trials consistently reported no significant differences in ACR, DAS, or radiological outcomes.[46,47] They included patients with disease duration of less than 1 year and again used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States.[46,47] The third trial included patients with RA duration of up to 10 years, and their DAS results favored the sulfasalazine-MTX combination therapy over monotherapy.[45]

One 52-week trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine and 7.5 mg/week to 15 mg/week MTX (n = 68), sulfasalazine (n = 68), or MTX (n = 69).[46] The combination group showed a trend towards greater improvement on the ACR 20 than either of the other groups, but the groups did not differ statistically (ACR: 65 percent combination; 59 percent sulfasalazine; 59 percent MTX; *P* = NS, NR). The DAS change favored combination therapy (DAS change: -1.26 combination; -1.15 sulfasalazine; -0.87 MTX; *P* = 0.019). However, when comparing combination therapy vs. monotherapy in a 5-year prospective followup of this cohort, the differences in DAS change scores became nonsignificant at year 5 (Table 11).[88] Additionally, radiological scores did not differ at 5 years; the total modified Sharp/van der Heijde score was 7.5 for combination therapy and 8.5 for single therapy (*P* = 0.7). A 52-week RCT (N = 105) also reported no significant differences in ACR or DAS results between combination and single therapy in this population.[47]

Finally, another trial included a population with disease duration of up to 10 years (mean, 1.6 to 1.8 years).[45] The investigators gave 687 patients sulfasalazine (up to 4 g/day) for 6 months. Those with DAS ≥ 2.4 were offered inclusion into a Phase II study and randomized to (1) sulfasalazine plus MTX (n = 56), (2) sulfasalazine (n = 55), and (3) MTX (n = 54) (maximum dose, 25 mg/week). At 18 months, the DAS was significantly better in the combination arm than in either the sulfasalazine or MTX arms (DAS change scores: -0.67, -0.30, -0.26; combination

vs. sulfasalazine; $P = 0.039$; combination vs. MTX; $P = 0.023$). The ACR 20, 50, and 70 responses were all higher in the combination arm, but they were not statistically different across the three arms. Additionally, the total modified Sharp/van der Heijde score, total erosions, and joint space narrowing also did not differ significantly across arms (data NR). However, 18 months is a short period for radiological outcomes, and this study was not powered for radiological progression.

MTX plus hydroxychloroquine plus sulfasalazine vs. one or two oral DMARDs. Two RCTs examined the combination of MTX, sulfasalazine, and hydroxychloroquine against either one or two drugs.[48,49] Both studies found that the combination of the three DMARDs to be more effective than either one or two DMARDs.

The more recent study randomized 171 patients over 2 years to (1) MTX 7.5 mg/week titrated to 17.5 mg/week plus sulfasalazine 2 g/day plus hydroxychloroquine 400 mg/day, (2) MTX plus hydroxychloroquine, or (3) MTX plus sulfasalazine.[48] Mean disease duration across groups was 5.8 to 7.9 years. After 2 years, patients receiving triple therapy had an ACR 20 of 78 percent; in contrast, those treated with MTX and hydroxychloroquine had an ACR 20 of 60 percent ($P = 0.05$), and those treated with MTX and sulfasalazine ($P = 0.002$) had an ACR 20 of 49 percent.

One oral DMARD plus corticosteroid vs. oral DMARD. Three studies, including a systematic review with meta-analyses,[50] RCT[51] and open label (non blinded) RCT[52] examined the combination of oral DMARD (MTX or SSZ) and a corticosteroid compared to oral DMARD alone. All studies found a reduction in x-ray progression lasting up to two years.

The systematic review with meta-analyses of 15 trials compared radiologic progression in groups treated with glucocorticoids with oral DMARDs vs. a comparator drug. The standard mean difference indicated less progression of erosion scores (Standard Mean Difference 0.40, 95% CI, 0.27-0.54)[50] in favor of glucocorticoids. The majority of the trials included in the meta-analyses examined an early RA population

Evidence for disease activity is conflicting. One RCT comparing MTX and prednisolone with methotrexate and found no significant difference in DAS scores at two years.[51] One open-label RCT (radiologic findings included in the meta-analyses) compared a combination therapy involving a oral DMARD (either MTX or sulfasalazine) and a corticosteroid with an oral DMARD only (N = 250).[52] This study suggested that, for patients with early RA, combining a oral DMARD with prednisolone may help extend remission. This 2-year, multicenter Swedish study compared prednisolone 7.5 mg/day added to a DMARD (n = 119) with a DMARD only (n = 131) in patients with early RA. Patients were eligible if they had been diagnosed with RA (1987 ACR criteria) in the past year and had been started by their treating rheumatologist on their first DMARD. The choice of DMARD had been left to the patient's primary rheumatologist and included MTX (mean dose 10 mg/week) or sulfasalazine (2 g/day). The combination group had higher remission than the DMARD only group (DAS 28 < 2.6, 55.5 percent vs. 43.8 percent; $P = 0.0005$).

Biologic DMARDs vs. biologic DMARDs. We identified one head-to-head RCT,[53] one nonrandomized, open-label effectiveness trial[54] and five prospective cohort studies (Table 13);[55-59] all but three studies[53,58,59] compared etanercept with infliximab. Other comparisons included adalimumab with infliximab,[58] abatacept with infliximab[53] and rituximab compared to other anti-TNF agents.[59] All studies had minimal exclusion criteria, enrolling patients who were starting treatments with biologic DMARDs. Mean disease durations ranged from 7.3 years to 14.5 years, indicating that most patients suffered from advanced RA; the proportion of patients with early

RA in these studies remains unclear. One study contained a multinational patient population,[53] one was conducted in the United States;[55] the other five were carried out in Sweden,[54,56,59] the Netherlands[58] and Spain.[57]

Table 13. Disease activity and remission for biologic DMARD vs. biologic DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Abatacept vs. Infliximab					
*Schiff, et al., 2008[53] ATTEST study	RCT 431 1 year	Patient who have failed MTX; active RA; mean disease duration 7.3-8.4 years	ABA (~10mg/kg every 4 weeks) vs. INF (3mg/kg every 8 weeks)	Greater decrease in DAS28 for ABA vs. INF at 1 year (estimate of difference -0.62 95% CI, -0.96, -0.29). Trend toward greater remission for ABA vs. INF at 1 year (estimate of difference 6.5%; 95% CI, -2.2, 15.2, P = NS, NR)	Fair
Etanercept vs. Infliximab					
Geborek et al., 2002[54]	Nonrandomized, open-label trial 369 1 year	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher)	Higher ACR 20 responses for ETN at 3 (data NR; *P* < 0.02) and 6 months (data NR; *P* < 0.05); no significant differences in ACR response rates at 1 year (data NR)	Fair
*Fernandez-Nebro et al., 2007[57]	Prospective cohort 161 6 years	Tertiary care center, Spain; Anti-TNF naïve patients; mean disease duration 9.5-9.9 years	ETN vs. INF (dosages NR)	Significantly greater decrease t in DAS28 at 6 months for ETN vs. INF (-1.7 vs. -1.3; *P* = 0.03); No difference in EULAR responses between ETN vs. INF at 6 months	Fair
*Kievit et al., 2008[58]	Prospective cohort 707 1 year	Population based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ETN vs. INF (dosages NR)	Greater decrease in DAS28 for ETN vs. INF at 1 year (ETN -1.8, INF -1.2; *P* < 0.05)	Fair
Kristensen et al., 2002[56]	Prospective cohort 949 3 years	Population based, Inadequate response to at least 2 DMARDs	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher)	No difference in ACR 50 response at 3 years (data NR)	Fair
Weaver et al., 2006[55]	Prospective cohort 1,371 1 year	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETN (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Higher mACR 20 response rates for ETN than INF at 1 year (41% vs. 26%; *P* = NR)	Fair

*New studies since last review.

ACR, American College of Rheumatology; ADA, adalimumab; ATTEST, Abatacept or infliximab vs. placebo, a trial for tolerability, efficacy, and safety in treating rheumatoid arthritis; CI, confidence interval; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; INF, infliximab; mg/kg, milligram/kilogram; mACR, modified American College of Rheumatology; NR, not reported; NS, not significant; PCS, physical component score; RA, rheumatoid arthritis; TNF, tumor necrosis factor; US, United States; vs., versus.

Table 13. Disease activity and remission for biologic DMARD vs. biologic DMARD studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Adalimumab vs. Infliximab					
*Kievit et al., 2008[58]	Prospective cohort 707 1 year	Population based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ADA vs. INF (dosages NR)	Greater decrease in DAS28 for ADA vs. INF at 1 year (ADA -1.8, INF -1.2; *P* < 0.05)	Fair
Rituximab vs. Anti-tumor necrosis factor therapies					
*Finckh et al., 2007[59]	Prospective cohort 116 6 months	Population based, Switzerland; Patients who have failed at least 1 Anti-TNF treatment; mean disease duration 9-10 yrs	RTX (2 infusions, 1000 mg) vs. anti-TNF agent (INF, ETN or ADA, dosages NR)	Greater reduction in DAS28 at 6 months for RTX vs. Anti-TNF (-1.6 vs. -0.98; *P* = 0.01)	Fair
Indirect analyses of placebo-controlled studies					
Clark et al., 2004[61]	Meta-analysis NR	Patients who have failed MTX treatment; mean disease duration varied	ANA vs. Anti-TNF as a class	Significantly lower ACR 20 response rates of anakinra than anti-TNF as a class. Risk difference: -0.21 (95% CI, -0.32-0.10)	Good
Gartlehner et al., 2006[60]	Meta-analysis 5,248	Patients who have failed MTX treatment; mean disease duration varied	ADA (40 mg every other week), ANA (100 mg/day), ETN (25 mg twice weekly), INF (3 to 10 mg every 8 weeks)	No difference in efficacy among anti-TNF drugs; greater efficacy of anti-TNF drugs than anakinra on ACR 20: RR, 0.61 (95% CI, 0.39-0.96)	Good
Hochberg et al., 2003[89]	Meta-analysis 1,053	Patients who have failed MTX treatment; mean disease duration varied	ADA (40 mg every other week), ETN (25 mg twice weekly), INF (3 to 10 mg every 8 weeks)	No difference in ACR 20 response rates among anti-TNF drugs	Fair
Wailoo et al., 2006[27]	Meta-analysis 6,694	Patients with RA; mean disease duration varied	INF, ETN, ANA, ADA	No difference in ACR 50 response rates among anti-TNF drugs	Fair

Abatacept vs. Infliximab. One head-to-head multinational RCT (N = 431) examined the effectiveness of abatacept (10mg/kg every 4 weeks) and infliximab (3mg/kg every 8 weeks) over one year.[53] All participants had active RA, were MTX resistant and continued on background MTX for the study. At one year abatacept had a greater reduction in DAS28 than infliximab (-2.88 vs. -2.55; estimate of difference -0.62; 95% CrI, -0.96, -0.29). There was also a nonsignificant trend in DAS, ESR (erythrocyte sedimentation rate) defined, remission (18.7% vs. 12.2%; estimate of difference 6.5; 95% CI, -2.2, 15.2). Additionally, ACR 20 response was significantly higher for abatacept than infliximab (72.4% vs. 55.8%, estimate of difference 16.7%; 95% CI, 5.5, 27.8) but ACR 50 and ACR 70 did not reach statistical significance. This study is limited by the fixed dosing of infliximab, which may be lower than generally used in

practice. Additionally the study was powered only to detect differences between the biologics with placebo at 197 days.

Etanercept vs. Infliximab. The nonrandomized, open-label effectiveness study (N = 369) assessed the effectiveness and safety of etanercept (25 mg twice weekly) and infliximab (3 mg/kg or higher every 8 weeks).[54] Study duration was 12 months. Comparisons of etanercept and infliximab with the leflunomide arm are reported in the section below comparing oral DMARDs with biologic DMARDs. Etanercept had significantly greater improvement on the ACR 20 at 3 months ($P < 0.02$; data NR) and 6 months ($P < 0.05$; data NR) and on the ACR 50 at 3 months ($P < 0.005$; data NR) than infliximab. The authors attributed these differences partly to a high need of dose adjustments (57 percent) in the infliximab group during the first months of the study. No significant differences between the therapy groups could be detected after 6 months.

Three prospective cohort studies provide similar results, initially favoring etanercept, but with differences lessening over longer time periods.[56-58] The first prospective cohort study (N = 161) in anti-TNF naïve patients found a higher change in DAS28 at 6 months for etanercept than infliximab (- 1.7 vs. -1.3; $P = 0.03$), but no differences in EULAR responses.[57] The second prospective cohort (N = 707) in anti-TNF naïve patients found a higher change in DAS28 at 12 months for etanercept than infliximab (-1.8 vs. -1.2, $P < 0.05$). A prospective cohort (N = 949) with longer follow up found that etanercept treatments led to greater improvement on the ACR 50 than infliximab during the first months of treatment, but no differences were noted thereafter for up to 36 months.[56] The authors of this study created an index called the LUNDEX (an index of drug efficacy in clinical practice developed at Lund University in Sweden, calculated as the proportion of starters still on the drug at time T times the proportion responding at time T), which takes adherence and efficacy together into consideration. Patients on etanercept achieved higher LUNDEX scores than patients on infliximab, which reflected a significantly lower level of adherence of patients on infliximab compared with those on etanercept (data NR; $P < 0.001$).

Findings from the U.S. prospective cohort study, which was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program and funded by the maker of etanercept, reported similar results.[55] Etanercept-treated patients had greater responses than infliximab-treated patients on the modified ACR 20 (mACR 20, which omits ESR and C-reactive protein [CRP] values because they are infrequently measured in clinical practice); percentage improvement rates were 43 percent for etanercept plus MTX, 41 percent for etanercept monotherapy, 35 percent for infliximab plus MTX, and 26 percent for infliximab monotherapy (P = NR).

Adalimumab vs. infliximab. In addition to examining the effects of etanercept, one prospective cohort study (N = 116) examined adalimumab with infliximab in anti-TNF naïve patients as part of the Dutch Rheumatoid Arthritis Monitoring (DREAM) register. Adalimumab-treated patients had a greater decrease in DAS28 than infliximab-treated patients at one year (-1.8 vs. -1.2, $P < 0.05$).[58]

Rituximab vs. anti-TNF. One cohort study (N = 116) examined the effectiveness of rituximab (1000 mg x 2 with concomitant IV glucocorticoids) compared to other anti-TNF agents in patients who had inadequate response to previous ant-TNF therapy.[59] The population included Swiss patients receiving anti-TNF therapy in 2003. Patients included in this analyses had an inadequate response to at least 1 anti-TNF agent (infliximab, etanercept or adalimumab) and initiated a second or third anti-TNF or rituximab. At 6 months, rituximab treated patients had a greater decrease in DAS28 than patients treated with an alternative anti-TNF agent (-1.6 vs. -0.98, $P = 0.01$).[59]

Indirect head-to-head comparisons of biologic DMARDs. Multiple placebo-controlled RCTs and meta-analyses[24,90] provide evidence on the general efficacy of abatacept,[53,91-96] adalimumab,[97-104] anakinra,[61,105-111] etanercept,[73,112-122] infliximab,[53,112,123-133], rituximab,[71,134-138] certolizumab pegol,[139-141] golimumab,[141,142] and tocilizumab.[64,139,143-146] Most of these studies were conducted in patients who previously failed oral DMARD treatment.

Using information from these placebo-controlled trials, four research groups did meta-analyses to produce adjusted indirect comparisons of biologic DMARDs.[27,60,61,89] The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[147] In the more recent analysis, findings suggested that efficacy does not differ substantially for adalimumab, etanercept, and infliximab.[60] However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty. Compared with anakinra, point estimates favored adalimumab, etanercept, and infliximab, but the results were not all statistically significantly different.[60] Adjusted indirect comparisons of anti-TNF drugs as a class with anakinra showed a statistically significantly greater efficacy of the anti-TNF drugs on ACR 20 but not on ACR 50.[60]

Our team conducted mixed treatment comparisons meta-analyses using Bayesian methods for ACR 20/50/70 which included randomized-controlled trials of abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, and tocilizumab in methotrexate resistant patients (Figure 2). Similar to previous studies, point estimates favor other biologics over anakinra; but the differences were only statistically significant for comparisons with adalimumab, certolizumab, and etanercept for ACR20 and only for certolizumab, and etanercept for ACR50. In addition point estimates for etanercept and certolizumab are favored over the other included biologics (ACR 50 OR range for etanercept 1.71 -5.01; ACR 50 OR range for certolizumab [not including etanercept] 1.37-2.62). The differences showed statistically significant improvements in disease activity with etanercept than with abatacept, adalimumab, anakinra, infliximab, or tocilizumab for ACR 50 (OR range 3.88 to 5.82), but no statistically significant differences between etanercept and certolizumab or golimumab for ACR50. The differences showed statistically significant improvements in disease activity with certolizumab than with abatacept, anakinra and infliximab for ACR 50 (OR range 2.62-2.89) but not statistically significant differences between certolizumab and adalimumab, etanercept, golimumab and tocilizumab.

These findings are consistent with a good-quality German retrospective cohort study based on the RABBIT (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) database, which reports higher discontinuation rates due to lack of efficacy for patients on anakinra than for patients on either etanercept or infliximab after 12 months of treatment (30 percent vs. 20 percent vs. 20 percent; P = NR).[75] In addition, they are consistent with several cohort studies reporting greater improvements in disease activity with etanercept than with infliximab.[55-58] Our MTC findings for etanercept are different than previous indirect analyses.[27,60,61,89] Potential reasons for these differences may be in part due to addition of newer studies and drugs (certolizumab, golimumab and tocilizumab), narrowing our studies to patient populations with inadequate response to methotrexate and excluding early RA, methotrexate naïve or who have failed anti-TNF therapy.

No indirect comparisons were available of rituximab with other biologic DMARDs.

Figure 2. ACR plots

Biologic DMARDs vs. oral DMARDs. Four RCTs, a nonrandomized trial, and a prospective cohort study determined the comparative efficacy and safety of various biologic and oral DMARDs. The RCTs compared adalimumab,[62] etanercept[63,73] and Tocilizumab[64] with MTX; the nonrandomized trial compared etanercept and infliximab with leflunomide;[54] and the cohort study assessed differences in class effects (Table 14).[65] No evidence exists on abatacept, anakinra, and rituximab, certolizumab, golimumab, or on oral DMARDs other than MTX and leflunomide. Disease activity and remission results are presented in Table 14 and radiographic damage in Table 15.

Table 14. Disease activity and remission for biologic DMARDs vs. oral DMARDs

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Adalimumab vs. Oral DMARD					
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Lower ACR 50 response rates for ADA than MTX (37% vs. 43%; *P* = NR)	Fair
Etanercept vs. Oral DMARD					
Bathon et al., 2000;[63] Genovese et al., 2002;[148] Genovese et al., 2005[149] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Similar ACR 20 at 12 months for ETN vs. MTX (72% vs. 65%; *P* = 0.16)	Fair
Klareskog et al., 2004[73] van der Heijde et al., 2006[113] van der Heijde et al., 2006[115] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 yrs	ETN (25 mg twice weekly) vs. MTX (7.5 titrated to 20 mg/week)	Higher area under curve of ACR-N for ETN than MTX(14.7%-years vs. 12.2%-years; *P*= NR) at 24 weeks; but similar ACR 20 at 52 weeks (76% vs. 75%, P = NR)	Fair
Geborek et al., 2002[54]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs; mean disease duration 14.5 years	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher) vs. LEF (20 mg/day)	Higher ACR 20/50 responses for ETN and INF vs. LEF at 3 months (data NR; *P* < 0.05) and for ETN vs. LEF at 6 months (data NR; *P* < 0.05); results for 12 months: NR	Fair
Tocilizumabvs. Methotrexate					
*Nishimoto et al., 2009[64] SATORI study	RCT 127 24 weeks	Active RA; inadequate response to MTX	TCZ (8 mg every 4 weeks) vs. MTX (8 mg/week)	Higher ACR20 response for TCZ than MTX (80.3% vs. 25.0%; *P* < 0.001)	Fair

*New studies since last review.

ACR, American College of Rheumatology; ADA, adalimumab; ANA, anakinra; CI, confidence interval; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ERA, early rheumatoid arthritis; ETN, etanercept; INF, infliximab; LEF, leflunomide; mg, milligram; MTX, methotrexate; NR, not reported; OR, odds ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; TCZ, tocilizumab; vs., versus

Table 15. Radiographic joint damage in biologic DMARDs vs. oral DMARD studies

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes	
Biologic class vs. DMARD class					
Listing et al., 2006[65]	Prospective cohort 1,083 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.6 years	Biologics as a class (ADA, ANA, ETN, INF; dose NR) vs. DMARDs as a class (dose NR)	Significantly higher chance of remission for biologics than oral DMARDs (OR, 1.95; 95% CI, 1.20-3.19)	Fair
Adalimumab vs. Oral DMARD					
Breedveld et al., 2006[62], *Hoff et al., 2009[150] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Total modified Sharp score change: 5.5 vs. 10.4; *P* < 0.001 Erosion score change: 3.0 vs. 6.4; *P* < 0.001 Joint space narrowing score change: 2.6 vs. 4.0; *P* < 0.001	
Etanercept vs. Oral DMARD					
Bathon et al., 2000;[63] Genovese et al., 2002;[148] Genovese et al., 2005[149] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Yes; MTX-naive patients with early, aggressive RA	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Total Sharp score change: 1.0 vs. 1.59; *P*= 9,111 Erosion score change: 0.47 vs. 1.03; P = 0.006	
Klareskog et al., 2004[73] van der Heijde et al., 2006[113] van der Heijde et al., 2006[115] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	No	ETN (25 mg twice weekly) vs. MTX (7.5 titrated to 20 mg/week)	At 1 year: Total modified Sharp score change: 0.52 vs. 2.80; *P* = 0.047 Erosion score change: 0.21 vs. 1.68; *P* < 0.008 Joint space narrowing score change: 0.32 vs. 1.12; *P* = NR (NS)	

*New studies since last review.

ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ERA, early rheumatoid arthritis; ETN, etanercept; INF, infliximab; LEF, leflunomide; mg, milligram; MTX, methotrexate; NR, not reported; RCT, randomized controlled trial; TCZ, tocilizumab; TEMPO, Trial of etanercept and Methotrexate with radiographic patient outcomes; vs., versus.

Biologic DMARDs as a class vs. oral DMARDs as a class. A prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab (n = 818) and oral DMARDs as a class (n = 265) in patients who had failed two previous DMARD treatments.[65] This study was population-based and part of RABBIT, a German long-term, prospective cohort study of RA patients who had required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. In a multivariate logistic regression, adjusting for baseline confounders, the investigators determined that patients on biologics had a statistically significantly greater chance of remission (DAS < 2.6) after 12 months of treatment (OR, 1.95; 95% CI, 1.20-3.19). Likewise, patients treated with biologics had an almost four times higher likelihood of achieving functional independence than patients treated with oral DMARDs (OR, 3.88; 95% CI, 1.71-8.79). Nevertheless, both groups had a substantial risk of relapse during the treatment period. Approximately one-half of the patients who were in remission at 6 months achieved a sustained remission until 12 months (biologics, 55 percent; oral DMARDs, 58 percent).

Adalimumab vs. MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA.[62] This multinational study randomized 799 patients with early RA to a combination of adalimumab (40 mg every other week) and MTX (20 mg/week), adalimumab monotherapy (40 mg every other week), or MTX monotherapy (20 mg/week). Two treatment arms of this 2-year study assessed differences in the efficacy of adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). After 2 years, the proportion of patients who met ACR 50 criteria was lower for those on adalimumab than for those on MTX monotherapy (37 percent vs. 43 percent; P = NR). In contrast, radiographic progression was statistically significantly lower in patients treated with adalimumab than with MTX (5.5 vs. 10.4 Sharp units; $P < 0.001$) (

Table 15). No difference was apparent in clinical remission (DAS 28 < 2.6) between the two treatment groups (both 25 percent); discontinuation rates due to lack of efficacy were similar in the adalimumab and MTX groups (19.0 percent vs. 17.9 percent; *P* = NR). We report on results of the other comparisons of the PREMIER study in the respective sections (below) on *Biologic DMARDs plus oral DMARDs vs. biologic DMARDs* and *Biologic DMARDs plus oral DMARDs vs. oral DMARDs.*

Etanercept vs. MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week) over 52 weeks.[63,73,113,115,148,149] The ERA (Early Rheumatoid Arthritis) study (N = 632) was conducted in patients with early RA who were MTX naive.[63,148,149] The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes)
trial[73,113,115] randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week MTX), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week).[73,113,115] Patients had active RA and had failed at least one DMARD other than MTX. About 57 percent of the study population was MTX naive. Patients who had either failed prior MTX treatment or experienced toxic effects were excluded from this study.

Both studies failed to show statistically significant differences between etanercept and MTX in clinical and health outcome measures (SF-36, the Health Assessment Questionnaire [HAQ], the Arthritis-Specific Health Index [ASHI]), and ACR 20/50/70 responses at study endpoints (52 weeks). By contrast, radiographic outcomes were significantly better in patients on etanercept than in those on MTX. For example, in the ERA trial, 72 percent of patients on etanercept and 60 percent on MTX had no radiographic progression of disease (*P* = 0.007). Improved radiographic outcomes were maintained during an open-label extension of the ERA study to 2 years[148] and 5 years.[149]

Etanercept or infliximab vs. leflunomide. No RCT compared biologic DMARDs to leflunomide. The only head-to-head evidence came from a nonrandomized, open-label study (N = 369) that accessed the efficacy and safety of etanercept (25 mg twice weekly), infliximab (3 mg/kg or higher every 8 weeks), and leflunomide (20 mg/day).[54] This study has been described in greater detail in the section (above) on *Biologic DMARDs vs. biologic DMARDs*. At 3 months and 6 months, a greater percentage of patients on etanercept met ACR 20 and ACR 50 criteria than those on leflunomide (data NR; *P* < 0.05). A greater percentage of patients on infliximab achieved ACR 20 and ACR 50 criteria at 3 months than those on leflunomide (data NR; *P* < 0.05). The authors did not report 12-month data. Both etanercept and infliximab led to significant reductions in prednisolone dosage; by contrast, the investigators did not find any reduction in prednisolone dosage with leflunomide. These findings must be viewed cautiously. Baseline characteristics of patients differed substantially between the leflunomide group and the biologic groups. Leflunomide patients were older and had significantly more joint damage than patients on etanercept or infliximab. Such differences can potentially confound results, introducing bias that would support differences in results among these treatment groups.

Tocilizumab vs. MTX. The SATORI study, a multisite RCT in Japan, examined 127 patients with active RA and an inadequate response to MTX.[64] Subjects were randomized to MTX (8 mg/week) plus placebo or to tocilizumab (8 mg/kg every 4 weeks) plus placebo. After 24 weeks, those treated with tocilizumab had significantly higher ACR 20 response than those treated with MTX (80.3% vs. 25.0%, *P* < 0.001). The study findings are limited by a high withdrawal rate; 48% of patients in the MTX group, compared with 11% in the tocilizumab group withdrew during the study, mostly due to unsatisfactory response.

Biologic combination strategies: Biologic DMARD plus biologic DMARD vs. biologic DMARD. A 24-week RCT did not detect any synergistic effects of a combination treatment of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy (Table 16).[66] Overall, 242 patients who were on stable doses of MTX treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept only. Furthermore, the frequency of serious adverse events was substantially higher in the combination groups (14.8 percent for 50 mg etanercept plus anakinra, 4.9 percent for 25 mg etanercept plus anakinra, and 2.5 percent for etanercept only; *P* = NR). Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6 percent vs. 7.4 percent; *P* = NR).

Table 16. Disease activity and remission for Biologic DMARD + Biologic DMARD vs. Biologic DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
ETN + AKA vs. ETN					
Genovese et al., 2004[66]	RCT 242 24 weeks	Inadequate control of disease with MTX; mean disease duration 9.9 years	ETN (25 mg twice weekly) + ANK (100 mg/day) vs. ETN (25 mg/week)	Higher ACR 50 response rates for ETN monotherapy (31% vs. 41%; *P* = 0.914)	Fair
ETN + ABA vs. ETN					
*Weinblatt, et al., 2007[67]	RCT 121 1 yr 2 yr long term extension	Patients on ETN; mean disease duration 12.8-13 yrs	ETN (25 mg twice weekly) + ABA 2g/kg increased to 10mg/kg after 1 year) vs. ETN (25 mg twice weekly)	No difference in mACR20/50/70 response rates at 1 year	Fair

*New studies since last review.

ABA, abatacept; ACR, American College of Rheumatology; ANK, anakinra; ETN, etanercept; kilogram, kg; mACR, modified American College of Rheumatology; milligram, mg; RCT, randomized controlled trial; vs., versus; yr, year.

Similarly, a 1 year RCT (N= 121) followed by a 2 year open label long term extension (N = 80) found no significant differences in modified ACR20 at six one year or at two and three years in the long term extension for patients treated with abatacept (2mg/kg for RCT, 10mg in long term extension) combined with etanercept (25mg twice weekly) compared to etanercept only (Table 16).[67] Although the initial RCT dosing of abatacept was lower than currently used clinically, the frequency of serious adverse events was higher in the abatacept combined with etanercept treated patients than in the etanercept only treated patients.

Biologic DMARD plus oral DMARD vs. biologic DMARD. The majority of trials assessed a combination of a biologic DMARD and MTX against a monotherapy of the respective biologic DMARD.[55,62,68,71,73,74] Only one trial used sulfasalazine as a oral DMARD in combination with a biologic DMARD.[72] No evidence is available on combination treatments of abatacept or anakinra. Disease activity and remission results are presented in Table 17 and radiographic joint damage in Table 18.

Table 17. Disease activity and Remission for Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs studies

Study	Study Design	Study Population	Comparison	Results	Quality

	N Duration		(dose)		Rating
Adalimumab +MTX vs. Adalimumab					
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. ADA (40 mg biweekly)	Significantly higher ACR 50 response rates for ADA + MTX than ADA (59% vs. 37%; *P* < 0.001)	Fair
Etanercept +DMARD vs. Etanercept					
Combe et al., 2006[72]	RCT 260 24 weeks	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. ETN (25 mg twice weekly)	Similar ACR 20 response rates between ETN + SSZ and ETN (74% vs. 74%; *P* = NR)	Fair
Klareskog et al., 2004;[73] van der Heijde et al., 2006;[113] van der Heijde et al., 2006[115], *Kavanaugh et al., 2008[151] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETN (25 mg twice weekly) + MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETN + MTX than ETN (18.3%-years vs. 14.7%-years; *P* < 0.0001) at 24 weeks	Fair
Van Riel et al., 2006[74]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX; mean disease duration 10.9 years	ETN (25 mg twice weekly) + MTX (>12.5 mg/week) vs. ETN (25 mg twice weekly)	Similar proportions of patients achieved an improvement of > 1.2 units of DAS 28 (75% vs. 73%; *P* = 0.66)	Fair
Hyrich et al., 2006[68]	Prospective cohort 2,711 6 months	Population-based; patients with active RA who required change in therapy; mean disease duration 14.3 years	ETN (25 mg twice weekly) + MTX (dose NR) vs. ETN (25 mg twice weekly) + other DMARD (dose NR) vs. ETN (25 mg twice weekly)	Significantly higher EULAR response rates for ETN + MTX than ETN (OR, 1.98; 1.45-2.71)	Good
Weaver et al., 2006[55]	Prospective cohort 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly) + MTX (dose NR) vs. ETN (25 mg twice weekly)	Similar mACR 20 response rates for ETN + MTX and ETN (43% vs. 41%; *P* = NR)	Fair

*New studies since last review.

ACR, American College of Rheumatology; ACR-N, American College of Rheumatology percent improvement from baseline to endpoint; ADA, adalimumab; CI, confidence interval; ETN, etanercept; EULAR, European League Against Rheumatism response; IFX, infliximab; kg, kilogram; mg, milligram; MTX, methotrexate; NR, not reported; NS, not significant; OR, odds ratio; RIT, rituximab; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 17. Disease activity and Remission for Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Zink et al., 2005[75]	Retrospective cohort 1,523	Patients with RA who had a change in treatment regimen	ETN + MTX vs. ETN (dosages NR)	Discontinuation due to lack of efficacy: Greater in ETN monotherapy vs. combination (ETN + MTX: 16.9%; ETN: 19.9%; *P* = NR)	Good
Infliximab + MTX vs. Infliximab					
Zink et al., 2005[75]	Retrospective cohort 1,523 1 year	Patients with RA who had a change in treatment regimen	INF + MTX vs. INF, (dosages NR)	Greater in IFX monotherapy than combination (INF + MTX: 17.9%, INF: 45%)	
Hyrich et al., 2006[68]	Prospective cohort 2,711 6 months	Population-based; patients with active RA who required change in therapy; mean disease duration 14.3 years	INF (3 mg/kg) + MTX (dose NR) vs. INF (3 mg/kg) + other DMARD (dose NR) vs. INF (3 mg/kg)	Higher EULAR response rates for IFX + MTX than INF (OR, 1.35; 0.92-2.00)	Good
Rituximab + MTX vs. MTX					
Edwards et al., 2004[71]	RCT 161 24 weeks	Active RA despite MTX treatment; mean disease duration 10.4 years	RIX (1,000 mg/days 1 & 15) + MTX (>10 mg/day) vs. RTX (1,000 mg/days 1 & 15)	Higher ACR 50 response rates for the RIT + MTX combination than for RTX monotherapy (43% vs. 33%; *P* = NR)	Fair

Table 18. Radiographic joint damage biologic DMARDs+ oral DMARDs vs. biologic DMARD studies

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Adalimumab + MTX vs. Adalimumab				
Breedveld et al., 2006[62], *Hoff et al., 2009[150] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) + MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 5.5; *P* < 0.001 Erosion score change: 1.0 vs. 3.0; *P* < 0.001 Joint space narrowing score change: 0.9 vs. 2.6; *P* < 0.001

*New studies since last review.

ADA, adalimumab; CI, confidence interval; ETN, etanercept; mg, milligram; MTX, methotrexate; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; vs., versus.

Table 18. Radiographic joint damage biologic DMARDs + oral DMARDs vs. biologic DMARD studies (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Etanercept + MTX vs. Etanercept				
Klareskog et al., 2004[73] van der Heijde et al., 2006[113] van der Heijde et al., 2006[115] TEMPO study	RCT 686 52 weeks	No	ETN (25 mg twice weekly) + MTX (20 mg/week) vs. ETN (25 mg twice weekly)	At 1 year: Total modified Sharp score change: -0.54 vs. 0.52; *P* = 0.0006 Erosion score change: -0.30 vs. 0.21; *P* < 0.0001 Joint space narrowing score change: -0.23 vs. 0.32; *P* = 0.0007 At 2 years: Total modified Sharp score change: -0.56 vs. 1.10; *P* < 0.05 Erosion score change: -0.76 vs. 0.36; *P* < 0.05 Joint space narrowing score change: 0.20 vs. 0.74; *P* = NR (NS)

Adalimumab plus MTX vs. adalimumab. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA.[62] Details of this study are reported above in *Biologic DMARDs vs. oral DMARDs.* After 2 years, significantly more patients on the combination therapy achieved response criteria on ACR 50 than patients on adalimumab monotherapy (59 percent vs. 37 percent; $P < 0.001$); in addition, they had statistically significantly less progression on a modified Sharp/van der Heijde score (1.9 vs. 5.5 Sharp units; $P < 0.001$). After 2 years of treatment, 49 percent of patients on the combination therapy and 23 percent on adalimumab monotherapy achieved remission (DAS 28 < 2.6; $P < 0.001$). Discontinuation rates because of lack of efficacy were lower in the combination group than in the monotherapy group (4.2 percent vs. 19.0 percent; *P* = NR). We report on results of the other comparisons of the PREMIER study in the respective sections on *Biologic DMARDs vs. oral DMARDs* and *Biologic DMARDs plus oral DMARDs vs. oral DMARDs*.

Etanercept plus MTX vs. etanercept. Two RCTs (in four publications)[73,74,113,115] and two prospective cohort studies[55,68] assessed differences in efficacy between an etanercept-MTX combination and etanercept monotherapy in patients with active, DMARD-resistant disease. Findings of these studies consistently supported greater efficacy for the combination therapy than for the etanercept monotherapy.

The TEMPO trial (described above in *Biologic DMARDs vs. oral DMARDs)* enrolled a mixed population of MTX-naive patients (about 57 percent) and patients who had been on prior MTX treatment (about 43 percent). Patients who had either failed prior MTX treatment or experienced toxic effects were excluded from this study. Results of the etanercept-MTX combination (25 mg twice weekly plus up to 20 mg/week) and the etanercept monotherapy (25 mg twice weekly) arms showed that the combination treatment was significantly more efficacious than etanercept alone. After 52 weeks, 69 percent in the combination group and 48 percent in the etanercept group achieved ACR 50 response criteria ($P < 0.0001$). Likewise, a statistically significantly higher proportion of patients in the combination than in the monotherapy group met ACR 20 and ACR 70 response criteria. The proportion of patients

achieving remission (DAS < 1.6) was 35 percent in the combination group and 16 percent in the monotherapy group ($P < 0.0001$). In addition, the combination regimen led to significantly better radiographic outcomes (changes in total Sharp score: -0.54 vs. 0.52; $P < 0.0001$) than the etanercept monotherapy.[113]

A German retrospective cohort study based on the RABBIT database did not find differences in discontinuation rates due to lack of efficacy between patients on etanercept monotherapy and those on an etanercept-MTX combination (19.9 percent vs. 16.9 percent; P = NR).[75]

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of findings from efficacy RCTs.[115] ACR response criteria, DAS remission rates, quality of life measures, and radiographic progression were statistically significantly better in the combination group than in the etanercept monotherapy group. Attrition was 39 percent after 2 years and could compromise the internal validity of the long-term results.

The other three studies included a 16-week, open-label RCT (N = 315),[74] a 12-month prospective cohort study,[55] and a 6-month prospective cohort study.[68] Their results were generally consistent with findings from the TEMPO trial. Both prospective cohort studies were population-based, one in the United States[55] and the other in the United Kingdom,[68] and both have a high generalizabilty.

The UK study also compared the effectiveness of the etanercept-MTX combination and a combination of etanercept and other DMARDs (leflunomide, azathioprine, sulfasalazine, hydroxychloroquine, cyclosporine A, penicillamine, gold, minocycline) as a class.[68] After adjusting for potential confounders, the investigators reported statistically significantly higher response rates for MTX as a cotherapy than for other DMARDs (OR, 1.66; 95% CI, 1.14-2.42).

Etanercept plus sulfasalazine vs. etanercept. A 24-week RCT assessed the comparative efficacy of etanercept and sulfasalazine combination therapy (respectively, 25 mg twice weekly plus 2, 2.5, or 3 g/day), etanercept monotherapy (25 mg twice weekly), and sulfasalazine monotherapy (2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[72] Because sulfasalazine monotherapy resembles a placebo treatment (patients had to have failed it to be eligible), we focus on results from the combination (n = 101) and etanercept monotherapy (n = 103) arms. After 24 weeks, both groups had similar clinical responses on multiple outcome measures (ACR 20/50/70, DAS 28). On ACR 20, the primary efficacy variable, 74 percent of patients in both groups met the relevant response criteria. Likewise, results on patient-reported measures of quality of life (HAQ, EuroQOL, general health VAS) were similar for patients on the combination and monotherapy interventions.

Infliximab plus MTX vs. infliximab. No RCT examined the comparative efficacy and effectiveness of a combination of infliximab and MTX against infliximab monotherapy in patients with RA. The only comparative evidence includes one U.S. and one U.K. prospective cohort study (already described).[55,68] Both studies indicated that EULAR and modified ACR response criteria were greater for patients in the studies' infliximab combination groups. Remission rates, however, were similar in both studies for the two regimens. At 6 months, U.K. patients in the combination group had higher EULAR response rates than those in the monotherapy group (OR, 1.35; 95% CI, 0.92-2.00).[68] At 12 months, mACR 20 responses were similar for U.S. patients in the combination and the monotherapy groups (OR, 0.96; 95% CI, 0.76-1.21; $P = 0.72$).[55]

A German retrospective cohort study assessing discontinuation rates in clinical practice reported findings similar to those noted above. Discontinuation rates because of lack of efficacy were higher among patients on an infliximab monotherapy than among those on an infliximab-

MTX combination regimen (45 percent vs. 18 percent; *P* = NR).[75] Overall discontinuation rates, however, were statistically significantly higher in the monotherapy than in the combination group (56 percent vs. 34 percent; hazard ratio, 1.9; 95% CI, 1.1-3.1).

Rituximab plus MTX vs. rituximab. One RCT enrolled patients with highly active, long-standing, DMARD-resistant RA to compare the efficacy of rituximab and MTX (1,000 mg on day 1 and day 15 plus MTX 10 mg or more/week), rituximab monotherapy (1,000 mg on day 1 and day 15), rituximab and cyclophosphamide, and MTX monotherapy.[71] Because cyclophosphamide is not a drug of interest for this report and because MTX monotherapy resembles a placebo treatment (patients had to have failed MTX treatment to be eligible), we focus on results of the rituximab-MTX combination (n = 40) and the rituximab monotherapy (n = 40) arms. After 24 weeks, patients on the combination intervention experienced changes in DAS outcomes similar to those for patients on rituximab monotherapy (-2.6 vs. -2.2; *P* = NR). A similar proportion of patients in both treatment groups achieved a good or moderate EULAR response (83 percent vs. 85 percent; *P* = NR). However, the proportion of patients meeting all three ACR response criteria was higher for patients treated with the rituximab combination treatment than for patients on rituximab monotherapy (ACR 20, 73 percent vs. 65 percent; ACR 50, 43 percent vs. 33 percent; ACR 70, 23 percent vs. 15 percent; *P* = NR). Higher ACR response rates for the combination treatment were maintained during a 48-week, double-blinded followup. After 48 weeks, 35 percent of patients on the combination regimen and 15 percent of patients on rituximab monotherapy met the ACR 50 response criteria.

Biologic combination strategies: Biologic DMARD plus oral DMARD vs. oral DMARD. The evidence is limited to five studies comparing a combination regimen of adalimumab plus MTX[62] or a combination of etanercept plus MTX[73,76] or a combination regimen of infliximab plus MTX[69] with MTX monotherapy. One study examined etanercept plus sulfasalazine versus sulfasalazine monotherapy.[72] Three studies were conducted in patients with early, aggressive RA.[62,69,76] Table 19 presents disease activity and remission results, followed by radiographic joint damage in Table 20.

Table 19. Disease activity and Remission for Biologic DMARDs + Oral DMARDs vs. Oral DMARDs

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Adalimumab + Methotrexate vs. Methotrexate					
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly higher ACR 50 response rates for ADA + MTX than MTX (59% vs. 43%; *P* < 0.001)	Fair

*New studies since last review.

ACR, American College of Rheumatology; American College of Rheumatology percent improvement from baseline to endpoint, ACR-N; ADA, adalimumab; ETN, etanercept; g. gram; INF, infliximab; kg. kilogram; mg, milligram; MTX, methotrexate; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 19. Disease activity and Remission for Biologic DMARDs + Oral DMARDs vs. Oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Etanercept + Methotrexate vs. Methotrexate					
*Emery et al., 2008[76] COMET study	RCT 542 52 weeks	MTX naïve patients; Early RA, mean disease duration 9 months	ETN (50mg/week) + MTX 7.5mg vs. MTX	Higher ACR 20 response rates between ETN +MTX vs. MTX (86%, 67%, *P* < 0.001) Higher remission between ETN + MTX vs. MTX (50%, 28%, *P* < 0.001)	Fair
Klareskog et al., 2004;[73] van der Heijde et al., 2006;[113] van der Heijde et al., 2006[115], *Kavanaugh et al., 2008[151] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETN (25 mg twice weekly) + MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETN + MTX than MTX (18.3%-years vs. 12.2%-years; *P* < 0.0001) at 24 weeks	Fair
Etanercept + Sulfasalazine vs. Sulfasalazine					
Combe et al., 2006[72] *Combe et al., 2009[122]	RCT 260 24 weeks 2 years	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. SSZ (2, 2.5, or 3 g/day)	Higher ACR 20 response rates between ETN + SSZ and SSZ (74% vs. 28%; *P* = NR) Higher remission at 2 years ETN + SSZ than SSZ (DAS <2.5; 57% vs.4.0%; *P* < 0.01)	Fair
Infliximab + Methotrexate vs. Methotrexate					
St Clair et al., 2004;[69] Smolen et al., 2006[70]; *Smolen et al., 2009[152] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks) + MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks) + MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly greater improvement of ACR-N for INF 3 mg + MTX and INF 6 mg + MTX than MTX (38.9% vs. 46.7% vs. 26.4%; *P* < 0.001) Higher remission in INF + MTX vs. MTX (DAS28-ESR < 2.6; 21.3%, 12.3%; *P* < 0.001)	Fair

Table 20. Radiographic joint damage of biologic DMARDs + oral DMARDs vs. oral DMARDs

Study	Study Design N Duration	Study Population	Comparison (dose)	Results
Adalimumab + Methotrexate vs. Methotrexate				
Breedveld et al., 2006[62], *Hoff et al., 2009[150] PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) + MTX (20 mg/week) vs. MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 10.4; *P* < 0.001 Erosion score change: 1.0 vs. 6.4; *P* < 0.001 Joint space narrowing score change: 0.9 vs. 4.0; *P* < 0.001
Etanercept + Methotrexate vs. Methotrexate				
*Emery et al., 2008[76] COMET study	RCT 542 52 weeks	MTX naïve patients; Early RA, mean disease duration 9 months	ETN (50mg/week) + MTX 7.5mg vs. MTX	Lower radiographic progression between ETN +MTX vs. MTX (mTSS -2.44, -0.27 *P* < 0.001)

*New studies since last review.

ADA, adalimumab; ETN, etanercept; mg, milligram; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; TEMPO, Trial of etanercept and Methotrexate with radiographic patient outcomes; vs., versus.

Adalimumab plus MTX vs. MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration < 3 years), aggressive RA[62] (see *Biologic DMARDs plus oral DMARDs vs. biologic DMARDs)*. Two treatment arms of this 2-year study assessed differences in efficacy between a combination of adalimumab (40 mg every other week) and MTX (20 mg/week) and MTX monotherapy (20 mg/week).[62] After 2 years, statistically significantly more patients on the combination therapy met ACR 50 response criteria than patients on MTX monotherapy (59 percent vs. 43 percent; *P* < 0.001); in addition, they had statistically significantly less progression on the modified SHS score (changes in total Sharp score: 5.5 vs. 10.4; *P* < 0.001). After 2 years of treatment, 49 percent of patients on the combination therapy and 25 percent on MTX monotherapy achieved remission (DAS 28 < 2.6; *P* < 0.001). Discontinuation rates because of lack of efficacy were lower in the combination than in the MTX group (4.2 percent vs. 17.9 percent; *P* = NR).

Etanercept plus MTX vs. MTX. Two trials (in five publications) compared etanercept (10 mg or 25 mg twice weekly or 50 mg weekly) with MTX (20 mg/week) over 52 weeks.[73,113,115,151] The COMET (combination of methotrexate and etanercept in active early rheumatoid arthritis) study (N =542) was conducted in patients with early RA who were MTX naïve.[76] The TEMPO trial,[73,113,115,151] described above in the section, *Biologic DMARD vs. Biologic DMARD* randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week).[73,113,115] The COMET trial[76] randomized 542 Early RA patients to Etanercept (50mg weekly) plus MTX (7.5 mg weekly) versus MTX.

Both studies showed statistically significant differences between etanercept plus MTX versus MTX in achieving ACR 20 response criteria at 24 weeks[73] and 52 weeks.[76] In the COMET study, patients treated with etanercept plus MTX had a higher remission (50% vs. 28%, *P* < 0.001) and less radiographic progression than MTX only.[76]

Infliximab plus MTX vs. MTX. The ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset) trial enrolled 1,049 patients

with early RA (disease duration < 3 years) who were MTX-naive.[69] This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or of using two different combinations of MTX and infliximab (3 mg/kg or 6 mg/kg) over 54 weeks. At endpoint, patients in the combination groups had significantly higher ACR-N (ACR-N is the percentage of ACR improvement from baseline to endpoint) scores than patients on MTX monotherapy (38.9 percent [3 mg infliximab plus MTX] vs. 46.7 percent [6 mg infliximab plus MTX] vs. 26.4 percent [MTX]; $P < 0.001$); remission rates were 31 percent, 21 percent, and 15 percent, respectively. The patients treated with infliximab plus MTX also had higher remission rates than patients treated with MTX alone (DAS28 ESR <2.6; 21.3% vs. 12.3%, $P < 0.001$).[152]

Biologic combination strategies: Biologic DMARD plus oral DMARD vs. Biologic DMARD plus oral DMARD. Three prospective cohorts compared patients taking an anti-TNF plus oral DMARD to patients taking another anti-TNF plus oral DMARD.[77,78,153] Each compared a different anti-TNF-oral DMARD combination and follow up ranged from 6 months to 17 months. Comparisons included anakinra plus MTX versus anakinra plus LEF,[77] etanercept plus oral DMARD versus infliximab versus oral DMARD,[153] and 'anti-TNF' (infliximab, etanercept or adalimumab) plus MTX versus anti-TNF plus MTX.[78] Overall, all three studies found similar disease activity responses (measured by ACR 20, EULAR and DAS**28**) for patients on anti-TNF plus oral DMARD compared to patients taking another anti-TNF plus oral DMARD. Similarly, radiographic progression was similar among anti-TNF + MTX groups.[78] Table 21 presents disease activity and remission while Table 22 presents radiographic joint damage.

Table 21. Disease activity and remission for biologic DMARDs + oral DMARDs vs. biologic DMARDs + oral DMARDs

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Anakinra + Methotrexate vs. Anakinra +Leflunomide					
*Karanikolas, et al., 2008[77]	Prospective cohort 128 48 weeks	Patients failed oral DMARD	ANK (100mg/day) +MTX (25 mg/week) vs. ANK + LEF (20 mg/week)	No significant difference in ACR 20 response between ANK +MTX and ANK + LEF (65%, 81%; *P* = NS, NR)	Fair
Etanercept +oral DMARD vs. Infliximab + oral DMARD					
*Hyrich, et al., 2006[153]	Prospective cohort 2879 6months	Population based, UK; patients failed at least 2 DMARDs; mean disease duration 14 years	ETN (dose NR) vs. INF (NR) (98% also received MTX)	Similar good EULAR response between ETN and INF (17.3% vs. 18.7%; *P* = NR	Fair
Anti-TNF + Methotrexate vs. Anti-TNF + Leflunomide					
*Finckh et al., 2009[78] SCQM cohort	Prospective Cohort 1218 17 months (mean)	Population based: Treatment with INF, ETN or ADA; mean disease duration 8.4-8.9 years	Anti TNF(INF or ETN or ADA)(dose NR) + MTX (NR) vs. Anti TNF (INF or ETN or ADA) (NR) + LEF	Similar DAS 28 improvement at 1 yr for anti-TNF + MTX and Anti-TNF + LEF (0.74; 95% CI, 0.63-0.84 vs. 0.63; 95% CI, 0.45 – 0.82, *P* = NR)	Fair

*New studies since last review.

ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; CI, confidence interval; DMARD, disease modifying anti-rheumatic drug; ETN, etanercept; EULAR, European League Against Rheumatism response; INF, infliximab; LEF, leflunomide; mg, milligram; NR, not reported; NS, not significant; SCQM, Swiss Clinical Quality Management; TNF, tumor necrosis factor; vs., versus.

Table 22. Radiographic joint damage for biologic DMARDs + oral DMARDs vs. biologic DMARDs + oral DMARDs

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Infliximab + Methotrexate vs. Infliximab +Methotrexate					
St Clair et al., 2004;[69] Smolen et al., 2006[70]; *Smolen et al., 2009[152] ASPIRE study	RCT 1,049 54 weeks	Yes; MTX-naive patients with early, aggressive RA	INF (3 mg/kg/8 weeks) + MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks) + MTX (20 mg/week) vs. MTX (20 mg/week)	Modified Sharp/van der Heijde score change: 0.4 vs. 0.5 vs. 3.7; *P* < 0.001 Erosion score change: 0.3 vs. 0.1 vs. 3.0; *P* < 0.001 Joint space narrowing score change: 0.1 vs. 0.2 vs. 0.6; *P* < 0.001	
Anti-TNF + Methotrexate vs. Anti-TNF + Leflunomide					
*Finckh et al., 2009[78] SCQM cohort	Prospective Cohort 1218 17 months (mean)	Population based: Treatment with INF, ETN or ADA; mean disease duration 8.4-8.9 years	Anti TNF(INF or ETN or ADA)(NR) + MTX (NR) vs. Anti TNF (INF or ETN or ADA) (NR) + LEF	Similar non significant radiographic progression for Anti-TNF +MTX and Anti-TNF + LEF (0.91%; 95% CI, 0.54 – 1.27 vs. 0.74%; 95% CI, 0.21-1.27, *P* = NS, NR)	

*New studies since last review.

ADA, adalimumab; ASPIRE, Active-Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; SCQM, Swiss Clinical Quality Management; INF, infliximab; kg, kilogram; LEF, leflunomide; mg, milligram; NR, not reported; NS, not reported; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor; vs., versus.

Strategies in Early RA. Disease activity and remission are presented in Table 23 and radiographic joint damage in Table 24.

Table 23. Disease activity and remission for early RA DMARD strategies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Two oral DMARDs + Corticosteroid vs. oral DMARD					
Boers et al., 1997;[79] Landewe et al., 2002[80] COBRA Study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2 g/day) + MTX (7.5 mg/day stopped after 40 weeks) + PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Pooled disease index: mean change better in combo group than SSZ alone at 28 weeks (1.4 vs. 0.8; *P* < 0.0001) vs. no longer significant at 52 weeks (1.1 vs. 0.9; *P* = 0.20) (Pooled index included tender joint count, grip strength, ESR, VAS, MACTAR questionnaire)	Good

*New studies since last review

BeST, Dutch acronym for Behandel Sstrategieen; COBRA, Combinatietherapie Bij Reumatoide Artritis; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ERA, early rheumatoid arthritis; ETN, etanercept; g, gram; HCQ, hydroxychloroquine; INF, infliximab; IQR, interquartile range; kilogram, kg; MACTAR, McMaster Toronto Arthritis Questionnaire mg, milligram; MTX, methotrexate; NR, not reported; NS, not significant; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; VAS, visual analog scale; vs., versus.

Table 23. Disease activity and remission for early RA DMARD strategies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Three oral DMARDs + Corticosteroid vs. oral DMARDs					
Mottonen et al., 1999;[81] Korpela et al., 2004[82] FIN-RACo study	RCT 199 24 months (5 year follow-up)	Multicenter; early RA; mean disease duration 7.3 to 8.6 months	MTX (7.5 to 10 mg/week) + HCQ (300 mg/day) + SSZ (2 g/day) + PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	Remission (defined by ACR preliminary criteria modified by authors) higher in combination group (37.9% vs. 18.4%; *P* = 0.011); ACR 50 higher in combination group (71% vs. 58%; *P* = 0.058); (5-year remission, NS, 28% vs. 22%; *P* = NS)	Fair
Other combination strategies					
Goekoop-Ruiterman et al., 2005;[83] *Allaart et al., 2006;[84] *Goekoop-Ruiterman et al., 2007;[85] *van der Kooij, et al., 2009;[86] *van der Kooij, et al., 2009;[154] *van der Kooij et al., 2008[155] BeSt study	RCT 508 12 months 2 years 4 years	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1to 5); median duration of symptoms 23 weeks (IQR 14 to 53)	DAS driven treatment; 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	DAS ≤ 2.4: 53%, 64%, 71%, 74%; *P* = 0.004 for 1 vs. 3; *P* = 0.001 for 1 vs. 4; *P* = NS for other comparisons Shorter time to DAS ≤ 2.4 for initial combination therapy groups (groups 3 and 4) than monotherapy groups (groups 1 and 2) (Median months; 3,3,9,9 *P* < 0.001) Similar remission among groups at 4 years (DAS <1.6; 50%, 41%, 38%, 42%; *P* = 0.40)	Good

Table 24. Radiographic joint damage in early RA strategy studies

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Two oral DMARDs + Corticosteroid vs. oral DMARD				
Boers et al., 1997;[79] Landewe et al., 2002[80] COBRA Study	RCT 155 (148) 56 weeks (5-year followup)	Yes	SSZ (2 g/day) + MTX (7.5 mg/day stopped after 40 weeks) + PNL (60 mg/day tapered over 28 weeks) vs. SSZ	56 week Modified Sharp/van der Heijde 5.6 vs. 8.6; *P* = 0.001

*New studies since last review.

BeST, Dutch acronym for Behandel Sstrategieen; COBRA, Combinatietherapie Bij Reumatoide Artritis; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; g, gram; HCQ, hydroxychloroquine; INF, infliximab; kg, kilogram; mg, milligram; MTX, methotrexate; NR, not reported; NS, not significant; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 24. Radiographic joint damage in early RA strategy studies (continued)

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes
Two oral DMARDs + Corticosteroid vs. oral DMARD				
Mottonen et al., 1999;[81] Korpela et al., 2004[82] FIN-RACo study	RCT 199 24 months (5 years)	Yes	MTX (7.5 to 10 mg/week) + HCQ (300 mg/day), + SSZ (2 g/day) + PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	2-year Larsen score change: 2 vs. 10; *P* = 0.002 2-year erosion score change: 2 vs. 3; *P* = 0.006 5-year median Larsen score: 11 vs. 24; *P* =0.001
Other combination strategies				
Goekoop-Ruiterman, 2005[83] *Allaart et al., 2006;[84] *Goekoop-Ruiterman et al., 2007;[85] *van der Kooij, et al., 2009;[86] *van der Kooij, et al., 2009;[154] *van der Kooij et al., 2008[155] BeST study	RCT 508 12 months (2 years, 4 years)	Yes	DAS driven treatment: 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/day-7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	Median modified Sharp/van der Heijde score change: 2.0, 2.5, 1.0, 0.5; *P* = 0.003 for 1 vs. 3, *P* < 0.001 for 1 vs. 4; *P* = 0.007 for 2 vs. 3; *P*< 0.001 for 2 vs. 4 In year 2, less joint damage in groups 3 and 4 (Median modified Sharp/van der Heijde score change: 2.0, 2.0, 1.0, 1.0; *P* = 0.004) In year 4, less joint damage in groups 3 and 4 (Median modified Sharp/van der Heijde score change: 5.0, 5.5, 3.0, 2.5; *P* < 0.05 for 1 and 2 vs. 4)

Two oral DMARDs plus corticosteroid vs. oral DMARD. One multicenter RCT, known as COBRA (Combinatietherapie Bij Reumatoide Artritis), assessed differences in efficacy between a combination of step-down prednisolone, MTX, and sulfasalazine and sulfasalazine only.[79] The investigators randomized 155 Dutch patients with early RA for 56 weeks. Patients with active RA were included if they had had symptoms for fewer than 2 years and had not used DMARDs in the past. Patients were then followed indefinitely in an open-label prospective cohort (5-year follow-up data reported).[80] Combination therapy included a stepped-down prednisolone treatment (60 mg/day tapered over 28 weeks), MTX (7.5 mg/week stopped after 40 weeks), and sulfasalazine (2 g/day). Mean duration of RA was 4 months. The authors applied a pooled index, which yielded a weighted change score of five disease activity measures: tender joint count, grip strength, erythrocyte sedimentation rate (ESR), assessor's global assessment by visual analog scale (VAS), and the McMaster Toronto arthritis questionnaire (MACTAR) (score range not given). At 28 weeks, patients on combination therapy had an improved change score in this index (mean change 1.4 vs. 0.8; $P < 0.0001$). At 52 weeks, however, the change results on the pooled index were no longer significant (mean change 1.1 vs. 0.9; $P = 0.20$). In terms of radiographic progression, patients on combination therapy had statistically significantly less progression than the monotherapy patients on the modified Sharp/van der Heijde score at 28 weeks (1 vs. 4; $P < 0.0001$), 56 weeks (2 vs. 6; $P < 0.004$), and 80 weeks (4 vs. 12; $P < 0.01$). Over 5 years, the modified Sharp/van der Heijde change score per year was lower for combination therapy than for monotherapy (5.6 vs. 8.6; $P = 0.001$).[80]

Three oral DMARDs plus corticosteroid vs. oral DMARDs. The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) RCT assessed the efficacy of a complex combination of prednisolone (5 to 10 mg/day), MTX (7.5 to 10 mg/week), sulfasalazine (2 g/day), and hydroxychloroquine (300 mg/day) against that of monotherapy with a DMARD with or without prednisolone.[81] The investigators randomized 199 patients with early RA to either combination therapy or monotherapy. Patients on monotherapy were initially started on sulfasalazine (2 to 3 g/day) but could be changed to MTX (7.5 to 15 mg/week), then changed to a third DMARD if needed (azathioprine, auranofin, hydroxychloroquine, injectable gold, penicillamine, or podophyllotoxin). If patients reached remission in the first year, they could be tapered and prednisolone and MTX could be discontinued at 9 months and 18 months, respectively. Adding prednisolone (up to 10 mg/day) in the monotherapy group was left up to the treating physician and allowed in patients with continuously active disease. After 2 years, remission (judged by the authors using modified ACR 20) was higher in the combination group than in the monotherapy group (37.9 percent vs. 18.4 percent; $P = 0.011$); the proportion achieving ACR 50 response criteria was higher in the combination group than in monotherapy group but did not reach statistical significance (71 percent vs. 58 percent; $P = 0.058$). Larsen Scale radiographic scores had also improved at 2 years in the combination group as compared to the monotherapy group (Larsen Scale score increase 2 vs. 10; $P = 0.002$). Subsequently, patients in this trial were followed for 5 years.[82] Those in the monotherapy group were allowed to be treated with combinations of DMARDs if their response was insufficient. At 5 years, the median Larsen Scale score remained lower in the combination therapy group than in the monotherapy group (11 vs. 24; $P = 0.001$). This trial can be considered an effectiveness trial given the flexibility of dosing in an effort to follow clinical practice.

Other combination strategies. One good-quality RCT examined four different treatment strategies over 12 months.[83] The BeSt Study (Dutch acronym for Behandel Strategieen, "treatment strategies") randomized 508 patients with early RA to one of four groups: (1) sequential DMARD, starting with MTX (15 mg/week), (2) step-up combination therapy with MTX (15 to 30 mg/week) followed by sulfasalazine (2 g/day), hydroxychloroquine, and prednisone, (3) initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone 60 mg/day to 7.5 mg/day in 7 weeks, and (4) initial combination therapy with MTX 25 to 30 mg/week and infliximab 3 mg/kg every 8 weeks (dose titrated up to 10 mg/kg dependent upon DAS 44 > 2.4). This design called for frequent changes in treatment strategy; the DAS (i.e., DAS in 44 joints) was calculated every 3 months and if it was greater than 2.4, the therapeutic strategies were adjusted. At 12 months, more patients in group 3 (MTX, sulfasalazine, tapered high-dose prednisone) and in group 4 (MTX with infliximab) reached a DAS of 2.4 or less. Respectively, these proportions were 53 percent, 64 percent, 71 percent, and 74 percent ($P = 0.004$ for group 1 vs. group 3; $P = 0.001$ for group 1 vs. group 4; $P =$ NS for other comparisons). Additionally, the median change in modified Sharp/van der Heijde score was lower for groups 3 and 4 than for groups 1 and 2 (2.0, 2.5, 1.0, and 0.5, respectively; $P = 0.003$ for group 1 vs. group 3; $P < 0.001$ for group 1 vs. group 4; $P = 0.007$ for group 2 vs. group 3; $P < 0.001$ for group 2 vs. group 4). Interestingly, at four years, the remission rates were similar among the groups (DAS < 1.6; 50%, 41%, 38%, 42%, $P = 0.40$).[154]

Key Question 2: Functional Capacity and Quality of Life

This question specifically examined the issue of whether, for patients with RA, drug therapies differed in their ability to improve functional capacity or quality of life. Findings are organized as for KQ 1. Table 17 (above) lists the abbreviated and full names of all instruments and scales referred to in this section. Functional capacity, functional status, and functional ability are three concepts often used interchangeably to refer to similar capabilities. Quality of life is a far broader construct comprising physical health, mental or emotional health, a variety of symptom states (e.g., pain, fatigue), and coping, spiritual and other domains. For the purposes of this report we divided outcomes into functional capacity and health-related quality of life. We use the terms *functional capacity, functional status,* or *functional ability* to refer to condition-specific measures, such as the Health Assessment Questionnaire (HAQ), developed to assess function in patients with RA or other rheumatic diseases. We use *health-related quality of life* when referring to generic measures, such as the Medical Outcomes Study Short Form 36 Health Survey (SF-36), that have been developed to assess quality of life in both healthy persons and those with different conditions. We also attempted to use terminology consistent with reporting from individual studies; if the authors used the term *functional ability* rather than *functional capacity,* we used the same term. Outcomes for functional capacity and health-related quality of life were often secondary outcomes in these studies; that is, not all studies were designed to detect a difference between groups for these types of outcomes.

Overview

A total of 27 RCTS, five observational studies, and one systematic review compared functional capacity or quality of life outcomes between active drugs or between active drugs and placebo. Details are found in Evidence Tables 3 and 4 in Appendix G. Overall results and strength of evidence are described below in Key Points and in Table 25. Table 26 provides information on comparisons made, functional capacity, health-related quality of life, and quality ratings. The main drug classes compared include corticosteroids, oral DMARDs, biologic DMARDs, and combined strategies. For each comparison, the table provides the strength of evidence for functional capacity and quality of life outcomes within a single row, if both outcomes were available. Information related to functional capacity is provided in the upper part of each row; information related to quality of life is provided in the lower part of each row, when available. If only one study provided all of the evidence for a comparison and had consistent results for functional capacity and quality of life outcomes (i.e. finding no difference or one treatment better than the other), we inserted a single set of entries in the row, rather than repeat the same information twice.

Table 25. Strength of evidence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD						
Corticosteroid vs. Corticosteroid 1 RCT N =143	Medium RCT/ fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with prednisolone than with budesonide	Low
Leflunomide vs. MTX 2 RCTs; N = 1481	Low RCTs/ 2 fair	Inconsistent	Direct	Imprecise	Mixed results for functional capacity	Insufficient
	Medium RCT/1 fair	Unknown, single study	Direct	Precise	Greater improvement in quality of life (SF-36 physical summary score, but not mental summary score) with LEF than MTX	Low
Leflunomide vs. Sulfasalazine 1 RCT; N =358	Low Meta-analysis/good RCT/fair	Consistent	Direct	Precise	Greater improvement in functional capacity with LEF than SSZ	Low
Sulfasalazine vs. MTX 3 RCTs; N = 479	Low RCTs/Fair	Consistent	Direct	Precise	No difference in functional capacity	Moderate
Oral DMARD Combinations vs. Monotherapy or Combinations with or without Corticosteroids						
SSZ + MTX vs. SSZ or MTX monotherapy 3 RCTs: N = 479	Low RCTs/Fair	Consistent	Direct	Precise	No difference in functional capacity	Moderate
Oral DMARD + corticosteroid vs. Oral DMARD 2 RCTs; N = 717	Low RCTs/ Good, Fair	Consistent	Direct	Precise	Greater improvement in functional capacity for subjects treated with oral DMARD plus prednisolone	Moderate
1 RCT; N = 467	Low RCT/Good	Unknown, single study	Direct	Imprecise	No difference in quality of life	Low
Biologic DMARD vs. Biologic DMARD						
ABA vs. INF 1 RCT; N = 431	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	No difference in functional capacity	Low
				Precise	Greater improvement in quality of life with ABA	Low
ETN vs. INF 3 prospective cohort studies; N = 2239	Medium Prospective cohorts/3 Fair	Inconsistent	Direct	Imprecise	Mixed results for functional capacity (2 of 3 studies reported no difference; 1 favored ETN)	Insufficient
	Medium Prospective cohort/1 Fair	Unknown, single study	Direct	Precise	Greater improvement in quality of life for ETN	Low

ABA, abatacept; ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; INF, infliximab; MTX, methotrexate; N, number; RCT, randomized controlled trial; TCZ, tocilizumab; vs., versus.

Table 25. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
ADA vs. ETN 1 prospective cohort; N = 707	Medium Prospective cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in functional capacity No difference in quality of life	Low
ADA vs. INF 1 prospective cohort; N = 707	Medium Prospective cohort/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with ADA Greater improvement in quality of life with ADA	Low
Biologic DMARD vs. Oral DMARD						
ADA vs. MTX 1 RCT; N = 799	Medium RCT/Fair	Unknown, single study	Direct	Precise	No difference in functional capacity for MTX naïve subjects with early RA	Low
ETN vs. MTX 2RCTs; N =1318	Low RCTs/1 Good, 1 Fair	Inconsistent	Direct	Imprecise	Mixed results for functional capacity	Insufficient
1 RCT; N = 632	Medium RCT/1 Fair	Unknown, single study	Direct	Imprecise	Faster improvement in quality of life with ETN (greater improvement at 12 weeks, but no difference from weeks 16 to 52)	Low
TCZ vs. MTX 1 RCT; N = 127	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with TCZ than MTX for patients with active RA and an inadequate response to MTX	Low
Biologic DMARD + Biologic DMARD vs. Biologic DMARD						
ETN + ABA vs. ETN 1 RCTs; N = 121	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	No difference functional capacity Greater improvement in physical, but not mental, health-related quality of life	Low
Biologic DMARD + MTX vs. Biologic DMARD in MTX naïve subjects or those not recently on MTX						
Any Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs 2RCTs; N = 1495	Low RCTs/1 Good, 1 Fair	Consistent	Direct	Precise	Greater improvement in functional capacity with biologic + MTX	Moderate
	Low RCT/1 Good	Unknown, single study	Direct	Precise	Greater improvement in quality of life with biologic + MTX	Low
ADA+ MTX vs. ADA 1 RCT; N = 799	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with ADA + MTX for MTX-naïve subjects with early RA.	Low

Table 25. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
ETN + MTX vs. ETN 1 RCTs, 1 cohort study; N = 696	Low RCT/ Good	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with ETN + MTX for subjects with active RA who failed at least 2 oral DMARDs, but were not on MTX for at least 6 months.	Low
Biologic DMARD + Oral DMARD vs. Biologic DMARD in subjects with active RA despite treatment with the same Oral DMARD						
ETN + DMARD vs. ETN 2RCTs, 1 cohort study; N = 3609	Low RCTs/2 Fair Cohort/Fair	Consistent	Direct	Precise	No difference in functional capacity No difference in quality of life	Moderate
Biologic DMARD + Oral DMARD vs. Oral DMARD						
Any Biologic DMARDs + Oral DMARD vs. Oral DMARD 5 RCTs, 1 cohort study; N = 6370	Low RCTs/ 4 Fair, 1Good Cohort/Fair	Consistent	Direct	Precise	Greater improvement in functional capacity with biologic + oral DMARD	Moderate
	Medium RCTs/1 Fair, 1 Good	Consistent	Direct	Precise	Greater improvement in quality of life with biologic + oral DMARD	Moderate
ADA + MTX vs. MTX 1 RCT; N = 799	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with ADA + MTX	Low
ETN + oral DMARD vs. oral DMARD (MTX or SSZ) 3 RCTs, 1 cohort study; N = 4522	Low RCTs/2 Fair, 1 Good Cohort/Fair	Consistent	Direct	Precise	Greater improvement in functional capacity with ETN + oral DMARD	Moderate
	Low RCT/Good	Unknown, single study	Direct	Precise	Greater improvement in quality of life with ETN + oral DMARD	Low
INF + MTX vs. MTX 1 RCT; N = 1049	Medium RCT/Fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity and quality of life with INF + MTX	Low
Biologic DMARD + Oral DMARD vs. Biologic DMARD + Oral DMARD						
Anti-TNF + MTX vs. anti-TNF vs. LEF 1 cohort; N = 1218	Medium Cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in functional capacity	Low

Table 25. Strength of evidence (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Strategies in Early RA						
Two oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT; N = 155	Low RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity (comparing groups at 28 weeks), but no difference by 56 weeks	Low
Three oral DMARDs plus corticosteroid vs. oral DMARD 1 RCT; N = 199	Medium RCT/Fair	Unknown, single study	Direct	Precise	Less work disability in the combination strategy group	Low
Other combination strategies: Sequential monotherapy vs. Step-up combination therapy vs. initial combination therapy with prednisone vs. initial combination therapy with infliximab RCT; N = 508	Low RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity in groups 3 and 4 than in groups 1 and 2(statistically significantly better at 3, 6, 9, and 12 months). By two years, improvement was maintained in all groups, but there were no statistically significant differences between groups Similar pattern was found for improvement in physical health-related quality of life	Low

Table 26. Oral DMARD vs. Oral DMARD studies: Functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Corticosteroid vs. Corticosteroid						
Kirwan et al., 2004[38]	RCT 143 12 weeks	Population-based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	Improvement in mean HAQ scores: PNL 0.393 units better than BUD 3 mg; $P < 0.001$ PNL 0.276 units better than BUD 9 mg; $P < 0.01$	Improvement in SF-36 physical component: mean change 5.4 units better for PNL than BUD 3 mg, $P < 0.01$; 3.7 units better than BUD 9 mg, $P < 0.05$	Fair

BUD, budesonide; combo, combination therapy; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; HCQ, hydroxychloroquine; INF, infliximab; LEF, leflunomide; mg, milligram; MTX, methotrexate; NHS, National Health Service; NR, not reported; NS, not significant; PNL, prednisolone; PRED, prednisone; RCT, randomized controlled trial; SF-36, Medical Outcomes Test, Short Form 36; SOFI, Signals of Functional Impairment Scale; SSZ, sulfasalazine.

Table 26. Oral DMARD vs. Oral DMARD studies: Functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Leflunomide vs. MTX						
Osiri et al., 2003[39]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week)	MHAQ scores improved significantly in LEF group compared with MTX at 6, 12, and 24 months; at both 12 and 24 months, no difference in improvement in HAQ At one year there was no difference in work productivity in LEF vs. MTX weighted mean difference -2.3 points: 95% CI, 6.37-1.77	LEF showed better improvement than MTX in SF-36 physical component but not mental component	Good
			LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	Data for LEF vs. SSZ under different heading in this table		
Emery et al., 2000[40]	RCT 999 1 year with optional 2nd year	Mean disease duration 3.5 to 3.8 years	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Change in HAQ at 12 months, minimal quantitative (data NR) but significant ($P < 0.05$); at 24 months, difference NS	NR	Fair
Strand, et al., 1999[41] Cohen, et al., 2001[42]	RCT 482 12 months (1 year continuation)	Mean disease duration 6.5 to 7 years	LEF (20 mg/day) vs. MTX (7.5 to 15 mg/week)	Mean improvement in HAQ-DI greater in LEF than MTX at 12 months (-0.45 vs. -0.26; $P \leq 0.01$) and MHAQ (-0.29 vs. -0.15; $P < 0.01$)	Mean improvement in SF-36 physical greater in LEF than MTX at 12 months (7.6 vs. 4.6; $P < 0.01$) but not mental component (1.5 vs. 0.9; P = NS)	Fair
Leflunomide vs. Sulfasalazine						
Osiri et al., 2003[39]	Systematic review and meta-analysis 1,732 2 years	6 trials; active RA	LEF (10 to 20 mg/day) vs. MTX (7.5 to 15 mg/week) LEF (10 to 20 mg/day) vs. SSZ (2 g/day)	Data for LEF vs. MTX under different heading in this table. At 6 and 24 months, LEF group had greater improvements in HAQ-DI than SSZ	Data for LEF vs. MTX under different heading in this table	Good
Smolen et al., 1999[43] Scott et al., 2001[156]	RCT 358 (146) 24 weeks (12 and 24 month followup)	Mean disease duration 5.7 to 7.6 years	LEF (20 mg/day) vs. SSZ (2 g/day)	Improvement in HAQ scores at 24 weeks greater in LEF than SSZ (-0.50 vs. -0.29; $P < 0.03$) and continued in 2-year followup group at 6 and 24 months (-0.50 vs. -0.29; -0.65 vs. -0.36; both $P < 0.01$)	NR	Fair

Table 26. Oral DMARD vs. Oral DMARD studies: Functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Sulfasalazine vs. MTX						
Capell et al., 2007[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	No significant difference between groups in change from baseline HAQ (SSZ: -0.25; MTX: -0.19; *P* = 0.99)	NR	Fair
Dougados et al., 1999[46]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ -0.74 vs. MTX -0.73; *P* = NS)	NR	Fair
Haagsma et al., 1997[47]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks not significant (SSZ -0.32; 95% CI, -0.53 to -0.10, MTX -0.46; 95% CI, -0.68 to -0.25; *P* = NR)	NR	Fair

Key Points

Oral DMARDs vs. oral DMARDs. Only one head-to-head RCT compared two corticosteroids, budesonide and prednisolone.[38] Prednisolone produced greater improvement in functional capacity and health-related quality of life than budesonide. The results are limited to one study. The strength of evidence is low.

The evidence from two RCTs is insufficient to determine whether leflunomide and MTX differ for functional capacity due to the inconsistent results.[40-42] Evidence from one study found greater improvement in quality of life (SF-36 physical component summary, but not mental component) with leflunomide than with MTX (low strength of evidence).

One RCT[43] with a 2-year followup[156] provides low strength of evidence that leflunomide yields greater improvements in functional capacity (measured by HAQ scores) at 24 weeks, 6 months, and 24 months than SSZ.

Evidence from three RCTs[45-47] provides moderate strength of evidence that there is no difference in functional capacity between patients treated with SSZ and MTX.

No fair or good evidence exists for comparing hydroxychloroquine to monotherapy with another oral DMARD.

Oral DMARD combinations. Three RCTs compared a combination of two oral DMARDs (SSZ plus MTX) to monotherapy with either drug and provide moderate strength of evidence that there is no difference in functional capacity.[45-47]

Two RCTs provide moderate strength of evidence that using corticosteroids and one oral DMARD results in greater improvements in functional capacity than using oral DMARD monotherapy. One RCT provides low strength of evidence supporting no difference between the combination of corticosteroids and one oral DMARD and oral DMARD monotherapy.

Biologic DMARDs vs. biologic DMARDs. We found one head-to-head RCT and three prospective cohort studies that compared one biologic DMARD with another.[53,55,57,58] Three of these included comparisons of etanercept with infliximab;[55,57,58] one study compared each of the following: adalimumab versus etanercept, abatacept versus infliximab, and adalimumab versus infliximab.[58] The head-to-head RCT[53] provides low strength of evidence that abatacept improves quality of life more than infliximab, but that there is no difference in functional capacity between those treated with abatacept and infliximab. Two of the three studies comparing etanercept with infliximab reported no difference in functional capacity outcomes; one reported greater improvement with etanercept.[55] Only one of the three studies reported a quality of life outcome, finding greater improvement in the SF-36 PCS with etanercept than with infliximab (low strength of evidence).[58] One cohort study provides low strength of evidence that adalimumab results in greater improvement in functional capacity and quality of life compared with infliximab.[58] One cohort study provides low strength of evidence that adalimumab and etanercept do not result in statistically significant differences in functional capacity or quality of life.[58] Because of the methodological limitations of observational studies, findings of these studies must be interpreted cautiously.

Biologic DMARDs vs. oral DMARDs. We found four RCTs[62-64,73] and one prospective cohort study[65] that included comparisons of monotherapy with a biologic DMARD to monotherapy with an oral DMARD. The evidence from these studies is mixed. Population-based, observational evidence from the cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than oral DMARDs as a class in patients with active RA who required a change in therapy.[65] Two of the RCTs, however, found no differences when comparing either adalimumab[62] or etanercept[73] with MTX. One RCT[63] found that etanercept resulted in better improvement of function and quality of life during the first 12 weeks of treatment, but it found no difference from week 16 to week 52. The study also reported that a greater percentage of patients treated with etanercept had significant improvements in functional capacity ($\geq$ 0.5 unit Disability Index of the Heath Assessment Questionnaire, HAQ-DI) at 24 months. One RCT found subjects treated with tocilizumab had significantly greater improvements in functional capacity than those treated with MTX.[64] All RCTs were funded by the makers of the biologic DMARDs. The strength of the evidence is insufficient for biologics as a class compared to oral DMARDs as a class.

We found no evidence on biologic DMARDs other than etanercept, adalimumab, and tocilizumab and no studies comparing biologics with oral DMARDs other than MTX.

No studies meeting our quality criteria compared biologic DMARDs with corticosteroids.

Biologic DMARD combinations. One RCT provides low strength of evidence that there is no difference in functional capacity between a combination of etanercept plus abatacept compared to etanercept alone.[67] The same RCT provides low strength of evidence that the combination results in statistically significantly greater improvement in physical, but not mental, health-related quality of life (as measured by the SF-36 PCS and MCS, respectively). Of note,

the study concluded that abatacept in combination with etanercept should not be used for patients with RA due to limited efficacy findings and safety concerns (more abatacept and etanercept-treated patients experiences serious adverse events).

For studies comparing a biologic DMARD plus an oral DMARD versus a biologic DMARD, we stratified by population because results differed based on the population enrolled. Three of the studies found no difference between combination therapy and biologic DMARD monotherapy;[55,72,74] two reported greater improvement with combination therapy.[62,73] The two RCTs that found combination therapy resulted in greater improvement in functional capacity or quality of life enrolled subjects that were MTX-naïve[62] or had not been on MTX for at least 6 months prior to enrollment.[73] The studies finding no difference enrolled subjects with active RA despite treatment with the same oral DMARD that was used in the combination therapy arm of the trial. We conclude that biologic DMARDs plus MTX result in greater improvements in functional capacity (moderate strength of evidence) and quality of life (low strength of evidence) than biologic DMARDs alone for MTX naïve subjects or those not recently on MTX. For subjects with active RA despite treatment with the same oral DMARD used in the combination therapy, we conclude that there is no difference in improvements in functional capacity (moderate strength of evidence) or quality of life (moderate strength of evidence) between a biologic DMARD plus an oral DMARD and biologic DMARDs monotherapy.

For most individual medications in these comparisons, however, the evidence is limited to a single study. All RCTs were funded by the makers of the biologic DMARDs. No evidence (for biologic DMARD plus oral DMARD vs. biologic DMARD) was available for biologic DMARDs other than adalimumab, etanercept, or infliximab and combinations with oral DMARDs other than MTX and sulfasalazine.

Five RCTs and one prospective cohort study found greater improvement in functional capacity with combination treatment with a biologic DMARD plus an oral DMARD than with oral DMARD monotherapy (moderate strength of evidence).[55,62,69,72,73,76,113,115,122] Three of the RCTs were conducted in subjects with early RA.[62,69,76] Two of the RCTs also reported quality of life outcomes, finding greater improvement in the biologic DMARD plus oral DMARD combination therapy group.[69,73,113,115] The specific comparisons in these studies were a combination regimen of adalimumab plus MTX,[62] infliximab plus MTX,[55,69] or etanercept plus MTX[55,73,76,113,115] with MTX monotherapy; and a combination of etanercept plus sulfasalzine with sulfasalazine monotherapy.[72,122]

Treatment strategies for early RA. We included two studies (three publications) that compared various combination strategies using corticosteroids and multiple oral DMARDs with oral DMARD monotherapy in subjects with early RA.[79,81,157] One RCT found that the combination of sulfasalazine, MTX, and prednisolone resulted in greater improvements in functional capacity at 28 weeks than in sulfasalazine alone, but the difference was no longer statistically significant at 56 weeks.[79] Thus, the combination group had more rapid improvement, but the groups reached similar improvement by 56 weeks. The second RCT compared a combination of three oral DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone with oral DMARD monotherapy.[81] The combination therapy group had significantly less work disability than patients in the monotherapy group at 5-year followup.[157] Of note, the randomized treatments were carried out for 2 years and treatments were then at the discretion of the treating physician. The data are limited to one study for each comparison. The strength of the evidence is low for each individual comparison. However, the strength of

evidence is moderate favoring combination strategies using corticosteroids plus multiple oral DMARDs over oral DMARD monotherapy.

One RCT (the BeSt study) in patients with early RA found that patients treated with initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab and MTX had more rapid improvement in functional ability than those treated with sequential DMARD monotherapy starting with MTX or with step-up combination therapy of MTX followed by sulfasalzine, hydroxychloroquin, and prednisone (statistically significantly greater improvements at 3, 6, 9, and 12 months).[83] However, the magnitude of difference was small, and the clinical significance of this result is uncertain. By two years, improvement was maintained in all groups, but there were no statistically significant differences between groups. The strength of the evidence is low.

Detailed Analysis

Oral DMARDs vs. oral DMARDs. Functional capacity and health related quality of life outcomes are presented in Table 26.

Corticosteroids vs. corticosteroids. One 12-week head-to-head RCT (N = 143) compared budesonide (3 mg/day or 9 mg/day; n = 37 and 36, respectively) and prednisolone (7.5 mg/day; n = 39).[38] Mean disease duration of RA was 9 years. Overall, prednisolone produced greater improvement in functional capacity and health-related quality of life than either dose of budesonide. At 12 weeks, those treated with prednisolone had better improvement in mean HAQ scores than budesonide (0.393 units better than budesonide 3 mg, $P < 0.001$; 0.276 units better than budesonide 9 mg, $P < 0.01$). A change of 0.22 units is generally considered the minimum clinically important difference.[158] Those treated with prednisolone also had better improvement in health-related quality of life as measured by the physical subscale of the SF-36 (difference in mean change of 5.4 units compared with budesonide 3 mg, $P < 0.01$; 3.7 compared with budesonide 9 mg, $P < 0.05$). Improvement on the mental subscale of the SF-36 was not statistically significantly different between groups. Of note, functional capacity and health-related quality of life were secondary outcome measures; the study had not been designed to compare differences in either the HAQ or the SF-36.

Leflunomide vs. methotrexate. We found two RCTs[40,41] comparing leflunomide (20 mg/day) with MTX (7.5 mg/week to 15 mg/week)[40,41] and one good systematic review with a meta-analysis of leflunomide.[39] The systematic review included only two trials comparing leflunomide with MTX and only one study for all but one of the functional capacity and quality of life outcomes. We describe the individual studies first.

The first trial randomized 482 patients to leflunomide (n = 182) or MTX (n = 182) over 12 months.[41,159] It is described in more detail in the KQ 1 section entitled *Oral DMARDs vs. Oral DMARDs.* Patients receiving leflunomide reported greater mean improvement in the HAQ-DI (-0.45 vs. -0.26; $P \leq 0.01$), modified HAQ (MHAQ: -0.29 vs. -0.15; $P < 0.01$), and the SF-36 physical component (7.6 vs. 4.6; $P < 0.01$) than those receiving MTX at 12 months. At 12 months, the two groups did not differ significantly in improvement in the SF-36 mental summary score (1.5 vs. 0.9; P = NS) or in work productivity. A 2-year followup of 235 patients (leflunomide, n = 98; MTX, n = 101) found greater mean improvement in the HAQ-DI (-0.60 vs. -0.37; $P = 0.005$) and MHAQ scores (-0.43 vs. -0.28; $P \leq 0.05$) with leflunomide than with MTX.[42] The groups did not differ significantly in mean improvement in the SF-36 physical or mental summary scores at 24 months. These 2-year results are limited by the high attrition rate (45 percent) from the initial study.

One multinational trial comparing leflunomide and MTX was a 1-year RCT of 999 subjects with an optional second year.[40,160] Mean disease duration was 3.5 years to 3.8 years. At 12 months, a statistically significant but minimal quantitative difference (number not reported, shown in bar graph)[40] for change in the HAQ ($P < 0.05$) was reported between the two groups; at 24 months, however, the groups did not differ significantly.

The systematic review with meta-analysis included six trials (N = 2,044) comparing leflunomide (10 to 20 mg/day) with other oral DMARDs in patients with active RA.[39] It included two studies relevant to this section.[40,41] MHAQ scores improved significantly more in patients treated with leflunomide than in those treated with MTX at 6, 12, and 24 months. The leflunomide group and the MTX group did not differ in improvement on the HAQ index at either 12 months or 24 months. Work productivity did not improve significantly in the leflunomide group when compared with the MTX group (weighted mean difference [WMD], -2.3 points; 95% CI, -6.37-1.77). When comparing leflunomide with MTX, changes in SF-36 scores showed better improvement in the physical summary score with leflunomide (WMD, -3.0 points; 95% CI, -5.41 - -0.59) but not the mental summary score (WMD, -0.6 points; 95% CI, -3.01-1.81). The only study that contributed to this outcome (SF-36 physical summary score) was the RCT (N = 482) described above in this section.[41,159] This systematic review was limited by the number of studies included for meta-analysis; only one study was available for each individual functional capacity or quality of life outcome measure except for change in HAQ scores, for which there were two studies.

Leflunomide vs. sulfasalazine. One RCT[43] with a 2-year followup[156] compared leflunomide (20 mg/day) with sulfasalazine (2 g/day) and placebo; one systematic review included a meta-analysis of leflunomide.[39] The RCT was a multinational, multicenter study of 358 patients (leflunomide, n = 133; sulfasalazine, n = 133; placebo, n=92).[43] Baseline HAQ scores were similar for all groups. The leflunomide group had significantly greater improvement in HAQ scores at 24 weeks than the sulfasalazine group (-0.50 vs. -0.29; $P < 0.03$). The 2-year followup found that the leflunomide group had significantly greater improvements in HAQ scores than the sulfasalazine group at 6 and 24 months (-0.50 vs. -0.29 and -0.65 vs. -0.36; both $P < 0.01$).[156] Subjects completing the first 6 months were given the option to continue. Those in the placebo group were switched to sulfasalazine if they continued in the study. The study was limited by only including 146 (leflunomide, n = 60; sulfasalazine, n = 60; placebo then sulfasalzine, n=26) of the original 358 subjects and having a 21 percent attrition rate (116 completed the study).

One systematic review with meta-analysis compared leflunomide (10 to 20 mg/day) with other DMARDs in patients with active RA.[39] For the comparison of leflunomide and sulfasalazine, the meta-analysis included one study (N = 229) with changes in HAQ at 6, 12, and 24 months.[156] At 6 and 24 months, the leflunomide group had greater improvements in the HAQ-DI than the sulfasalazine group (WMD -0.25 point; 95% CI, -0.42 - -0.08; WMD -0.29 point; 95% CI, -0.57 - -0.01, respectively). This evidence is limited because the meta-analysis included only one study for this outcome; they did not pool data from multiple studies.

Sulfasalazine vs. MTX. Three RCTs compared sulfasalazine with MTX.[45-47] Their findings are consistent and do not support a difference in functional capacity between the groups receiving these two pharmaceuticals. A multinational 52-week RCT of 209 DMARD-naive subjects failed to find a statistically significant difference in change in the HAQ from baseline to 1 year (sulfasalazine -0.74; MTX -0.73; P = NS).[46] A 52-week RCT of 105 DMARD-naive subjects in academic and peripheral clinics in the Netherlands reported a change in HAQ scores from baseline to 52 weeks of -0.32 (95% CI, -0.53 - -0.10) for sulfasalazine and a change of -

0.46 (95% CI, -0.68 - -0.25; *P* = NR) for MTX.[47] HAQ was a secondary outcome in this study; HAQ changes for the different groups were not compared statistically. An 18-month RCT of 165 subjects at eight sites in Scotland found no significant difference between the sulfasalazine and MTX groups on the HAQ between baseline and endpoint (-0.25 vs. -0.19; *P* = 0.99).[45]

Oral DMARD combinations. MTX plus sulfasalazine vs. monotherapy with MTX or sulfasalazine. Three RCTs (four publications) compared MTX plus sulfasalazine to either drug alone.[45-47,88] Two of the RCTs included patients with disease duration of less than 1 year;[46,47] the third included patients with RA of up to 10 years.[45] Findings of these studies do not support a difference in functional capacity between combination therapy and either monotherapy. Study data is presented in Table 27.

Table 27. Oral DMARD combination studies: Functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Sulfasalazine + MTX vs. Sulfasalazine or MTX Monotherapy						
Capell et al., 2007[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤ 4 g/day) + MTX (≤ 25 mg/week) vs. SSZ (≤ 4 g/day) vs. MTX (≤ 25 mg/week)	Change from baseline HAQ: no significant difference between groups (SSZ + MTX -0.50 vs. SSZ -0.25; *P* = 0.51), (SSZ + MTX -0.50 vs. MTX -0.19; *P* = 0.57)	NR	Fair
Dougados et al., 1999[46] Maillefert et al., 2003[88]	RCT 209 (146) 52 weeks (5 year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) plus MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ + MTX -0.70 vs. SSZ -0.74 vs. MTX -0.73; *P*= NS) or in mean HAQ at 5 years (combination 0.6 vs. either single therapy 0.6; *P* = 0.9)	NR	Fair
Haagsma et al., 1997[47]	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) + MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks NS (SSZ + MTX -0.51: 95% CI, -0.76 - -0.26 vs. SSZ -0.32: 95% CI, -0.53 - -0.10 vs. MTX -0.46: 95% CI, -0.68 - -0.25; *P* = NR)	NR	Fair

*New studies since last review.

CI, confidence interval; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; g, gram; HAQ, Health Assessment Questionnaire; mg, milligram; MTX, methotrexate; NHS, National Health Service; NR, not reported; NS, not significant; PCS, physical component score; PNL, prednisolone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Test, Short Form 36; SOFI, Signals of Functional Impairment Scale; SSZ, sulfasalazine; vs., versus; yrs, years.

Table 27. Oral DMARD combination studies: Functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Oral DMARD + Corticosteroid vs. Oral DMaRD						
*Choy et al., 2008[51]	RCT 467 2yrs	England/Wales, Multicenter: early RA; mean disease duration 2.7-5.1 months	MTX (≤ 15mg/week) + PNL (60mg/day stepped down and stopped at 34 weeks) vs. MTX	Difference in mean change in HAQ: -0.28 with additional PNL compared to MTX alone (*P* = 0.02)	Mean change in SF-36 PCS and MCS: No difference between groups (*P* = 0.22 and NR, respectively)	Good
Svensson et al., 2005[52]	Open-label trial 250 2 years	Population-based; active RA; duration 1 year or less	DMARD (SSZ or MTX, dosages NR) + PNL (7.5 mg/day) vs. DMARD	Greater improvement in DMARD + PNL group than DMARD-only group (from mean HAQ of 1.0 to 0.4 at 1 year and 0.5 at 2 years vs. 1.0, 0.6, and 0.7; *P* = NR) Mean SOFI index decreased from 8 at baseline to 4 at 1 year and 4 at 2 years vs. 9, 6, and 7 respectively; *P* = NR)	NR	Fair

A multinational RCT of 209 DMARD-naive subjects compared sulfasalazine (2 g/day to 3 g/day; n = 68), MTX (7.5 mg/week to 15 mg/week; n = 69), and the sulfasalazine-MTX combination (n = 68) for 52 weeks. No statistically significant difference in changes in HAQ scores occurred from baseline to 1 year (combination -0.70; sulfasalazine -0.74; MTX -0.73; *P* = NS).[46] A long-term followup comparing the combination therapy to monotherapy (combining the two monotherapy groups) did not find a significant difference in mean HAQ scores at 5 years (combination 0.6; monotherapy 0.6; *P* = 0.9).[88]

A 52-week RCT of 105 DMARD-naive subjects in Dutch academic and peripheral clinics reported a change in HAQ scores between baseline and 52 weeks of -0.51 (95% CI, -0.76 - -0.26) for the MTX-sulfasalazine combination therapy, a change of -0.32 (95% CI, -0.53 - -0.10; *P* = NR) for sulfasalazine, and a change of -0.46 (95% CI, -0.68 - -0.25; *P* = NR) for MTX.[47] The HAQ was a secondary outcome in this study; the authors did not attempt to explain these results or compare the values.

The third study was an 18-month RCT of 165 subjects at eight sites in Scotland. The investigators found no significant difference between the combination therapy and the monotherapy groups in changes from baseline HAQ scores (combination -0.50; sulfasalazine -0.25; MTX -0.19; combination vs. sulfasalazine, *P* = 0.51; combination vs. MTX, *P* = 0.57).[45]

Oral DMARD plus corticosteroid vs. oral DMARD. We found two RCTs.[51,52] The first was a 2-year RCT (N= 467) comparing MTX plus prednisolone (60mg/day stepped down and

stopped at 34 weeks) with MTX monotherapy in subjects with early RA.[51] The study reported greater improvements in functional capacity for subjects treated with MTX plus prednisolone than subjects treated with MTX alone (difference in mean change in HAQ -0.28, $P = 0.02$), but found no difference in quality of life between groups.

One open-label RCT compared oral DMARD use with and without prednisolone in patients with active RA for 1 year or less.[52] This 2-year study compared prednisolone (7.5 mg/day) added to an initial DMARD (chosen by the treating physician) with an oral DMARD only in patients with early RA**.** The authors reported greater improvement in functional capacity for the prednisolone group than the nonprednisolone group. The DMARD plus prednisolone group had a decrease in HAQ scores from a mean of 1.0 at baseline to 0.4 at 1 year and 0.5 at 2 years. The corresponding values for the DMARD-only group were 1.0, 0.6, and 0.7 (P = NR). The DMARD plus prednisolone group also had greater improvement in the mean Signals of Functional Impairment (SOFI) index (mean decrease from 8 at baseline to 4 at 1 year and 4 after 2 years compared to values of 9, 6, and 7, respectively; P = NR). Scores on the HAQ and the SOFI index were not statistically compared for the two groups; the clinical relevance of these results is uncertain. In addition, the results should be interpreted cautiously, given the open-label design and potential for bias.

Biologic DMARD vs. biologic DMARD. We identified one head-to-head RCT and three prospective cohort studies meeting our inclusion criteria.[53,55,57,58] Three of these included comparisons of etanercept with infliximab;[55,57,58] one study compared each of the following: adalimumab versus etanercept,[58] abatacept versus infliximab,[53] and adalimumab versus infliximab.[58] Mean disease durations ranged from 6 years to 9.9 years; the proportion of patients with early RA in these studies remains unclear. One study was conducted in the United States;[55] the others were carried out in the Netherlands,[58] Spain,[57] or were multinational.[53] The design, results, and quality ratings of these studies are summarized in Table 28.

Abatacept vs. infliximab. One head-to-head multinational RCT (N = 431) conducted in subjects with active RA who had an inadequate response to MTX failed to find a difference in functional capacity between those treated with abatacept and infliximab, but found greater improvement in health-related quality of life for those treated with abatacept (SF-36 PCS: difference of 1.93 at 1 year, 95% CI, 0.02-3.84).[53]

Etanercept vs. infliximab. Two of the three cohort studies comparing etanercept with infliximab reported no difference in functional capacity outcomes; one reported greater improvement with etanercept.[55] Only one of the three studies reported a quality of life outcome, finding greater improvement in the SF-36 PCS with etanercept than with infliximab.[58]

The first cohort study (N = 161) was conducted in anti-tumor necrosis factor (TNF) naïve patients and found no difference in functional capacity between etanercept than infliximab (mean change in HAQ at 6 months; $P = 0.218$).[57] The second cohort study (N = 707) was conducted in anti-TNF naïve patients that had failed at least two DMARDs and also found no difference in functional capacity between etanercept than infliximab (mean change in HAQ at 12 months; P = NS), but reported greater improvement in health-related quality of life for those treated with etanercept.[58]

Table 28. Biologic DMARD vs. biologic DMARD studies: functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
ABA vs. INF						
*Schiff et al., 2008[53] ATTEST	RCT 431 1 year	Multinational; Active RA with inadequate response to MTX	ABA (~10mg/kg every 4 weeks) vs. INF (3 mg/kg every 8 weeks) Study also had a third arm (placebo)	Percentage of patients with improvement in HAQ-DI at 1 year: 57.7% vs. 52.7%; estimate of difference (95% CI, 5.0 (-6.5, 16.5)	SF-36 PCS: ABA patients had significantly greater improvement than INF at 1 year (difference of 1.93, 95% CI, 0.02-3.84) SF-36 MCS: ABA patients had numerically greater improvement, but the difference was not statistically significantly different (difference of 1.92, 95% CI, -0.30-4.15)	Fair
ETN vs. INF						
*Fernandez-Nebro et al., 2007[57]	Prospective cohort 161 6 years	Tertiary care center, Spain; Anti-TNF naïve patients; mean disease duration 9.5-9.9 years	ETN vs. INF (dosages NR)	Mean change in HAQ at 6 months: -0.46 vs. -0.32; *P* = 0.218	NR	Fair
*Kievit et al., 2008[58] DREAM register	Prospective cohort study 707 1 year	Population based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ETN vs. INF (dosages NR)	Mean change in HAQ at 12 months: -0.35 vs. -0.26; *P* = NS	SF-36 PCS: ADA and ETN patients had significantly greater improvement than INF; *P* = 0.001 (data NR, in Figure only)	Fair

*New studies since last review.

ADA, adalimumab; CI, confidence interval; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; INF, infliximab; MCS, mental component score; mg/kg, milligram/killigram; NR, not reported; NS, not significant; PCS, physical component score; RA, rheumatoid arthritis; SF-36, Medical Outcomes Test, Short Form 36; TNF, tumor necrosis factor; US, United States; vs., versus.

Table 28. Biologic DMARD vs. biologic DMARD studies: functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Weaver et al., 2006[55]	Prospective cohort study 1,371 12 months	Population-based, US; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETN (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Mean percentage improvements in HAQ at 12 months: 17% vs. 1%; *P* = NR	NR	Fair
ADA vs. ETN						
*Kievit et al., 2008[58] DREAM register	Prospective cohort study 707 1 year	Population based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ADA vs. ETN (dosages NR)	Mean change in HAQ at 12 months: -0.42 vs. -0.35; *P* = NS	SF-36 PCS: ADA and ETN patients had significantly greater improvement than INF; *P* = 0.001 (data NR, in Figure only)	Fair
ADA vs. INF						
*Kievit et al., 2008[58] DREAM register	Prospective cohort study 707 1 year	Population based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6-7.7 years	ADA vs. INF (dosages NR)	Mean change in HAQ at 12 months: -0.42 vs. -0.26; *P* < 0.05)	SF-36 PCS: ADA and ETN patients had significantly greater improvement than INF; *P* = 0.001 (data NR, in Figure only)	Fair

The third cohort study comparing etanercept with infliximab was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program. RADIUS was a primary care-based U.S. study that enrolled patients who were initiating any new DMARD at study entry.[55] Mean disease duration was 9.3 years, indicating that most patients suffered from advanced RA. The percentage of patients with early RA was not reported. Patients treated with etanercept had a greater mean percentage improvement on the HAQ at 12 months than patients treated with infliximab (17% vs. 1%; *P* = NR). Among patients older than 65 years, after adjusting for baseline covariates, the authors reported that the etanercept-treated patients had a greater mean percentage improvement in the HAQ at 12 months than infliximab-treated patients (22% vs. 4%; *P* = NR). However, the authors did not describe direct statistical comparisons between etanercept and infliximab. The study was designed to compare combinations of etanercept or infliximab with MTX to monotherapy with etanercept, infliximab, or MTX.

Adalimumab vs.etanercept. One cohort study (N = 707) conducted in anti-TNF naïve patients that had failed at least two DMARDs reported no difference in functional capacity or health-related quality of life between adalimumab and etanercept.[58]

Adalimumab vs. infliximab. One cohort study (N = 707) conducted in anti-TNF naïve patients that had failed at least two DMARDs reported greater improvement in both functional capacity (mean change in HAQ at 12 months: -0.42 vs. -0.26, $P < 0.05$) and health-related quality of life (data NR, $P = 0.001$) for subjects treated with adalimumab than for those treated with infliximab.[58]

Placebo-controlled studies. Multiple placebo-controlled RCTs provide evidence on the general efficacy of abatacept,[53,91-96,161-165] adalimumab,[97-104] anakinra,[61,105-111] etanercept,[73,112-122] infliximab,[53,112,123-133] rituximab,[71,134-138,166] certolizumab pegol,[139,140,167] golimumab,[141,142] and tocilizumab.[64,139,143-146] Most of these studies were conducted in patients who had failed oral DMARD treatment.

Biologic DMARDs vs. oral DMARDs. We found four RCTs and one prospective cohort study that included comparisons of biologic DMARD monotherapy with oral DMARD monotherapy (Table 29). The RCTs compared etanercept with MTX,[63,73] adalimumab with MTX,[62] and tocilizumab with MTX;[64] the cohort study assessed differences in class effects.[65] No head-to-head evidence exists for the other biologic DMARDs or for oral DMARDs other than MTX (although anakinra and infliximab were included in the prospective cohort study comparing biologics as a class to oral DMARDs as a class).

Biologic DMARDs as a class vs. oral DMARDs as a class. The prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab; n = 818) and oral DMARDs as a class (n = 265) in patients who had failed two previous oral or biologic DMARD treatments.[65] This study was population-based and part of the RABBIT study, a German long-term, prospective cohort study of RA patients who required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. Severely disabled patients receiving biologic therapies were more likely to achieve physical independence, defined as ≥ 67 percent of full function as measured by the Hanover Functional Status Questionnaire (FFbH, or Funktionsfragebogen Hannover), than controls on conventional oral DMARD therapy (OR, 3.88; 95% CI, 1.7-8.8). Functional remission (≥ 83 percent of full function) was more often achieved in patients receiving biologics than in controls (OR, 2.18; 95% CI, 1.04-4.6).

Adalimumab vs. MTX. The only data come from the PREMIER study, a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX.[62] Two treatment arms of this 2-year study were adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). Details of this study are reported in the KQ 1 section on *Biologic DMARDs plus oral DMARDs vs. biologic DMARDs.* After 1 year, the adalimumab and MTX monotherapy groups had similar improvements in functional status measured using the HAQ-DI (mean: -0.8; -0.8; P = NR). Improvements remained similar after 2 years (-0.9; -0.9; P = NR). After 2 years, 19 percent of patients in both monotherapy groups had HAQ-DI scores of zero. We report on results of the other comparisons of the PREMIER study for functional status outcomes in the respective KQ 2 sections on *Biologic DMARDS plus oral DMARDs vs. biologic DMARDs* and *Biologic DMARDs plus oral DMARDs vs. oral DMARDs*.

Table 29. Biologic DMARD vs. oral DMARD studies: functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab vs. MTX						
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	At 1 year, ADA and MTX monotherapy groups had similar improvement in HAQ-DI (-0.8 vs. -0.8; *P* = NR). Improvements remained similar after 2 years	NR	Fair
Etanercept vs. MTX						
Bathon et al., 2000;[63] Genovese al., 2002;[148] Genovese al, 2005;[149] Kosinski et al., 2002[168] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Better improvement in HAQ early in treatment (first 12 weeks) for ETN than MTX (*P* < 0.0001). No significant difference in HAQ scores during weeks 16 to 52 Significantly greater percentage of patients with at least a 0.5 unit improvement in HAQ-DI at 24 months for ETN 25 mg than for either ETN 10 mg or MTX (55% vs. 43% vs. 37%; *P* = 0.021 and *P* < 0.001, respectively)	Better improvement in SF-36 physical summary and SF-36 arthritis-specific health index for ETN group than the MTX group during first 12 weeks (*P* < 0.0001) No significant difference in weeks 16 to 52	Fair
Klareskog et al., 2004;[73] van der Heijde et al., 2006;[113] van der Heijde et al., 2006[115] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly) vs. MTX (20 mg/week)	Similar improvement in mean HAQ scores for MTX and ETN (scores fell from 1.7 to 1.1 and 1.7 to 1.0; *P* = 0.3751)	NR	Good

*New studies since last review.

ADA, adalimumab; ANA, anakinra; CI, confidence interval; DMARD, disease modifying antirheumatic drug; ERA, early rheumatoid arthritis; ETN, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; INF, infliximab; mg, milligram; MHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; NR, not reported; OR, odds ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Test, Short Form 36; TCZ, tocilizumab.

Table 29. Biologic DMARD vs. oral DMARD studies: functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
TCZ vs. MTX						
*Nishimoto et al., 2009[64] SATORI	RCT 127 24 weeks	Active RA with inadequate response to MTX	TCZ (8mg every 4 weeks) +placebo vs. MTX (8mg/week) + placebo	Percentage of patients with a decrease of at least 0.22 units in MHAQ at last observation: 67% vs. 34% (P < 0.001)	NR	Fair
Biologic class vs. Oral DMARD class						
Listing et al., 2006[65]	Prospective cohort study 1,083 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 9.6 years	Biologics as a class (ADA, ANA, ETN, INF; dose NR) vs. DMARDs as a class (dose NR)	Severely disabled patients (≤ 50% of full function) in biologic group more likely to achieve physical independence (≥ 67% of full function, Hanover Functional Status Questionnaire) than DMARD group (OR, 3.88; 95% CI, 1.7-8.8) Functional remission (≥ 83% of full function) more often achieved in biologic group than in DMARD group (OR, 2.18; 95% CI, 1.04-4.6)	NR	Fair

Etanercept vs. MTX. Two trials (seven publications) compared etanercept with MTX (20 mg/week) over 52 weeks.[63,73,113,115,148,149,168] The ERA (Early Rheumatoid Arthritis) study (N = 632) was conducted in patients with early RA who were MTX-naive.[63,148,149] The other study was the TEMPO trial (see KQ 1 section on *Biologic DMARDs plus oral DMARDs vs. biologic DMARDs).*[73,113,115] Patients had active RA and had failed at least one DMARD other than MTX. About 60 percent of the study population was MTX-naive.

ERA was a 52-week multicenter RCT of 632 patients with early RA in the United States that compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week).[63,148,149,168] The treatment groups were similar at baseline. Most patients were female, white, and rheumatoid factor positive and had had RA for fewer than 18 months. Patients treated with etanercept had better early responses for functional status and health-related quality of life. Compared with patients treated with MTX, patients treated with etanercept showed better improvement early in treatment (during the first 12 weeks) on the HAQ (P < 0.0001), the SF-36 physical subscale (P < 0.0001), and the SF-36 arthritis-specific health index (ASHI) (P < 0.0001). From weeks 16

to 52, these measures did not differ significantly; both groups showed similar improvement. These results may be attributed to an earlier response to etanercept than to MTX and the fact that patients were increased to the maximum MTX dose over 2 months. After 12 months, approximately 55 percent of patients in both the MTX and the 25-mg etanercept groups had at least a 0.5 unit improvement in the HAQ-DI. At 24 months, 55 percent of the 25-mg etanercept group had this level of improvement, as did 37 percent of the MTX group ($P < 0.001$) and 43 percent of the 10-mg etanercept group ($P = 0.021$).

The 52-week TEMPO RCT of RA patients who had failed previous DMARD therapy compared patients treated with etanercept (25 mg twice weekly) with those treated with MTX (20 mg/week) and those given combination therapy with both drugs.[73] Baseline HAQ scores were similar for all three groups. At 52 weeks, improvement of functional status did not differ significantly between the MTX group and the etanercept group (mean HAQ scores fell from 1.7 to 1.1 and from 1.7 to 1.0, respectively; $P = 0.3751$). We report on comparisons of etanercept with the combination group in the KQ 2 section below on *Biologic DMARD plus oral DMARD vs. biologic DMARD*.

Tocilizumab vs. MTX. The only data come from the Study of Active controlled TOcilizumab monotherapy for Rheumatoid arthritis patients with an Inadequate response to methotrexate (SATORI), a 24 week RCT of 127 patients with active RA and an inadequate response to MTX conducted at 25 sites in Japan.[64] Subjects were randomized to MTX monotherapy (8 mg/week) plus tocilizumab placebo or to tocilizumab (8mg/kg every 4 weeks) plus MTX placebo. After 24 weeks, those treated with tocilizumab had significantly greater improvements in the percentage of subjects achieving at least a 0.22 unit improvement in MHAQ scores (67% vs. 34%, $P < 0.001$), which was considered significant clinical improvement and the minimum clinically important difference.

Biologic combination strategies: Biologic DMARD plus biologic DMARD vs. biologic DMARD. We found a single 1 year RCT (N = 121) followed by a 2 year open label long term extension (N = 80) that reported no significant differences in functional capacity for patients treated with abatacept (2mg/kg for RCT, 10mg in long term extension) combined with etanercept (25mg twice weekly) compared to etanercept only (Table 30).[67] The study reported greater improvement in quality of life measured by the physical component summary of the SF-36 (data NR), but not the mental component summary (3.9 point improvement vs. 1.06 point, P = NS). Although the initial RCT dosing of abatacept was lower than currently used clinically, the frequency of serious adverse events was higher in the abatacept combined with etanercept treated patients than the etanercept only treated patients. The study concluded that abatacept in combination with etanercept should not be used for patients with RA due to limited efficacy findings and safety concerns (more abatacept and etanercept-treated patients experiences serious adverse events).

Table 30. Biologic DMARD plus Biologic DMARD vs. Biologic DMARD studies: Functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
ETN + ABA vs. ETN						
*Weinblatt, et al., 2006[67]	RCT 121 1 yr double-blind phase, 2yr long term extension	Patients with active RA despite ETN; mean disease duration 12.8-13 yrs	ETN (25 mg twice weekly) + ABA 2 g/kg increased to 10 mg/kg after 1 year) vs. ETN (25 mg twice weekly)	Mean change in mHAQ at 12 months: -0.3 vs. -0.2; *P* = NR Mean change in mHAQ from 1 yr to 2 yr: -0.1 vs. 0; *P* = NR)	Greater improvement in the SF-36 PCS for ETN + ABA group (data NR) Mean change in SF-36 MCS: 3.9 vs.1.06; *P* = NS	Fair

*New studies since last review.

ABA, abatacept; ETN, etanercept; g/kg, gram/killigram; MCS, mental component score; mg, milligram; mg/kg, milligram/killigram; MHAQ, modified health assessment questionnaire; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Test, Short Form 36; vs., versus; yr, year.

Biologic combination strategies: biologic DMARD plus oral DMARD vs. biologic DMARD. We found five studies, four RCTs[62,72,73,169] and one prospective cohort study,[55] comparing the combination of a biologic DMARD plus an oral DMARD with biologic DMARD monotherapy (Table 31). The majority of these studies compared a combination of a biologic DMARD and MTX with monotherapy of the same biologic DMARD.[55,62,73,169] One trial used sulfasalazine as a oral DMARD in combination with a biologic DMARD.[72] Three of the studies found no difference between combination therapy and biologic DMARD monotherapy; two reported greater improvement with combination therapy. The two RCTs finding that combination therapy resulted in greater improvement in functional capacity or quality of life enrolled subjects that were MTX-naïve[62] or had not been on MTX for at least 6 months prior to enrollment.[73] The studies finding no difference enrolled subjects with active RA despite treatment with the same oral DMARD that was used in the combination therapy arm of the trial.

Adalimumab plus MTX vs. adalimumab. The PREMIER study was conducted in MTX-naive patients with early (< 3 years), aggressive RA.[62] This 2-year multinational study randomized 799 patients to a combination of adalimumab (40 mg every other week) and MTX (20 mg/week), adalimumab monotherapy (40 mg every other week), or MTX monotherapy (20 mg/week). After 1 year, the combination group had greater improvements in HAQ-DI scores (mean: -1.1 units) than the adalimumab group (-0.8; $P = 0.002$). After 2 years, the combination group (-1.0) and the adalimumab-only group (-0.9) did not differ significantly ($P = 0.058$) for improvements in the HAQ-DI. After two years, more patients in the combination group (72 percent) had achieved improvement of ≥ 0.22 (considered the clinically relevant threshold) in HAQ-DI than the adalimumab group (58%; $P < 0.05$). In addition, 33 percent of patients in the combination group and 19 percent of those in the adalimumab group had HAQ-DI scores of zero ($P < 0.001$). For functional capacity outcomes, we report on results of the other comparisons of the PREMIER study in the KQ 2 sections on *Biologic DMARDs vs. oral DMARDs* and *Biologic DMARDs plus oral DMARDs vs. oral DMARDs.*

Table 31. Biologic DMARD plus oral DMARD vs. biologic DMARD studies: functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab +MTX vs. Adalimumab						
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. ADA (40 mg biweekly)	At 1 year, ADA + MTX group had greater improvements in HAQ-DI than ADA alone (mean, -1.1 units vs. -0.8; *P* = 0.002). After 2 years, there was no difference (-1.0 vs. -0.9; *P* = 0.058) After 2 years, more ADA + MTX patients had improvement of ≥ 0.22 in HAQ-DI than ADA patients (72% vs. 58%; *P* < 0.05); had a greater percentage with HAQ-DI scores of 0 (33% vs. 19%; *P* < 0.001)	NR	Fair
Etanercept + Oral DMARD vs. Etanercept						
Combe et al., 2006[72] *Combe et al., 2009[122]	RCT 260 24 weeks 2 years	Europe multicenter; active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. ETN (25 mg twice weekly)	Mean percentage improvements in HAQ were similar for ETN + SSZ and ETN alone at 24 weeks (40.2% vs. 35.3%, *P* = NS). At 2 years, clinically significant improvement in HAQ was seen for 78% vs. 76% (*P* = NS)	Mean percentage improvements in EuroQOL VAS were similar for ETN + SSZ and ETN alone at 24 weeks (67.6% vs. 64.6%; *P* = NS)	Fair
Klareskog et al., 2004;[73] van der Heijde et al., 2006;[113] van der Heijde et al., 2006[115] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly) + MTX (20 mg/week) vs. ETN (25 mg twice weekly)	At 52 weeks ETN + MTX was more likely to attain HAQ-DI scores similar to population norms (< 0.5) than ETN alone (*P* < 0.05). Combination group had greater improvement in mean HAQ scores (mean fall from 1.8 to 0.8 vs. 1.7 to 1.0; *P* < 0.001; mean improvement from baseline HAQ 1.0 vs. 0.7; *P* < 0.01)	ETN + MTX patients reported better quality of life than ETN-only patients (mean EQ-5D VAS 72.7 vs. 66.8; *P* < 0.05)	Good

*New studies since last review.

ADA, adalimumab; CI, confidence interval; EuroQOL VAS, European Quality of Life Health Status Visual Analogue Scale; ETN, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; MTX, methotrexate; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; vs., versus.

Table 31. Biologic DMARD plus oral DMARD vs. biologic DMARD studies: functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
*Van Riel et al., 2008[169] ADORE trial	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX; mean disease duration 10.9 years	ETN (25 mg twice weekly) + MTX (>12.5 mg/week) vs. ETN (25 mg twice weekly)	Mean change in HAQ DI at 16 wks: -0.59 vs. -0.59; difference between groups (95% CI, 0.029 (-0.115-0.172)	Mean change in EQ-5D VAS: 21.00 vs. 19.76; difference between groups (95% CI, -2.593 (-7.667-2.482)	Fair
Weaver et al., 2006[55]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly) + MTX (dose NR) vs. ETN (25 mg twice weekly)	Patients treated with ETN + MTX had similar improvements in functional capacity to those treated with ETN only (mean percentage improvements in HAQ at 12 months: 17% vs. 17%; *P* = NR)	NR	Fair

Etanercept plus MTX vs. etanercept. Two RCTs (four publications)[73,113,115,169] and one prospective cohort study[55] assessed differences in efficacy between a combination of etanercept and MTX and etanercept monotherapy in patients with active, DMARD-resistant RA. One RCT showed greater improvements for functional capacity and quality of life for combination therapy; one RCT found no difference; the cohort study found no difference. The study showing greater improvements for combination therapy enrolled subjects who had not taken MTX during the prior six months. The studies that found no difference enrolled subjects with active RA despite current MTX use.

The first RCT, the 52-week TEMPO trial, involved 686 patients with active RA who had failed previous DMARD therapy.[73,113-115] Subjects were included only if they had not taken MTX for the six months prior to enrollment. We focus here on results of the etanercept-MTX combination and the etanercept monotherapy arms; their baseline HAQ scores were similar. The combination therapy group had better improvement in functional status than the etanercept monotherapy group. At 52 weeks, patients in the combination group were significantly more likely to attain HAQ-DI scores similar to population norms (< 0.5) than patients in the monotherapy group ($P < 0.05$). The combination group had greater improvement in functional capacity than the monotherapy group (mean HAQ changes from 1.8 to 0.8 vs. 1.7 to 1.0; $P < 0.001$; mean improvement from baseline HAQ 1.0 vs. 0.70; $P < 0.01$). In addition, those receiving combination therapy achieved better quality of life scores than etanercept monotherapy (mean European Quality of Life Health Status Visual Analogue Scale [EQ 5-D VAS] 72.7 vs. 66.8; $P < 0.05$).[113] Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings.[115] Improvement in disability (based on HAQ) remained significantly better in the combination group than in the etanercept monotherapy group ($P < 0.01$). However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

The second RCT, the ADORE trial,[169] randomized subjects (N = 315) with active RA despite MTX treatment to 16 weeks of etanercept plus MTX or to etanercept monotherapy. The study reported no difference in change in functional capacity (mean change in HAQ DI -0.59 vs. -0.59)

or quality of life between groups. Unlike the TEMPO trial described above, that enrolled subjects who had not been on MTX for the prior six months, the ADORE trial enrolled patients with active RA despite MTX use.

The prospective cohort study was based on the RADIUS program[55] (see *Biologic DMARD vs. biologic DMARD* above). Mean percentage improvements in HAQ at 12 months did not differ between patients treated with etanercept plus MTX and those treated with etanercept monotherapy (17 percent vs. 17 percent; *P* = NR).

Etanercept plus sulfasalazine vs. etanercept. A 24-week multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy (25 mg twice weekly), sulfasalazine monotherapy (2, 2.5, or 3 g/day), and an etanercept-sulfasalazine combination (25 mg twice weekly plus 2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[72] Two year outcomes were also published for the trial.[122] This study is described in greater detail in the corresponding section for KQ 1. We focus on results of the etanercept monotherapy (n = 103) and the combination (n = 101) arms. Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. The mean percentage improvement for HAQ was similar for the combination group (40.2 percent) and the etanercept group (35.3 percent; *P* = NS). The mean percentage improvement for health-related quality of life measured by the EuroQOL VAS was also similar (67.6 percent vs. 64.6 percent; *P* = NS). After two years, a clinically significant improvement in functional capacity (HAQ improvement of ≥ 0.22) was similar for both groups (78 percent vs. 76 percent; *P* = NS).[122]

Infliximab plus MTX vs. infliximab. No RCT compared the infliximab-MTX combination to infliximab monotherapy. The only comparative evidence comes from a cohort study from the RADIUS program (see *Etanercept plus MTX vs. etanercept*).[55] The mean percentage improvements in the HAQ at 12 months were similar for patients treated with the infliximab-MTX combination and those treated with infliximab monotherapy (3% vs. 1%; *P* = NR).

Biologic combination strategies: biologic DMARD plus oral DMARD vs. oral DMARD. We included five studies comparing a biologic DMARD plus an oral DMARD with oral DMARD monotherapy (Table 32). We found three RCTs[62,69,76] and one prospective cohort study[55] comparing a combination regimen of adalimumab plus MTX,[62] infliximab plus MTX,[55,69] or etanercept plus MTX[55,76] with MTX monotherapy. We found one RCT comparing a combination of etanercept plus sulfasalzine with sulfasalazine monotherapy.[72,122] Three RCTs were conducted in patients with early RA.[62,69,76] All of the RCTs found greater improvement in functional capacity with combination therapies than with monotherapy. The prospective cohort study found the etanercept-MTX combination improved functional capacity more than MTX monotherapy, but the infliximab-MTX group did not differ from the MTX-only group.[55]

Adalimumab plus MTX vs. MTX. The PREMIER study was a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX; it compared adalimumab monotherapy, MTX monotherapy, and the combination of adalimumab plus MTX[62] (see KQ 1 section on *Biologic DMARDs plus oral DMARDs vs. biologic DMARDs*). After 1 year, the combination group had greater improvements in HAQ-DI scores (mean: -1.1) than the methotrexate group (-0.8; $P < 0.001$). After 2 years, the combination (-1.0) was superior to MTX (-0.9; $P < 0.05$). More patients in the combination group (72%) had achieved improvement

Table 32. Biologic DMARD plus Oral DMARD vs. Oral DMARD studies: Functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab + MTX vs. MTX						
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (< 3 years)	ADA (40 mg biweekly) + MTX (20 mg/week) vs. MTX (20 mg/week)	At 1 year, ADA + MTX had greater improvement in HAQ-DI than MTX alone (mean -1.1 units vs. -0.8; *P* < 0.001). After 2 years, ADA + MTX remained statistically greater (-1.0 vs. -0.9; *P* < 0.058) After 2 years, more ADA + MTX patients had improvement of ≥ 0.22 in HAQ-DI than MTX patients (72% vs. 63%; *P* < 0.05). Had greater percentage with HAQ-DI scores of 0 (33% vs. 19%; *P* < 0.001)	NR	Fair
Etanercept + MTX vs. MTX						
*Emery et al., 2008[76] COMET study	RCT 542 52 weeks	MTX naïve patients; Early RA, mean disease duration 9 months	ETN (50mg/week) + MTX 7.5mg vs. MTX	Percent improvement in HAQ DI: 61% vs. 44%; *P* < 0.0001 Percent of subjects achieving normal HAQ-DI (score < 0.5): 55% vs. 39%; *P* = 0.0004	Percentage of patients who were working full-time or part-time at baseline who reported stopping work at least once by wk 52: 9% vs. 24%; *P* = 0.004	Fair
Klareskog et al., 2004;[73] van der Heijde et al., 2006;[113] van der Heijde et al., 2006[115] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly) + MTX (20 mg/week) vs. MTX (20 mg/week)	Combination group had greater improvement in mean HAQ scores (mean improvement from baseline HAQ 1.0 vs. 0.65; *P* < 0.01)	ETN + MTX patients reported better quality of life than MTX-only patients (mean EQ-5D VAS 72.7 vs. 63.7; *P* < 0.01)	Good

*New studies since last review.

ADA, adalimumab; ETN, etanercept; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; INF, infliximab; MTX, methotrexate; NR, not reported; NS, not significant; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine.

Table 32. Biologic DMARD plus Oral DMARD vs. Oral DMARD studies: Functional capacity and health-related quality of life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Weaver et al., 2006[55]	Prospective cohort study 3,034 12 months	Population-based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly) + MTX (dose NR) vs. MTX	Greater mean percentage improvements in HAQ at 12 months for ETN + MTX than MTX (17% vs. 7%; *P* < 0.01) Similar mean percentage improvements in HAQ at 12 months for INF + MTX and MTX (3% vs. 7%; *P* = NS)	NR	Fair
Etanercept + SSZ vs. SSZ						
Combe et al., 2006[72], *Combe et al., 2009[122]	RCT 260 24 weeks 2 years	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly) + SSZ (2, 2.5, or 3 g/day) vs. SSZ (2, 2.5, or 3 g/day)	Percentage of patients who achieved a clinically significant improvement in HAQ at 2 years: 78% vs. 40%; *P* < 0,01	NR	Fair
Infliximab + MTX vs. MTX						
St Clair et al., 2004;[69] Smolen et al., 2006[70] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks) + MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks) + MTX (20 mg/week) vs. MTX (20 mg/week)	Greater mean decrease in HAQ from weeks 30 to 54 for combination groups than MTX group (INF 3 mg + MTX and INF 6 mg + MTX vs. MTX: 0.80 and 0.88 vs. 0.68; *P* = 0.03; *P* < 0.001). Combination therapy was more effective for improving HAQ by at least 0.22 units (76.0% and 75.5% vs. 65.2%; *P* = 0.003; *P* = 0.004) Patients on combination treatment had a higher probability of improvement in employability than those on MTX alone (*P* < 0.001)	Significantly greater improvement in SF-36 physical component summary scores for INF 6 mg + MTX vs. MTX (13.2 vs. 10.1; *P* = 0.003) but not for INF 3 mg + MTX vs. MTX (11.7 vs. 10.1; *P* = 0.10)	Fair

of ≥0.22 (considered the clinically relevant threshold) in the HAQ-DI than the MTX group (63 percent; $P < 0.05$). In addition, 33 percent of patients in the combination group and 19 percent of those in the MTX group had HAQ-DI scores of zero ($P < 0.001$). We report on results of the other comparisons of the PREMIER study in the sections on *Biologic DMARDs plus oral DMARDs vs. biologic DMARDs* and *Biologic DMARDs vs. oral DMARDs.*

Etanercept plus MTX vs. MTX. The COMET study randomized 542 subjects with active, early, moderate to severe early RA to 52 weeks of MTX monotherapy or a combination of MTX and etanercept.[76] Subjects in the combination therapy group had greater improvements in functional capacity (percent improvement in HAQ DI: 61% vs. 44%, $P < 0.001$; percent of subjects achieving normal HAQ DI score: 55% vs. 39%, $P = 0.004$). In addition, among subjects that were working full- or part-time at baseline, fewer patients needed to stop work for at least one week in the combination therapy group (9% vs. 24%, $P = 0.004$).

The the 52-week TEMPO trial, involved 686 patients with active RA who had failed previous DMARD therapy.[73,113-115] Subjects were included only if they had not taken MTX for the six months prior to enrollment. We focus here on results of the etanercept-MTX combination and the MTX monotherapy arms; their baseline HAQ scores were similar. The combination therapy group had better improvement in functional status than the MTX monotherapy group. At 52 weeks, the combination group had greater improvement in functional capacity than the monotherapy group (mean improvement from baseline HAQ 1.0 vs. 0.65; $P < 0.01$). In addition, those receiving combination therapy achieved better quality of life scores than MTX monotherapy (mean EQ 5-D VAS 72.7 vs. 63.7; $P < 0.01$).[113] Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings.[115] Improvement in disability (based on HAQ) remained significantly better in the combination group. However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

A prospective cohort study from the RADIUS program showed that patients treated with the etanercept-MTX combination had greater mean percentage improvements in HAQ scores at 12 months than those treated with MTX alone (17% vs. 7%; $P < 0.01$).[55]

Etanercept plus sulfasalazine vs. sulfasalazine. A 2-year multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy (25 mg twice weekly), sulfasalazine monotherapy (2, 2.5, or 3 g/day), and an etanercept-sulfasalazine combination (25 mg twice weekly plus 2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment.[72] Two year outcomes were also published for the trial.[122] Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. A greater percentage of subjects treated with combination therapy achieved a clinically significant improvement in functional capacity (HAQ improvement of $\geq$ 0.22) at two years (78 percent vs. 40 percent; $P < 0.01$).[122]

Infliximab plus MTX vs. MTX. The ASPIRE trial enrolled 1,049 patients with early RA (disease duration < 3 years) who were MTX-naive.[69] This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or with a combination of MTX and infliximab (3 mg/kg or 6 mg/kg) over 52 weeks. HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX-only group. The mean decrease in the HAQ score from week 30 to week 54 was greater for the combination groups (0.80 for 3 mg/kg group and 0.88 for the 6 mg/kg group) than for the MTX-only group (0.68; $P = 0.03$ and $P < 0.001$, respectively). In addition, more patients in the combination groups (76.0 percent and 75.5 percent, respectively) improved their HAQ scores by at least 0.22 units than in the MTX-only group (65.2 percent; $P = 0.003$ and $P = 0.004$, respectively). The mean increases in SF-36 physical component summary scores were 11.7 and 13.2 for the combination groups and 10.1 for the MTX-only group ($P = 0.10$ and $P = 0.003$, respectively). Patients on the combination treatment also had a higher probability of maintaining their employability than did those on MTX alone.[70]

One prospective cohort study from the RADIUS program in the United States (described above in the *Etanercept plus MTX vs. etanercept section)* involved patients who were initiating any new DMARD.[55] The mean percentage improvements in the HAQ at 12 months were not significantly different between patients treated with the infliximab-MTX combination and those treated with MTX monotherapy (3 percent vs. 7 percent; *P* = NS).

Biologic combination strategies: Biologic DMARD plus oral DMARD vs. biologic DMARD plus oral DMARD. One prospective cohort compared patients taking an anti-TNF plus oral DMARD to patients taking another anti-TNF plus oral DMARD (Table 33).[78] The study compared 'anti-TNF' (infliximab, etanercept or adalimumab) plus MTX versus anti-TNF plus leflunomide.[78] The study reported no difference in functional capacity between groups (Mean improvement in HAQ at one year: 0.12 vs. 0.14; *P* = 0.09).[78]

Table 33. Biologic DMARD plus oral DMARD vs. biologic DMARD plus oral DMARD studies: functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Anti-TNF + MTX vs. Anti-TNF + LEF						
*Finckh et al., 2008[78] SCQM cohort	Prospective Cohort 1,218 17 months (mean)	Population based: Treatment with INF, ETN or ADA; mean disease duration 8.4-8.9 years	Anti TNF (INF or ETN or ADA) (NR) + MTX (NR) vs. Anti TNF (INF or ETN or ADA) (NR) + LEF	Mean improvement in HAQ at 1 yr: 0.12 vs. 0.14; *P* = 0.09	NR	Fair

*New studies since last review.

ADA, adalimumab; ETN, etanercept; HAQ, Health Assessment Questionnaire; INF, infliximab; LEF, leflunomide; NR, not reported; SCQM, Swiss Clinical Quality Management; TNF, tumor necrosis factor.

Strategies in early RA. Functional capacity and health related quality of life outcomes are presented in Table 34.

Two oral DMARDs plus corticosteroid vs. oral DMARD. The COBRA study assessed differences in efficacy between a combination of sulfasalazine, MTX, and prednisolone and sulfasalazine only.[79] This RCT evaluated 155 patients with early RA over 56 weeks. Combination therapy included sulfasalazine (2 g/day), MTX (7.5 mg/week stopped after 40 weeks), and prednisolone treatment (60 mg/day tapered over 28 weeks). Compared with patients treated with sulfasalazine alone, patients treated with combination therapy had greater improvements in functional capacity at 28 weeks (mean change in HAQ of -1.1 vs. -0.6; $P < 0.0001$). The difference was no longer statistically significant at 56 weeks (mean change in HAQ, -0.8 vs. -0.6; $P < 0.06$).

Three oral DMARDs plus corticosteroid vs. oral DMARD. The FIN-RACo RCT assessed the efficacy of a combination of MTX, sulfasalazine, hydroxychloroquine, and prednisolone against monotherapy with a DMARD with or without prednisolone.[81] This study randomized 199 patients with early RA to combination therapy or monotherapy. Combination therapy included sulfasalazine (2 g/day), MTX (7.5 mg/week to 10 mg/week), hydroxychloroquine (300 mg/day), and prednisolone (5 mg/day to 10 mg/day). Patients on monotherapy were initially started on sulfasalazine (2 g/day to 3 g/day), but they could be changed to MTX (7.5 mg/week to 15

Table 34. Early RA strategies: Functional capacity and health-related quality of life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Two Oral DMARDs + Corticosteroid vs. Oral DMaRD						
Boers et al., 1997;[79] Landewe et al., 2002;[80] COBRA study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2g/day) + MTX (7.5 mg/day stopped after 40 weeks) + PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Mean change in HAQ: SSZ + MTX combination had greater improvements in functional capacity at 28 weeks (mean change in HAQ -1.1 vs. -0.6; *P* < 0.0001) but difference not significant at 56 weeks (-0.8 vs. -0.6; *P* < 0.06)	NR	Good
Two Oral DMARDs + Corticosteroid vs. Oral DMaRD						
Mottonen et al., 1999;[81] Korpela et al., 2004;[82] Puolakka et al., 2004;[157] FIN-RACo study	RCT 199 24 months (5 year followup)	Multicenter; early RA; mean disease duration 7.3 to 8.6 months	MTX (7.5 to 10 mg/week) + HCQ (300 mg/day) + SSZ (2 g/day) + PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd DMARD) ± PNL	Less work disability for combination group than monotherapy group (median 12.4 days per patient-observation year vs. 32.2; *P* = 0.008)	NR	Fair
Other Combination Strategies						
Goekoop-Ruiterman et al., 2005;[83] *Allaart et al., 2006;[84] Goekoop-Ruiterman et al., 2007;[85] van der Kooij, et al., 2009;[86] van der Kooij, et al., 2009;[154] BeSt study	RCT 508 12 months 2 years 4 years	Multicenter; early RA; median duration between diagnosis and inclusion 2 weeks (IQR 1 to 5), median duration of symptoms 23 weeks (IQR 14 to 53)	DAS driven treatment; 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/d) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	All groups improved; better functional ability after 12 months for patients in group 3 or 4 than in group 1 (mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.9, and 0.9, respectively; *P* < 0.05 for 1 vs. 3 and 4, NS for other comparisons); No difference between groups at 24 months (0.7, 0.8, 0.9, and 0.9; *P* = 0.26); Improvements were maintained at 4 years, with no significant differences between groups (0.8, 0.7, 0.8, 0.8; *P* = 0.64)	SF-36 PCS: Greater improvement at 3 months and 6 months for groups 3 and 4 than groups 1 and 2 (*P* < 0.001); no at 1 and 2 years (*P* = 0.10 and 0.95, respectively) difference SF-36 MCS: No differences between groups at 3 months, 6 months, 1 year, or 2 years (*P* = 0.73, 0.22, 0.17, 0.83, 0.97, respectively)	Good

*New studies since last review.

BeST, Dutch acronym for Behandel Sstrategieen; COBRA, Combinatietherapie Bij Reumatoide Artritis; DAS, disease activity score; D-HAQ, Health Assessment Questionnaire – Disability Index; DMARD, disease modifying antirheumatic drug;; ERA, early rheumatoid arthritis; ETA,; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; g/day, gram per day; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; INF, infliximab; MCS, mental component score; mg/d, milligram per day; MTX, methotrexate; NR, not reported; NS, not significant; PCS, physical component score; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; SF-36, Medical Outcomes Test, Short Form 36; SSZ, sulfasalazine.

mg/week) or to a third DMARD if needed. The study is described further in the KQ 1 section entitled *Three oral DMARDs plus corticosteroid vs. oral DMARDs*. The initial publication reported no functional capacity or quality of life outcomes at 2 years. A 5-year follow-up trial reported that patients in the combination therapy group had significantly less work disability than patients in the monotherapy group (median 12.4 days per patient-observation year vs. 32.2 days; $P = 0.008$, sex- and age-adjusted $P = 0.009$).[157] After 2 years, the drug treatment strategy was no longer restricted and was left to the discretion of individual physicians.

Other combination strategies. The BeSt RCT examined four different treatment strategies over 12 months.[83] Patients (N = 508) with early RA were randomized to one of four strategies: (1) sequential DMARD starting with MTX (15 mg/week); (2) step-up combination therapy of MTX (15 to 30 mg/week) followed by sulfasalazine (2 g/day), hydroxychloroquine, and prednisone; (3) initial combination therapy of MTX, and sulfasalazine with tapered high-dose prednisone (60 mg/day to 7.5 mg/day in 7 weeks); and (4) initial combination therapy with infliximab (3 mg/kg) and MTX (25 to 30 mg/week). Adjustments were made in each strategy when the DAS 44 (disease activity score in 44 joints) was greater than 2.4. All groups had similar D-HAQ (Dutch version of the HAQ) scores at baseline (1.4 ± 0.7 or 1.4 ± 0.6). Functional ability, measured by the D-HAQ, was a primary end point. Subjects in groups 3 and 4 had more rapid improvement in functional ability (statistically significant greater improvements at 3, 6, 9, and 12 months). After 12 months of treatment, patients treated with strategy 3 or 4 had statistically significant better functional ability than those treated with strategy 1; (mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.5, and 0.5, respectively; $P < 0.05$ for group 1 vs. groups 3 and 4, NS for other comparisons). By two years, improvement was maintained in all groups, but there were no statistically significant differences between groups (0.7, 0.8, 0.9, and 0.9, respectively; $P = 0.26$). Improvements were maintained at 4 years, with no significant differences between groups (0.8, 0.7, 0.8, 0.8; $P = 0.64$). Subjects in groups 3 and 4 had more rapid improvement in physical health-related quality of life; with greater improvement at 3 months and 6 months for groups 3 and 4 than groups 1 and 2 on the SF-36 PCS ($P < 0.001$); but all groups had similar improvement by the end of 1 and 2 years ($P = 0.10$ and 0.95, respectively). There were no differences at any point in mental health-related quality of life as measured by the SF-36 MCS.

Key Question 3: Harms, Tolerability, Adverse Effects or Adherence

This key question examines overall harms for both diseases. Specifically, for patients with rheumatoid arthritis, do drug therapies differ in harms, tolerability, or adverse effects? We describe overall tolerability, then specific adverse events for each drug class, followed by studies reporting on adherence for each disease. Evidence Tables 8 and 9 in Appendix E describe details about these studies, some of which were described for efficacy in KQ 1, above.

Overview

A total of 28 randomized controlled trials (RCTs), one nonrandomized controlled trial, 48 observational studies, and four systematic reviews reported on tolerability, harms and adherence (see Evidence Tables 8 and 9 in Appendix E). Table 35 provides information on Food and Drug Administration (FDA) black box warnings and warnings in bold letters as well as toxicities

requiring monitoring according to the American College of Rheumatology (ACR). A black box warning is a type of warning that the FDA requires on the labels of prescription drugs that may cause serious adverse effects, and it signifies that clinical studies have indicated that the drug carries a significant risk of serious or even life-threatening side effects. Its name comes from the black border that typically surrounds the text of the warning. A bold letter (or "bolded") warning is text prominently displayed on the main panel of the drug label that warns users about possible side effects and other cautions. Adding a bold-text warning is a lesser step than a black box warning, even if it does relate to the possibility of serious adverse effects.

Table 35. Drug toxicities and Food and Drug Administration warnings

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Corticosteroids	Hypertension, hyperglycemia, osteoporosis	No black box warnings[170-174]	Dosage requirements are variable and must be individualized on basis of disease under treatment and response of the patient[170-174]
Synthetic DMARDs			
Leflunomide	Diarrhea, alopecia, rash, headache, theoretical risk of immunosuppressi on infection	Pregnancy must be excluded before start of treatment; pregnancy must be avoided during treatment or prior to completion of treatment[175]	Hepatotoxicity; rare cases of severe liver injury, including cases with fatal outcome, have been reported[175]
Hydroxychloro-quine	Macular damage	Physicians should be completely familiar with complete contents of package insert before prescribing[176]	No bold letter warnings[176]
Methotrexate	Myelosuppres-sion, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis	Physicians should be familiar and experienced in the use of antimetabolite therapy; Only use in patients with severe disease who are unresponsive to other forms of therapy; Should not be used by pregnant women due to fetal death and/or congenital anomalies; Patients with impaired renal function, ascities, or pleural effusions require monitoring for toxicity; Bone marrow supression, aplastic anemia, and GI toxicity reported with concomitant NSAID use; Hepatotoxicity, fibrosis and cirrhosis; elevated liver enzymes; Methotrexate-induced lung diease; diarrhea and ulcerative stomatitis; malignant lymphoma; severe to fatal skin reactions; fatal opportunistic infections; malignant lymphoma; induction of TLS; and death have been reported' Concomitant use with radiotherapy may increase risk of soft tissue necrosis and osteonecrosis[177]	No bold letter warnings[177]
Sulfasalazine	Myelosuppression	No black box warning[178]	No bold letter warnings[178]

† Toxicities requiring monitoring according to ACR guidelines.[179]

Table 35. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Biologics DMARDs			
Abatacept	No ACR recommendations about monitoring	No black box warning[180]	No bold letter warnings[180]
Adalimumab	No ACR recommendations about monitoring	Risk of infections (TB, invasive fungal infections, bacterial sepsis, other opportunistic infections) leading to hospitalization or death; patients should discontinue treatment if a serious infection or sepsis occurs; patients should be closely monitored for development of infection during and after treatment, including signs of active and latent TB; risks and benefits should be carefully considered before treating patients with chronic or recurring infections; lymphoma and other malignancies, some fatal, have been reported in young adults[181]	No bold letter warnings.[181]
Anakinra	No ACR recommendations about monitoring	No black box warning[182]	No bold letter warnings[182]
Certolizumab Pegol	No ACR recommendations about monitoring	Risk of serious infections (TB, invasive fungal infections, bacterial sepsis, other opportunistic infections) leading to hospitalization or death; patients should discontinue treatment if a serious infection or sepsis occurs; patients should be evaluated for latent TB; patients should be monitored for signs of active TB during treatment; risks and benefits should be carefully considered before treating patients with chronic or recurring infections; lymphoma and other malignancies have been reported; some have been fatal	No bold letter warnings
Golimumab	No ACR recommendations about monitoring	Risk of infections (TB, invasive fungal infections, bacterial sepsis, other opportunistic infections) leading to hospitalization or death; patients should discontinue treatment if if a serious infection or sepsis occurs; patients should be evaluated for latent TB; patients should be monitored for signs of active TB during treatment; risks and benefits should be carefully considered before treating patients with chronic or recurring infections; lymphoma and other	No bold letter warnings

Table 35. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
		malignancies have been reported; some have been fatal	
Etanercept	None recognized by ACR guidelines	Risk of infections (TB, bacterial sepsis) leading to hospitalization or death; patients should discontinue treatment if a serious infection occurs; patients should be evaluated for latent TB; patients should be monitored for signs of active TB during treatment; risks and benefits should be carefully considered before treating patients with chronic or recurring infections; lymphoma and other malignancies have been reported; some have been fatal[183]	No bold letter warnings[183]
Infliximab	None recognized by ACR guidelines	Increased risk for infections, including progression to serious infections leading to hospitalization or death; these infections include bacterial sepsis, TB, invasive fungal and other opportunistic infections; increased risk for TB; patients should discontinue treatment if a serious infection occurs; patients should be evaluated for TB risk factors and tested for latent TB prior to treatment; TB, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, other bacterial, mycobacterial and fungal infections observed; monitor patients for signs and symptoms of TB; lymphoma and other malignancies have been reported; fatal hepatosplenic T-cell lymphoma reported in adolescent and young adult patients with Crohn's disease[184]	No bold letter warnings[184]
Rituximab	No ACR recommendations about monitoring	Fatal infusion reactions can occur within 24 hours with 80% of fatal reactions occurring with first infusion; monitor and discontinue treatment in patients with severe reactions; TLS—acute renal failure requiring dialysis; severe mucocutaneous reactions; PML—JC virus infection resulting in PML and death has been reported[185]	No bold label warnings[185]

Table 35. Drug toxicities and Food and Drug Administration warnings (continued)

Drug	Toxicities†	Warnings Black Box	Warnings Bold Letter
Tocilizumab	No ACR recommendations about monitoring	Risk of infections (TB, invasive fungal infections, other opportunistic infections) leading to hospitalization or death; patients should interrupt treatment if a serious infection occurs until infection is controlled; patients should be evaluated for latent TB; patients should be monitored for signs of active TB during treatment	No bold label warnings

As with earlier KQs, the main drug classes examined are corticosteroids, oral DMARDs, and biologic DMARDs.

Most studies that examined the comparative efficacy of our drugs of interest also determined their harms. Methods of adverse events assessment, however, differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often, determining whether assessment methods were unbiased and adequate was difficult. Rarely were adverse events pre-specified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events.

Because few studies used the term *serious adverse events* as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,[186] we describe serious adverse events as the individual studies identified and reported them.

Rheumatoid Arthritis: Key Points

Tolerability and adverse events. *Corticosteroids.* Comparative tolerability and overall adverse events between corticosteroids were similar but comparative data were limited to one 3-month trial.[38] The strength of evidence is low (Table 36).

Mixed results from 1 RCT and 4 observational studies suggest that corticosteroids may increase risk of cardiovascular events.[51,187-190] One study showed a protective effect with corticosteroids.[188] The strength of the evidence is low.

Corticosteroid use significantly predicted the risk of serious infections, with increased risk of infection demonstrated in eight observational studies.[191-198] The strength of evidence for risk of infection with corticosteroids is moderate.

Low strength evidence suggests that corticosteroid treatment is associated with an increased risk of septic arthritis[199] and interstitial lung disease.[200]

Table 36. Strength of evidence for corticosteroids

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability						
Corticosteroid vs. Corticosteroid 1 RCT N = 143	Medium RCT/ fair	Unknown, single study	Direct	Precise	Similar tolerability with budesonide and prednisolone	Low
Corticosteroid vs. no corticosteroid 1 cohort study; N = 224	Medium Retrospective cohort/1 fair	Unknown, single study	Indirect	Imprecise	Dose dependent increased risk of fracture, infection, and GI events	Insufficient
Cardiovascular and Cerebrovascular Events						
Corticosteroid vs. no corticosteroid 1 RCT; N = 467 4 observational N = 122,817	Medium RCT/fair; observational/ 4 fair	Inconsistent	Indirect	Imprecise	Mixed results; decreased cardiovascular risk in one study, but increased risk of cardiovascular events and stroke in others	Low
Infection						
Corticosteroid vs. no corticosteroid 8 observational N = 260,412	Low observational/ 6 fair, 2 good	Consistent	Indirect	Precise	Corticosteroids increase risk of serious infection, TB, and herpes zoster	Moderate
Other Adverse Events						
Corticosteroid vs. no corticosteroid 3 observational N = 161,838	Medium observational/ 3 fair	Unknown, single studies	Indirect	Imprecise	Risk of septic arthritis and interstitial lung disease increased with corticosteroids	Low

RCT, randomized controlled trial; TB, tuberculosis; vs., versus.

Oral DMARDs and combinations. Three efficacy trials and one meta-analysis indicated similar tolerability and discontinuation rates of leflunomide, MTX, and sulfasalazine in data up to 2 years.[39-41,43] A retrospective cohort study found improved tolerability with leflunomide.[201] In another meta-analysis, the proportion of patients who stayed on MTX was higher than the proportion remaining on sulfasalazine at 5 years based on analysis of 71 RCTs and 88 observational studies (36 percent vs. 22 percent, P = NR).[202] The strength of evidence for comparisons of monotherapy with oral DMARDs is low (Table 37).

Seven studies involving combinations of two or three DMARDs, including sulfasalazine, MTX, hydroxychloroquine, and etanercept (a biologic DMARD), vs. one or two DMARDs have similar withdrawal rates attributable to adverse events.[45-49,79,203] Although discontinuation rates were similar for these pharmaceuticals, the number of patients with adverse events (nausea, erythema, elevated transaminases) were higher in two studies of sulfasalazine plus MTX than in monotherapy with either drug.[46,47] The strength of evidence comparing combinations of DMARDs with DMARD monotherapy is low.

Table 37. Strength of evidence for oral DMARDs

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability						
Oral DMARD vs. Oral DMARD 3 RCT N = 1839 1 observational N = 40594; 2 meta-analysis N = 6025	Low RCTs/3 fair; Retrospective cohort/1 fair; meta-analysis/1 good, 1 fair	Inconsistent	Direct	Precise	Similar tolerability and discontinuation rates for HCQ, LEF, MTX, and SSZ, with the exception of one study noting better tolerability for LEF and one study noting better tolerability with MTX	Low
Oral DMARD vs. Oral or Biologic DMARD combination 6 RCT N = 841 1 observational N = 119	Low RCTs/2 good, 4 fair; prospective cohort/1 fair	Inconsistent	Direct	Precise	Similar withdrawal rates due to adverse events; DMARD combination may have more adverse events	Moderate
Oral DMARD + Corticosteroid vs. Oral DMARD 4 RCT N = 1202 1 observational N = 154	Low RCTs/1 good, 3 fair; retrospective cohort/1fair	Consistent	Direct	Precise	Similar tolerability and rates of serious adverse events; addition of corticosteroid to oral DMARD lowered withdrawal due to adverse events	Moderate
Cardiovascular and Cerebrovascular Events						
Oral DMARD vs. Oral DMARD vs. Oral DMARD combination 4 observational N = 119,929	Medium observational/ 4 fair	Consistent	Indirect	Imprecise	Oral DMARDs and combinations of oral DMARDS may reduce cardiovascular risk; risk reductions were larger in magnitude with LEF	Low
Hepatic Events						
Oral DMARD vs. Oral DMARD vs. Biologic DMARD 2 observational N = 82,479	Medium observational/ 2 fair	Consistent	Indirect	Imprecise	Similar hepatic event rates for LEF, MTX, and other oral DMARDs	Low
Infection						
Oral DMARD vs. Oral DMARD 4 observational N = 105,645	Medium observational/ 3 fair, 1 good	Inconsistent	Direct	Imprecise	Mixed results; inconsistent differences for infection rates for comparisons of HCQ, LEF, MTX, and SSZ	Insufficient
Oral DMARD vs. no Oral DMARD 6 observational N = 236,151	Medium observational/ 6 fair	Inconsistent	Indirect	Imprecise	Mixed results; increased risk of infection in some studies, while other show decreased infection risk	Insufficient

DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; RCT, randomized controlled trial; SSZ, sulfasalazine.

Table 37. Strength of evidence for oral DMARDs (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Interstitial Lung Disease						
Oral DMARD vs. Oral DMARD 2 observational N = 80,332	Medium observational/ 2 fair	Inconsistent	Direct	Imprecise	Mixed results; increased risk with LEF in one study, while another study found no differences among HCQ, LEF, MTX, and SSZ	Insufficient
Malignancy						
Oral DMARD vs. Oral DMARD vs. corticosteroid 2 observational N = 16,545	Medium observational/ 1 good, 1 fair	Consistent	Direct	Imprecise	No differences in lymphoma for MTX and SSZ, and no difference in non-melanoma skin cancer for LEF and MTX	Low
Other Adverse Events						
Oral DMARD vs. Oral DMARD 3 observational N = 80,332	Medium observational/ 3 fair	Unknown, single studies	Indirect	Imprecise	Oral DMARDs increase risk of septic arthritis; LEF + corticosteroids increase risk of wound healing complications; no association of oral DMARDs with sinus problems	Low

Three studies of combinations including prednisone with one or more DMARDs indicated similar discontinuation rates between groups.[52,82-85,154] The BeST study, compared various strategies of combing corticosteroids with oral and biologic DMARDs found similar rates of serious adverse events among various drug strategies for early RA.[83-85,154] A retrospective cohort study of 154 patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months ($P<0.05$).[204] The level of evidence is moderate.

Four observational studies assessed cardiovascular or cerebrovascular outcomes with monotherapy or combinations of oral DMARD treatment.[187,188,205,206] All found either a decrease or no difference in risk of these events for patients treated with oral DMARDs. The reduction in risk was largest for leflunomide based on two studies.[188,205] The strength of the evidence is low.

Hepatic events appeared to be similar among patients treated with MTX, leflunomide, hydroxychloroquine, sulfasalazine, infliximab, and etanercept in two retrospective studies over 2 years to 3 years.[201,207] Longer term evidence is lacking. The level of evidence is low.

Mixed evidence from 10 studies suggests that oral DMARDs do not significantly affect risk of infections.[191,193,194,196,197,201,208-210] Evidence is inconclusive for comparing among oral DMARDs. One good-rated nested case-control study showed a lower rate of infection with MTX and hydroxychloroquine. Four other observational studies found no difference in risk with oral DMARDs,[191,193,194,210] while five fair-rated observational studies risk of infection was increased with oral DMARDs. Because of these inconsistencies, the level of evidence is insufficient.

In one 5-year retrospective cohort, interstitial lung disease appeared to be significantly higher with leflunomide use than with use of other DMARDs (RR, 1.9; 95% CI, 1.1-3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8-2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4-1.5).[190] Overall, the rate of hospitalizations because of interstitial lung

disease in the entire cohort was 8.1 per 10,000 patient years. In a second study, the risk of interstitial lung disease was similar for leflunomide and other oral DMARDs. The level of evidence is insufficient.

Estimates of cancer risk were limited to retrospective cohort studies. No risk of lymphoma was found for MTX or sulfasalazine in a 30-year retrospective cohort.[211] For the comparison of oral DMARDs, the strength of the evidence is low. Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR, 1.28; $P = 0.014$).[212]

Additional studies suggest that oral DMARDs increase risk of septic arthritis,[199] and that leflunomide increases risk of wound healing complications compared with MTX,[213] but hydroxychloroquine, leflunomide, MTX, and sulfasalazine do not increase risk of sinus problems[214] The strength of this evidence is low because only a single study addresses each of these questions.

Meta-analysis of withdrawal rates from placebo-controlled trials indicate that fewer patients randomized to a biologic DMARD discontinue treatment compared with patients randomized to placebo or MTX monotherapy (OR of discontinuation, 0.47; 95% CI, 0.36-0.62). This difference is largely driven by withdrawals because of lack of efficacy. In a meta-analysis of withdrawals because of lack of efficacy, the patients treated with a biologic DMARD were much less likely to withdraw than placebo- or MTX-treated patients (OR, 0.21; 95% CI, 0.16-0.28). Withdrawals because of adverse events were higher among patients treated with a biologic DMARD compared with placebo- or MTX-treated patients (OR, 1.44; 95% CI, 1.19-1.74). Because the *overall* withdrawals rates favored biologic DMARDs over placebo, we concluded that efficacy had a stronger influence on the likelihood of treatment continuation than adverse events. A summary of results from these quantitative analyses can be found in Figure 3.

Adjusted indirect comparisons based on the same efficacy trials found no difference in overall withdrawals, with the exception of a more favorable withdrawal profile for certolizumab pegol, etanercept, and rituximab compared with other biologic DMARDs. Similarly, most comparisons suggest no difference in withdrawals due to lack of efficacy. Similar to the analysis of overall withdrawals, certolizumab pegol had lower rates of withdrawals due to lack of efficacy and withdrawals due to adverse events, with a few exceptions. Certolizumab pegol, etanercept, and rituximab had fewer withdrawals due to lack of efficacy for some comparisons. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals.

Strength of evidence is presented in Table 38; overall, the strength of evidence is low.

Overall tolerability: *studies on discontinuation rates not otherwise covered in quantitative analyses.* Studies that assessed overall tolerability but were not eligible for inclusion in quantitative analyses are summarized in (Table 39). One good-quality RCT compared etanercept with the combination of etanercept and abatacapt.[67] Withdrawals due to adverse events occurred more in the combination group (11.8%) than in the monotherapy etanercept group (2.8%). Additional evidence on comparative discontinuation rates is provided by observational studies.[75,77,215-219] While some studies did not find clinically or statistically significant differences in drug discontinuation rates,[215,217] others did, generally suggesting higher discontinuation rates with infliximab.[75,216,218,219]

Figure 3. Meta-analysis of overall withdrawals from randomized controlled trials of biologic DMARDs.

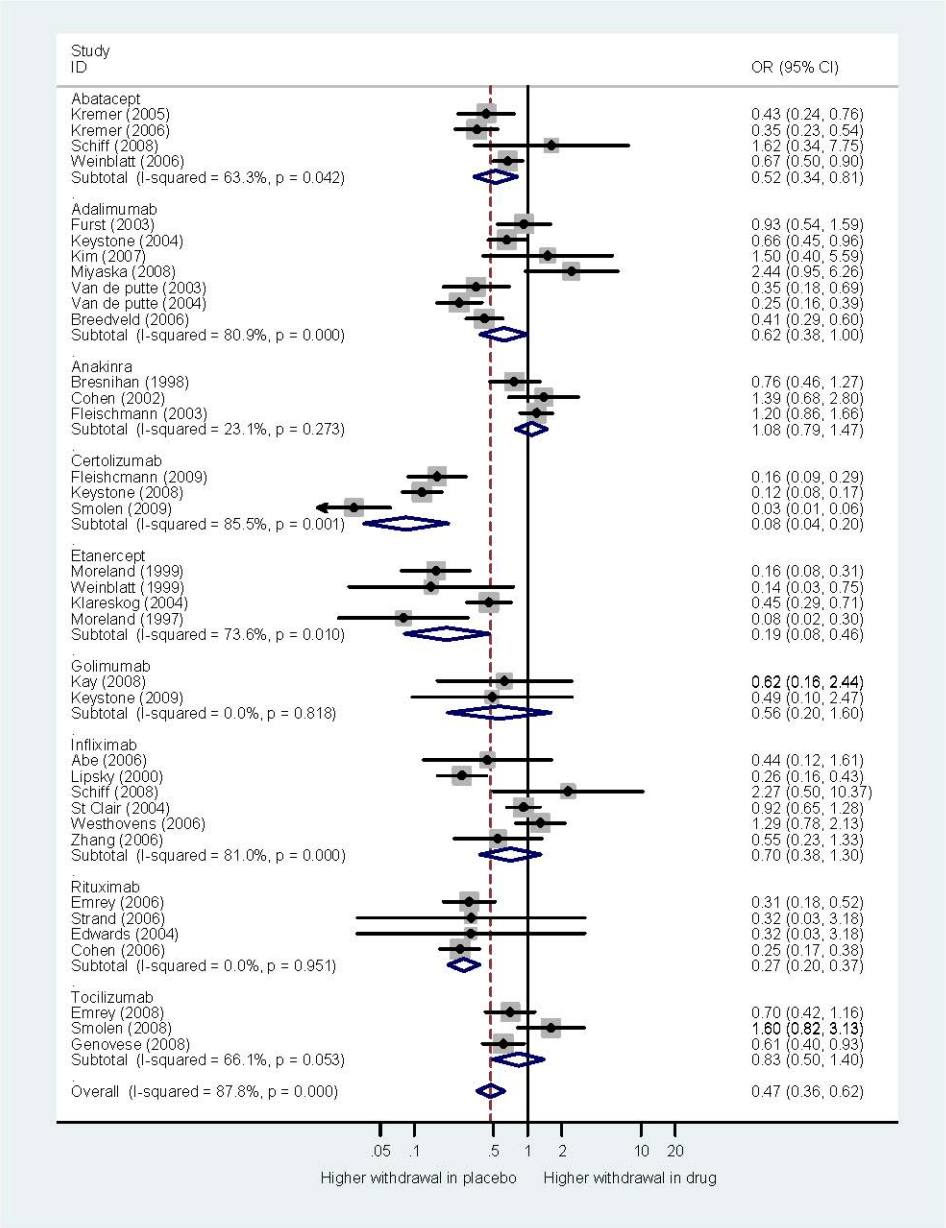


Table 38. Strength of evidence for biologic DMARDs

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability: Withdrawals Total						
Biologic DMARD vs. Placebo 38 RCT N = 15,959 Studies included in mixed treatment comparison meta-analysis	Medium RCTs*	Inconsistent	Indirect	Precise	Odds ratio of withdrawal overall: 0.47 (0.36-0.62) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol, etanercept, and rituximab had more favorable overall withdrawal profiles than most other biologic DMARDs	Low
Overall Tolerability: Withdrawals due to Lack of Efficacy						
Biologic DMARD vs. Placebo 28 RCT N = 9,819 Studies included in mixed treatment comparison meta-analysis	Medium RCTs*	Consistent	Indirect	Precise	Odds ratio of withdrawal due to lack of efficacy: 0.21 (0.16-0.28) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol, etanercept, and rituximab had more favorable profile for withdrawal due to lack of efficacy compared with most other biologic DMARDs	Low
Overall Tolerability: Withdrawals due to Adverse Events						
Biologic DMARD vs. Placebo 36 RCT N = 7,983 Studies included in mixed treatment comparison meta-analysis	Medium RCTs*	Consistent	Indirect	Precise	Odds ratio of withdrawal due to adverse events: 1.44 (1.19-1.74) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab	Low

ABA, abatacept; ADA, adalimumab; ANK, anakinra; CTZ, certolizumab; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; GOL; golimumab; INF, infliximab; RCT, randomized controlled trial; RR, relative risk; RTX, rituximab; TCZ, tocilizumab.

Table 39. Strength of evidence for biologic DMARDs tolerability and adverse events

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall and Serious Adverse Events						
Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 1 observational N = 2,364	Medium RCT/fair; retrospective cohort/fair	Consistent	Direct	Precise	Serious adverse events were more common with INF than with ABA, ADA, or ETN	Low
Biologic DMARD vs. No Biologic DMARD 19 RCT N = 10,742 4 observational N = 7,455	Low RCT/16 fair; 3 good; retrospective cohort/fair	Inconsistent	Indirect	Precise	Mixed results; similar adverse event profiles among biologic DMARDs, with some studies indicating higher adverse event rates for biologic DMARDs given alone or in combination with oral DMARDs compared with placebo or no treatment.	Low

ABA, abatacept; ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; NF, infliximab; RCT, randomized controlled trial.

Two studies compared adverse event rates and serious adverse events with biologic DMARDs; one randomized controlled trial[53] and one retrospective cohort study.[220] Both studies found more serious adverse events among patients treated with infliximab compared with abatacept, adalimumab, and etanercept. No other studies directly compared one biologic DMARD with another biologic DMARD with regard to tolerability or serious adverse events. The strength of this evidence is low.

Indirect evidence from additional efficacy trials and cohort studies suggests that the overall tolerability profiles are similar among biologic and oral DMARDs, or combinations of biologic and oral DMARDs.[54,57,62,71,73,74,76,96,100,113,115,133,145,221] However, several studies suggested that adverse events were more common with biologic DMARDs, given alone or in combination with an oral DMARD.[64,99,122,139-141,222] One prospective cohort study found a slightly lower rate of serious adverse events among patients who had an oral DMARD added to adalimumab, compared with patients who only received adalimumab (5.3% vs. 7.3%, respectively; P = NR).[223] Four RCTs were designed to assess adverse events as primary outcomes.[100,132,224,225] Overall, adverse event rates were similar for abatacept,[224] adalimumab,[100] anakinra,[225] or infliximab[132] and placebo. Other efficacy trials suggested that overall adverse events are higher with biologic DMARDs than with placebo.

Two trials indicated that a combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy.[66,224] The evidence, however, is limited to combinations of anakinra with etanercept and abatacept with anakinra, adalimumab, etanercept, or infliximab. The strength of the evidence is moderate.

Five long-term extension studies of adalimumab,[103] anakinra,[106] etanercept,[226] and infliximab[126,227] indicated that the rate of adverse events does not increase over time. The strength of the evidence is moderate. No evidence is available on the long-term tolerability of abatacept and rituximab.

Specific adverse events. The risk for long-term, rare but serious adverse events such as serious infections, malignancies, congestive heart failure, or autoimmunity is a cause of concern for all biologic DMARDs. We could not, however, reliably assess the *comparative* risk among biologic DMARDs for most serious adverse events because of insufficient evidence. A summary of studies assessing specific events can be found in Table 40.

Table 40. Strength of evidence for biologic DMARDs specific adverse events

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Cardiovascular and Cerebrovascular Events						
Biologic DMARD vs. No Biologic DMARD 1 RCT N = 150 11 observational N = 159,735	High RCT/1 fair; cohort, case-control, or other design/ 8 fair, 3 good	Inconsistent	Indirect	Imprecise	Mixed results; 1 cohort study found protective effect for heart failure, while 3 others found increased risk of heart failure with biologic DMARDs. 1 nested-case control study found no difference in risk for cardiovascular events, while 2 other studies found a protective effect with biologic DMARDs. 1 case-control study found no increased risk of stroke, and 2 cohort studies found no increased risk of MI.	Low
Infections						
Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 2 observational N = 14,013 3 AERS data	Medium RCT/1 fair; prospective cohort/1 fair, 1 good; AERS data/3 fair	Inconsistent	Direct	Imprecise	Mixed results; 1 RCT reported more infections with INF than ABA (*P* = NR). 1 prospective cohort study reported no differences in risk of serious infections among ADA, ETA, and INF. Risk of herpes zoster infection greater with ADA and INF than with ETA. Analysis of AERS data indicates that INF might have a higher risk of granulomatous infections than ETA	Low
Biologic DMARD vs. No Biologic DMARD 6 RCT N = 4514 16 observational N = 335,376 2 meta-analysis	Low RCT/5 fair; 1 good; cohort, case-control, or other design/ 13 fair, 3 good; meta-analysis/2 fair	Inconsistent	Indirect	Precise	Mixed results; most studies found either a trend towards increased infections or statistically significant increase in infections with biologic DMARDs. One meta-analysis reported a pooled odds ratio for serious infections of 2.0 (95% CI, 1.3-3.1) relative to placebo, but a second meta-analysis found an increased risk of infection only with ANK	Moderate

* Quality ratings not assigned to studies otherwise included in good-rated meta-analyses; ABA, abatacept; ADA, adalimumab; AERS, adverse event reporting system; ANK, anakinra; CTZ, certolizumab; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; GOL; golimumab; HR, hazard ratio; INF, infliximab; LEF, leflunomide; MI, myocardial infarction; MTX, methotrexate; NR, not reported; RCT, randomized controlled trial; RR, relative risk; RTX, rituximab; TCZ, tocilizumab.

Table 40. Strength of evidence for biologic DMARDs specific adverse events (continued)

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Infusion and Injection Site Reactions						
Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 1 observational N = 14,013 1 meta-analysis	Medium RCT/1 fair; prospective cohort/1 fair, meta-analysis/1 good	Consistent	Direct	Precise	Mixed results; 1 RCT reported more infusion reactions with INF than ABA (*P* = NR) and 1 retrospective cohort study reported more infusion reactions INF than with ADA and ETA. 1 meta-analysis found more reactions with ANK than ADA or ETA.	Low
Interstitial Lung Disease						
Biologic DMARD vs. Biologic DMARD 1 observational N = 17,598	Medium prospective cohort/1 fair	Unknown	Direct	Imprecise	Current treatment with ETA and INF not associated with hospitalization for interstitial lung disease; Past treatment was for ETA (HR, 1.7; 95% CI, 1.0-3.0; *P* = 0.056) and INF (HR, 2.1; 95% CI, 1.1-3.8; *P* = 0.019)	Low
Malignancies						
Biologic DMARD vs. Oral DMARD 4 observational N = 124,012	Medium Retrospective cohort/3 fair, 1 good	Inconsistent	Indirect	Imprecise	Mixed results; higher risk of lymphoma with biologic DMARDs in 1 study, but no difference in risk in another study. No increased risk of solid cancers or other malignancies for biologic DMARDs	Low
Biologic DMARD vs. no Biologic DMARD 5 observational N = 69,263 1 meta-analysis 1 AERS data	Medium cohort, case-control, or other design/ 5 fair, meta-analysis/1 fair	Unknown	Direct	Imprecise	Mixed results; some studies suggest small increased risk of malignancies including: lymphoma, nonmelanotic skin cancer, and melanoma	Low
Adherence						
Biologic DMARD vs. Biologic DMARD 3 observational N = 6,534	High cohort/3 fair	Inconsistent	Direct	Imprecise	Better adherence for INF than ETA in 1 study, similar adherence for INF and ETA in a second study, worse adherence for INF than ETA in a third study	Insufficient
Biologic DMARD vs. Oral DMARD 1 observational N = 6,018	High Cohort/1 fair	Unknown	Direct	Imprecise	Better adherence for LEF, ADA, ETN, and INF monotherapy compared with MTX	Low
Biologic DMARD vs. placebo 2 RCT N = 2,066	Medium RCT/1 good, 1 fair	Consistent	Indirect	Imprecise	No apparent differences in adherence	Insufficient

Cardiovascular and cerebrovascular events. No studies compared the risk of cardiovascular or cerebrovascular events with one biologic DMARD to another. Studies assessing class effects or individual biologic DMARDs provide mixed results. For example, one observational study reported lower rates of congestive heart failure[228] for RA patients on anti-TNF therapy than for those on conventional RA therapies. This study is contrasted by three other cohort studies that found an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with no treatment or oral DMARD.[229-231] Three observational studies assessed the risk of broadly defined cardiovascular events.[188,189,232] One study found no statistically significant association between use of biologic DMARDs and cardiovascular events,[189] while two studies reported a decreased risk of cardiovascular events with biologic DMARDs.[188,232] One nested case-control study found a slight decrease in the risk of stroke with adalimumab, etanercept, and infliximab (OR, 0.79; 95% CI, 0.34-1.82; *P* = NS),[187] and two cohort studies found no statistically significant differences in the risk of MI (although results trended towards an increased risk of MI for these biologic DMARDs).[205,233]

Infection. The best comparative evidence for risk of infection stems from an RCT[53] and a prospective cohort study.[234] The trial abatacept plus MTX with infliximab plus MTX and reported that serious infections were more common in the infliximab group than the abatacept group (*P* = NR).[53] One prospective cohort study suggested that risks do not differ for adalimumab, etanercept, and infliximab;[235] it showed that, compared with oral DMARDs as a class, anti-TNF drugs as a class did not lead to a higher overall risk for serious infections (53.2 vs. 41.1 events/1000 person years incidence rate ratio [IRR], 1.03; 95% CI, 0.68-1.57). Three observational studies indicated that infliximab might have a higher risk of granulomatous infections than etanercept.[236-238] Two studies indicated that the general risk of biologic DMARDs for serious infections is dose dependent. The evidence, however, is limited to adalimumab[239] and infliximab.[132] The strength of comparative evidence is low.

Infusion and injection site reactions. In efficacy studies, infusion reactions (abatacept, infliximab, rituximab, tocilizumab) and injection site reactions (adalimumab, anakinra, certolizumab, etanercept, golimumab) were the two most commonly and consistently reported adverse events. Some infusion reactions appeared to be more serious than injection site reactions. Overall, 0.5 percent of patients treated with infliximab had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions.[240] Fatal infusion reactions have also occurred with rituximab.[185] Of existing comparative evidence, reactions with infliximab were reported more commonly than with other biologic DMARDs in an RCT comparing abatacept and infliximab,[53] and in a retrospective cohort study comparing adalimumab, etanercept, and infliximab.[220] A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1-27.9) for adalimumab, 22.4 percent (95% CI, 8.5-36.3) for etanercept, and 67.2 percent (95% CI, 38.7-95.7) for anakinra.[60]

Interstitial lung disease. Only one study assessed the risk of interstitial lung disease with biologic DMARDs. This prospective cohort study found that current treatment with etanercept and infliximab was not associated with hospitalization for interstitial lung disease.[200] However, past treatment with etanercept (HR, 1.7; 95% CI, 1.0-3.0; *P* = 0.056) and infliximab (HR, 2.1; 95% CI, 1.1-3.8; *P* = 0.019) was associated with hospitalization for interstitial lung disease.[200]

Malignancies. Data from controlled trials do not provide sufficient evidence concerning an increase in the risk of cancer attributable to the use of either biologic DMARDs or a combination of biologic and oral DMARDs. In a large prospective cohort study the risk of lymphoma was

higher for patients on anti-TNF therapies than for those on oral DMARDs, although not statistically significantly so (standardized incidence ratio: MTX, 1.7 (95% CI, 0.9-3.2); infliximab, 2.6 (95% CI, 1.4-4.5); and etanercept, 3.8 (95% CI, 1.9-7.5).[241] An update of this analysis with additional patients and follow-up time confirmed that the risk of lymphoma was not increased among patients taking adalimumab, etanercept, and infliximab.[242] Similarly, three retrospective cohort studies did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on oral DMARDs.[243-245] The largest study included 4,160 patients treated with anti-TNF drugs.[244] Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6-2.1) for anti-TNF patients relative to patients on oral DMARDs. Results regarding an increased risk for overall malignancies in patients treated with biologic DMARDs relative to placebo are also mixed. The best evidence comes from a meta-analysis of data from more than 5,000 RA patients in adalimumab and infliximab efficacy trials, the pooled odds ratio for malignancies was 3.3 (95% CI, 1.2-9.1).[239] Two large retrospective cohort studies, however, do not support such findings.[244,245] The strength of the evidence is low.

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity. Reports based on data from the FDA's AERS indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[246,247] Similar cases have been seen in regulatory trials of adalimumab.[181] Reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases.[184,240,248,249] Lupus-like syndromes have also been reported for adalimumab.[246]

Hepatotoxicity has been reported for infliximab.[184] One study also reported elevated liver enzymes in patients treated with tocilizumab.[144]

A prospective cohort study indicated that patients on anti-TNF treatments were more likely to develop dermatological conditions (skin infections, eczema, drug-related eruptions).[250] Another retrospective cohort study found no overall association of anti-TNF drugs with risk of psoriasis.[251] Among the three biologic DMARDs included, adalimumab had a significantly increased risk of psoriasis compared with those treated with etanercept (IRR, 4.6; 95% CI, 1.7-12.1) and infliximab (IRR, 3.5; 95% CI, 1.3-9.3).

One cross-sectional analysis of data from 7,243 patients reported a small elevated risk of sinus problems with etanercept (OR, 1.21; 95% CI, 1.02-1.42).[214] No statistically significant increased risk of sinus problems was observed with adalimumab (OR, 1.09; 95% CI, 0.79-1.51) or infliximab (OR, 1.00; 95% CI, 0.88-1.15).

Adherence. Few efficacy studies reported rates of adherence. Results of efficacy trials do not indicate any differences in adherence among drug therapies used to treat RA. However, the quality of reporting and assessment of adherence was limited.

Findings from highly controlled efficacy studies may have limited generalizability to "real world" practice, especially because of the overall short duration of these trials. The evidence is insufficient to draw any conclusions about adherence from effectiveness studies.

For the comparison of one biologic DMARD with another, three observational studies provided mixed results. A review of a large, managed care database suggested that infliximab might have greater adherence than etanercept or MTX.[252] In contrast, a prospective cohort study found that etanercept had better adherence than infliximab. This also is supported by an observational study that suggested that etanercept had a better response rate than infliximab

attributable to greater adherence.[56] Another prospective cohort study failed to find any differences in adherence between etanercept and infliximab. Overall strength of evidence is low or insufficient for adherence (Table 41).

Table 41. Strength of evidence for adherence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD 5 RCT N = 1,924	High RCT/5 fair	Inconsistent	Direct	Imprecise	No apparent differences in adherence among oral DMARDs	Low
Biologic DMARD vs. Biologic DMARD 3 observational N = 6,534	High cohort/3 fair	Inconsistent	Direct	Imprecise	Better adherence for INF than ETN in 1 study, similar adherence for INF and ETN in a second study, worse adherence for INF than ETN in a third study	Insufficient
Biologic DMARD vs. Oral DMARD 1 observational N = 6,018	High Cohort/1 fair	Unknown	Direct	Imprecise	Better adherence for LEF, ADA, ETN, and INF monotherapy compared with MTX	Low
Biologic DMARD vs. placebo 2 RCT N = 2,066	Medium RCT/1 good, 1 fair	Consistent	Indirect	Imprecise	No apparent differences in adherence	Insufficient

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; N, number; RCT, randomized controlled trial; vs., versus.

Detailed Analysis

Tables 42 to 61 provide information on harms, divided into separate sections for the three main categories of drugs covered in this review. In each section, we cover overall tolerability and then specific adverse events. When sufficient data are available, we break out specific events by type (e.g., hepatic, infection, etc). The overall tolerability section for biologic DMARDs is divided further to present results of quantitative analyses.

Corticosteroids: overall tolerability. Corticosteroids are associated with several well-known side effects (noted already in Table 35). The prescription information for long-term use of corticosteroids highlights precautions including osteoporosis with secondary fractures, infection, glucose intolerance, peptic ulcer disease, gastrointestinal bleeding, cataracts, and glaucoma.[170-174]

Comparatively, the tolerability for corticosteroids appears to be similar among different corticosteroids, although the information is limited by short study duration and the fact that only one study is available (Table 42). One head-to-head RCT, described more in detail for KQ 1, compared budesonide (3 mg/day), high-dose budesonide (9 mg/day), prednisolone (7.5 mg/day), and placebo over 12 weeks.[38] Overall rates of adverse events were similar among groups (89 percent, 3 mg/day budesonide; 94 percent, 9 mg/day budesonide; 85 percent, prednisone; 90 percent, placebo; *P* = NR). Few adverse events caused patients to discontinue the drug; gastrointestinal symptoms, heart symptoms, and mood swings or insomnia were similar in all patient groups (*P* = NR).

Table 42. Overall tolerability in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Kirwan et al., 2004[38]	RCT 143 12 weeks	Active RA	BUD PNL	Similar in all groups	Fair
Saag et al., 1994[253]	Retrospective cohort 224 ≥ 1 year	RA patients on low-dose PRED (15 mg/day or less)	PRED No PRED	PRED 10 mg to 15 mg/day most related to development of AE (OR, 32.3; 95% CI, 4.6-220) PRED 5 mg to 10 mg/day (OR, 4.5; 95% CI, 2.1-9.6) No increase in AE for PRED < 5 mg/day Fracture: OR, 3.9 (95% CI, 0.8-18.1; *P* < 0.09) First infection: OR, 8.0 (95% CI, 1.0-64.0; *P* < 0.05) First GI event: OR, 3.3 (95% CI, 0.9-12.1; *P* < 0.07)	Fair

* Studies added during update; AE, adverse event; BUD, budesonide; CI, confidence interval; DMARD, disease-modifying antirheumatic drugs; GI, gastrointestinal; mg, milligram; HR, hazard ratio; OR, odds ratio; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial.

One retrospective cohort study of 224 RA patients directly assessed the toxicity of low-dose, long-term corticosteroid therapy (mean 4.9 years).[253] In three outpatient rheumatology clinics, 112 patients on low-dose prednisone (< 15 mg/day) for more than 1 year were matched with 112 patients not using prednisone. Investigators abstracted records from the date of prednisone initiation to the date of a predetermined adverse event (fracture, avascular necrosis of bone, new onset diabetes or diabetes out of control, infection requiring hospital or surgical intervention, herpes zoster, myocardial infarction, cerebrovascular event, gastrointestinal (GI) bleeding or peptic ulcer disease, cataracts, glaucoma, and death). Low-dose and high-dose long-term prednisone use (> 5 mg/day) was correlated with dose-dependent specific adverse events (adverse event at 10 to 15 mg/day: OR, 32.3; 95% CI, 4.6-220; $P = 0.0004$; adverse event at 5 to 10 mg/day: OR, 4.5; 95% CI, 2.1-9.6; $P = 0.0001$; and adverse event at 0 to 4 mg/day: OR, 1.9; 95% CI, 0.8-4.7; $P = 0.15$). Patients on long-term prednisone (any dose) were at higher risk for fracture (OR, 3.9; 95% CI, 0.8-18.1; $P < 0.09$), infection (OR, 8.0; 95% CI, 1.0-64; $P < 0.09$) and GI event (OR, 3.3; 95% CI, 0.9-12.1; $P < 0.07$) than were those on shorter-term prednisone use.

Corticosteroids: specific adverse events. We found no comparative study of corticosteroids directly assessing specific serious adverse events. Sixteen studies assessed single agents or class effects of corticosteroids, and these studies are highlighted here for cardiovascular and cerebrovascular events (Table 43), infection (Table 44), and other specific events (Table 45).

Cardiovascular and cerebrovascular events. Four observational studies[187-189,205] and one RCT[51] provide mixed evidence that corticosteroid treatment in patients with RA increases risk of cardiovascular events, and possibly cerebrovascular events (Table 43). Of the studies of cardiovascular outcomes, one fair-rated cross-sectional analysis of 4,363 patients with RA sampled from 15 countries reported a small reduction in risk of cardiovascular morbidity (HR,

0.95; 95% CI, 0.92-0.98).[188] Three studies reported an increased risk of cardiovascular events.[51,189,205] A fair-rated RCT of patients with early RA reported that prednisolone was associated with an increased risk of developing hypertension (OR, 2.16; 95% CI, 1.07-4.36).[51] A fair-rated nested-case control study of Pennsylvania Medicare enrollees with RA found a glucocorticoid-related increased risk of cardiovascular events (OR, 1.5; 95% CI, 1.1-2.1),[189] and a fair-rated retrospective cohort study of US commercially insured patients found that glucocorticoid use was associated with small increased risk of acute MI (RR, 1.32; 95% CI, 1.02-1.72).[205] Only one study assessed cerebrovascular outcomes; this nested case-control study from the National Data Bank for Rheumatic Diseases found a statistically non-significant increased risk of ischemic stroke with prednisolone treatment (OR, 1.75; 95% CI, 0.87-3.53).

Table 43. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Cardiovascular and Cerebrovascular Events					
*Choy et al., 2008[51] CARDERA trial	RCT 467 2 years	Pts with early, active RA	MTX+PNL	The number need to harm (NNH) with added PNL for any adverse event leading to withdrawal was 14 (95% CI, 6-65). PNL use associated with hypertension (OR, 2.16; 95% CI, 1.07-4.36).	Fair
*Nadareishvili et al., 2008[187]	Nested case-control 269 cases among 7,045 patients 8 years	RA pts in National Data Bank for Rheumatic Diseases	PRED	Association of PRED therapy with ischemic stroke: OR,1.75; 95% CI, 0.87-3.53; *P* = 0.114)	Fair
*Naranjo et al., 2008[188]	Cross-sectional 4,363 Clinician and patient recall	Sample of RA pts across 15 countries	Glucocorticoids	Glucocorticoids associated with reduced risk for CV morbidity (HR, 0.95; 95% CI, 0.92-0.98).	Fair
*Solomon et al., 2006[189]	Nested case-control study 3,501 24 months	Pennsylvania Medicare enrollees with RA	Glucocorticoids	Glucocorticoid monotherapy associated with increased risk for cardiovascular events (OR, 1.5; 95% CI, 1.1-2.1).	Fair
*Suissa et al, 2006[205]	Retrospective cohort 107,908 14 months	RA pts from PharMetrics data (US)	Glucocorticoids	Glucocorticoid use associated with acute MI (RR,1.32; 95% CI, 1.02-1.72)	Fair

* Studies added during update; AE, adverse event; BUD, budesonide; CI, confidence interval; CV, cardiovascular; DMARD, disease-modifying antirheumatic drugs; GI, gastrointestinal; mg, milligram; HR, hazard ratio; MI, myocardial infarction; MTX, methotrexate; NNH, number needed to harm; OR, odds ratio; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial.

*Infection***.** Eight observational studies (Table 44) provide consistent evidence that corticosteroid use in patients with RA is associated with an increased risk of infection, including tuberculosis and herpes zoster.[191-198] These studies represent large treated populations with RA, varying in setting from US commercially insured populations, Medicare patients in a single US state, and populations in the UK and Canada. A risk of serious bacterial infection was shown in four fair quality studies[191,193-195] and one good quality study.[196] One fair-[197] and one good-rated study[198] demonstrated an increased risk of herpes zoster infection with corticosteroids, and one fair-rated study[192] demonstrated an increased risk of tuberculosis with corticosteroids. Across all of these studies of patients with RA (regardless of type of infection), the risk of infection increased by approximately 50% to 150% with use of corticosteroids.

Table 44. Infection in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et al., 2007[191]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Glucocorticoids	The risk for all infections requiring hospitalization was most elevated with glucocorticoid agents (RR, 2.6; 95% CI, 2.3 - 2.9); Similar effects were seen with pneumonia as the outcome (RR, 2.1; 95% CI, 2.4-3.1).	Fair
*Brassard et al., 2006[192]	Retrospective cohort study 112,300 Up to 5 years	RA pts from PharMetrics data (US)	Several oral DMARDs, biologic DMARDs, corticosteroids	Adjusted rate ratio of developing TB with corticosteroids: 1.7 (95% CI, 1.3-2.2).	Fair
Doran, et al., 2002[193]	Retrospective cohort 609 39 years	RA patients	Several oral DMARDs, corticosteroids	In patients hospitalized for infection, corticosteroid use increased risk (HR, 1.56; 95% CI, 1.20-2.04)	Fair
*Lacaille et al., 2008[194]	Retrospective cohort 27,710 162,720 person years	Pts with RA from British Columbia, Canada	Oral DMARDs, corticosteroids	Adjusted Rate Ratio for serious infections: DMARDs + corticosteroids:1.63 (95% CI, 1.5-1.77); corticosteroids alone: 1.9 (95% CI, 1.75-2.05)	Fair
*Schneeweiss et al., 2007[195]	Retrospective cohort 15,597 Up to 8 years	Medicare beneficiaries ages 65 and older with RA	Glucocorticoids	Compared with MTX use, glucocorticoid use associated with serious bacterial infections (RR, 2.25; 95% CI, 1.57-3.22)	Fair

* Studies added during update; AE, adverse event; BUD, budesonide; CI, confidence interval; DMARD, disease-modifying antirheumatic drugs; GI, gastrointestinal; GPRD, General Practice Research Database; mg, milligram; HR, hazard ratio; MTX, methotrexate; OR, odds ratio; PM, Pharmetrics; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; TB, tuberculosis.

Table 44. Infection in patients with rheumatoid arthritis treated with corticosteroids (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Smitten et al., 2008[196]	Retrospective cohort 24,530 26.6 months	RA pts from PharMetrics data (US)	Corticosteroids	Oral corticosteroid use increased risk of hospitalized infection (RR, 1.92; 95% CI, 1.67-2.21). Risk increased with dose.	Good
*Smitten et al., 2007[197]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	RA pts from PM database and UK GPRD	Corticosteroids	Risk of herpes zoster infection with corticosteroids only: (PM: OR, 2.51 ; 95% CI, 2.05-3.06 GPRD: 1.46 ; 95% CI, 1.24-1.70)	Fair
*Strangfeld et al., 2009[198]	Prospective cohort 5,040 up to 36 months	RA pts initiating biologic therapy or switching to another DMARD	Glucocorticoids	Adjusted HR for Herpes Zoster. Glucocorticoids 1 mg to 9 mg (HR, 1.86; 95% CI, 0.92-3.78); Glucocorticoids 10+mg (HR, 2.52; 95% CI, 1.12-5.65)	Good

*Other adverse events***.** Three additional observational studies assessed the risk of specific adverse events with corticosteroid treatment in patients with RA; one of septic arthritis;[199] one of sinus problems;[214] and one of interstitial lung disease (Table 45).[200] A large fair-rated retrospective cohort study found that prednisolone was associated with roughly a 3-fold increased risk of developing septic arthritis compared with those not receiving any DMARD (IRR, 2.94; 95% CI, 1.93–4.46).[199] A cross-sectional analysis of 6-month questionnaires from 7,243 patients enrolled in the National Data Bank for Rheumatic Diseases (NDB) study found that prednisone use was not associated with an increased risk of sinus problems.[214] Analysis of a larger group of patients from the NDB study (n = 17,598) found that current and past prednisone use was associated with hospitalization for interstitial lung disease (respectively, HR, 2.5; 95% CI, 1.5-4.1, $P < 0.001$, and HR, 3.0; 95% CI, 1.0-8.9, $P = 0.044$).[200]

Oral DMARDs: overall tolerability. MTX, sulfasalazine, hydroxychloroquine and leflunomide all can produce several well-known, and similar, reactions (Table 35). Frequently reported adverse reactions for these drugs found in package inserts include the following:

- MTX: ulcerative stomatitis, nausea and abdominal distress, fatigue, chills and fever, dizziness, leukopenia, and decreased resistance to infection;[177]
- Sulfasalazine: stomatitis, nausea, dyspepsia, rash, headache, abdominal pain or vomiting, fever, dizziness, pruritus, and abnormal liver function tests.[178]
- Hydroxychloroquine: dizziness, headache, abdominal pain/nausea/vomiting/diarrhea, pruritus, weight loss, hair bleaching, and alopecia;[176] and
- Leflunomide: diarrhea, rash, elevated liver enzymes, and alopecia.[175]

Table 45. Other specific harms in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Edwards et al., 2007[199]	Retrospective cohort 136,997 15 years	RA pts (n = 34,250)	Several oral DMARDs, PNL	PNL (adjusted IRR, 2.94; 95% CI, 1.93–4.46, *P* < 0.001) was associated with an increased incidence of septic arthritis when compared with those not receiving any DMARD.	Fair
*Michaud and Wolfe, 2006[214]	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the NDB study	PRED	Association of PRED treatment with visits to physician for sinus problems was OR,0.98; 95% CI, 0.86-1.11; *P* = 0.776).	Fair
*Wolfe et al., 2007[200]	Prospective cohort 17,598 up to 3.5 years	RA pts in the NDB	PRED	Current treatment with PRED associated with hospitalization for interstitial lung disease (HR, 2.5; 95% CI, 1.5-4.1, *P* < 0.001). Past treatment with PRED was also associated with hospitalization for interstitial lung disease (HR, 3.0; 95% CI, 1.0-8.9, *P* = 0.044)	Fair

* Studies added during update; AE, adverse event; BUD, budesonide; CI, confidence interval; DMARD, disease-modifying antirheumatic drugs; GI, gastrointestinal; mg, milligram; HR, hazard ratio; NDB, National Data Bank for Rheumatic Diseases; OR, odds ratio; PNL, prednisolone; PRED, prednisone; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Tables 21-27 describe studies providing information on tolerability and various adverse events. Studies reporting overall tolerability of oral DMARDs and oral DMARD combinations are summarized in Table 46. For monotherapy with oral DMARDs, three trials[40,41,43] and one meta-analysis with up to 2 years of data,[39] all described in more detail for KQ 1, indicated similar levels of general tolerability among leflunomide, MTX, and sulfasalazine, including similar discontinuation rates and frequency of serious adverse events. A retrospective cohort study found leflunomide given as monotherapy or in combination with MTX had fewer adverse event reports than MTX alone or other oral DMARDs.[201] However, another meta-analysis of withdrawal rates from 71 RCTs and 88 observational studies, which included data up to 5 years, found that patients with RA stayed on MTX significantly longer than on either sulfasalazine or hydroxychloroquine.[202] At 5 years, 36 percent of patients had remained on MTX to continue their treatment; 22 percent had remained on sulfasalazine. Patients on sulphasalazine were more likely to have withdrawn from medication because of toxicity than those on MTX (52% vs. 35%; RR, 1.68; *P* < 0.0001). Withdrawal rates were not found to differ between samples reported in observational studies and RCTs.

Table 46. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Oral DMARDs Overall Tolerability					
Cannon, et al., 2004[201]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	AE rates in LEF, LEF + MTX were lower than or similar to AE rates for MTX and other DMARDS	Fair
Emery et al., 2000[40]	RCT 999 1 year with optional 2nd year	RA 4 months to 10 years	LEF, MTX	Frequency of SAEs similar between groups	Fair
Maetzel, et al., 2000[202]	Meta-analysis (RCT and observational) 159 studies MTX = 2,875 SSZ = 1,418 5 years	RA pt studies including withdrawal information	MTX SSZ HCQ (and gold)	Withdrawals due to toxicity for 5 years: MTX 35%, SSZ 52% Pts treated with SSZ were 1.68 times more likely to fail therapy due to toxicity than MTX (RR, 1.68; $P < 0.0001$)	Fair
Osiri et al., 2002[39]	Systematic review and meta-analysis 1,732 2 years	Active RA	LEF, MTX, SSZ	Discontinuation rates from AEs were similar for LEF, MTX and SSZ	Good
Smolen et al., 1999[43]	RCT 358 24 weeks	Active RA	LEF, SSZ	Withdrawal due to AEs 14% vs. 19%	Fair
Strand, et al., 1999[41,42]	RCT 482 12 months (1 year continuation)	RA for at least 6 months, MTX-naive	LEF, MTX	AEs constant over time LEF and MTX 12 months: Higher discontinuation rate for LEF (22% vs. 10.4%, P = NR)	Fair
Oral DMARD Combinations Overall Tolerability					
Boer et al., 1997[79] COBRA study	RCT 155 56 weeks	Early RA, DMARD naive	PNL taper + MTX + SSZ vs. SSZ	Lower withdrawal rate due to AEs (2.6% vs. 7.6%, P = NR)	Fair
Capell et al., 2006[45]	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥ 2.4 at 6 months)	Active RA	SSZ + MTX vs. SSZ or MTX	Similar withdrawal rate due to AEs	Fair

* Study added during the 2010 update search; AEs, adverse events; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoids; hydroxychloroquine; HR, hazard ratio; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; PNL, prednisolone; PRED, prednisone; Pts, patients; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; SAEs, serious adverse events; SSZ, sulfasalazine.

Table 46. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Dougados et al., 1999[46]	RCT 209 (146) 52 weeks (5 year followup)	DMARD naive, early RA	SSZ +MTX vs. SSZ or MTX	Discontinuation rate due to AEs similar among groups AEs higher in SSZ+MTX vs. SSZ vs. MTX (91% vs. 75% vs. 75%, *P* = 0.025)	Fair
*Goekoop-Ruiterman et al., 2005[83-85,154] BeSt study	RCT 508 12 months	Early RA	Sequential monotherapy (starting with MTX) vs. step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. combination (MTX, SSZ, tapered high-dose PRED) vs. combination with INF (3 mg/kg – could be titrated to 10 mg/kg based on DAS)	No significant differences in serious AEs in all groups	Good
Haagsma et al., 1997[47]	RCT 105 52 weeks	DMARD naive, early RA	SSZ + MTX vs. SSZ or MTX	No significant difference in number of withdrawals due to AEs	Fair
Korpela et al., 1999[82] FIN-RACo study	RCT 199 24 months	Early RA	MTX + HCQ + SSZ + PNL vs. DMARD ± PNL	Frequency of serious AEs similar in both groups Discontinuation due to AEs similar in both groups	Fair
*Malyshev a et al., 2008[204]	Retrospective cohort 154 2-62 months	RA Pts	MTX vs. MTX +glucocorticoids vs. HCQ vs. HCQ+glucocorticoids	Use of GC significantly increased the time until withdrawal of DMARD therapy due to AE (18.6 ± 2.3 months; *P* < 0.05) compared with no use of GC (12.5 ± 1.4 months)	Fair
O'Dell et al., 2006[203]	Prospective cohort 119 48 weeks	Active RA, previous use of DMARDs	ETA +SSZ vs. ETA + HCQ	Similar discontinuation rates due to AEs	Fair
O'Dell et al., 2002[48]	RCT 171 2 years	RA pts not previously treated with combination drugs	MTX + SSZ + HCQ vs. MTX + HCQ vs. MTX + SSZ	Similar withdrawal rate due to AEs across groups	Good
O'Dell et al., 1996[48]	RCT 102 2 years	RA and poor response to at least 1 DMARD	MTX + SSZ+ HCQ vs. MTX vs. SSZ + HCQ	Similar withdrawal rate due to AEs across groups	Good
Svensson et al., 2005[52]	Open-label RCT 250 2 years	Early RA	DMARD + PNL vs. DMARD	Similar number of discontinuations between groups	Fair

Table 46. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Svensson et al., 2003[254]	Open-label RCT 245 2 years	Early RA	MTX + PRED SSZ + PRED	Lower withdrawal rate due to AEs or inefficacy for PRED + MTX group vs. PRED + SSZ group (11.5% vs. 33.3%, *P* = 0.0005)	Fair

For combination therapies, five studies of DMARD combinations (one up to 5 years[46]) included MTX, sulfasalazine, hydroxychloroquine, and etanercept (described in detail under KQ 1). They had similar withdrawal rates attributed to adverse events.[45-49,203] Although discontinuation rates were similar, rates of adverse events were higher in two studies for sulfasalazine plus MTX vs. monotherapy (adverse events for combination therapy range from 53 percent to 91 percent; adverse events for monotherapy range from 50 percent to 75 percent).[46,47] Side effects included nausea, erythema, and elevated transaminases. Three RCTs of combination therapy including prednisone with one or more DMARDs (described in detail in KQ 1) showed similar discontinuation rates between groups.[52,82,83] One open-label RCT of 155 patients comparing a prednisolone taper plus MTX plus sulfasalazine actually had a lower withdrawal rate because of adverse events than sulfasalazine only (2.6 percent vs. 7.6 percent, *P* = NR).[79] Another open-label RCT of 245 patients found the withdrawal rate for adverse events to be lower in the prednisone plus MTX group than in the prednisone plus sulfasalazine group (11.5% vs. 33.3%, *P* = 0.0005).[254] A retrospective cohort study of 154 patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months ($P<0.05$).[204]

Oral DMARDS: specific adverse events. Synthetic DMARDs can produce several serious adverse events (Table 35). The package inserts for MTX give several warnings.[177] It has been reported to cause congenital abnormalities. Severe and sometimes fatal bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of MTX and NSAIDS. MTX-induced lung disease can occur in doses as low as 7.5 mg per week. Malignant lymphoma may also occur in patients on low-dose MTX. Severe, occasionally fatal skin reactions have also been reported.

Less common but severe adverse and potentially fatal events for sulfasalazine include blood dyscrasias, hypersensitivity reactions including Stevens-Johnson syndrome, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis.[178] The package insert for hydroxychloroquine describes irreversible retinal damage in some patients on long-term therapy or high dosage. Other serious reactions include blood dyscrasias, seizures, hypersensitivity reactions, and hepatotoxicity.[176] Potentially severe adverse reactions for leflunomide include blood dyscrasias, hepatotoxicity, and hypersensitivity reactions including Stevens-Johnson syndrome.[175] Studies of adverse events with oral DMARDs are summarized in Tables 47-52.

Cardiovascular and cerebrovascular events. Four observational studies assessed cardiovascular or cerebrovascular outcomes with oral DMARD treatment (Table 47).[187,188,205,206] All found either a decrease or no difference in risk of these events for patients treated with oral DMARDs compared with no treatment or other comparator treatments.

Table 47. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Naranjo et al., 2008[188]	Cross-sectional 4,363 Clinician and patient recall	Sample of RA pts across 15 countries	MTX, LEF, SSZ	MTX, LEF, and SSZ associated with reduced risk for CV morbidity (HR, 0.85; 95% CI, 0.81-0.89; HR, 0.59; 95% CI, 0.43-0.79; HR, 0.92; 95% CI, 0.87-0.98; respectively).	Fair
*Nadareishvili et al., 2008[187]	Nested case-control 269 cases among 7045 patients 8 years	RA pts in National Data Bank for Rheumatic Diseases	MTX	Association of treatment with ischemic stroke: MTX: OR,0.63; 95% CI, 0.32-1.26; *P* = 0.191)	Fair
*Suissa et al, 2006[205]	Retrospective cohort 107,908 14 months	RA pts in PharMetrics US data	Traditional DMARDs	Traditional DMARD use associated with decreased acute MI: MTX: RR, 0.8; 95% CI, 0.60-1.08 LEF: RR, 0.28; 95% CI,0.12-0.64	Fair
*van Halm et al., 2006[206]	Case-control 613 Eligible diagnosis from 1953-2004	Pts with RA treated in a single clinic in Netherlands	MTX, HCQ, SSZ, MTX+HCQ, MTX+SSZ, SSZ+HCQ, MTX+HCQ+SSZ	Cardiovascular events compared with no DMARD treatment: MTX OR:0.47 (95% CI, 0.07-3.23), SSZ: 0.31 (95% CI, 0.07-1.33), HCQ: 0.45 (95% CI, 0.10-2.04), MTX+ SSZ: 0.24 (95% CI, 0.07-0.85, *P* < 0.05), MTX+HCQ: 0.54 (95% CI, 0.08-3.66), SSZ+ HCQ: 0.34 (95% CI, 0.05-2.16), MTX + SSZ + HCQ: 0.27 (95% CI, 0.07-0.99, *P* < 0.05)	Fair

* Study added during the 2010 update search; CV, cardiovascular; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GI, gastrointestinal; HCQ, hydroxychloroquine; HR, hazard ratio; INF, infliximab; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; Pts, patients; RA, rheumatoid arthritis; RR, rate ratio; SSZ, sulfasalazine;.

Two studies found a decreased risk of broadly defined cardiovascular events with oral DMARDs.[188,206] One study, the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) project, was a cross-sectional review of 4,363 patient records from 15 countries.[188] This fair-rated study reviewed clinical history and surveyed patients for information about cardiovascular events, including myocardial infarction, angina, coronary disease, coronary bypass surgery, and stroke. Risk of all types of cardiovascular events was reduced among patients taking MTX, leflunomide, and sulfasalazine. The second study was a retrospective chart review of 613 patients from a single rheumatology clinic in the Netherlands.[206] Cardiovascular disease was defined as a verified medical history of coronary, cerebral, or peripheral arterial disease. Regression models considered patients treated with oral

DMARD monotherapy, as well as combinations of MTX, hydroxychloroquine, and sulfasalazine. All oral DMARD monotherapy and combinations showed a decreased risk of cardiovascular disease (compared with no oral DMARD), although the risk reduction was only statistically significant for patients ever taking MTX and sulfasalazine (OR, 0.24; 95% CI, 0.07-0.85, P < 0.05) and MTX, sulfasalazine, and hydroxychloroquine (OR, 0.27; 95% CI, 0.07-0.99, *P* < 0.05).

One fair-rated retrospective cohort study of 107,908 commercially insured patients with RA found a decreased risk of acute myocardial infarction amount patients taking MTX (RR, 0.81; 95% CI, 0.60-1.08) or leflunomide (RR, 0.28; 95% CI, 0.12-0.65).[205] A decreased risk also was observed among a heterogeneous group of "all other traditional DMARDs" (RR, 0.67; 95% CI, 0.46-0.97); this group included hydroxychloroquine and sulfasalazine among numerous other agents.

A fair-rated nested case-control study of 7,045 patients with RA from the National Data Bank for Rheumatic Diseases found that while overall patients with RA have a significantly increased risk of stroke (OR, for all strokes 1.64; 95% CI, 1.16-2.30; OR, for ischemic strokes 2.66; 95% CI, 1.24-5.70), treatment with the oral DMARDs MTX, hydroxychloroquine, leflunomide, and sulfasalazine does not increase this risk.[187]

Hepatic events. Two retrospective cohorts examined hepatic events in patients with rheumatoid arthritis.[201,207] Both studies found similar hepatic event rates for leflunomide and MTX (Table 48).

Table 48. Hepatic events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Cannon et al., 2004[201]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Hepatic event: LEF 4.1/1,000PY, MTX 6.2/1,000PY, Other 4.2/1,000PY, LEF + MTX 4.6/1,000PY	Fair
Suissa et al., 2004[207]	2 retrospective cohorts (claims data) 41,885 3 years	RA diagnosis	LEF, biologics, traditional DMARDs, MTX	Serious hepatic events compared with MTX: LEF rate ratio: 0.9 (95% CI, 0.2-4.9), traditional DMARD: 2.3 (95% CI, 0.8-1.4), biologic DMARD: 5.5 (95% CI, 1.2-24.6)	Fair

* Study added during the 2010 update search; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; LEF, leflunomide; MTX, methotrexate; Pts, patients; PY, person years; RA, rheumatoid arthritis;.

A 2-year retrospective cohort from a U.S. insurance claims database (N = 40,594) examined the incidence rates of serious hepatic events in patients treated with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept).[201] The hepatic event rate for leflunomide was similar to that for other DMARDs (leflunomide, 4.1/1,000 person-years [95% CI, 2.4-7.0], MTX, 6.2/1,000 person-years [95% CI, 5.1-9.3]; other DMARDs, 4.2/1,000 person-years [95% CI, 3.3, 5.3], *P* = NS, NR).

Another group examined data from claims databases for two retrospective cohorts of 41,885 patients over 3 years for serious hepatic events associated with treatment with leflunomide, MTX, traditional DMARDs (hydroxychloroquine, sulfasalazine, gold, minocycline, penicillamine, chlorambucil, cylcophosphamide and cyclosporine), or biologic DMARDs

(infliximab, etanercept).[207] Overall, the rate of serious hepatic events for all drugs was 4.9 per 10,000 patient years. Using MTX as the reference, they observed no higher rates in serious hepatic events for leflunomide (RR, 0.9; 95% CI, 0.2-4.9) or for traditional DMARDs (RR, 2.3; 95% CI, 0.8-6.5), but they did report higher rates for biologic DMARDs (RR, 5.5; 95% CI, 1.2-24.6).

Infection. Mixed evidence from 10 studies suggests that oral DMARDs do not significantly affect risk of infections (Table 49).[191,193,194,196,197,201,208-210] A good-rated retrospective cohort study found that some oral DMARDs may decrease risk of infection.[196] In this study, 24,530 US commercially insured patients with RA were evaluated for hospitalized infection. A nested case-control analysis was conducted on 1,993 cases of infection and 9,965 controls. The adjusted rate ratio showed a statistically significantly lower rate of infection for MTX- (RR, 0.81; 95% CI, 0.70-0.93) and hydroxychloroquine-treated patients (RR, 0.74; 95% CI, 0.62-0.89). Risk of infection was not increased with leflunomide (RR, 1.02; 95% CI, 0.79-1.32) or sulfasalazine (RR, 0.82; 95% CI, 0.58-1.16).

Four other fair-rated studies showed no difference in infection rates with oral DMARDs.[191,193,194,210] A 39-year population-based study of the Rochester, Minnesota, cohort examined potential risk factors for hospitalization for infection in RA patients (N = 609).[193] The use of corticosteroids increased hospitalization for infection (HR, 1.56; 95% CI, 1.20-2.04), but oral DMARDs (including MTX, hydroxychloroquine, sulfasalazine, and leflunomide) had no increased risk of infection-related hospitalizations. This finding was similar in a retrospective cohort study of 27,710 patients with RA from British Columbia,[194] where oral DMARDs given in combination with corticosteroids were associated with an increased risk of infection (RR, 1.63; 95% CI, 1.5-1.77), but oral DMARDs alone were not associated with an increased risk of infection (RR, 0.92; 95% CI, 0.85-1.0). A nested case-control study of 23,733 patients with RA from a Quebec database[191] and a retrospective cohort study of 20,357 patients with RA treated at the US Veterans Affairs healthcare system[210] also found no increased risk of infection with oral DMARDs.

Two fair-rated cohort studies examined the risk of hospitalization for pneumonia infection.[201,208] One study examined 16,788 patients from U.S. rheumatology practices and followed up semi-annually with questionnaires for 3.5 years.[208] Both prednisone and leflunomide use increased the risk of hospitalization for pneumonia compared with RA patients not on these drugs (HR, 1.7; 95% CI, 1.5-2.1; HR 1.3; 95% CI, 1.0-1.5); MTX, hydroxychloroquine, sulfasalazine, infliximab, etanercept, or adalimumab did not increase risks. A 2-year retrospective database study examined RA patients to determine the incidence rates of adverse events during treatment with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept).[201] Respiratory infection rates per person-year were highest in the MTX group (38.9/1,000 person-years), next highest in the other DMARD group (36.9/1,000 person-years), and lowest in the leflunomide group (20/1,000 person-years) ($P < 0.0001$).

Two retrospective cohort studies examined the risk of TB with oral DMARDs.[192,209] Both showed an increased risk of TB with oral DMARD treatment. One study examined 24,282 patients with RA from Quebec, Canada and found the risk of TB to be increased among oral DMARD users (RR, 3.0; 95% CI, 1.6-5.8).[209] The risk was highest among leflunomide-treated patients (RR, 11.7; 95% CI, 2.1-65.1), although the sample size for this group was only 10 patients (3 cases, 7 controls). A similarly designed study using a US claims database identified

Table 49. Infection in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et al., 2007[191]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Oral DMARDs including: MTX, LEF, HCQ, SSZ	Relative risk for infections requiring hospitalization: MTX 1.10 (95% CI, 0.98-1.23); all other DMARDs (includes LEF, SSZ) 0.99 (95% CI, 0.84-1.16); Anti-malarial (includes HCQ) 1.06 (95% CI, 0.92 - 1.22)	Fair
*Brassard et al., 2009[209]	Retrospective cohort study 24,282 1980-2003 for cohort and 1992-2003 for TB incidence rates	RA pts from Quebec	Traditional DMARDs including MTX and LEF, corticosteroids	Rate ratio of TB associated with any DMARD use: 3.0 (95% CI, 1.6-5.8).	Fair
*Brassard et al., 2006[192]	Retrospective cohort study 112,300 Up to 5 years	RA pts from the PharMetrics Patient-Centric database	Several oral DMARDs, biologic DMARDs, corticosteroids	Adjusted rate ratio of developing TB with use of traditional DMARDs: 1.2 (95% CI, 1.0 - 1.5).	Fair
Cannon et al., 2004[201]	Retrospective cohort 40,594 2 years (claims database)	RA pts	LEF, MTX, other DMARD	Respiratory infection: LEF 20/1,000PY, MTX 38.9/1,000PY, Other 36.9/1,000PY	Fair
Doran et al., 2002[193]	Retrospective cohort 609 39 years	RA pts	Several oral DMARDs, corticosteroids	Compared with oral DMARDS, corticosteroids increased risk of hospitalized infection (HR, 1.56; 95% CI, 1.20-2.04)	Fair
*Lacaille et al., 2008[194]	Retrospective cohort 27,710 162,720 person years	Pts with RA from British Columbia, Canada	Oral DMARDs, corticosteroids	Adjusted Rate Ratio for serious infections: DMARDs + corticosteroids:1.63 (95% CI, 1.5-1.77); DMARDs alone: 0.92 (95% CI, 0.85-1.0)	Fair
*McDonald et al., 2009[210]	Retrospective cohort 20,357 7 years	Pts with RA in the Veterans Affairs healthcare system	Traditional DMARDs	No increased risk of infection with oral DMARDs; SSZ associated with a lower risk of herpes zoster infection (HR, 0.44; 95% CI, 0.21-0.91)	Fair
*Smitten et al., 2008[196]	Retrospective cohort 24,530 26.6 months	Pts with RA from US PharMetrics data	MTX, LEF, HCQ, SSZ	MTX and HCQ decreased risk of hospitalized infection (RR, 0.81; 95% CI, 0.70-0.93; RR, 0.74; 95% CI, 0.62-0.89; respectively).	Good

* Study added during the 2010 update search; ADA, adalimumab; AERS, adverse events reporting system; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GI, gastrointestinal; GPRD, General Practict Research Database; HCQ, hydroxychloroquine; HR, hazard ratio; INF, infliximab; LEF, leflunomide; MTX, methotrexate; N/A, not applicable; NR, not reported; OR, odds ratio; PM, PharMetrics; PNL, prednisolone; PRED, prednisone; Pts, patients; PY, person years; RA, rheumatoid arthritis; RR, rate ratio; SSZ, sulfasalazine; TB, tuberculosis.

Table 49. Infection in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Smitten et al., 2007[197]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	Pts with RA the PM database and UK GPRD	Corticosteroids, traditional DMARDs, biologic DMARDs	Risk of herpes zoster infection with traditional DMARDS alone (PM: OR,1.37; 95% CI, 1.18-1.59; GPRD: 1.27; 95% CI, 1.10-1.48)	Fair
Wolfe et al., 2006[208]	Prospective cohort 16,788 3.5 years	RA diagnosis	PRED, LEF, SSZ, MTX, ETA, INF, ADA	Risk for hospitalization for pneumonia: PRED HR 1.7 (95% CI, 1.5-2.0), LEF HR 1.2 (95% CI, 1.0-1.5). No significant differences for SSZ, MTX	Fair

112,300 patients with RA and found only a slight increase in risk of developing TB among oral DMARD users (RR, 1.2; 95% CI, 1.0-1.5).[192] Subgroup analyses from this study illustrate that the risk of developing TB is lower among patients concomitantly receiving corticosteroids (RR, 0.6; 95% CI, 0.4-1.0) compared with patients not receiving corticosteroids (RR, 1.4; 95% CI, 1.1-1.8).

One fair-rated retrospective cohort study examined the risk of herpes zoster infection with oral DMARDs.[197] This study analyzed data from a US commercial claims database as well as data from the UK General Practice Research Database. Analyses from both databases revealed an increased risk of herpes zoster infection with oral DMARDs (US data: OR, 1.37; 95% CI, 1.18-1.59; UK data: OR, 1.27; 95% CI, 1.10-1.48).

Interstitial lung disease. Two fair-rated observational studies evaluated the risk of interstitial lung disease with oral DMARD treatment (Table 50).[190,200] One 5-year retrospective cohort study examined claims data from 62,734 patients with RA given a DMARD 1 year prior to the date of diagnosis of interstitial lung disease.[190] Patients were divided into four categories: leflunomide, methotrexate, biologic agents (infliximab, etanercept, adalimumab, anakinra), and traditional DMARDs (antimalarials, sulfasalazine, gold salts, minocycline, penicillamine, azathioprine, cyclosporine, other cytotoxic agents). In patients diagnosed with interstitial lung disease, those prescribed leflunomide were at increased risk compared to patients prescribed other DMARDs (RR, 1.9; 95% CI, 1.1-3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8-2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4-1.5).[190] The second study analyzed data from 17,598 patients with RA followed prospectively in the National Databank for Rheumatic Diseases.[200] Cases of interstitial lung disease were identified by searching patient descriptive reports, hospital records, physician records, and mortality records. The incidence of hospitalization for interstitial lung disease was 260 per 100,000 patient years. No significant association was observed between current or past treatment with MTX, hydroxychloroquine, leflunomide, or sulfasalazine. Current and past treatment with prednisone, as well as current treatment with infliximab, etanercept, and cyclophosphamide was associated with an increased risk of interstitial lung disease.

Table 50. Interstitial lung disease in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Suissa et al., 2006[190]	Retrospective cohort (claims data) 62,734 5 years	RA diagnosis, on DMARD	MTX, LEF, biologics, traditional DMARDs	Risk of interstitial lung disease in LEF compared to other DMARDs: OR, 1.9 (95% CI, 1.1-3.6). No elevation noted in LEF pts with no history of MTX or no history of interstitial lung disease	Fair
*Wolfe et al., 2007[200]	Prospective cohort 17,598 up yo 3.5 years	RA pts in the National Databank for Rheumatic Diseases	MTX,LEF,HCQ,SSZ	No significant association between current and past MTX, LEF, HCQ, and SSZ use and hospitalization for interstitial lung disease.	Fair

* Study added during the 2010 update search; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; Pts, patients; RA, rheumatoid arthritis; SSZ, sulfasalazine;.

Malignancies. Two observational studies assessed the risk of malignancy with oral DMARDs (Table 51). One retrospective study examined 756 patients with RA to determine the risk of lymphoma over a 30-year period.[211] This was a matched case-control of consecutive Swedish RA patients in whom lymphoma was diagnosed. Controls were RA patients matched for sex, year of birth, year of RA diagnosis, and county of residence. The investigators found no association between lymphoma and use of DMARDs, including MTX (OR, 0.7; 95% CI, 0.3-1.6) or sulfasalazine (OR, 0.6; 95% CI, 0.3-1.1).

Table 51. Malignancies in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Baecklund et al., 2006[211]	Retrospective cohort 756 30 years	RA pts with diagnosis of lymphoma	MTX, SSZ	No significant risk for lymphoma for MTX or SSZ	Good
Chakravarty et al., 2005[212]	Retrospective cohort 15,789 (RA) 4 years	RA pts	PRED, LEF, MTX	PRED was associated with increased risk for non melanoma skin cancer PRED: HR 1.28 (95% CI, 1.05-1.55, *P* = 0.014)	Fair

* Study added during the 2010 update search; CI, confidence interval; HR, hazard ratio; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; PRED, prednisone; Pts, patients; RA, rheumatoid arthritis; SSZ, sulfasalazine;.

Another retrospective cohort study examined the risk of nonmelanoma skin cancer in 15,789 U.S. patients with RA who were participating in a registry and returned semi-annual questionnaires over a 4-year period in which they reported any current malignancies.[212] Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR, 1.28; $P = 0.014$). They found no association between this neoplasm and leflunomide plus MTX.

Other adverse events. Three studies provided additional data on oral DMARD-related adverse events (Table 52). One study evaluated the relationship of treatment with the incident

rate of septic arthritis;[199] one study examined whether MTX and leflunomide increased the risk of wound healing complications (both in combination with corticosteroids) in RA patients undergoing elective orthopedic surgery;[213] and one study assessed whether oral DMARDs were related to sinus problems.[214]

Table 52. Other specific adverse events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Edwards et al., 2007[199]	Retrospective case-control 136,997 15 years	RA pts (n = 34,250)	Several oral DMARDs, including MTX, LEF, HCQ, SSZ	Incident rate of septic arthritis in RA pts receiving DMARDs: 2.14 (95% CI, 1.64–2.78; *P* < .001) times greater than in patients with RA not receiving DMARDs.	Fair
*Fuerst et al., 2006[213]	Prospective cohort 201 6 weeks+	Pts with RA or PsA (n = 8) undergoing elective orthopedic surgery	MTX, LEF, both in combination with corticosteroids	LEF+corticosteroids significantly increased the risk for wound healing complications compared to MTX+corticosteroids (40.6% vs. 13.6%, *P* = 0.01).	Fair
*Michaud and Wolfe, 2006[214]	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the National Data Bank for Rheumatic Diseases (NDB) study	MTX, HCQ, LEF, SSZ	Association (OR) of treatment with visits to physician for sinus problems was MTX: 1.06 (95% CI, 0.93-1.20; *P* = 0.371); HCQ: 1.08 (95% CI, 0.93-1.25; *P* = 0.313) LEF: 0.84 (95% CI, 0.70-0.99; *P* = 0.041) SSZ: 0.68 (95% CI, 0.51-0.90; *P* = 0.007)	Fair

* Study added during the 2010 update search; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; Pts, patients; RA, rheumatoid arthritis; SSZ, sulfasalazine

In a retrospective cohort study of 136,977 patients with RA from the UK General Practice Research Database, the incidence rate of septic arthritis was increased for patients receiving oral DMARDs compared with patients not receiving oral DMARDs (IR, 2.14; 95% CI, 1.64-2.78; $P < 0.001$).[199] The increased incidence rate varied by drug, and was highest for penicillamine (IRR, 2.51; 95% CI, 1.29-4.89), sulfasalazine (IRR, 1.74; 95% CI, 1.04-2.91), and prednisolone (IRR, 2.51; 95% CI, 1.93-4.46).

A prospective cohort study of 201 patients with RA undergoing orthopedic surgery assessed whether leflunomide or methotrexate given in combination with corticosteroids increased the risk of wound healing complications.[213] In comparison with patients who received MTX, the risk of postoperative wound healing complications was significantly higher than in patients who received leflunomide (13.6% vs. 40.6%; $P = 0.01$).

A cross-sectional analysis of 7,243 patients followed in the National Data Bank for Rheumatic Diseases assessed whether treatment with oral DMARDs was associated with physician visits for sinus problems. Treatment with MTX and hydroxychloroquine were not

associated with an increased risk of sinus problems, and leflunomide and sulfasalazine had a slight protective effect (respectively, OR, 0.84; 95% CI, 0.70-0.99; $P = 0.041$; and OR, 0.68; 95% CI, 0.51-0.90; $P = 0.007$).

Biologic DMARDs. This section follows a similar format as the detailed analysis of corticosteroid and oral DMARD sections above, where results for overall tolerability are presented first, followed by general adverse events and then specific adverse events. This section follows a slightly different format to accommodate the presentation of quantitative analyses and detailed adverse event data. Data on tolerability and adverse events for biologic DMARDs are presented as follows: (1) results of quantitative analyses for withdrawal data; and (2) additional discontinuation data not captured by the quantitative analyses, (3) overall adverse event rates and reports of serious adverse events (not otherwise discussed in the specific adverse events section but that are reflective of tolerability profile), and (4) specific adverse events.

Overall tolerability quantitative analyses. Randomized controlled trials identified by our systematic literature search were screened for inclusion in the meta-analysis of overall tolerability. This included mostly fair-to-good quality efficacy trials, as well as some RCTs otherwise included in a good quality meta-analysis covered in KQ1 or KQ2 of this report. Trials were excluded if they did not meet pre-established eligibility criteria for study design or duration, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest. Eligible studies had to compare one more biologic DMARD with placebo. Concomitant use of MTX was allowed, as long as it was consistently used in the biologic DMARD and placebo groups. The outcome of interest was withdrawal (total, due to adverse events and due to lack of efficacy) of biologic DMARD treatment. Trials had to be at least 12 weeks in duration. If multiple withdrawal rates were reported for more than one time point, we used the time point identified for the primary outcome measure. We limited included data to FDA approved dosage ranges to achieve better equivalency across drugs. Note that sample sizes may not match sample sizes reported in individual trials since we excluded dosing arms outside of the FDA recommend range. We identified a total of 37 studies that were relevant for 9 biologics. These included 4 studies for abatacept, 8 for adalimumab, 4 for anakinra, 3 for certolizumab, 4 for etanercept, 2 for golimumab, 6 for infliximab, 4 for rituximab and 3 for tocilizumab. Table 53 lists trials included in the meta-analyses, along with the corresponding withdrawal rates overall and by reason.

Table 53. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses

				Number of Withdrawals by Reason		
Author, year	**Duration (weeks)**	**Comparison**	**N**	**Overall**	**Tolerability**	**Efficacy**
Kremer, 2005[92]	52	Abatacept	115	26‡	6‡	13‡
		Placebo	119	48	11	30
Kremer, 2006[94]	52	Abatacept	433	48‡	18‡	13‡
		Placebo	219	57	4	40
Schiff, 2008[53]	26	Abatacept	156	9‡	2‡	2‡
		Placebo	55	3	1	1
Weinblatt, 2006(Weinblatt, 2006 #2031}	52	Abatacept	959	123‡	52‡	NR
		Placebo	482	87	20	NR
Breedveld, 2006[62]	104	Adalimumab	268	65**	32	13
		Placebo	257	112	19	46

Kg, kilogram; mg, millogram; NR, not reported; NS, not significant
$P < 0.05$; **$P < 0.01$; † P = NS; ‡ P = NR

Table 53. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses (continued)

Author, year	Duration (weeks)	Comparison	N	Number of Withdrawals by Reason		
				Overall	Tolerability	Efficacy
Furst,2003[100]	24	Adalimumab	318	28‡	9‡	5‡
		Placebo	318	30	8	14
Kim, 2007[255]	18	Adalimumab	65	6‡	4‡	NR
		Placebo	63	4	4	NR
Keystone,2004[99]	52	Adalimumab 20 mg	212	44‡	16‡	6‡
		Adalimumab 40 mg	207	48‡	26‡	6‡
		Placebo	200	60	13	23
Miyasaka, 2008[104]	24	Adalimumab	91	16‡	12‡	NR
		Placebo	87	7	4	NR
Van de putte, 2003[98]	12	Adalimumab 20 mg	72	10‡	0‡	2‡
		Adalimumab 40 mg	70	12‡	3‡	0‡
		Placebo	70	24	1	1
Van de putte, 2004[101]	26	Adalimumab 20 mg	112	33‡	3‡	27‡
		Adalimumab 40 mg biweekly	113	32‡	6‡	20‡
		Adalimumab 40 mg weekly	103	15‡	3‡	10‡
		Placebo	110	62	1	56
Weinblatt, 2003[102]	16	Adalimumab	67	NR	0‡	NR
		Placebo	62	NR	2‡	NR
Breshnihan, 1998[105]	24	Anakinra 75 mg/day	116	22‡	7‡	14‡
		Anakinra 150 mg/day	116	28‡	11‡	11‡
		Placebo	121	32	5	24
Cohen, 2002[108]	24	Anakinra 1 mg/kg/day	59	13‡	8‡	4‡
		Anakinra 2 mg/kg/day	72	19‡	11‡	4‡
		Placebo	74	14	3	5
Cohen, 2004[110]	24	Anakinra	250	NR	14‡	NR
		Placebo	251	NR	13‡	NR
Fleishmann, 2003[225]	24	Anakinra	1116	241‡	149‡	NR
		Placebo	283	53‡	26‡	NR
Fleishmann, 2009[140]	24	Certolizumab	111	35‡	5‡	24**
		Placebo	109	81	2	75
Keystone, 2008[167]	52	Certolizumab	390	116‡	22‡	68‡
		Placebo	199	156	3	125
Smolen, 2009[222]	24	Certolizumab	246	65‡	6‡	53‡
		Placebo	127	110	2	107
Klareskog, 2004[73]	52	Etanercept	231	38‡	24‡	6‡
		Placebo	228	69	32	21
Moreland,1997[121]	12	Etanercept	44	3‡	NR	2‡
		Placebo	44	21	NR	19
Moreland,1999[117]	26	Etanercept	78	19**	2†	12**
		Placebo	80	54	3	42
Weinblatt,1999[119]	24	Etanercept	59	2‡	2‡	0‡
		Placebo	30	6	1	4
Kay, 2008[141]	16	Golimumab	35	4‡	2‡	2‡
		Placebo	35	6	3	3
Keystone, 2009[142]	16	Golimumab	89	2‡	2‡	0‡
		Placebo	133	6	4	0
Abe, 2006[130]	14	Infliximab 3 mg/kg	49	3‡	1‡	0‡
		Infliximab 10 mg/kg	51	3‡	4‡	0‡
		Placebo	47	5	1	3
Lipsky, 2000[128]	54	Infliximab 3 mg/kg every 8 wks	86	23‡	5‡	17‡
		Infliximab 3 mg/kg every 4 wks	86	20‡	9‡	19‡
		Infliximab 10 mg/kg every 8 wks	87	12‡	4‡	6‡
		Infliximab 10 mg/kg every 4 wks	81	16‡	8‡	7‡
		Placebo	88	44	7	32

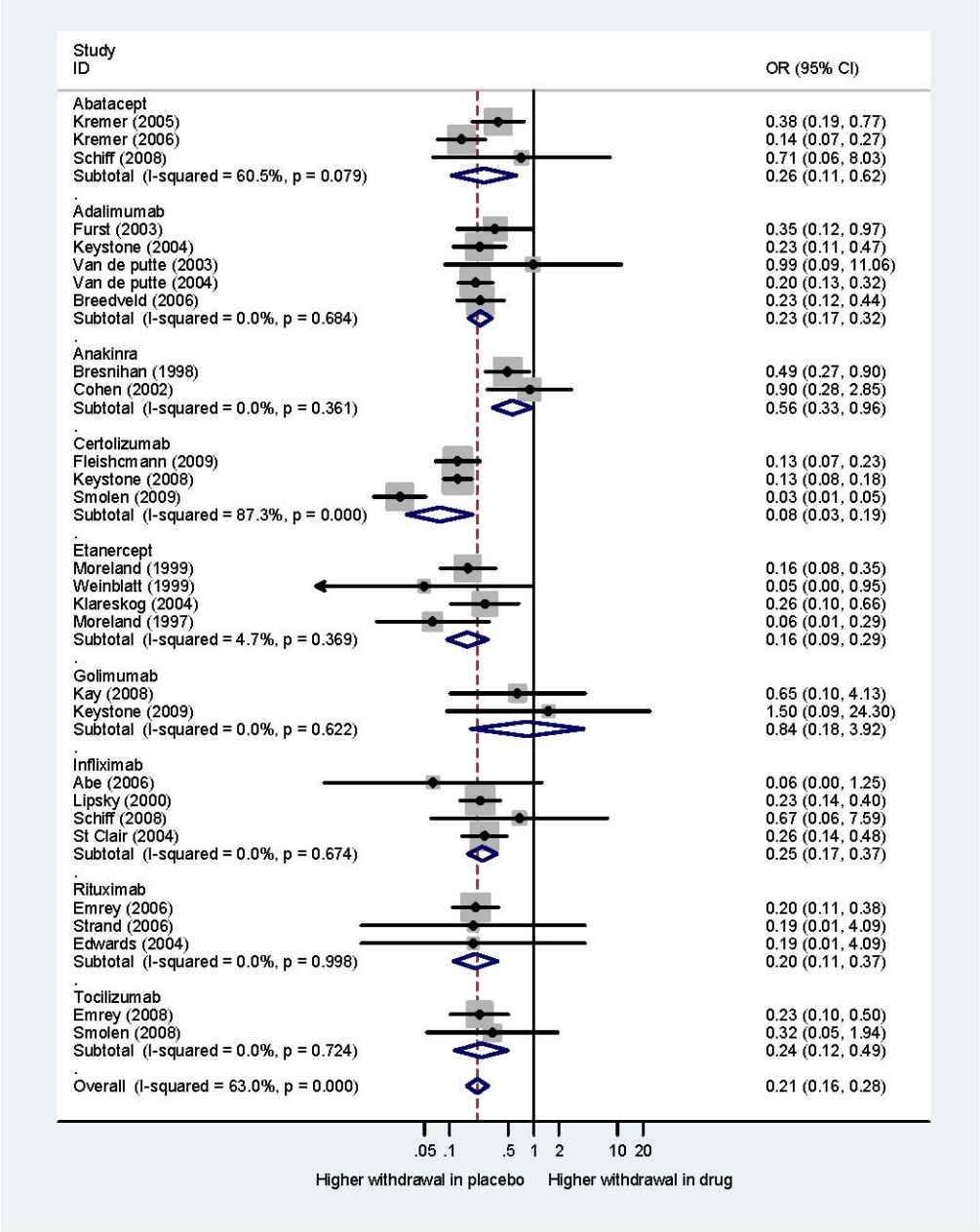
Table 53. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses (continued)

Author, year	Duration (weeks)	Comparison	N	Number of Withdrawals by Reason		
				Overall	Tolerability	Efficacy
Schiff, 2008[53]	26	Infliximab	165	13‡	8‡	2‡
		Placebo	55	2	1	1
St Clair, 2004[69]	54	Infliximab 3 mg/kg	373	66‡	34‡	7‡
		Infliximab 6 mg/kg	375	75‡	35‡	12‡
		Placebo	298	60	9	27
Westhovens, 2006[132]	22	Infliximab 3 mg/kg	360	26‡	18‡	NR
		Infliximab 10 mg/kg	361	32‡	20‡	NR
		Placebo	363	23	8	NR
Zhang, 2006[133]	18	Infliximab	87	9‡	6‡	NR
		Placebo	86	15	4	NR
Cohen, 2006[135]	24	Rituximab	309	55‡	2‡	NR
		Placebo	208	96	8	16
Edwards, 2004[71]	24	Rituximab	40	1‡	1‡	1‡
		Placebo	40	3	0	2
Emery, 2006[134]	24	Rituximab	192	27‡	6‡	16‡
		Placebo	149	52	0	46
Strand, 2006[256]	24	Rituximab	40	1‡	1‡	0‡
		Placebo	40	3	1	2
Emery, 2008[145]	24	Tocilizumab 4 mg/kg	163	24‡	10‡	6‡
		Tocilizumab 8 mg/kg	175	23‡	11‡	4‡
		Placebo	160	30	10	19
Genovese, 2008[146]	16	Tocilizumab	805	53‡	32‡	NR
		Placebo	415	43	8	NR
Smolen, 2008[139]	24	Tocilizumab 4 mg/kg	214	25‡	14‡	2‡
		Tocilizumab 8 mg/kg	205	13‡	12‡	0‡
		Placebo	204	12	6	3

Overall tolerability: quantitative analysis of total withdrawals for biologic DMARD vs. placebo. Using random effects models, we calculated the pooled odds ratios of total treatment withdrawal for each biologic relative to placebo (Figure 4). Overall, patients on biologics were approximately half as likely to withdraw from the treatment as compared to the patients on placebo. Among the individual biologics, the pooled estimates were statistically significant for abatacept (OR, 0.52; 95% CI, 0.34-0.81), adalimumab (OR, 0.62; 95% CI, 0.38-1.00), certolizumab (OR, 0.08; 95% CI, 0.04-0.20), etanercept (OR, 0.19; 95% CI, 0.08-0.46) and rituximab (OR, 0.27; 95% CI, 0.20-0.37). Patients taking these drugs were less likely to withdraw from a trial than patients taking placebo. The likelihood of withdrawal of anakinra, infliximab, tocilizumab, and golimumab was not statistically significantly different than placebo. We estimated heterogeneity using I^2 statistic. I^2 was found to be 88%, which suggested a high amount of heterogeneity among the studies. This heterogeneity may be attributed to several reasons. First, real heterogeneity may exist across study designs and patient populations. Second, the withdrawal outcome—which measures a combination of withdrawals due to adverse events and withdrawals due to lack of efficacy—can be a potential source of heterogeneity. These reasons for withdrawal may not be in agreement with each other, and introduce measurement concerns when combining studies. For example, total withdrawal for one drug can be higher due to the fact that it is less efficacious while for another drug, it might just be because of high adverse events. This can lead to potential heterogeneity concerns when looking across all studies. We assessed publication bias using funnel plots. Visual examination of funnel plots illustrated

potential for some publication bias. However, given the small number of component studies, results of these tests must be viewed cautiously.

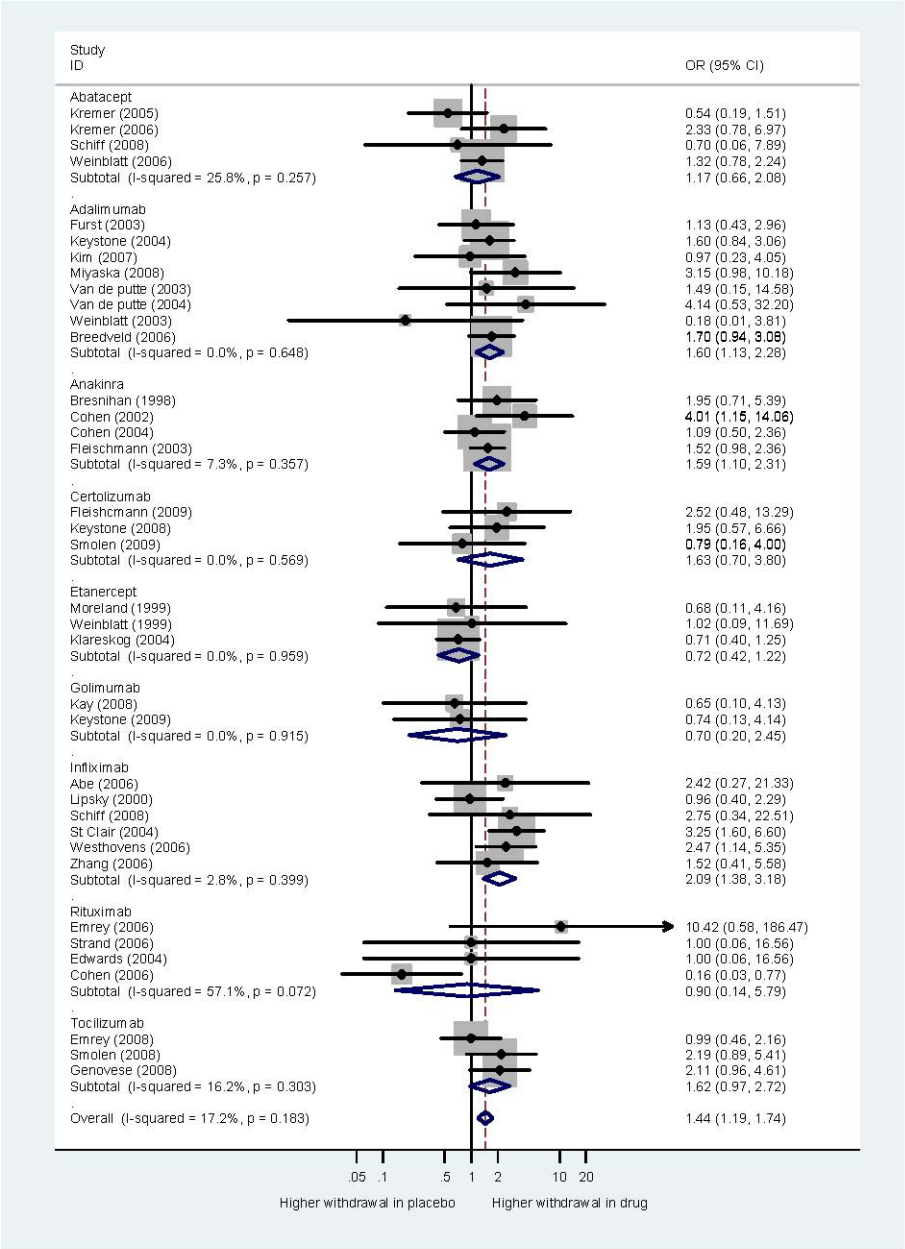
Figure 4. Meta-analysis of withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs.



Overall tolerability: quantitative analysis of withdrawals due to lack of efficacy for biologic DMARD vs. placebo. We also calculated the pooled odds ratios of treatment withdrawal because of lack of efficacy for each biologic relative to placebo (Figure 5). Patients randomized to biologic DMARDs were nearly 5 times less likely to withdraw from the treatment due to lack of efficacy as compared to the patients on placebo (OR, 0.21; 95% CI, 0.16-0.28). All individual biologics, except golimumab, were less likely to be withdrawn compared to placebo for lack of efficacy. I^2 was found to be 63%, which suggested slightly lower heterogeneity when just

looking at lack of efficacy. This suggests that some of the heterogeneity with the total withdrawals analysis was probably due to combining withdrawals for all the reasons together. Visual examination of funnel plots did not show evidence of publication bias.

Figure 5. Meta-analysis of withdrawals due to adverse events in randomized controlled trials of biologic DMARDs.



Overall tolerability: quantitative analysis of withdrawals due to adverse events for biologic DMARD vs. placebo. We also calculated the pooled odds ratios of treatment withdrawal because of adverse events for each biologic relative to placebo. It was found that patients on biologics were 44% more likely to withdraw from the treatment due to adverse events as compared to the patients on placebo (OR, 1.44; 95% CI, 1.19-1.74). Among individual biologics, the pooled estimates for adalimumab (OR, 1.60; 95% CI, 1.13-2.28), anakinra (OR, 1.59; 95% CI, 1.10-

2.31), and infliximab (OR, 2.09; 95% CI, 1.38-3.18) were statistically significant, suggesting that patients on these drugs were more likely to withdraw from the trial due to adverse events than patients on placebo. Heterogeneity I^2 was found to be 17.2%, which suggests low heterogeneity among this outcome in these studies. Visual examination of funnel plots did not show evidence of publication bias.

Overall tolerability: mixed treatment comparisons for overall withdrawals. Indirect comparisons were made using the studies described in Table 29 and shown in meta-analyses (Figures 6 and 7). Thirty-four studies contributed data to the analysis of overall withdrawals. Results are presented for each possible drug-drug comparison (Figure 6). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer total withdrawals for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable withdrawal rate. Most comparisons suggest no difference in overall withdrawals. A couple exceptions were found. Namely, certolizumab pegol, etanercept, and rituximab had more favorable overall withdrawal profiles than most other biologic DMARDs. For certolizumab pegol, results were statistically significant for the comparison with abatacept (OR, 0.21; 95% CI, 0.07-0.48), adalimumab (OR, 0.18; 95% CI, 0.07-0.38), anakinra (OR, 0.11; 95% CI, 0.03-0.26), golimumab (OR, 0.14; 95% CI, 0.04-0.89), infliximab (OR, 0.15; 95% CI, 0.33), and tocilizumab (OR, 0.11; 95% CI, 0.04-0.34). For etanercept, results were statistically significant for the comparison with abatacept (OR, 0.41; 95% CI, 0.13-0.93), adalimumab (OR, 0.35; 95% CI, 0.12-0.75), anakinra (OR, 0.16; 95% CI, 0.06-0.50), infliximab (OR, 0.29; 95% CI, 0.10-0.65), and tocilizumab (OR, 0.21; 95% CI, 0.08-0.66). For rituximab, results were statistically significant for only the comparison with anakinra (OR, 0.22; 95% CI, 0.09-0.75), infliximab (OR, 0.42; 95% CI, 0.14-0.97), and tocilizumab (OR, 0.29; 95% CI, 0.11-0.99). These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals.

Overall tolerability: mixed treatment comparisons for withdrawals due to lack of efficacy. Indirect comparisons were made using the studies described in Table 29 and shown in meta-analyses (Figure 4). Twenty-six studies contributed data to the analysis of withdrawals due to lack of efficacy. Results are presented for each possible drug-drug comparison (Figures 8 and 9). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer withdrawals due to lack of efficacy for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable efficacy-related withdrawal rate. Most comparisons suggest no difference in withdrawals due to lack of efficacy. Similar to the analysis of overall withdrawals, certolizumab pegol had lower rates of withdrawals due to lack of efficacy than abatacept (OR, 0.43; 95% CI, 0.16-0.89), adalimumab (OR, 0.41; 95% CI, 0.18-0.77), anakinra (OR, 0.14; 95% CI, 0.06-0.40), and infliximab (OR, 0.32; 95% CI, 0.15-0.79). Both etanercept (OR, 0.20; 95% CI, 0.08-0.63) and rituximab (OR, 0.23; 95% CI, 0.08-0.92) had fewer withdrawals due to lack of efficacy than anakinra, but results were not statistically significant for other comparisons with these drugs. These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals.

Overall tolerability: mixed treatment comparisons for withdrawals due to adverse events. Indirect comparisons were made using the studies described in Table 53 and shown in meta-analyses (Figure 5). Thirty-six studies contributed data to the analysis of withdrawals due to adverse events. Results are presented for each possible drug-drug comparison (Figures 10 and 11). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that

Figure 6. Mixed treatment comparisons for overall withdrawals in randomized controlled trials of biologic DMARDs (Part 1)

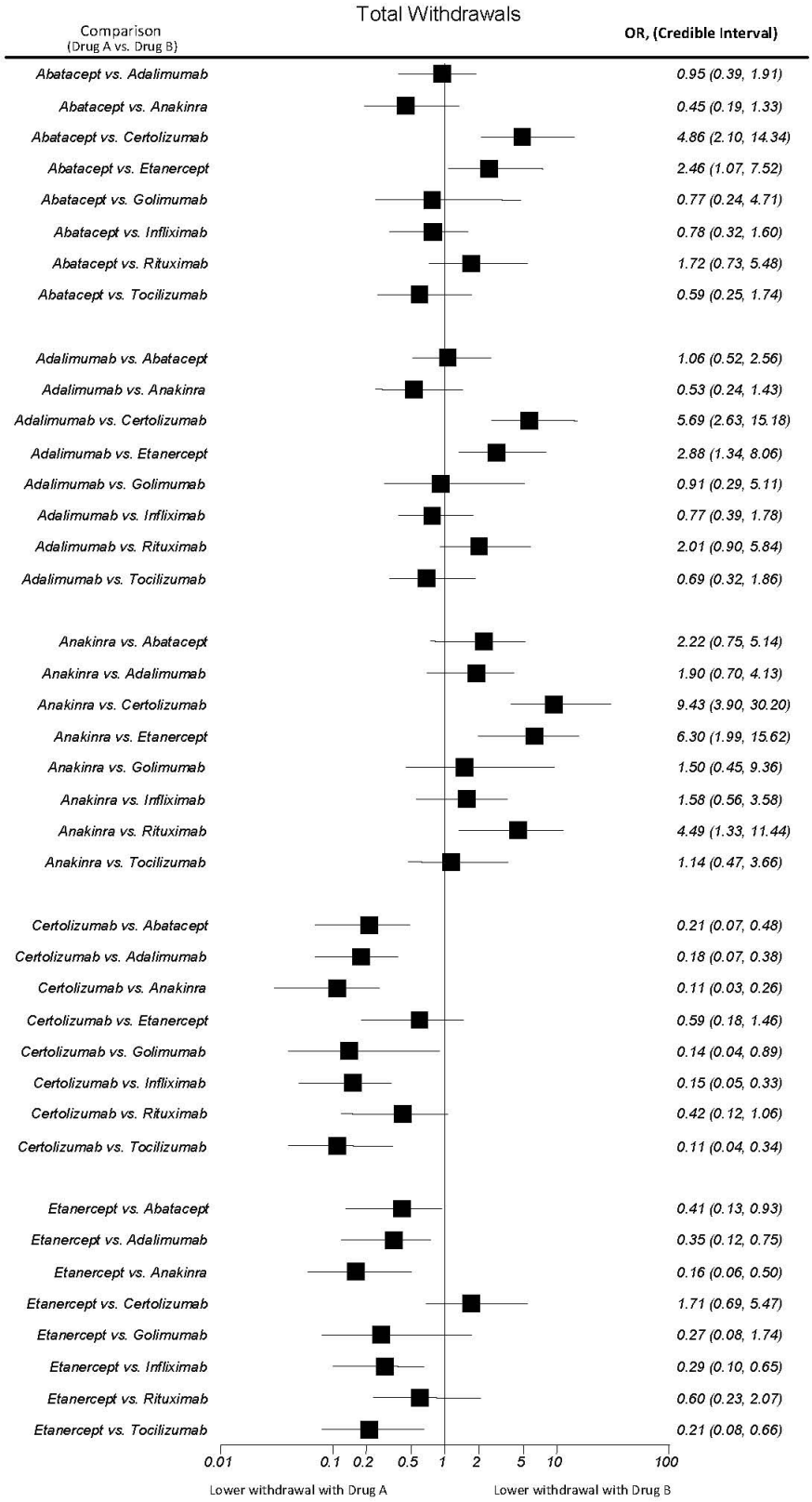


Figure 7. Mixed treatment comparisons for overall withdrawals in randomized controlled trials of biologic DMARDs (Part 2)

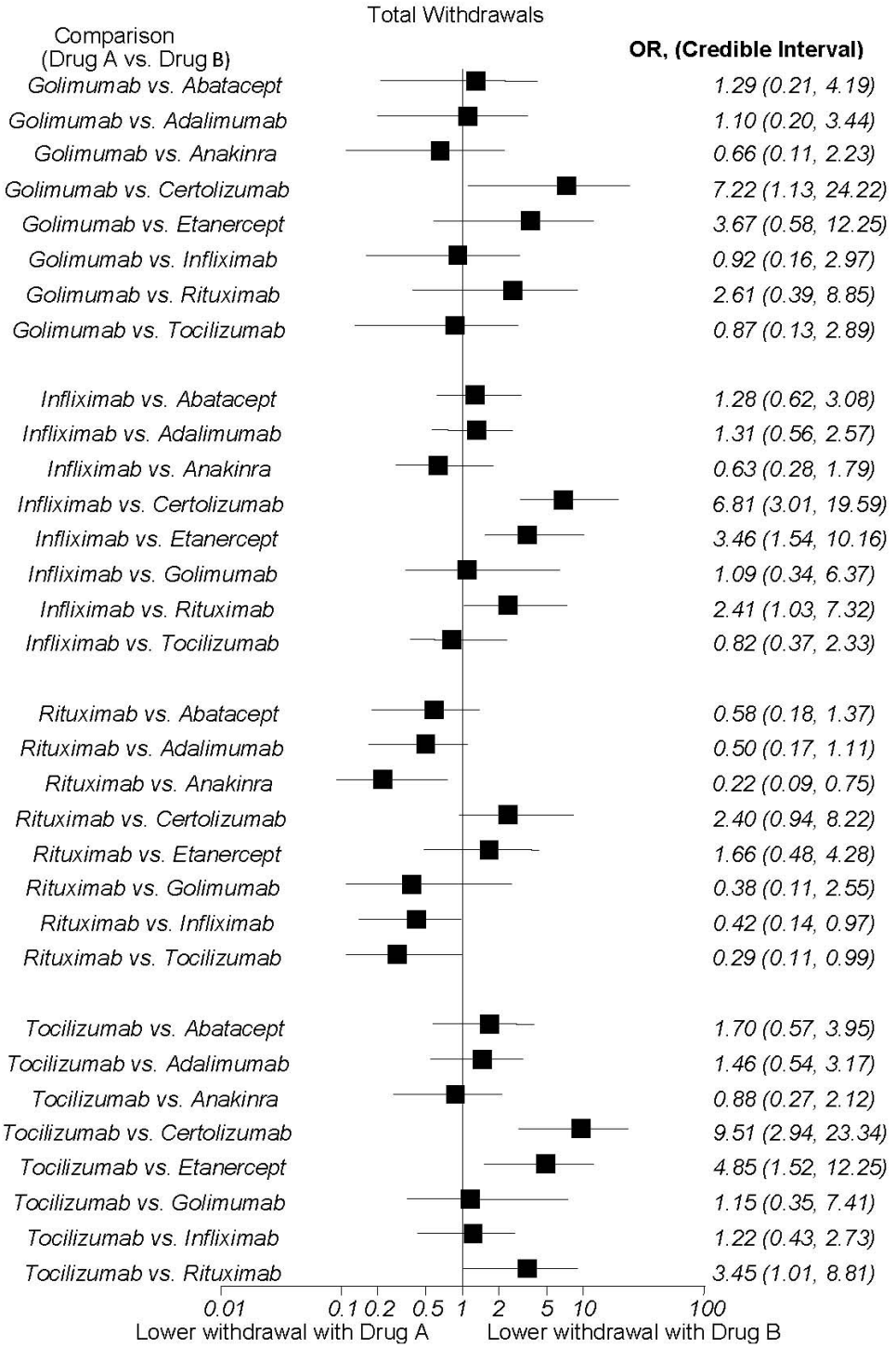


Figure 8. Mixed treatment comparisons for withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs (Part 1)

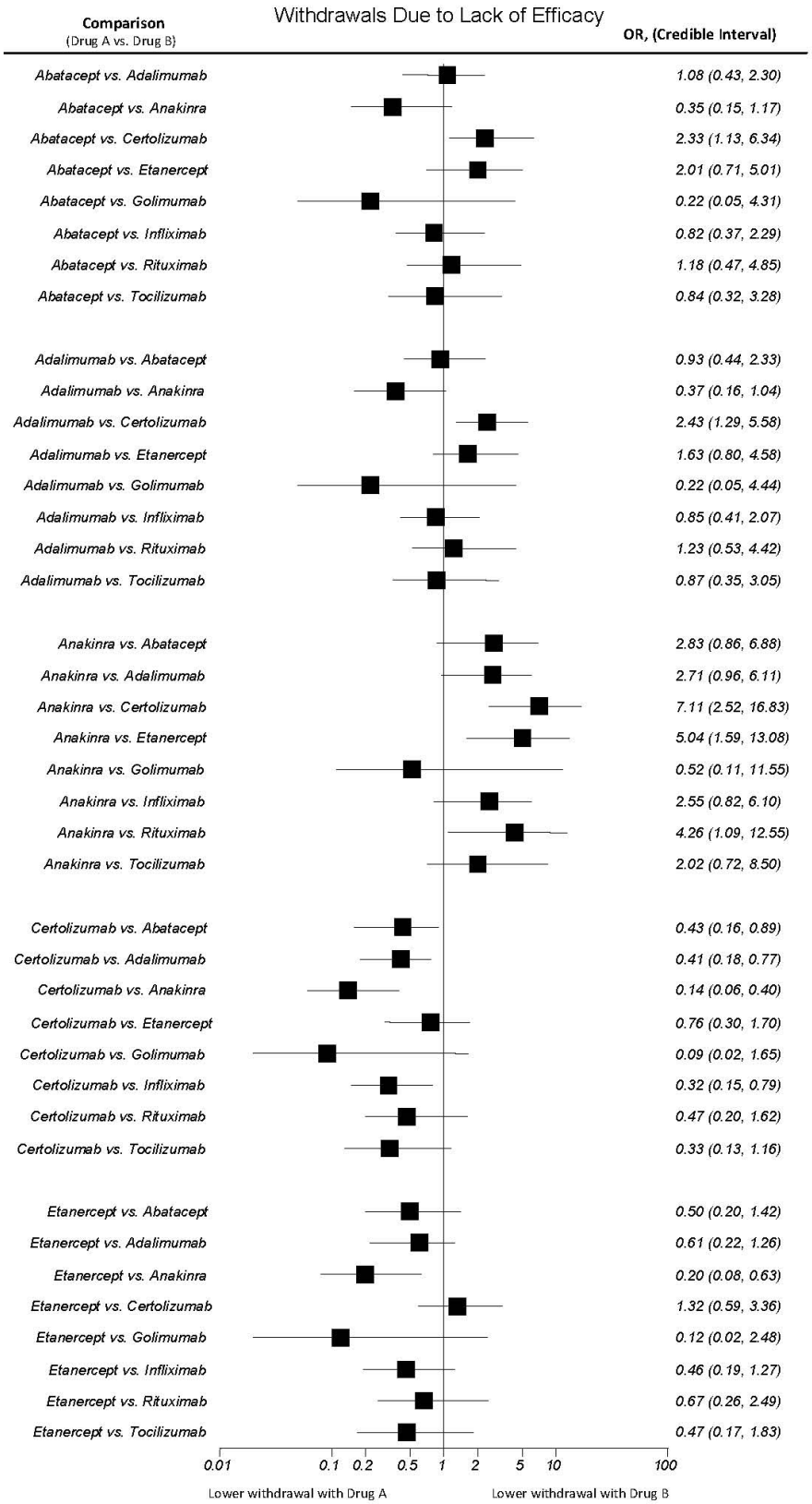


Figure 9. Mixed treatment comparisons for withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs (Part 2)

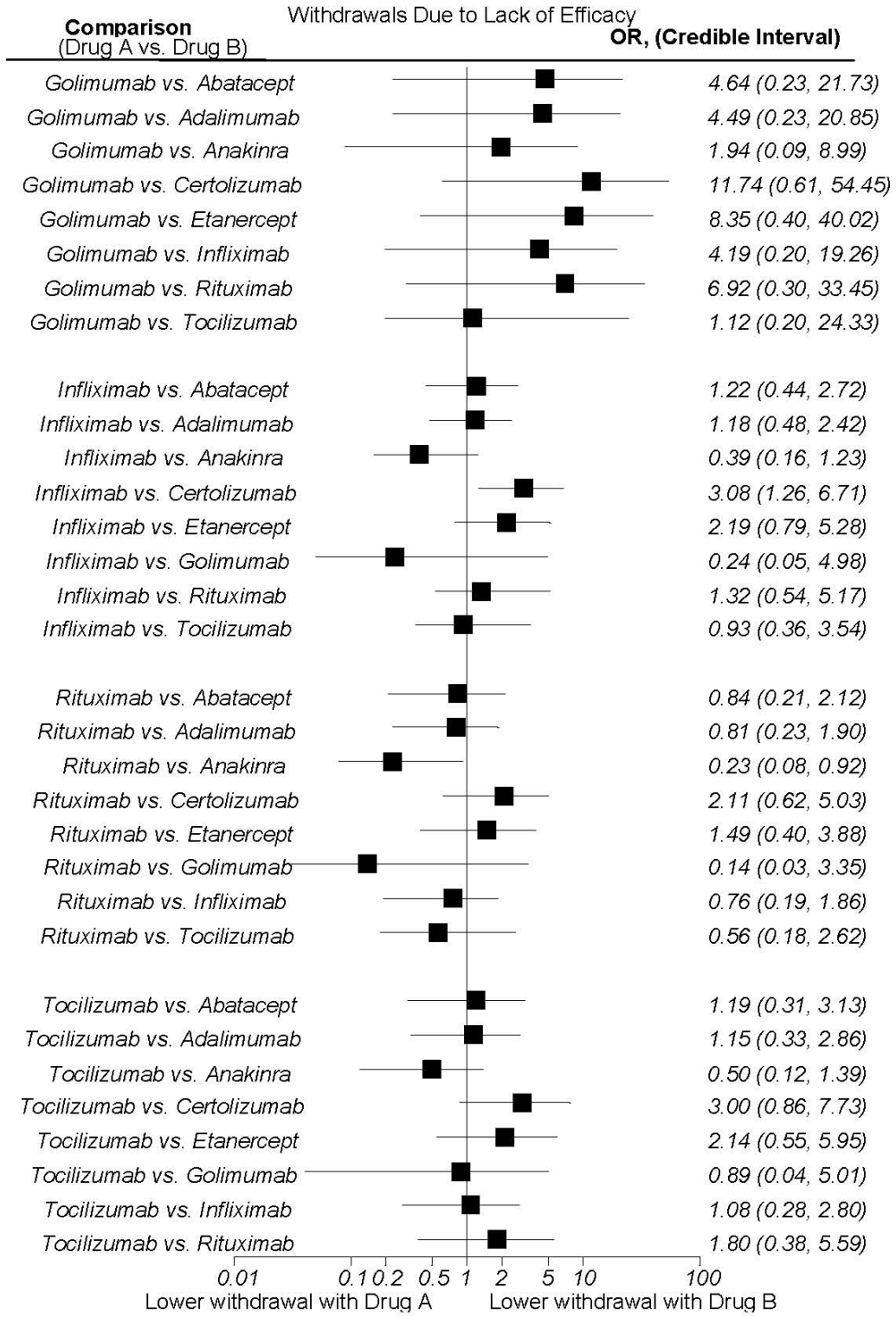


Figure 10. Mixed treatment comparisons for withdrawals due to adverse events in randomized controlled trials of biologic DMARDs (Part 1)

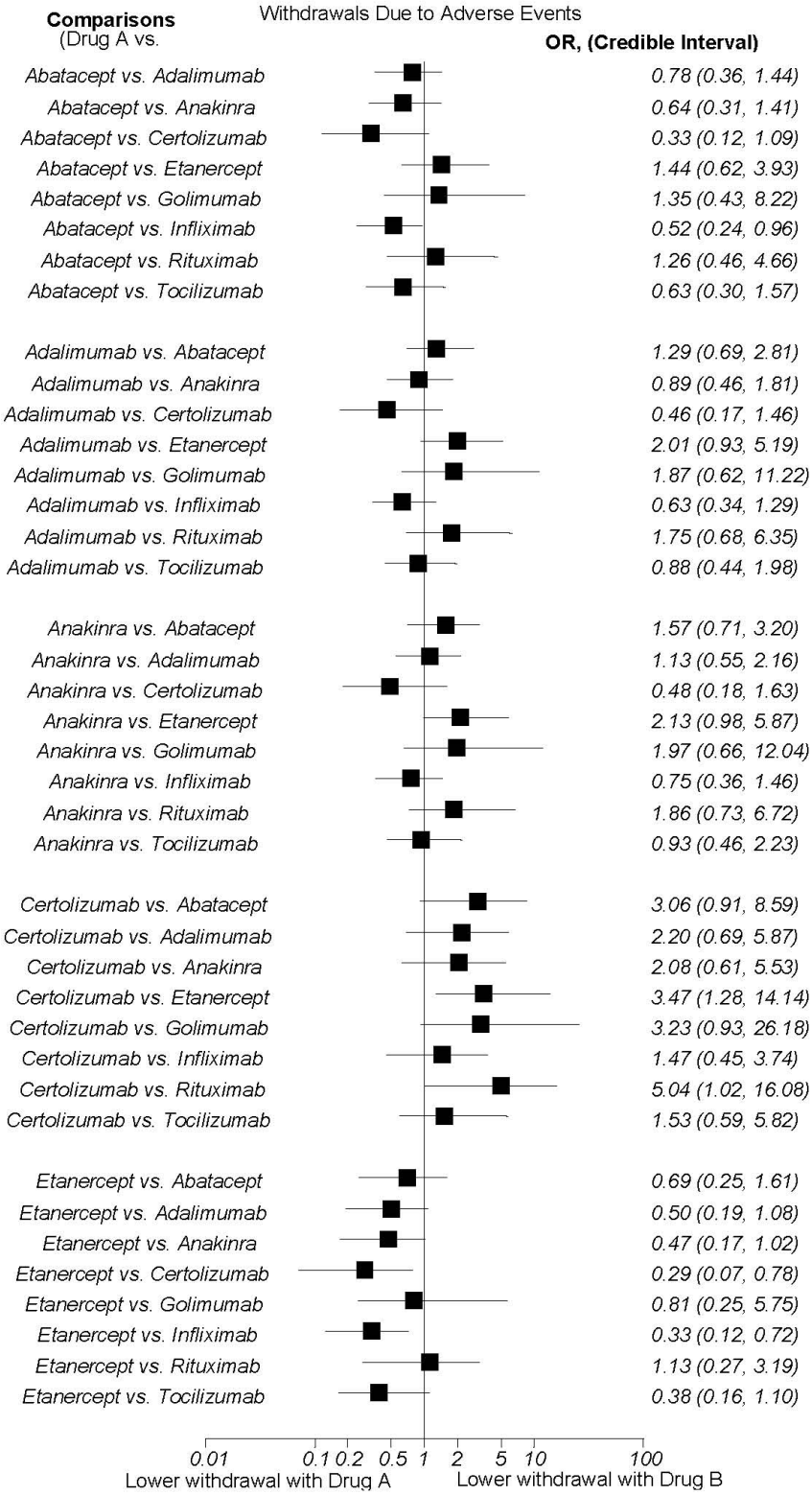
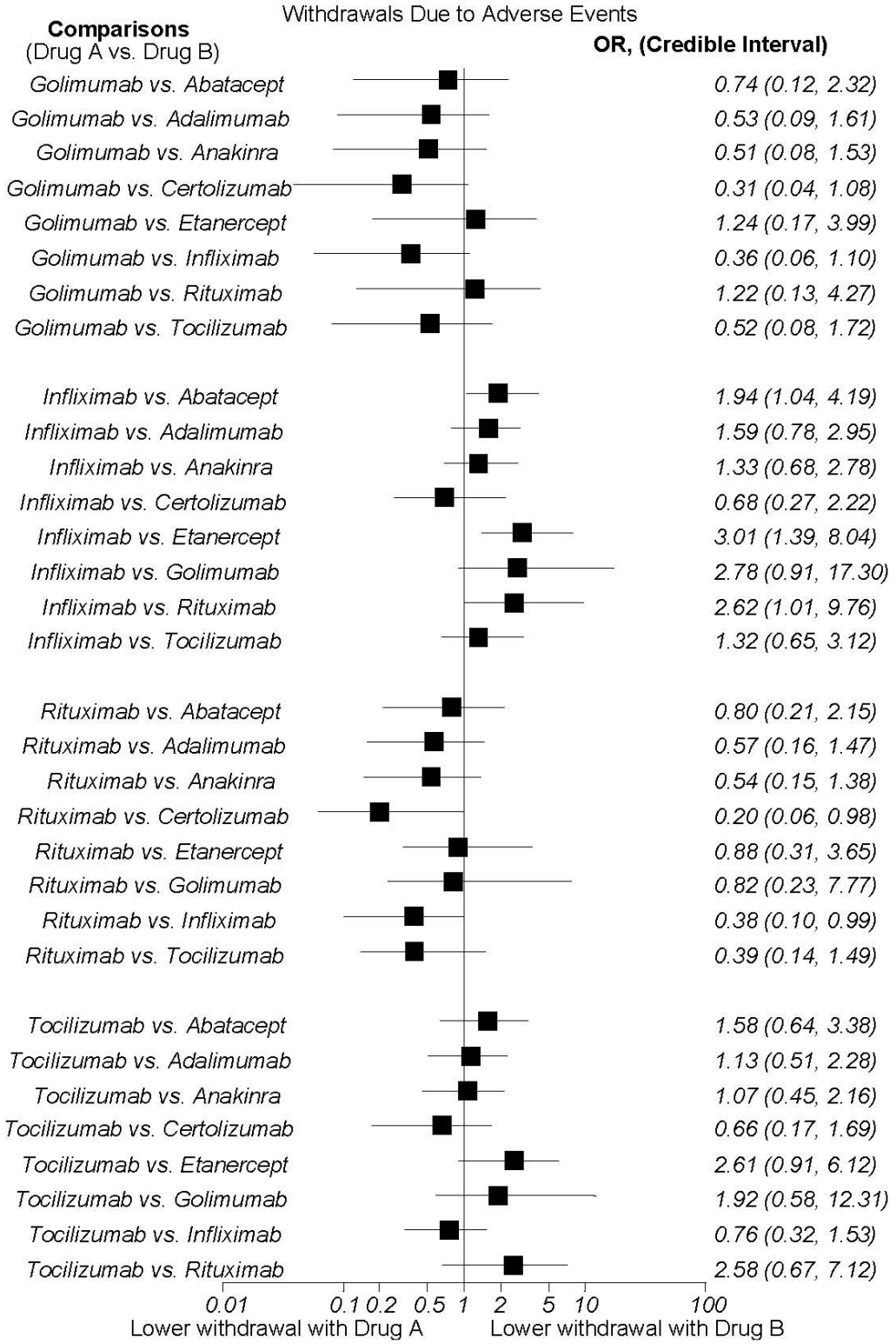


Figure 11. Mixed treatment comparisons for withdrawals due to adverse events in randomized controlled trials of biologic DMARDs (Part 2)



there were fewer withdrawals due to adverse events for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable adverse-event-related withdrawal rate. Most comparisons suggest no difference in withdrawals due to adverse events, with a couple exceptions. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. For certolizumab, the likelihood of withdrawal because of an adverse event was 3.5 times the likelihood with etanercept (OR, 3.47; 95% CI, 1.28-14.14) and 5 times the likelihood with rituximab (OR, 5.04; 95% CI, 1.02-16.08). For infliximab, the likelihood of withdrawal because of an adverse event was 3 times the likelihood with etanercept (OR, 3.01; 95% CI, 1.39-8.04) and 2.6 times the likelihood with rituximab (OR, 2.62; 95% CI, 1.01-9.76). Withdrawals because of adverse events trended towards being lower with etanercept and rituximab when comparing with other drugs, but results were not statistically signficant. All of these results should be interpreted cautiously because of the relatively small number of contributing studies and the very wide confidence intervals.

Biologic DMARDs – overall tolerability: studies on discontinuation rates not otherwise covered in quantitative analyses. Table 54 presents studies providing discontinued data not otherwise covered by quantitative analyses. One good-quality RCT compared etanercept with the combination of etanercept and abatacapt.[67] This RCT was not included in our meta-analysis of withdrawal rates because it compared two biologic DMARDs with a single biologic DMARD. Withdrawals due to adverse events occurred more in the combination group (11.8%) than in the monotherapy etanercept group (2.8%).

Table 54. Overall tolerability: discontinuation data not otherwise covered by quantitative analyses

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Duclos et al., 2006[216]	Retrospective cohort 770 7 years	Pts with inflammatory rheumatism (mostly RA) that received an anti-TNF agent	ADA, ETA, INF	ETA and ADA were better tolerated compared with INF (*P* = 0.06)	Fair
Flendrie et al., 2003[215]	Retrospective cohort study 230 NR	Pts with RA initiating therapy with biologic DMARDs	ADA, ETA, INF	No significant differences in discontinuation rates among anti-TNF drugs	Fair
*Hjardem et al., 2007[217]	Retrospective cohort 235 Varied	RA pts who had received 2+ biologics (INF, ETA, or ADA only)	ADA,ETA, INF	Similar reasons for switching treatments: Lack of efficacy; ADA 54%; ETA 44%; INF 45%. Adverse events: ADA 21%; ETA 22%; INF 34%	Fai
*Hyrich et al., 2007[218]	Prospective cohort 6,739 Minimum 6 months	Pts with RA in the British Society for Rheumatology Biologics Register	ADA, ETA, INF	Differences in reason for discontinuation (*P* = NR): Lack of efficacy; ADA 6.7%; ETA 4.8%; INF 10%. Adverse events: ADA 2.9%; ETA 2.6%; INF 8.4%	Fair

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; AE, adverse event; ANK, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; NR, not reported; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Table 54. Overall tolerability: discontinuation data not otherwise covered by quantitative analyses (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Karanikolas et al., 2008[77]	Prospective cohort 128 48 weeks	Pts with RA with inadequate response to traditional DMARD	MTX+ANK, LEF+ANK	No statistically significant differences in number of withdrawals due to AEs	Fair
Kristensen et al., 2006[219]	Prospective cohort 1,161 Up to 6 years	Pts with RA in Southern Sweden	ETA, ETA + MTX, INF, INF + MTX, other DMARDS	Early discontinuation 3-fold higher for INF than for ETA (P<0.001). Addition of MTX improved treatment continuation rates (P<0.01).	Fair
*Mertens and Singh, 2009[111]	Meta-analysis 2876 5 trials	Pts with RA included in placebo-controlled RCTs	ANK	No difference in total number of withdrawals, adverse events, or serious adverse events for ANK vs. placebo	Fair
*Weinblatt et al., 2007[67]	RCT 121 1 year (LTE: 2 years)	Pts with active RA	ETA, ABA+ETA	Discontinuation due to adverse events occurred more in ABA+ETA group (11.8%) vs. ETA group (2.8%).	Good
Zink et al., 2005[75]	Retrospective cohort study 1,523 1 year	Pts with RA who had a change in treatment regimen	ANK, ETA, INF, LEF	Significantly higher overall discontinuation rates for ANK than ETA and INF after 12 months; no differences in discontinuation rates due to adverse events	Good

Additional evidence on comparative discontinuation rates is provided by observational studies.[75,77,215-219] While some studies did not find clinically or statistically significant differences in drug discontinuation rates,[215,217] others did, generally suggesting higher discontinuation rates with infliximab.[75,216,218,219] A Swedish population-based, prospective cohort study reported statistically significantly higher rates of overall discontinuation (HR, 2.92; 95% CI, 2.32-3.69; $P < 0.001$) for patients on infliximab than for those on etanercept.[219] These differences were not statistically significant for discontinuations due to adverse events or due to lack of efficacy. These findings are consistent with those from a German retrospective, population-based cohort study, based on the RABBIT database. This study reported that overall discontinuation rates among biologics were significantly higher for anakinra-treated patients (41%) than for patients on etanercept (31%; $P = 0.004$ for anakinra vs. etanercept) or those on infliximab (35%; $P = 0.03$ for anakinra vs. infliximab).[75] Treatment discontinuations because of adverse events, after 12 months of treatment, were lowest for etanercept (13 percent for etanercept, 16 percent for anakinra, and 19 percent for infliximab; P = NR). This also is consistent with a retrospective cohort study of patients treated with adalimumab, etanercept, and infliximab, where adalimumab and etanercept were better tolerated than infliximab.[216] Another prospective cohort study reported higher rates of switching treatments with infliximab compared with adalimumab and etanercept (P = NR).[218]

Biologic DMARDs – overall tolerability: adverse event rates and serious adverse events. Table 55 presents the comparative harms for biologic DMARDs. Only two studies compared adverse event rates and serious adverse events with biologic DMARDs; one randomized controlled trial[53] and one retrospective cohort study.[220] Both studies found more serious adverse events among patients treated with infliximab. The randomized controlled trial included 431 patients with RA who were receiving MTX and were naïve to biologic DMARDs. Patients were randomized to abatacept plus MTX, infliximab plus MTX, or placebo plus MTX. At 6 months, serious adverse events were reported by 5.1% of the abatacept group, but 11.8% and 11.5% of the placebo and infliximab groups, respectively (*P* = NR). After 1 year, 18.2% of infliximab-treated and 9.6% of abatacept-treated reported a serious adverse event (*P* = NR; placebo arm stopped at 6 months). Acute infusional events were lower with abatacept (7.1%) than with infliximab (24.8%). The retrospective cohort study followed 2,364 patients with RA newly treated with an anti-TNF agent in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry. There was an increased risk of adverse events in the infliximab compared with adalimumab and etanercept groups (HR, 1.4; 99% CI, 1.0-1.96). More specifically, there was an increased risk of infusion or systemic allergic reactions with infliximab compared with adalimumab and etanercept (*P* = 0.018).

Table 55. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
		Biologic DMARDs Overall Tolerability			
Bathon et al., 2000[63,148,149] ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive	ETA, MTX	Significantly more patients on MTX than on ETA had nausea (29% vs. 15%; *P* < 0.05) or mouth ulcers (14% vs. 5%; *P* < 0.05)	Fair
Breedveld et al., 2006[62] PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive	ADA, MTX, ADA + MTX	No statistically significant differences in adverse events	Fair
*Burmester et al., 2007[223] ReACT trial	Prospective cohort 6,610 12 weeks	Pts with RA with treatment failure to at least one traditional DMARD	ADA, ADA + DMARDs	Serious adverse events occurred in 7.3% of pts treated with ADA vs. 5.3% treated with ADA+DMARDs	Fair
*Combe et al., 2009[122]	RCT 260 2 years	Pts with active RA despite treatment with sulfasalazine	ETA, SSZ, ETA+SSZ	Non-infectious serious adverse events were significantly greater in patients receiving ETA (20.8% for the combination and 20.4% for ETA alone) compared with 4% for patients receiving SSZ (*P* <0.01)	Fair

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; AE, adverse event; AERS, adverse event reporting system; ANK, anakinra; CTZ, certolizumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; INF, infliximab; IR, incidence rate; IRR, incidence rate ratio; LEF, leflunomide; MTX, methotrexate; NA, not applicable; OR, odds ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; RTX, rituximab; SSZ, sulfasalazine; TCZ, tocilizumab; TNF, tumor necrosis factor.

Table 55. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Edwards et al., 2004[71]	RCT 161 24 weeks	Active RA despite MTX treatment	RTX,MTX, RTX+MTX, RTX+CYP	No significant differences in adverse events	Fair
*Emery et al., 2008[145] RADIATE study	RCT 499 24 weeks	Pts with active RA resistant to 1 or more TNF-alpha antagonist agents	MTX, TCZ +MTX	The overall occurrence of adverse events was similar among groups.	Fair
*Emery et al., 2008[76] COMET trial	RCT 542 52 weeks	Early, moderate to severe RA; MTX-naive	MTX,ETA +MTX	Serious adverse events were similar among groups	Fair
Feltelius et al., 2005[226]	Case series 1,073 2 years	Pts with RA initiating ETA therapy	ETA	Incidence of serious adverse events remained constant over time	Fair
*Fernandez-Nebro et al., 2007[57]	Prospective cohort 161 6 years	RA pts with no response to DMARDs, including MTX	ADA, ETA, INF	No difference in adverse events among groups	Fair
*Fleischmann et al., 2009[140] FAST4WARD	RCT 220 24 weeks	Pts with RA treatment resistant to at least one DMARD	CTZ	Overall, adverse events occurred in 75.4% of pts treated with CTZ and 57.8% of placebo pts	Fair
Fleischmann et al., 2003[225]	RCT 1,414 6 months	Pts with active RA despite MTX treatment	ANK	No statistically significant differences in adverse events (except infusion reactions)	Fair
Fleischmann et al., 2006[257]	Open-label extension of RCT 1,346 Up to 3 years	Pts with active RA despite MTX treatment	ANK	Incidence of serious adverse events remained constant over time	Fair
Furst et al., 2003[100] STAR study	RCT 636 6 months	Pts with active RA despite MTX treatment	ADA	No statistically significant differences in adverse events	Fair
Geborek et al., 2002[54]	Nonrandomized, open-label trial 369 12 months	Population-based; active RA; had failed at least 2 DMARDs	ETA, LEF, INF	No statistically significant differences in adverse events	Fair

Table 55. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Genovese et al., 2002[148]	Open-label extension of RCT 632 2 years	Pts with early, aggressive RA; MTX-naive	ETA	Incidence of serious adverse events remained constant over time	Fair
Genovese et al., 2004[66]	RCT 242 24 weeks	Inadequate control of disease with MTX	ETA, ETA+AKA	Significantly higher rates of serious adverse events in combination group	Fair
Genovese et al., 2005[149]	Uncontrolled extension of RCT 369 5 years	Pts with early, aggressive RA; MTX-naive	ETA	Rates of serious adverse events did not increase with long-term exposure	Fair
*Karanikolas et al., 2008[77]	Prospective cohort 128 48 weeks	Pts with RA with inadequate response to traditional DMARD	MTX+ANK, LEF+ANK	No statistically significant differences in adverse events	Fair
*Kay et al., 2008[141]	RCT 172 52 weeks	Pts with active RA despite treatment with MTX	MTX, GOL+MTX,	Serious adverse events occurred in 9% of pts treated with GOL versus 6% in pts treated with MTX alone	Fair
*Keystone et al., 2004[99]	RCT 619 52 weeks	Pts with active RA on MTX therapy	MTX, ADA + MTX	Serious adverse events occurred more frequently in ADA pts (3.8%) vs. MTX pts (0.5%; $P \leq 0.02$)	Fair
Klareskog et al., 2004[73,113,115] TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 2 DMARDs	ETA, MTX, ETA+MTX	No statistically significant differences in adverse events	Good
Langer et al., 2003[258]	Postmarketing surveillance 454 6 months	Pts with RA, initiating AKA treatment	AKA	Rate of adverse events was generally similar to those reported in efficacy trials	Fair
Maini et al., 2004[129]	Open-label extension of RCT 259 2 years	Pts with active RA despite MTX treatment	INF	Incidence of serious adverse events remained constant over time	Fair

Table 55. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Martin Du Pan et al., 2009[220]	Retrospective cohort 2,364 9 years	Pts with RA in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry treated with an anti-TNF agent	ADA, ETA, INF	Increased overall risk for adverse events in INF vs. ETA and ADA (HR, 1.4; 99%CI,1.00-1.96)	Fair
Moreland et al., 2006[227]	Open-label extension of clinical trials 714	Pts treated with ETA	ETA	Incidence of serious adverse events remained constant over time	Fair
*Nishimoto et al., 2009[64] SATORI	RCT 127 24 weeks	Pts with active RA despite MTX treatment	TCZ, MTX	Adverse events occurred in 91.8% of pts treated with TCZ vs. 71.9% of those treated with MTX	Fair
Nuki et al., 2002[106]	Uncontrolled extension of RCT 309 19 months	Pts with active RA despite MTX treatment	AKA	Incidence of serious adverse events remained constant over time	Fair
O'Dell et al., 2006[203]	Nonrandomized, open-label trial 119	Pts with active RA despite treatment with SSZ, HCQ, or gold	ETA + SSZ ETA + HCQ ETA + gold	No differences in adverse event rates among 3 treatment groups	Fair
*Russell et al., 2007[96,221] AIM	RCT 652 12 months	Pts with RA despite treatment with MTX	ABA, ABA+MTX	Incidence of serious adverse events similar between groups	Good
*Schiff et al., 2008[53]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA +MTX, INF +MTX, MTX	The occurrence of serious adverse events was lower in those treated with ABA (9.6%) versus INF(18.2%).	Fair
Schiff et al., 2006[246]	Retrospective data analysis of clinical trials; postmarketing surveillance 10,050 12,506 pt years	Pts treated with ADA	ADA	Incidence of serious adverse events remained constant over time	Fair
*Smolen et al., 2008[139] OPTION study	RCT 623 32 weeks	Pts with RA that failed treatment with MTX	MTX, TCZ+MTX	Adverse events occurred more frequently in pts treated with TCZ (71%) vs. MTX monotherapy (63%)	Fair

Table 55. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Smolen et al., 2009[222] RAPID 2 study	RCT 619 24 weeks	Pts with RA with prior MTX use for ≥ 6 months	MTX, CTZ+MTX	Serious adverse events occurred more frequently in CTZ pts vs. pts treated with MTX monotherapy	Fair
Van Riel et al., 2006[74]	Open-label RCT 315 16 weeks	Inadequate control of disease with MTX	ETA, ETA+MTX	No statistically significant differences in adverse events	Fair
Weinblatt et al., 2006[224] ASSURE study	RCT 1,456 1 year	Pts with active RA despite background biologic or synthetic DMARD treatment	ABA	Higher incidence of serious adverse events in pts on ABA and a biologic background DMARD	Fair
Weinblatt et al., 2006[103]	Uncontrolled extension of RCT 162 3.4 years	Pts with active RA despite MTX treatment	ADA	Incidence of serious adverse events remained constant over time	Fair
Westhovens et al., 2006[132] START study	RCT 1,084 22 weeks	Pts with active RA despite MTX treatment	INF + MTX, MTX	No statistically significant differences in adverse events, except infection (higher in 10mg/kg)	Good
*Zhang et al., 2006[133]	RCT 173 18 weeks	Pts with active RA despite treatment with MTX	MTX, INF+MTX	Rate of adverse events similar between groups	Fair

Four RCTs were designed to assess adverse events as primary outcomes.[100,132,224,225] Overall, adverse event rates were similar for abatacept,[224] adalimumab,[100] anakinra,[225] or infliximab,[132] and placebo. Other efficacy trials suggested that overall adverse events are higher with biologic DMARDs than with placebo.

In placebo-controlled efficacy trials of biologic DMARDs, injection site reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were commonly reported adverse events.[60] Indirect evidence from additional efficacy trials and cohort studies suggests that the overall tolerability profiles are similar among biologic and oral DMARDs, or combinations of biologic and oral DMARDs.[54,57,62,71,73,74,76,96,100,113,115,133,145,221] However, several studies suggested that adverse events were more common with biologic DMARDs, given alone or in combination with an oral DMARD.[64,99,122,139-141,222] One prospective cohort study found a slightly lower rate of serious adverse events among patients who had an oral DMARD added to adalimumab, compared with patients who only received adalimumab (5.3% vs. 7.3%, respectively; P = NR).[223]

The combination of two biologic DMARDs consistently had more adverse events than monotherapy. A 24-week RCT, described in more detail for KQ 1, assessed a combination treatment of etanercept (25 mg or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy.[66] The frequency of serious adverse events was substantially higher in

the combination groups than the etanercept-only group (14.8 percent for 50 mg etanercept plus anakinra; 4.9 percent for 25 mg etanercept plus anakinra; 2.5 percent for etanercept only; *P* = NR). Furthermore, a study determining the efficacy of abatacept combined with different background treatments found substantially higher rates of serious adverse events in patients on abatacept combined with a biologic background treatment (22.3%) than in those not on a combination of two biologic DMARDs (12.5%).[224]

One nonrandomized open-label trial determined the comparative harms among combinations of biologic DMARDs and oral DMARDs other than MTX.[203] No differences in adverse events could be detected between a combination of etanercept and either sulfasalazine or hydroxychloroquine. Similar evidence of similarities in adverse events among background oral DMARDs comes from an RCT comparing rituximab, MTX, rituximab plus MTX, and rituximab ply cyclophosphamide,[71] and a prospective cohort study comparing anakinra plus MTX with anakinra plus leflunomide.[77] Both studies reported no significant differences in adverse events among these combinations of biologic and oral DMARDs.

The ERA study, described in more detail in KQ 1, had an open-label extension of up to 2 years,[148] and an uncontrolled extension with etanercept (25 mg twice weekly) of up to 5 years.[149] The rates of adverse events for etanercept did not rise during long-term treatment compared with rates reported from the short-term RCT. These results are consistent with findings from long-term extension studies of efficacy RCTs on adalimumab,[103] anakinra,[106,257] and infliximab.[126,227] Likewise, safety analyses of postmarketing surveillance data showed that the incidence of adverse events did not rise over time in patients treated with adalimumab[246] and etanercept.[226]

Biologic DMARDS – specific adverse events. Biologic DMARDs can produce several serious adverse events (Table 4). Studies of adverse events with biologic DMARDs are summarized in Tables 56-61.

Cardiovascular and cerebrovascular events. No direct evidence compared the risk of cardiovascular or cerebrovascular events for one biologic DMARD with another. Eleven observational studies[187,189,205,228-233,259] and one RCT conducted in a population with CHF[260] provide general evidence for the risk of cardiovascular and cerebrovascular events with biologic DMARD (Table 56).

Table 56. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Chung et al., 2003[260]	RCT 150 28 weeks	Pts with CHF	INF	INF (10 mg)-treated pts were more likely to die than placebo-treated pts	Fair
*Curtis et al., 2007[229]	Retrospective cohort study 2,121 5 years	Pts with RA (Also Crohn's Disease but excluded here)	ETA, INF	Cumulative incidence of heart failure among pts treated with ETA or INF versus those not: 4.4 cases per 1000 persons and 1.0 case per 1000 persons in the unexposed group (RR, = 4.3; *P* = NS.	Fair

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; AE, adverse event; AERS, adverse event reporting system; ANK, anakinra; CHF, congestive heart failure; CV, cardiovascular; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HF, heart failure; HR, hazard ratio; INF, infliximab; IR, incidence rate; IRR, incidence rate ratio; LEF, leflunomide; MI, myocardial infarction; MTX, methotrexate; NA, not applicable; OR, odds ratio; Pts, patients; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, rate ratio; TCZ, tocilizumab; TNF, tumor necrosis factor.

Table 56. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Dixon et al., 2007[233] BSRBR	Prospective cohort 10,755 1.66 years median follow-up	Pts with RA in the British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF, oral DMARDs	IRR, of MI among anti-TNF users compared with oral DMARDs:1.44 (95% CI, 0.56 - 3.67)	Good
Jacobsson et al., 2005[232]	Retrospective cohort study 983 NR	Pts with RA in daily clinical care in Sweden	ETA, INF	Pts on anti-TNF treatment had a lower rate of cardiovascular events than pts on traditional RA therapy	Fair
*Listing et al., 2008[230]	Prospective cohort 4,248 5 years	Pts with RA enrolled in the RABBIT German biologics register	ADA, ETA, INF, oral DMARDs	HR for incident HF among those using anti-TNFs vs. conventional DMARDs: 1.66, (95% CI, 0.67-4.10;*P* = 0.28); HR for worsening HF among prevalent cases: 1.18, (95% CI, 0.30-4.73;*P* = 0.81)	Good
*Nadareishvili et al., 2008[187]	Nested case-control 269 cases among 7045 patients 8 years	RA pts in National Data Bank for Rheumatic Diseases	ADA, ETA, INF	Association of treatment with ischemic stroke: Anti-TNF: OR,0.79; 95% CI, 0.34-1.82; *P* = 0.584)	Fair
*Naranjo et al., 2008[188]	Cross-sectional 4,363 Clinician and patient recall	Sample of RA pts across 15 countries	TNF-alpha antagonists (not specified)	Anti-TNF agents associated with reduced risk for CV morbidity (HR, 0.64; 95% CI, 0.49-0.83).	Fair
Kwon et al., 2003[259]	Database analysis AERS 47 cases of CHF NA, AERS data	Pts on ETA or INF therapy	ETA, INF	Most pts with CHF did not have preexisting conditions	Fair
*Setoguchi et al., 2008[231]	Retrospective cohort 5,593 10 years	Medicare pts with RA from 2 states	ADA, ETA, INF, MTX	Effect of anti-TNFs compared to MTX on heart failure and/or death;HR,1.70; 95% CI, 1.07 - 2.69	Good
*Solomon et al., 2006[189]	Case-control study 3,501 24 months	Pennsylvania Medicare enrollees with RA	Biologic DMARDs	No statistically significant association between use of biologic DMARDs and cardiovascular events	Fair

Table 56. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Suissa et al, 2006[205]	Prospective cohort 107,908 14 months	RA pts in US PharMetrics data	ADA,ETA, INF	Biologic DMARD use slightly associated with acute MI (RR,1.30; 95% CI, 0.92-1.83)	Fair
Wolfe et al., 2004[228]	Retrospective cohort study 13,171 2 years	Pts with RA in daily clinical care in U.S.	ADA, ETA, INF	Pts on anti-TNF treatment had a lower rate of CHF than pts on traditional RA therapy	Fair

The evidence on the risk of CHF with anti-TNF therapy is mixed. One observational study reported lower rates of CHF[228] for RA patients on anti-TNF therapy than for those on conventional RA therapies. This large retrospective cohort study (N = 13,171) reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 - -0.5; *P* = NR) for patients treated with anti-TNF therapy compared with those not treated with anti-TNF medications over a 2-year period.[228] This study is contrasted by three other cohort studies that found an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with no treatment or oral DMARD.[229-231] While the increased risk was not statistically significant in two of these studies,[229,230] one good-rated retrospective cohort study of 5,593 Medicare patients with RA from 2 US states reported statistically significant increases in the risk heart failure and death (HR, 1.70; 95% CI, 1.07-2.69).[231]

An analysis of the FDA Adverse Event Reporting System (AERS) data reported that half of the patients who developed new onset CHF under etanercept or infliximab treatment did not have any identifiable risk factors.[259] Indirect evidence comes from three trials, two on etanercept[261] and one on infliximab,[260] that evaluated the efficacy of these drugs for the treatment of CHF. Study populations did not have any rheumatoid illnesses. One of the two etanercept trials was terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.[260] The package insert of infliximab issues a contraindication regarding use in patients with CHF; the package inserts of etanercept and adalimumab emphasize precaution.

Three observational studies assessed the risk of cardiovascular events (broadly defined).[188,189,232] One case-control study of Medicare patients with RA found no statistically significant association between use of biologic DMARDs and cardiovascular events,[189] while two studies reported a decreased risk of cardiovascular events with biologic DMARDs.[188,232] A good-quality Swedish retrospective cohort study (N = 983), using data from population-based databases, reported a statistically significantly lower risk of cardiovascular events in patients treated with anti-TNF medications than in those on conventional therapy (age-sex adjusted rate ratio: 0.46/1,000 person-years; 95% CI, 0.25-0.85; *P* = 0.013).[232] A cross-sectional analysis of patients from 15 countries participating in the QUEST-RA study reported that patients exposed

to biologic DMARDs had a reduced risk of cardiovascular morbidity (HR, 0.42; 95% CI, 0.21-0.81; $P < 0.05$).[188]

One nested case-control study assessed the risk of stroke with adalimumab, etanercept, and infliximab,[187] and two cohort studies assessed the risk of MI with these same biologic DMARDs.[205,233] The study assessing stroke was conducted in the National Data Bank for Rheumatic Diseases, finding a slight decrease in the risk of stroke with adalimumab, etanercept, and infliximab (OR, 0.79; 95% CI, 0.34-1.82; P = NS).[187] The two studies assessing risk of MI also found no statistically significant differences in the risk of MI, although results trended towards an increased risk of MI for these biologic DMARDs. In a good rated analysis of 10,755 patients from the British Society for Rheumatology Biologics Register, the incidence rate ratio was 1.44 (95% CI, 0.56-3.67) for biologic DMARDs compared with oral DMARDs. In a larger fair-rated analysis of 107,908 patients from a US claims database, biologic DMARDs were associated with a similar non-statistically significant increase in the risk of MI (RR, 1.30; 95% CI, 0.92-1.83).[205]

Infections. Because of the immunosuppressive nature of biologic DMARDs, serious infections including tuberculosis, pneumonia, osteomyelitis, progressive multifocal leucoencephalopathy (PML), and sepsis are of special concern. The FDA has issued black box warnings about an increased risk of infections for adalimumab and infliximab. The package inserts of anakinra and etanercept also contain bold letter warnings. Recently, the FDA issued an alert for health care professionals highlighting the death of two patients from PML who had been treated with rituximab for systemic lupus erythematosus.[262] The available head-to-head evidence is insufficient to draw firm conclusions about the comparative risk of biologic DMARDs.

The best evidence stems from an RCT[53] and a prospective cohort study.[234] The trial randomized 431 patients with RA to MTX, abatacept plus MTX, or infliximab plus MTX. Serious infections were reported more often in the infliximab group than the abatacept group (P = NR).[53] The cohort study enrolled 8,973 patients with severe RA from the British Society for Rheumatology Biologics Register. Patients were treated with adalimumab (n = 1,190), etanercept (n = 3,596), infliximab (n = 2,878), or oral DMARDs (n = 1,354). The overall followup included 11,220 patient-years. Results indicated no differences in risks among anti-TNF drugs. Compared with oral DMARDs, anti-TNF drugs did not lead to a higher overall risk for serious infections (IRR, 1.03; 95% CI, 0.68-1.57). The frequency of serious skin infections, however, was fourfold higher in patients treated with anti-TNF drugs than with synthetic DMARDs (IRR, 4.28; 95% CI, 1.06-17.17). Although the statistical analysis controlled for multiple confounding factors, residual confounding in such a study design is likely. Results, therefore, must be interpreted cautiously. Event rates of serious infections in efficacy trials comparing anti-TNF drugs with oral DMARDs were generally too low to draw meaningful conclusions.

The following paragraphs summarize the evidence on the general risk of biologic DMARDs for serious infections (i.e., the risk of biologic DMARDs compared with that of placebo treatment). Table 57 presents studies reporting on infections in those patients treated with biologic DMARDs.

Table 57. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Askling et al., 2005[263]	Retrospective cohort study 62,321 467,770 person-years	Pts with RA in daily clinical care in Sweden	ETA, INF	4-fold increase of risk for TB for ETA and INF compared with conventional DMARDs	Good
Bergstrom et al., 2004[264]	Retrospective cohort study 985 3 years	Pts with inflammatory arthritis in daily clinical care, U.S.	ETA, INF	Pts treated with INF or ETA are more likely to develop symptomatic coccidiomycosis than pts on synthetic DMARDs	Fair
*Bernatsky et al., 2007[191]	Nested case-control 23,733 Up to 23 years	RA pts registered in claims databases in Quebec	Anti-TNFs (not specified), oral DMARDs, corticosteroids	No statistical association between anti-TNF use and risk for all infections requiring hospitalization (RR: 1.9; 95% CI, 0.7-5.3)	Fair
Bongartz et al., 2006[239]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of serious infections for ADA and INF compared with placebo (3.6% vs. 1.7%; OR, 2.0; 95% CI, 1.3-3.1)	Fair
*Brassard et al., 2006[192]	Retrospective cohort 112,300 Up to 5 years	RA pts with ≥ 1 claim for anti-RA drugs in U.S. database	Several oral DMARDs, ANK, ETA, INF, corticosteroids	Adjusted rate ratio of developing TB: Biologic DMARDs:1.5 (95% CI, 1.1 - 1.9); INF:1.6 (95% CI, 1.0 - 2.6) ETA:1.2 (95% CI, 0.9 - 1.8) ANK:1.3 (95% CI, 0.8 - 2.1)	Fair
*Cohen et al., 2006[135] REFLEX Trial	RCT 520 24 weeks	Pts with RA with inadequate response to previous or current treatment with anti-TNF agents	RTX+MTX, MTX	The rate of serious infection was 5.2 and 3.7 per 100 pt-yrs in the RTX+MTX and MTX groups, respectively	Fair
Combe et al., 2006[72]	RCT 260 24 weeks	Active RA despite SSZ treatment	ETA, SSZ, ETA+SSZ	Significantly more infections in ETA and ETA+SSZ than in SSZ group (47% vs. 31% vs. 13%; $P < 0.05$)	Fair
*Curtis et al., 2007[265,266]	Retrospective Cohort Study 5,326 Up to 67 months	Pts with RA enrolled in a large US health care organization	MTX, TNF-alpha antagonists	Risk of hospitalization with a bacterial infection for those receiving TNF-alpha antagonists was 1.94 (95% CI, 1.32 - 2.83) compared with pts that received MTX only; risk highest in first 6 months – ETA: 1.61, 95% CI, (0.75-3.47) INF 2.40, 95% CI, (1.23-4.68)	Good

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; AE, adverse event; AERS, adverse event reporting system; ANK, anakinra; CI, confidence interval; CTZ, certolizumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HR, hazard ratio; INF, infliximab; kg, kilogram; LEF, leflunomide; mg, milligram; MTX, methotrexate; NA, not applicable; OR, odds ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, rate ratio; RTX, rituximab; SSZ, sulfasalazine; TB, tuberculosis; TCZ, tocilizumab; TNF, tumor necrosis factor.

Table 57. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*den Broeder et al., 2007[267]	Retrospective cohort 1,219 1 year follow-up	RA pts that were TNF-alpha antagonist naïve	TNF-alpha antagonists	Perioperative continuation of anti-TNFs not associated with increased risk of surgical site infection. Wound dehiscence in patients that continued anti-TNFs compared to patients that temporarily discontinued anti-TNF treatment (OR,11.2; 95% CI, 1.4-90).	Fair
Dixon et al., 2006[234]	Prospective cohort study 8,973 11,220 pt-years	Pts with active RA despite MTX treatment	ADA, ETA, INF	No differences among anti-TNF drugs for risk of serious infections. Similar risk for serious infections between anti-TNF drugs and oral DMARDs	Fair
Gomez-Reino et al., 2003[268]	Retrospective cohort study 1,540 1.1 years	Pts with RA in daily clinical care in Spain	ETA, INF	Higher risk of TB for ETA and INF than oral DMARDs	Fair
Keane et al., 2001[269]	Database analysis 70 cases of TB NA, AERS data	Pts treated with INF	INF	TB may develop soon after initiation of INF treatment	Fair
*Keystone et al., 2008[167] RAPID-1 Trial	RCT 982 52 weeks	Pts with RA that received MTX for ≥ 6 months prior to baseline	MTX, CTZ+MTX	Occurrence of serious infections was higher in pts treated with CTZ than those on MTX alone	Fair
Lee et al., 2002[237]	Database analysis 10 cases of histo-plasmosis NA, AERS data	Pts treated with ETA and INF	ETA, INF	Histoplasmosis infections may be a serious complication of treatment with anti-TNF agents; pts on INF had a higher rate of infections than pts on ETA	Fair
Listing et al., 2005[270]	Prospective cohort study 1,529 Up to 12 months	Pts with RA in daily clinical care in Germany	AKA, ETA, INF	Higher risk of infections for AKA, ETA, INF compared with DMARDs	Fair
Mohan et al., 2004[271]	Database analysis 25 cases of TB NA, AERS data	Pts treated with ETA	ETA	Median interval between first dose and diagnosis of TB was 11.5 months	Fair
*Salliot et al., 2009[272]	Meta-analysis 12 RCTs	RA patients receiving ABA, ANK, or RTX	ABA, ANK, RTX	No increase in risk of serious infection for ABA or RTX; high doses of ANK increased risk of serious infection	Fair

Table 57. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Salliot et al., 2006[273]	Case series 709 NR	Pts with different rheumatic diseases; primary care-based cohort	ADA, ETA, INF	Rates of serious infections in daily practice were higher than ones reported in efficacy trials	Fair
*Schiff et al., 2008[53]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA +MTX, INF +MTX, MTX	Serious infections were reported more with INF (8.5%) than ABA (1.9%)	Fair
*Schneeweiss et al., 2007[195]	Retrospective cohort 15,597 Up to 8 years	Medicare beneficiaries ages 65 and older with RA	TNF-alpha antagonists (ADA, ETA, INF)	Compared with MTX use, TNF-alpha did not increase risk of serious bacterial infections (RR, 1.04; 95% CI, 0.63-1.72)	Fair
Slifman et al., 2003[238]	Database analysis 15 cases of listeria infection NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of infections than pts on ETA	Fair
*Smitten et al., 2008[196]	Retrospective cohort 24,530 26.6 months	Pts with RA from US PharMetrics data	ADA, ANK, ETA, INF	Biologic DMARDs slightly increased risk of hospitalized infection (RR, 1.21; 95% CI, 1.02-1.43).	Good
*Smitten et al., 2007[197]	Retrospective cohort 12,272 (PM) 38,621 (GPRD) 12.3 to 38.8 months	Pts with RA from the PharMetrics (PM) database and UK General Practice Research database (GPRD)	ANK, ETA, INF	Risk of herpes zoster infection with biologic DMARD: (PM: OR,1.54; 95% CI, 1.04-2.29)	Fair
*Smolen et al., 2009[222] RAPID 2 study	RCT 619 24 weeks	Pts with RA with prior MTX use for ≥ 6 months	MTX, CTZ+MTX	Serious infection occurred more frequently in CTZ pts vs. pts treated with MTX monotherapy	Fair
St. Clair et al., 2004[69,70] ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX-naive	MTX, INF, INF+ MTX	Significantly more patients in the INF than in the MTX group had more than one serious infection (5.3 vs. 2.1%; $P < 0.05$)	Fair
*Strangfeld et al., 2009[198]	Prospective cohort 5,040 up to 36 months	RA pts initiating biologic therapy or switching to another DMARD	ADA, ETA, INF	Adjusted HR for Herpes Zoster. All anti-TNFs: (HR, 1.63; 95% CI, 0.97-2.74) ADA or INF (HR, 1.82; 95% CI, 1.05-3.15) ETA (HR, 1.36; 95% CI, 0.73-2.55)	Good

Table 57. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Wallis et al., 2004[236]	Database analysis 649 cases of granulomatous infections NA, AERS data	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of granulomatous infections than pts on ETA	Fair
Westhovens et al., 2006[132] START study	RCT 1,084 22 weeks	Pts with active RA despite MTX treatment	INF + MTX, MTX	Risk of serious infections was similar between placebo and 3 mg/kg infliximab. 10 mg/kg infliximab led to increased risk of serious infections	Good
Wolfe et al., 2004[274]	Prospective cohort study with historic control 17,242 3 years	Pts with RA in daily clinical care in U.S.	INF, oral DMARDs	TB was more common in pts treated with INF than with oral DMARDs	Fair
Wolfe et al., 2006[208]	Prospective cohort study 16,788 3.5 years	Pts with RA	ADA, ETA, INF	No increased risk for hospitalization for pneumonia for ADA, ETA, and INF compared to a historic control	Fair

Most studies defined serious infections as those that required antibiotic treatment or led to hospitalization or death. In placebo-controlled safety RCTs, the incidence of serious infections was consistently higher in biologic-treated than in placebo-treated patients. Although clinically significant, these differences rarely reached statistical significance because of low power. For example, in one large safety RCT (N = 1,414), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1% vs. 0.4%; $P = 0.068$).[225] The START (Trial for Rheumatoid Arthritis with Remicade) study, another safety RCT (N = 1,084) conducted to assess the risk of serious infections during infliximab treatment for RA, indicated a dose-dependent risk for patients on infliximab.[132] After 22 weeks of treatment, patients on 3 mg/kg infliximab had similar rates of serious infections as patients on placebo (1.7% vs. 1.7%; RR, 1.0; 95% CI, 0.3-3.1). Patients treated with 10 mg/kg infliximab had a significantly higher rate of serious infections than patients on placebo (5.0% vs. 1.7%; RR, 3.1; 95% CI, 1.2-7.9). The REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab) trial randomized 520 patients to 24 weeks of treatment with MTX or rituximab plus MTX.[135] The rate of serious infections was slightly higher among rituximab-treated patients (5.2 vs. 3.7 per 100 patient-years). In both the RAPID1 and RAPID2 (RA Prevention of Structural Damage) trials,[167,222] two trials assessing the efficacy of certolizumab in RA patients previously treated with MTX, serious infections occurred more frequently among the certolizumab-treated patients.

A fair meta-analysis of efficacy studies confirmed this finding and reported a similar dose-dependent risk for a combined population of adalimumab- and infliximab-treated patients.[164]

This meta-analysis pooled data of more than 5,000 RA patients from adalimumab and infliximab efficacy trials.[239] The pooled odds ratio for serious infections was 2.0 (95% CI, 1.3-3.1) relative to placebo. The number needed to harm (NNH) was 59 (95% CI, 39-125) within a treatment period of 3 months to 12 months. Another fair meta-analysis of 12 RCTs did not find an increased risk of serious infections with abatacept or rituximab, but found that high doses of anakinra did increase risk.[272]

Most long-term observational studies support these findings.[135,191,195,196,240,265,266,270,273,275] A large, French case series of 709 patients with various rheumatic diseases treated with adalimumab, etanercept, or infliximab in daily clinical practice reported a substantially higher rate of serious infections (10.5 per 100 patient-years) than rates reported in phase 3 efficacy trials (3 to 4 per 100 patient-years).[273] A larger good-rated US cohort study (N = 5,326) of patients with RA enrolled in a US healthcare organization found an increased risk of hospitalization with bacterial infection for those treated with adalimumab, etanercept, or infliximab (HR, 1.94; 95% CI, 1.32-2.83) compared with patients that only received MTX.[265,266] This is in contrast to a large retrospective cohort study of 15,597 US Medicare patients receiving adalimumab, etanercept, or infliximab;[195] compared with MTX use there was no increased risk of serious infection with these biologic DMARDs. Another good-rated retrospective cohort study using US administrative claims data showed a slightly increased risk of hospitalized infection with adalimumab, anakinra, etanercept, and infliximab (RR, 1.21; 95% CI, 1.02-1.43).Smitten, 2008 #2784}

The most common serious infections were cases of tuberculosis.[269] In addition, observational studies reported infections with coccidiomycosis,[264] histoplasmosis,[237] pneumocystis carinii,[276] listeriosis,[238] candida,[269] and herpes.[197,198]

Six retrospective cohort studies determined the risk of tuberculosis or granulomatous infections during treatment with infliximab or etanercept.[192,236,263,268,269,271,274] All studies reported a significant increase in risk attributable to biologic DMARDs relative to placebo. For example, in a fair-rated retrospective cohort study of 112,300 US patients with RA, the rate ration for developing tuberculosis was 1.5 with biologic DMARDS (95% CI, 1.1-1.9).[192] For the individual agents, the rate ratio was highest with infliximab (RR, 1.6; 95% CI, 1.0-2.6) compared with etanercept and anakinra (respectively, RR, 1.2; 95% CI, 0.9-1.8; and RR, 1.3; 95% CI, 0.8-2.1).

Other evidence regarding the risk of tuberculosis comes from Spanish, Swedish, and U.S. databases that collected data on patients treated with biologic DMARDs.[263,268,274] The U.S. study, using data from the National Data Bank of Rheumatic Diseases (NBI), reported an eightfold higher rate of tuberculosis in patients treated with infliximab than in patients in a historic control group who had been treated with synthetic DMARDs.[274] The analysis yielded rates of 6.2 cases per 100,000 patient-years in the control group and 52.5 cases per 100,000 patient-years in patients on infliximab. The other two studies were based on the Spanish BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia)[268] and several Swedish databases.[263] Both studies analyzed data on infliximab and etanercept and indicated a substantially higher risk for tuberculosis in patients treated with etanercept or infliximab than in those on synthetic RA therapy. The Swedish study reported a fourfold increased risk of tuberculosis (RR, 4.0; 95% CI, 1.3-12) for patients on anti-TNF treatment compared with the risk for RA patients not exposed to etanercept or infliximab.[263] The incidence of tuberculosis in patients treated with infliximab was 145 per 100,000 (95% CI, 58-299) person years; in patients treated with etanercept, the incidence was 80 (95% CI, 16-232) per 100,000 person years.

Three studies based on spontaneously reported adverse events from the FDA adverse event reporting system (AERS) database provided similar results.[236,269,271] One analysis of AERS data focused on granulomatous infections in general. It indicated a higher rate among patients treated with infliximab (239 cases per 100,000 patients) than with etanercept (74 cases per 100,000 patients).[236] The rate of tuberculosis in this study was 144 cases per 100,000 patients for infliximab and 35 cases per 100,000 patients for etanercept. However, incidence rates must be compared cautiously because this study reported cases per treated patients and not per patient years.[236] Another AERS analysis reported histoplasmosis to be related to treatment with etanercept and infliximab.[237]

Two observational studies assessed the risk of herpes zoster infection with biologic DMARDs.[197,198] A good-rated prospective cohort study of 5,040 patients with RA initiating treatment with adalimumab, etanercept, or infliximab reported a statistically non-significant but potentially clinically significant increase in the risk of herpes zoster infection (HR, 1.63; 95% CI, 0.97-2.74).[198] This risk was greatest among patients treated with adalimumab or infliximab (HR, 1.82; 95% CI, 1.03-3.15) in comparison with those treated with etanercept (HR, 1.36; 95% CI, 0.73-2.55). A fair-rated retrospective cohort study of patient in a US claims database and patients from the UK General Practice Research Database found a risk of herpes zoster infection of similar magnitude (OR, 1.54; 95% CI, 1.04-2.29).[197]

Infusion and Injections Site Reactions. Infusion reactions (abatacept, infliximab, rituximab, tocilizumab) and injection site reactions (adalimumab, anakinra, certolizumab, etanercept, golimumab) were the more commonly and consistently reported adverse events. Most infusion reactions were nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. Studies reporting infusion or injection site reactions in patients treated with biologic DMARDs are presented in Table 58.

Table 58. Infusion or injection site reactions in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Cohen et al., 2006[135] REFLEX Trial	RCT 520 24 weeks	Pts with RA with inadequate response to previous or current treatment with anti-TNF agents	RTX+MTX, MTX	Infusion reactions occurred in 23% of RTX+MTX pts versus 18% in MTX alone.	Fair
*Emery et al., 2006[138] DANCER trial	RCT 465 24 weeks	Pts with RA that failed prior treatment with at least 1 but not more than 5 DMARDs (other than MTX) and/or biologic response modifiers	RTX + MTX, MTX	Acute infusion reaction occurred more frequently in pts treated with RTX (23% and 32% in the 500-mg and 1000-mg groups, respectively) vs. MTX alone (17%)	Fair
Fleischmann et al., 2003[225]	RCT 1,414 6 months	Pts with active RA despite MTX treatment	ANK	Higher rates of injection site reactions with ANK than placebo	Fair

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; ANK, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; MTX, methotrexate; NA, not applicable; OR, odds ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; RTX, rituximab; TNF, tumor necrosis factor.

Table 58. Infusion or injection site reactions in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Gartlehner et al., 2006[60]	Meta-analysis 5,248 NA	Patients who have failed MTX treatment; mean disease duration: varied	ADA, ANK, ETA,INF	Higher rates of injection site reactions for ANK than ADA and ETA (56% vs. 19% vs. 25%)	Good
Langer et al., 2003[258]	Postmarketing surveillance 454 6 months	Pts with RA, initiating ANK treatment	ANK	Lower rates of injection site reactions than in clinical trials	Fair
*Martin Du Pan et al., 2009[220]	Retrospective cohort 2,364 9 years	Pts with RA in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry treated with an anti-TNF agent	ADA, ETA, INF	Increased risk for infusion or systemic allergic reaction in INF vs. ETA and ADA (HR, 2.11;99%CI,1.23-3.62; *P* = 0.018)	Fair
*Miyasaka et al., 2008[104] CHANGE study	RCT 352 24 weeks	Pts with RA that failed 1 DMARD, including MTX	ADA	Injection site reactions occurred more frequently in ADA pts vs. placebo (*P*<0.05); Placebo 2.3%; ADA 20mg 31%; ADA 40mg 30.8%; ADA 80mg 33.3%	Fair
Schaible et al., 2000[240]	Retrospective data analysis of clinical trials 913 12 weeks to 3 years	Pts with RA or Crohn's disease	INF	17% of pts on INF in clinical trials had acute infusion reactions	Fair
*Schiff et al., 2008[53]	RCT 431 1 year	Pts with RA despite treatment with MTX, anti-TNF therapy naive	ABA + MTX, INF + MTX, MTX	Acute infusional events occurred in 7.1% of those treated with ABA versus 24.8% treated with INF.	Fair
Wasserman et al., 2004[277]	Prospective cohort study 113 15 months	Pts with RA starting INF treatment in a clinical care setting	INF	53% of pts on INF experienced at least one infusion reaction	Fair

In clinical trials of infliximab for the treatment of RA or Crohn's disease, 17 percent of patients experienced infusion reactions; 0.5 percent were severe and resembled acute anaphylactic conditions or led to convulsions.[240] In these trials, however, less than 2 percent of patients discontinued because of infusion reactions.[240] A prospective cohort study of infliximab in a Canadian clinical care setting reported substantially higher rates of reactions than did the clinical trials.[277] Specifically, in the community study (113 patients with 1,183 infusions), 53

percent of patients experienced at least one infusion reaction during the course of the therapy (mean 15 months). Reactions with infliximab were reported more commonly than with other biologic DMARDs in an RCT comparing abatacept and infliximab,[53] and in a retrospective cohort study comparing adalimumab, etanercept, and infliximab.[220] In the randomized trial, 7.1% of those treated with abatacept and 24.8% of those treated with infliximab had an infusion reaction.[53] In the retrospective cohort study, the risk of infusion reaction (or systemic allergic reaction with adalimumab) was more than 2-fold greater with infliximab compared with adalimumab and etanercept (HR, 2.11; 95% CI, 1.23-3.62; $P = 0.018$).[220] While comparative data on infusion reactions were not available for rituximab and tocilizumab, two RCTs reported similar rates of infusion reactions; 23%[135] and 28%.[138]

Injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity, and they were the most common reason for discontinuation blamed on adverse events. A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1-27.9) for adalimumab, 22.4 percent (95% CI, 8.5-36.3) for etanercept, and 67.2 percent (95% CI, 38.7-95.7) for anakinra.[49] Injection site reactions for adalimumab were slightly higher than this estimate (31.7%) in an RCT of 352 patients with RA.[104] The substantially higher incidence of injection site reactions for anakinra than for adalimumab and etanercept is consistent with rates reported in the respective package inserts.[181-183] A German retrospective study based on postmarketing surveillance data, however, reported a lower incidence of injection site reaction for anakinra than was reported in clinical trials (20 percent).[258]

Interstitial Lung Disease. The risk of interstitial lung disease with biologic DMARDs was assessed by one fair-quality prospective cohort study conducted in 17,598 patients with RA in the US National Databank for Rheumatic Diseases (Table 59).[200] This study found that current treatment with etanercept and infliximab was not associated with hospitalization for interstitial lung disease. However, past treatment with etanercept (HR, 1.7; 95% CI, 1.0-3.0; $P = 0.056$) and infliximab (HR, 2.1; 95% CI, 1.1-3.8; $P = 0.019$) was associated with hospitalization for interstitial lung disease.

Table 59. Interstitial lung disease in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Wolfe et al., 2007[200]	Prospective cohort 17,598 up to 3.5 years	Pts with RA in U.S. National Databank for Rheumatic Diseases	ETA, INF	Current treatment with ETA and INF not associated with hospitalization for interstitial lung disease. Past treatment with ETA and INF was associated with hospitalization for interstitial lung disease (HR, 1.7; 95% CI, 1.0-3.0; $P = 0.056$; HR, 2.1; 95% CI, 1.1-3.8; $P = 0.019$	Fair

* Study added during the 2010 update search; ETA, etanercept; HR, hazard ratio; INF, infliximab.

Malignancies. The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with RA compared with the general population.[278] Data from controlled trials do not provide sufficient evidence concerning a further increase in their risk of

cancer attributable to the use of either biologic DMARDs or a combination of biologic and synthetic DMARDs. Findings from retrospective observational studies are mixed (Table 60).

Table 60. Malignancies in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Askling et al., 2005[275]	Retrospective cohort study 60,930 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, oral DMARDs	No increase in solid cancers for pts treated with anti-TNF drugs	Fair
Askling et al., 2005[244]	Retrospective cohort study 53,067 NR	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, oral DMARDs	No increase in lymphoma for pts treated with anti-TNF drugs	Fair
Bongartz et al., 2006[239]	Meta-analysis 5,014 3 to 12 months	Pts with active RA despite MTX treatment	ADA, INF	Statistically significantly higher risk of malignancies for ADA and INF compared with placebo (0.8% vs. 0.2%; OR, 3.3; 95% CI, 1.2-9.1)	Fair
Brown et al., 2002[279]	Database analysis AERS 26 cases of lymphoma NA, AERS data	RA or CD pts treated with ETA and INF	INF, ETA	Median interval between initiation of therapy and lymphoma 8 weeks; some spontaneous remissions after discontinuation of therapy reported	Fair
Chakravarty et al., 2005[212]	Retrospective cohort study 15,789 NR	RA or osteoarthritis pts treated with ETA or INF	ETA, INF	Statistically significant association between anti-TNF (HR, 1.97; 95% CI, NR; *P* = 0.001) and corticosteroid (HR, 1.28; 95% CI, NR; *P* = 0.014) use and nonmelanoma skin cancer	Fair
Geborek et al., 2005[243]	Retrospective cohort study 1,557 5,551 pt-years	Pts with RA in daily clinical care in Sweden	ETA, INF	Higher risk of lymphoma for anti-TNF drugs than oral DMARDs	Fair
Lebwohl et al., 2005[280]	Postmarketing database review 1,442 3.7 years	Pts with RA treated with ETA	ETA	No increase in the incidence of cutaneous squamous cell carcinoma for ETA-treated pts	Fair

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; AE, adverse event; AERS, adverse event reporting system; ANK, anakinra; CD, Crohns disease; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HR, hazard ratio; INF, infliximab; MTX, methotrexate; NA, not applicable; OR, odds ratio; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

Table 60. Malignancies in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Setoguchi et al., 2006[245]	Retrospective cohort study 8,458 2,940 pt-years (Biologic DMARD) to 30,300 pt-years (MTX)	Pts with RA in daily clinical care in U.S. and Canada	ADA, ETA, INF	No increased risk of hematologic and overall malignancies for pts treated with anti-TNF drugs compared with those on oral DMARDs	Good
*Wolfe et al., 2007[281]	Prospective cohort 13,869 4. years (mean)	Pts with RA in U.S. National Data Bank for Rheumatic Diseases	ADA, ANK, ETA, INF	Biologics were associated with an increased risk of nonmelanotic skin cancer (OR, 1.5; 95% CI, 1.2-1.8) and melanoma (OR, 2.3; 95% CI, 0.9-5.4). No other malignancy was associated with biologic use. The overall risk of any cancer was 1.0 (95% CI, 0.8-1.2).	Fair
Wolfe et al., 2004[241]	Prospective cohort study with external control 18,572 Up to 3 years	Pts with RA in daily clinical care in U.S.	INF, ETA	Pts with RA treated with INF or ETA are more likely to develop lymphoma than the general population	Fair
*Wolfe and Michaud, 2007[242] * Updates Wolfe 2004[241]	Prospective cohort 19,591 89,710 person-years	Pts with RA in U.S. National Data Bank for Rheumatic Diseases	MTX, ADA, ETA, INF	Pts treated with any anti-TNFs did not have an increases risk for lymphoma compared to RA pts who had not received anti-TNFs.	Fair

A large prospective cohort study followed 18,572 RA patients in a registry for up to 3 years.[241] The risk of lymphoma was higher for patients on anti-TNF therapies than for those on synthetic DMARDs, although not statistically significantly so. Confidence intervals for treatment groups overlapped and the results were insufficient to establish a causal relationship between RA treatments and lymphoma or to delineate differences in risks among treatments. The standardized incidence rate (SIR) in the overall cohort was 1.9 cases per 100,000. The SIR for patients not receiving MTX or any biologic agents was 1.0. The SIRs for patients on specific drugs were as follows: MTX, 1.7 (95% CI, 0.9-3.2); infliximab, 2.6 (95% CI, 1.4-4.5); and etanercept, 3.8 (95% CI, 1.9-7.5). An update of this analysis with additional patients and follow-up time confirmed that the risk of lymphoma was not increased among patients taking adalimumab, etanercept, and infliximab.[242]

Three community-based, retrospective cohort studies from Sweden, Canada, and the United States, however, did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on synthetic DMARDs.[243-245] The largest study included 4,160

patients treated with anti-TNF drugs.[244] Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6-2.1) for anti-TNF patients relative to patients on synthetic DMARDs.

Results regarding an increased risk for overall malignancies in patients treated with biologic DMARDs relative to placebo are also mixed. The best evidence comes from a fair meta-analysis that pooled data of more than 5,000 RA patients from adalimumab and infliximab efficacy trials.[239] The pooled odds ratio for malignancies was 3.3 (95% CI, 1.2-9.1). The NNH was 154 (95% CI, 91-500) within a treatment period of 3 months to 12 months. Two large retrospective cohort studies, however, do not support such findings.[245,275] The larger of these two studies, based on data on more than 60,000 Swedish patients, found SIRs for solid cancers to be similar for RA patients treated with anti-TNF medications and those on conventional therapy using both a contemporary and a historic control group.

A clinical trial database review did not detect a higher incidence of squamous cell carcinoma in 1,442 RA patients (4,257 patient-years) treated with etanercept (crude rate: 2.8 cases/1,000 patients) than for those on placebo;[280] the median follow-up time was only 3.7 years. A larger retrospective cohort study (N = 15,789), however, reported a statistically significant association of a combination of anti-TNF and MTX treatment and nonmelanoma skin cancer (hazard ratio [HR]: 1.28; 95% CI, NR; $P = 0.014$).[212] This finding also was observed in a large prospective cohort study of 13,869 patients in the US National Data Bank for Rheumatic Diseases taking adalimumab, anakinra, etanercept, and infliximab.[281] These biologic DMARDs were associated with an increased risk of nonmelanotic skin cancer (OR, 1.5; 95% CI, 1.2-1.8) and melanoma (OR, 2.3; 95% CI, 0.9-5.4).

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity (Table 61). Reports based on data from the FDA's AERS indicated that adalimumab, etanercept, and infliximab might be associated with demyelination.[246,247] Similar cases have been seen in regulatory trials of adalimumab.[181] All neurologic events partially or completely resolved after discontinuation of treatment.

Table 61. Other specific adverse events in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
De Bandt et al., 2005[248]	Case series 22 cases with lupus syndrome	Pts with RA in daily clinical care in France	ETA, INF	Similar incidence of lupus syndrome between ETA and INF	Fair
Flendrie et al., 2005[250]	Prospective cohort study with historic control 578 911 pt-years	Pts with RA starting anti-TNF therapy	ADA, ETA, INF	Higher rates of dermatological conditions in pts on anti-TNF drugs compared to DMARDs	Fair

* Study added during the 2010 update search; ABA, abatacept; ADA, adalimumab; AE, adverse event; AERS, adverse event reporting system; ANK, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab; IR, incidence rate; IRR, incidence rate ratio; LEF, leflunomide; MTX, methotrexate; NA, not applicable; OR, odds ratio; RA, rheumatoid arthritis; RCT, randomized controlled trial; TCZ, tocilizumab; TNF, tumor necrosis factor.

Table 61. Other specific adverse events in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Harrison et al., 2009[251] BSRBR	Retrospective cohort study 12,706 1 to 2 years	Pts with severe RA from The British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF, oral DMARDs	Anti-TNF vs. oral DMARDs: IR 1.04 (95% CI, 0.67-1.54); Among anti-TNF: ADA had a significantly increased risk of psoriasis compared to those treated with ETA (IRR, 4.6; 95% CI, 1.7-12.1) and INF (IRR, 3.5; 95% CI, 1.3-9.3)	Fair
*Maini et al., 2006[144] CHARISMA	RCT 359 20 weeks	Pts with RA despite MTX treatment	MTX, TCZ+MTX, TCZ	Liver enzymes (AST) increased with TOC use but was highest in TOC+MTX. No change in liver enzymes occurred with MTX alone	Fair
*Michaud and Wolfe, 2006[214]	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the National Data Bank for Rheumatic Diseases (NDB) study	ADA, ETA, INF	Association (OR) of treatment with visits to physician for sinus problems: ADA: 1.09 (95% CI, 0.79-1.51; *P* = 0.600) ETA: 1.21 (95% CI, 1.02-1.42; *P* = 0.025) INF: 1.00 (95% CI, 0.88-1.15; *P* = 0.973)	Fair
Mohan et al., 2001[247]	Database analysis AERS 19 cases of demyelination NA, AERS data	Pts on anti-TNF therapy	ETA, INF	Discontinuation of therapy led to partial or complete resolution of all cases	Fair
Shin et al., 2006[282]	Database analysis AERS 15 cases of Guillain-Barre and Miller Fisher syndromes NA, AERS data	Pts on anti-TNF therapy	ADA, ETA, INF	Demyelination is a potential adverse event of anti-TNF therapy	Fair

Similarly, reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases.[184,240,248,249] Lupus-like syndromes have also been reported for adalimumab.[246] Development of antinuclear, antidouble-stranded DNA, or antihistone antibodies have also been reported in regulatory trials of other anti-TNF-α drugs.[181,182] The infliximab package insert reports that 34 percent of patients treated with infliximab and MTX experienced transient elevations of liver function parameters.[184] Severe liver injury, including acute liver failure, has been reported. Only one study, the Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) trial,[144] reported data on liver function tests. This trial compared MTX, tocilizumab plus MTX, and tocilizumab monotherapy over 20 weeks in 359 patients with RA. Both tocilizumab groups

had elevated liver enzymes compared with MTX monotherapy. Liver enzymes were most elevated in the tocilizumab plus MTX group.

A prospective cohort study (N = 578) indicated that patients on anti-TNF treatments developed dermatological conditions (skin infections, eczema, drug-related eruptions) statistically significantly more often than anti-TNF-naive patients over a median treatment time of 2.3 years (25% vs. 13%; $P < 0.0005$).[250] Another retrospective cohort study of 12,076 patients with severe RA from the British Society for Rheumatology Biologics Register (BSRBR) failed to find an overall association of Anti-TNF drugs with risk of psoriasis.[251] Among the three biologic DMARDs included, adalimumab had a significantly increased risk of psoriasis compared with those treated with etanercept (IRR, 4.6; 95% CI, 1.7-12.1) and infliximab (IRR, 3.5; 95% CI, 1.3-9.3).

One cross-sectional analysis of data from 7,243 patients in the prospective cohort of the National Data Bank for Rheumatic Diseases assessed the relationship of treatment with adalimumab, etanercept, and infliximab with physician visits for sinus problems.[214] A small elevated risk was observed among patients treated with etanercept (OR, 1.21; 95% CI, 1.02-1.42). No statistically significant increased risk of sinus problems was observed with adalimumab (OR, 1.09; 95% CI, 0.79-1.51) or infliximab (OR, 1.00; 95% CI, 0.88-1.15).

Adherence. The published literature in this area frequently uses the terms *compliance* and *adherence* interchangeably. *Compliance* has traditionally been used to describe a patient's ability to take medications as prescribed. Some authors argue, however, that *adherence* better represents the more complex relationship among patients, providers, and medications; it is meant to reflect the fact that following a medication regimen is not necessarily a simple choice.[283] Given the lack of a clear definition, we use the term *adherence*. Table 62 summarizes studies for adherence.

The majority of RCTs that reported adherence stated a rate between 85 percent and 100 percent. Seven published studies reported levels of adherence in RCTs.[40,47,79,83,96,158,221,225] Most, however, contained only minimal information, and many did not stratify by treatment. Furthermore, they provided little or no information on the methods of assessment. For example, one study reported that adherence was satisfactory in 85 percent of patients, but the investigators did not describe their method of determining adherence.[79] Only four of the seven RCTs reported adherence rates for different treatment arms.[40,96,158,221,225] None of these studies noted a significant difference in adherence (although there differences in discontinuation rates were noted in many trials). To what extent results from these highly controlled efficacy trials can be extrapolated to effectiveness settings remains unclear.

A retrospective database analysis used a large U.S. health plan, which included commercial and Medicare insurance, to examine adherence levels in 2,662 patients being treated with infliximab, etanercept, or MTX from November 1999 to December 31, 2001.[252] The primary outcome measured was the number of drug administrations or prescriptions filled, divided by the expected number during a 365-day period. Their primary finding was that patients on infliximab were significantly more adherent than patients on etanercept or MTX. After controlling for baseline covariates (age, sex, baseline cost, insurance type, health plan region, history of therapy of RA, comorbidities, type of physician), 81 percent of the patients receiving infliximab were adherent compared with 68 percent of the etanercept and 64 percent of the MTX patients ($P < 0.05$ for infliximab vs. both other drugs) over 1 year. This finding was contradicted by a prospective cohort study of 1,161 patients taking etanercept or infliximab, where infliximab-treated patients were less adherent than etanercept-treated patients ($P < 0.001$).[219] Adherence at 5 years was 69% for the infliximab group and 89% for the etanercept group.

Table 62. Studies assessing adherence in patients with rheumatoid arthritis

Author, Year	Study Type and Interventions	N	Results
Boers et al., 1997[79]	RCT MTX + SSZ + prednisolone vs. SSZ	155	Compliance satisfactory in 85%
Emery et al., 2000[40]	RCT LEF vs. MTX	999	Reason for withdrawal: noncompliance in the 1st year: LEF 11 (2%) vs. MTX 14 (3%) noncompliance in the 2nd year: LEF 6 (2%) vs. MTX 6 (2%)
Fleischmann et al., 2003[225]	RCT AKA vs. placebo	1,414	AKA vs. placebo: 100% adherent with use of study drug: 43.8% vs. 47.8% <70% adherent with use of study drug: 0.8% vs. 1.7% >40% missed no injections >90% received at least 90% of intended doses
Goekoop-Ruiterman et al., 2005[83]	RCT Four treatment strategies	508	24 (5%) were nonadherent
*Grijalva et al., 2007[284]	Retrospective cohort study Oral and Biologic DMARDs	6,018	SSZ, MTX+HCQ, MTX+IFX, MTX+ETN, MTX+ADA, and ANK or ANK+MTX less adherent than MTX (P = 0.014; P <0.001; P <0.001; P <0.001; P = 0.001; P = 0.008; respectively) LEF, INF, ETN, ADA more adherent than MTX (P <0.001; P <0.001; P <0.001; P = 0.005; respectively)
Haagsma et al., 1997[47]	RCT SSZ + MTX vs. SSZ or MTX	105	Percentage of tablets taken > 90% (pill count)
Harley et al., 2003[252]	Retrospective database analysis INF vs. ETN vs. MTX	2,662	INF more adherent than ETA or MTX (P < 0.05)
Hyrich et al., 2006[68]	Prospective observational study	2,711	Adherence at 6 months: ETN 80% vs. INF 79% ETN subgroups (22% monotherapy, 16% MTX co-therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy, vs. 22% DMARD co-therapy)
*Kristensen et al., 2006[219]	Prospective cohort study ETN vs. IFX	1,161	INF less adherent than ETN for all subgroups (P <0.001). Adherence at 5 years 69% for IFX+MTX vs. 89% for ETN+MTX (P <0.001).
Kremer et al., 2002[158]	RCT LEF + MTX vs. placebo + MTX	263	Overall, 98% adherent Adherence rates 80%-120% LEF, 87.7% placebo 90.2%
*Russell et al.,2007[96,221]	RCT ABA + MTX vs. placebo + MTX	652	ABA + MTX adherence 89% MTX placebo adherence 74%
Strand et al., 1999[41]	RCT LEF vs. MTX vs. placebo	402	Nonadherence as the reason for withdrawal: LEF (1) MTX (1)

ABA, abatacept; ADA, adalimumab; AKA, anakinra; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; HCQ, hydroxychloroquine; INF, infliximab; LEF, leflunomide; MTX, methotrexate; RCT, randomized controlled trial; SSZ, sulfasalazine.

A 5-year observational study from March 1999 to January 2004 with 949 patients in Sweden, prospectively evaluated the long-term efficacy and tolerability of treatment with infliximab and etanercept in adults with RA using the LUNDEX.[56] The LUNDEX, a new index combining the proportion of responders with the proportion of patients adhering to treatment, was designed to compare the efficacy of the different therapies based on continued adherence and continuation of treatment. The study found that the etanercept group had a greater LUNDEX value, attributable primarily to better treatment adherence or survival time in the active treatment group, than did the infliximab group (P = NR).

A retrospective cohort study of 6,018 patients measured adherence with multiple oral DMARDs, biologic DMARDs, and combinations of DMARDs. Compared with patients on MTX monotherapy, patients taking monotherapy sulfasalazine or anakinra, and patients taking methotrexate plus hydroxychloroquine, adalimumab, anakinra, etanercept, and infliximab had lower adherence.[284] Patients on monotherapy leflunomide, adalimumab, etanercept, or infliximab had better adherence than patients on monotherapy methotrexate. However, these differences might also be capturing decrements in adherence related to measurement or to behavior with taking more than one treatment at the same time (since combination treatments had lower adherence).

Key Question 4: Benefits and Harms for Selected Populations

This key question addressed the comparative benefits and harms of drug therapies for rheumatoid arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities. Early RA as a stage of disease and history of prior therapy were addressed under KQ 1, however, we present one study here that grouped subjects by early RA vs. more advanced RA. We did not find studies that exclusively compared MTX-naive RA groups with those with RA who were MTX-experienced.

Overview

We did not find any studies directly comparing efficacy, effectiveness, or harms of drug therapies between subgroups of RA patients and the general population. Our findings are limited to results from subgroup analyses, a weaker form of evidence. Overall, we included five good or fair quality studies to address this key question: two RCTs, one subgroup analysis of multiple RCTs, one database analysis, and one systematic review.

We focused on groups defined by stage of disease, demographics (age, sex, race, or ethnicity), concomitant therapies, and comorbidities (any comorbidity, cardiovascular disease, osteoporosis, and renal disease).

We present key points and detailed analyses below for the population groups noted above. Details about included studies are presented by subgroup analysis in Tables 63 to 67 (listed alphabetically within outcome sections).

Key Points

Strength of evidence is low for comparative efficacy and effectiveness for stage of disease, age, concomitant therapies, and comorbidities. Only single studies exist for each of the drug comparisons (Table 63).

Table 63. Strength of evidence

Number of Studies; # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Stage of Disease						
MTX vs. ETA vs. MTX+ETA N = 1,091	Medium 1 Posthoc analysis/fair	Unknown, single study	Direct	Imprecise	Moderate RA groups on MTX monotherapy or combinations had better DAS28 scores than those with severe disease; HAQ scores better in moderate RA groups on monotherapy; severe RA monotherapy groups had greater mean change scores in DAS28 from baseline than moderate RA	Low
Age						
MTX in age groups N = 496	Medium 1 Systematic Review/fair	Unknown, single study	Direct	Imprecise	Inverse relationship between age and risk for major clinical improvement	Low
Various agents in the elderly N= 946	Medium 1 Case control study/fair	Unknown, single study	Direct	Imprecise	Oral glucocorticoids and cytotoxic immunosuppressive agents (such as LEF) increased risks for cardiovascular events. No differences in cardiovascular events for biologics (ADA, ETN, INF, ANK)	Low
Concomitant Therapies						
ANK N=1,399	Medium 1 RCT/fair	Unknown, single study	Direct	Imprecise	No differences in adverse events when taking antihypertensive, antidiabetic, or statin pharmacotherapies	Low
Comorbidities						
ANK use in those with high risk comorbid conditions N=951	Medium 1 RCT/fair	Unknown, single study	Direct	Imprecise	No differences between treatment groups in regard to serious adverse events or overall infectious events	Low
MTX use in those with renal impairment N = 496	Medium 1 Systematic Review/fair	Unknown, single study	Direct	Imprecise	Risk of severe toxicity and respiratory toxicity higher in those with greater renal impairment	Low

AKA, anakina; CHF, congestive heart failure; DAS, disease activity score; ETA, etanercept; HAQ, health assessment questionnaire, MTX methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Stage of disease. One fair quality post hoc analysis of two RCTs[285] compared those treated with MTX or etanercept or a combination of both in patients with moderate RA with those in a severe disease activity state. Generally, patients with moderate RA achieved significantly better DAS28 and HAQ results than those with severe RA, however, those with severe disease activity on etanercept or MTX monotherapies had greater change scores from baseline in DAS28.

Demographics. We found no studies that conducted comparisons by sex, race, or ethnicity, but we did include one fair systematic review that addressed age,[286] one pooled analysis of RCTs[246] and a secondary database analysis of Medicare patients.[189]

One systematic review by the Rheumatoid Arthritis Clinical Trial Archive Group found an inverse relationship between age and major clinical improvement.[286] Of the three trials reviewed, the differences between the odds ratios was small.[286] One study directly compared the efficacy of etanercept in elderly RA patients (65 years of age or older) with younger RA patients (under 64 years of age and older than 18) and found no significant difference in functional status between age groups.[246] The secondary database analysis reported that in the elderly, the risk of cardiovascular events was higher in those who were treated with oral glucocorticoids or cyctotoxic immunosuppressant agents such as leflunomide, whereas biologic agents (abatacept, intanercept, infliximab, anakina) were found to have no beneficial or harmful effect.[189]

Concomitant therapies. We found no evidence from head-to-head comparisons, placebo-controlled trials, or observational studies on other treatment therapies. Differences based on comparisons of various combinations of RA medications are addressed in key questions 1 through 3. An analysis of data from one placebo-controlled trial involving RA patients receiving anakinra determined that the safety profiles did not differ in subjects receiving antihypertensive, antidiabetic, or statin medication treatments.[287]

Comorbidities. We identified two studies that addressed outcomes of RA patients with comorbidities. For RA patients with various high-risk conditions, one large placebo-controlled RCT of anakinra reported that there was no difference in serious adverse events or infections between the treated and placebo groups.[288] A systematic review of 11 MTX trials of RA patients determined that those with renal impairment were directly at greater risk for experiencing MTX toxicity, and the greater the renal impairment the greater the toxicity effects.[286]

Detailed Analysis

Stage of disease. A fair post hoc analysis of TEMPO and ERA study data (Table 64)[285] looked at response to etanercept or MTX, or a combination of both, in regard to the patient's stage of RA - moderate (DAS20 > 3.2 and ≤ 5.1) or severe (DAS28 > 5.1) Though there were similarities between the two trial populations, the TEMPO subjects in this analysis had RA longer (6.6 versus 1 mean years) and greater prior MTX use (43% versus 0%) than the ERA group. Both analysis groups were primarily patients with severe RA (94% versus 84.3%), however, the percentage of ERA patients with moderate RA was more than twice that in the TEMPO group (15.7% versus 6%), making the TEMPO analysis group a more severe population than the ERA group overall. The authors did not report any *P* values for differences between groups on baseline characteristics.

Table 64. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by stage of disease

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Keystone et al., 2009[285]	Posthoc analysis of 2 RCTs 1,091 12 months	Adults with moderate versus severe RA treated with MTX, etanercept monotherapies or combinations	MTX (dose NR), ETN (25 mg twice weekly), MTX + ETA	Significant differences favored those with moderate RA in DAS28 and HAQ scores versus those with severe stage, but greater gains from baseline scores for DAS28 were seen in the those with severe RA	Fair

Investigators reported significant differences in DAS28 remission at six months in TEMPO patients with moderate RA treated with MTX or etanercept monotherapies or combination compared with those with severe RA. This significant trend continued for the MTX-only or MTX-etanercept combination groups at 12 months, but not for those treated with etanercept alone (MTX: $P = 0.0035$; MTX plus etanercept: $P = 0.0006$). In the ERA analysis, both those treated with MTX or etanercept monotherapies for moderate RA, achieved significant DAS28 improvements at both six (MTX: $P = 0.0058$; etanercept: $P = 0.0003$) and 12 months (MTX: $P = 0.0094$; etanercept: $P < 0.0001$).[285]

A significant difference in low disease activity level was achieved by those with moderate RA in both trial groups at both six and 12 months in all treatment groups except those treated with etanercept monotherapy in the TEMPO study. Mean DAS28 scores were consistently lower in moderate RA groups in comparison with those with severe RA, however, mean changes in DAS28 scores at 12 months were significantly greater in those with severe RA (ERA trial: MTX only: 1.2 versus 2.4, $P < 0.0001$; etanercept only: 1.7 versus 2.4 $P < 0.0110$; TEMPO trial: MTX only: 1.6 versus 2.6, $P < 0.0076$; etanercept only: 1.5 versus 2.7, $P < 0.0268$; MTX plus etanercept 2.5 versus 3.5, $P < 0.0069$).[285]

Twelve month changes in HAQ scores from baseline showed significant differences between moderate and severe disease activity in the MTX-only group from the TEMPO trial and the two monotherapies in the ERA trial (TEMPO trial: MTX only 0.29 versus 0.68, $P = 0.0138$; etanercept only 0.42 versus 0.74, $P = 0.1329$; MTX plus etanercept 0.74 versus 1.00, $P = 0.0895$; ERA trial: MTX only 0.44 versus 0.77, $P = 0.0107$; etanercept only 0.45 versus 0.75, $P = 0.0070$).[285]

In regard to radiographic changes, only the MTX monotherapy group in the TEMPO trial showed significant differences in median change of total sharp scores between moderate and severe RA patients (1.00 versus 2.57, $P = 0.014$).[285]

Demographics. We identified one study analyzing MTX use in the elderly and one database analysis of various agents of a Medicare population.[189,286]

Table 65 presents the studies of adults with RA that conducted comparisons by age groups.

Table 65. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by age

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Rheumatoid Arthritis Clinical Trial Archive Group 1995[286]	Systematic review 496 ≥ 12 weeks	Adults with RA by age subgroups: under 60 years of age; 60 to 64 years; 65 to 69 years; and 70 years or above	MTX	Adjusted analysis demonstrated that as age increases, the odds ratio for major clinical improvement decreases; no effect found on toxicity	Fair
Solomon et al., 2006[189]	Nested case control database analysis (Medicare and PACE) 946 ≤ 24 months	Elderly adults with RA	MTX, ADA, ETA, INF, AKA, AZA, CSA, LEF, HCQ, SSZ, gold, and all oral glucocorticoid agents	Oral glucocorticoids and cytotoxic immunosuppressive agents increased risks for cardiovascular events, biologics neither increased risk or decreased risk	Fair

ADA, adalimumab; AERS, adverse events reporting system; AKA, anakinra; AZA, azathioprine; CHF, congestive heart failure; CSA, cyclosporine A; ETA, etanercept; HCQ, hydroxychloroquine ;INF, infliximab; LEF, leflunomide; MTX, methotrexate; NA, not applicable; PACE, pharmaceutical assistance contract for the elderly; RA, rheumatoid arthritis; RCT, randomized controlled trial; SSZ, sulfasalazine; TNF, tumor necrosis factor.

The Rheumatoid Arthritis Clinical Trial Archive Group 1995 review of 11 MTX trials for adults with RA evaluated the effects of age or renal impairment on adverse events or treatment efficacy.[286] Although the authors reported that the odds for major clinical improvement dropped slightly as age increases, among all clinical trial patients, age did not affect MTX efficacy or the rate of side effects. Using the group under age 60 as the referent, the odds of major clinical improvement for those 60 to 64 years of age was 1.4 (95% CI, 0.7-2.6), 1.0 (95% CI, 0.5-2.2) for those 65 to 69 years of age, and 0.7 (95% CI, 0.3-1.7) for those 70 years of age or older (P = NR).

A fair quality nested case control study investigating cardiovascular events in 946 RA patients was conducted using data from Medicare enrollees also receiving benefits from the state of Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program.[189] Index dates were established as the first cardiovascular event within patients who had a diagnosis of RA on at least two visits and a prescription of an immunosuppressant agent (MTX, adalimumab, etanercept, infliximab, anakinra, azathioprine, cyclosporine, leflunomide, gold, hydroxychloroquine, sulfasalazine, and all oral glucocorticoid agents) within 90 days of the index event. Using MTX as the reference group, oral glucocorticoids (monotherapy: OR, 1.5; 95% CI, 1.1-2.1; combinations: OR, 1.3; 95% CI, 0.8-2.0) and cytotoxic immunosuppressive agents: azathioprine, cyclosporine and leflunomide (OR, 1.8; 95% CI, 1.1-3.0) were associated with an increased risk for cardiovascular events. Biologics (adalimumab, etanercept, infliximab), on the other hand, had no effect on risk for developing or preventing a cardiovascular event (monotherapy: OR, 1.0; 95% CI, 0.5-1.9; combination with MTX: OR 0.8; 95% CI, 0.3-2.0; combination with other immunosuppressive agents OR, 1.2; 95% CI, 0.7-2.2).[189]

Concomitant therapies. One placebo-controlled trial of 1,399 adults with active RA disease examined safety profiles of those treated with 100 mg/day anakinra (Table 66). Investigators failed to find anydifferences in the adverse event profiles of the subjects taking or not taking

concomitant antihypertensive, antidiabetic, or statin pharmacotherapies. Even when the analysis compared those treated with anakinra with those on placebo, no differences emerged (*P* = NR).[287]

Table 66. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: by concomitant therapies

Study	Study Design N Duration	Study Population	Intervention	Outcomes	Quality Rating
Tesser et al., 2004[287]	RCT 1,399 6 months	Adults with RA taking or not taking antihypertensive, antidiabetic, or statin pharma-cotherapies	ANK, 100 mg/day	No significant difference found in safety profiles	Fair

ANK, anakinra; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Comorbidities. Table 67 presents three studies identified as addressing comorbidities.

Any comorbidity. We did not identify any study specifically designed to assess the comparative efficacy and risk of biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab) in RA patients with common comorbidities. A post-hoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with various comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, and central nervous system-related events).[288] Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

Table 67. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis by comorbidities

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Rheumatoid Arthritis Clinical Trial Archive Group, 1995[286]	Systematic review of 11 RCTs 454 NA	RA patients with impaired renal function treated with MTX	MTX	Severe toxicity (severe upper abdominal pain, renal failure, proteinurea, cytopenias and liver toxicity) and respiratory toxicity (cough, pneumonitis, dyspnea, wheezing) worse with greater renal impairment	Fair
Schiff et al., 2004[288]	RCT 951 6 months	RA patients with high-risk comorbid conditions	ANK, 100 mg/day	In patients with comorbid conditions, no differences were found between treatment groups in regard to incidence of serious adverse events or overall infectious events	Fair

ANK, anakinra; MTX, methotrexate; NA, not applicable; RA, rheumatoid arthritis; RCT, randomized controlled trial.

*Cardiovascular morbidity***.** No direct evidence exists on the comparative risk of biologic DMARDs in patients with both RA and cardiovascular disease.

Renal function. A systematic review of 11 RCTs of MTX use in 496 adults with RA concluded that toxicity worsened with greater renal impairment. Patients with high renal impairment had a fourfold risk (OR, 4.5; 95% CI, 0.9-22.6) for severe toxicity (severe upper

abdominal pain, renal failure, proteinurea, cytopenias, and liver toxicity) than those with no renal impairment. Slightly more (4% versus 1%) had respiratory toxicity (cough, pneumonitis, dyspnea, wheezing). No effect was found between renal impairment and increased liver toxicity.[286] Baseline renal function was found to be a significant predictor of toxicity, with the lower creatinine clearances ending up with greater toxicity ($P = 0.027$).[286]

Chapter 4. Discussion

This report provides a comprehensive review of the comparative efficacy, effectiveness, and harms of members of the main classes of drugs used to treat adult patients with rheumatoid arthritis (RA). These include oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. The objective of our report was to evaluate the comparative efficacy, effectiveness, and harms of monotherapies, combination therapies, and different treatment strategies.

Table 68 summarizes our findings and the strength of evidence for three key questions (KQs) addressed by this report. In brief, the KQs involved benefits of these drugs, alone or in combination, in terms of slowing or limiting disease activity or radiographic joint damage (KQ 1); improving functional capacity and quality of life (KQ 2) and harms and risks of these drugs (KQ 3). The benefits or harms in various patient subpopulations (KQ 4) are described within the text. Most of the evidence meeting inclusion criteria focuses on comparative efficacy.

Table 68. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses LOW	No consistent differences in tolerability and discontinuation rates LOW
	Mixed results for functional capacity INSUFFICIENT	Mixed results for specific adverse events INSUFFICIENT
	Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide LOW	
Leflunomide vs. sulfasalazine	Mixed ACR response rates INSUFFICIENT	No differences in tolerability and discontinuation rates LOW
	No differences in radiographic changes LOW	Mixed results for specific adverse events INSUFFICIENT
	Greater improvement in functional capacity for leflunomide LOW	
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and functional capacity MODERATE	No differences in tolerability; more patients stayed on MTX long-term LOW
	No differences in radiographic changes LOW	Mixed results for specific adverse events INSUFFICIENT

Table 68. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. SSZ or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes MODERATE No differences in functional capacity MODERATE	Withdrawal rates attributable to adverse events higher with combination LOW Insufficient evidence for specific adverse events INSUFFICIENT
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity INSUFFICIENT Less radiographic progression In patients on DMARD plus prednisone LOW In patients with early RA, significantly lower radiographic progression and fewer eroded joints LOW Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy MODERATE No difference in quality of life LOW	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment MODERATE No differences in specific adverse events, except addition of corticosteroid may increase wound healing complications LOW
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity and quality of life for abatacept, but no difference in remission or functional capacity LOW	Discontinuation rates and severe adverse events higher with infliximab LOW
Biologic vs. Biologic *(indirect comparisons)*	Less improvement in disease activity (ACR 20/50) for anakinra compared to certolizumab and etanercept in MTC analyses. Comparisons with abatacept, adalimumab, golimumab, infliximab and tocilizumab did not reach statistical significance. LOW Greater improvement in disease activity (ACR 20/50) for certolizumab compared to abatacept, anakinra, infliximab in MTC analyses. No significant differences when compared with adalimumab, etanercept, golimumab and tocilizumab LOW Greater improvement in disease activity (ACR 20/50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab and tocilizumab in MTC analyses. No significant differences when compared with certolizumab (ACR 20/50) and golimumab (ACR 50) LOW	Risk for injection site reactions apparently highest with anakinra LOW Indirect comparisons consistently showed better tolerability for certolizumab and etanercept. LOW Observational evidence suggests discontinuation rates and severe adverse events may be higher with infliximab than other biologic DMARDs LOW Risk of infusion reactions most common with infliximab LOW Mixed results for specific adverse events INSUFFICIENT

Table 68. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
	No significant differences in disease activity for abatacept, adalimumab, golimumab, infliximab and tocilizumab in MTC analyses LOW	
Biologic DMARDs vs. Oral DMARDs		
Anti-TNF drugs vs. MTX	In patients with early RA, no differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs MODERATE No difference in functional capacity between adalimumab and MTX for MTX naïve subjects with early RA; mixed results for ETN vs. MTX LOW; INSUFFICIENT Faster improvement in quality of life with ETN than MTX LOW In patients who had failed initial RA treatment, greater functional independence and remission for anti-TNF drugs as a class than oral DMARDs as a class MODERATE	No differences in adverse events in efficacy studies LOW Insufficient evidence on differences in the risk for rare but severe adverse events INSUFFICIENT
Other Biologic DMARDs vs. Oral DMARDs	Greater improvement in disease activity and functional capacity with TCZ than MTX for patients with active RA and an inadequate response to MTX LOW	Insufficient evidence on differences in tolerability and in the risk for rare but severe adverse events INSUFFICIENT
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with ETN plus ABA vs. ETN LOW	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy MODERATE
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (ADA, ETN,INF,RTX) plus MTX than from monotherapy with biologics MODERATE In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group LOW	No differences in adverse events in efficacy studies LOW Insufficient evidence on differences in the risk for rare but severe adverse events INSUFFICIENT

Table 68. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
	In MTX naïve subjects or those not recently on MTX, greater improvement in functional capacity (MODERATE) and quality of life (LOW) with combination therapy In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life LOW	
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy LOW	No differences in adverse events in efficacy studies LOW Insufficient evidence on differences in the risk for rare but severe adverse events INSUFFICIENT
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy MODERATE, LOW for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis LOW Mixed evidence on differences in the risk for rare but severe adverse events INSUFFICIENT
Strategies in early RA		
2 oral DMARDs plus prednisone vs. oral DMARD	In patients on 3 oral DMARDs, improved ACR 50 response rates, disease activity scores, and less radiographic progression LOW In patients with early RA, significantly lower radiographic progression and fewer eroded joints LOW	No differences in discontinuation rates MODERATE
3 oral DMARDs plus prednisone vs. 1 oral DMARD	In patients on 3 oral DMARDs, improved ACR 50 response rates, disease activity scores, and less radiographic progression LOW In patients with early RA, significantly lower radiographic progression and fewer eroded joints LOW	No differences in discontinuation rates MODERATE

Table 68. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of evidence	Harms Strength of evidence
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high- dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 yrs LOW	No differences in serious adverse events between groups LOW

Key Findings

Over the past few years, treatment strategies for RA have changed considerably. Early use of DMARDs is now considered crucial to avoid persistent and erosive arthritis. Clinicians frequently start treatment regimens with DMARD monotherapies and adjust dosages as appropriate to achieve a low disease activity.

Existing comparative evidence permits us to draw some conclusions for monotherapies of oral and biologic DMARDs. Overall, the evidence supports similar efficacy and effectiveness for methotrexate (MTX) and sulfasalazine.[45-47] The evidence is insufficient to draw conclusions about disease activity for sulfasalazine and leflunomide, but improvement in functional capacity is greater for patients on leflunomide (low strength of evidence).[43,156] All three drugs have similar discontinuation rates attributed to adverse events in short-term efficacy trials up to 2 years.[39-41,43]

The evidence comparing biologic DMARDs is limited to one head-to-head RCT, several observational studies, indirect analyses, and our mixed treatment comparisons (MTC) meta-analyses. Based on one RCT, abatacept lessens disease activity more than infliximab, but remission rates are not significantly different at one year (low strength of evidence).[53] Discontinuation rates and severe adverse events appear higher with infliximab; these results are also supported by observational studies.[135,216,218,219] Our MTC of randomized-controlled trials of subjects with active RA despite MTX treatment found a higher odds of reaching the ACR 20/50 for etanercept compared to abatacept, adalimumab, anakinra, infliximab, or tocilizumab (low strength of evidence), but no statistically significant difference for etanercept compared to certolizumab (ACR 20/50) or golimumab (ACR 50). The same analyses found higher odds of reaching ACR 20/50 for certolizumab compared to abatacept, anakinra, and infliximab (low strength of evidence). Similarly, our indirect analyses from randomized trials indicate that patients taking certolizumab or etanercept are less likely to withdraw treatment than patients taking other biologic DMARDs. In contrast prior analyses found no differences among the set of anti-tumor necrosis factor (anti-TNF) drugs (namely, etanercept, infliximab, and adalimumab).[27,60,61,89] The differences between our results and those of previous indirect analyses may be attributed to newer studies and drugs (certolizumab, golimumab, and tocilizumab) added to the analyses, which provide additional data. Further, unlike previous indirect analyses, our MTC meta-analysis uses methods that do not rely solely on placebo-controlled trials; it also

allows the inclusion of data from head-to-head studies or those with active comparators, thus increasing statistical power. In addition, we limited our studies to patient populations who had an inadequate response to methotrexate and excluded studies with methotrexate naïve populations, those with early RA, or those who had failed anti-TNF therapy. Our MTC meta-analysis indicates that anakinra is less efficacious than certolizumab and etanercept. Prior indirect comparisons consistently indicated that anakinra is less efficacious than biologics for patients with RA.[60,61] Adjusted indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be verified, particularly the similarity of study populations.

The evidence comparing monotherapy using a biologic DMARD with monotherapy using an oral DMARD is mixed. Monotherapies of adalimumab in early RA[62] and etanercept in longstanding RA[63,73] generally did not reveal a benefit relative to MTX monotherapy for response rates and had mixed results for functional capacity. There was faster improvement in quality of life for etanercept. Radiographic outcomes were also significantly better in patients on biologic DMARDs than on MTX. Whether such differences are clinically relevant and can alter the long-term progression of the disease remains unclear. Tocilizumab showed greater improvement in both disease activity and functional capacity in patients with active RA and an inadequate response to MTX. Other biologic DMARDs have not been directly compared with MTX.

Population-based, observational evidence from one study suggests that biologic DMARDs as a class resulted in better functional capacity than oral DMARDs as a class (low strength of evidence).[65] No studies were available comparing biologics with oral DMARDs other than MTX.

Although a substantial percentage of patients respond well to DMARD monotherapy,[39,62,63,73,113,115] some patients do not achieve an acceptable treatment response. As the BeSt study (Dutch acronym for Behandel Strategieen, "treatment strategies"), a Dutch effectiveness trial assessing different treatment strategies for RA, has indicated, tight disease control and an individualized treatment approach are paramount in achieving a satisfactory treatment response or remission.[83] Therefore, if dose escalation of a monotherapy does not achieve low levels of disease activity, combination therapies have to be taken into consideration. This is supported by multiple efficacy studies that indicate that combinations of biologic and oral DMARDs appear to be more efficacious than monotherapy of either drug in populations failing DMARD therapy.

The existing evidence supports combination strategies of up to three oral DMARDs, including corticosteroids, compared with strategies using one or two drugs. The data are limited, however, by the number of supporting studies for each drug combination. Moderate strength evidence from two efficacy trials reported higher proportions of patients meeting American College of Rheumatology (ACR) 20 criteria at 2 years for the combination of MTX plus sulfasalazine and hydroxychloroquine than for one or two drugs.[48,49]

Combination therapy of biologic DMARDs with MTX achieved better results in clinical outcomes, functional capacity, and quality of life than monotherapy with biologic DMARDs in patients not on methotrexate.[62,73,74,113,115] Whether these results can be extrapolated to combinations of biologic DMARDs with other oral DMARDs is uncertain. In clinical practice, patients often receive biologic DMARDs as an add-on therapy to an existing regimen of various oral DMARDs.

Combinations of two biologic DMARDs did not yield an additional treatment benefit but rather led to substantially higher rates of serious adverse events than with biologic DMARD monotherapies (14.8% vs. 2.5%; *P* = NR).[66,67,224]

The evidence is limited to draw firm conclusions about whether one combination strategy is better than another in early RA. Current evidence also suggests improved functional capacity[52,79,81,157] and less radiographic progression[52,79-82] for combination strategies with corticosteroids and one or more oral DMARDs compared with oral DMARD monotherapy. For most of these comparisons, the evidence is limited to a single study. One effectiveness trial for patients with early RA reported less radiographic progression over 12 months with either (1) combination therapy of MTX, sulfasalazine, and high-dose tapered prednisone or (2) MTX and infliximab versus (3) sequential DMARD therapy or (4) step-up combination therapy.[83] At two years,[85] results of this study reinforced the conclusion that patients on initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with MTX and infliximab had less radiographic progression. They also had more rapid improvement in disease activity functional capacity and quality of life, although the differences between groups were no longer present by two years. By four years, there was no difference in remission among the groups.[154]

Evidence of moderate strength suggests that studies of combinations of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had similar withdrawal rates attributable to adverse events. Studies of combinations including prednisone with one or more DMARDs had similar discontinuation rates between groups.

Similarly, patients on combinations of biologic and oral DMARDs were less likely than patients on oral DMARD monotherapy to withdraw from trials because of lack of efficacy. Combinations of biologic and oral DMARDs had similar rates of adverse events than monotherapies of either drugs However, because biologic DMARDs are relatively new medications, long-term data on safety are generally still missing. Especially rare but severe adverse events such as serious infections, lymphoma, autoimmunity, or congestive heart failure are of concern. One obvious difference among biologic DMARDs that might be clinically useful for choosing a particular drug involves dosing and administration. Abatacept, infliximab, and rituximab require intravenous administration at different intervals and present the danger of rare but severe infusion reactions. Adalimumab, anakinra, and etanercept can be administered subcutaneously by the patient. Administration intervals differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, and etanercept once or twice per week. The route of administration is also the cause of the main differences in short-term tolerability. Anakinra appears to have a substantially higher rate of injection site reactions than anti-TNF drugs. Abatacept, infliximab, and rituximab carry the risk of severe infusion reactions that cannot occur in drugs administered subcutaneously. Fatal infusion reactions have been reported for infliximab and rituximab.[184,185]

The existing evidence remains insufficient to draw firm conclusions on the best treatment regimen for patients with early RA. Studies conducted in patients with early RA suggested that an early start of a biologic DMARD can improve radiographic findings compared to an oral DMARD, but did not differ for disease activity, functional capacity, or quality of life. Because the studies were of limited duration, however, they do not allow conclusions on whether early initiation of a biologic regimen can improve the long-term prognosis of RA. Currently, clinical

practice guidelines recommend that clinicians start biologic DMARDs if patients have suboptimal response to oral DMARDs.[179,289]

Applicability

A considerable limitation of our conclusions is that we have had to derive them primarily from efficacy trials that typically enroll a narrow spectrum of patients and are conducted in ideal settings. However, the direction and effect sizes of findings from effectiveness trials and observational studies were generally consistent with those from efficacy trials. Nonetheless, differences in the incidence of reported adverse events and discontinuation rates were obvious between clinical trials and population-based observational studies.

For example, clinical efficacy trials of infliximab reported infusion reactions, on average, in 17 percent of patients.[240] A prospective cohort study in a Canadian clinical care setting, however, reported substantially higher percentages.[277] In this study (113 patients with 1,183 infusions), 53 percent of patients experienced at least one infusion reaction during their therapy (mean, 15 months).

Patients who were enrolled in efficacy trials usually suffered from more severe disease than the average patient in clinical practice.[290] For example, a recent study found that only a small proportion of consecutive patients with RA who were under the care of a private practice rheumatologist in Nashville, Tennessee, would have met eligibility criteria of the ERA (Early Rheumatoid Arthritis) trial;[63] only 31 percent of patients with early RA who had not taken MTX would have met the ERA criteria. The same pattern was true for the ATTRACT (anti-TNF trial in RA with concomitant therapy) study trials;[125,290] only 5 percent of patients in a long-term RA database would have been eligible for this trial. Therefore, the applicability of results from efficacy trials to the average patient in community practice appears to be limited.

Furthermore, we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups. Several studies conducted subgroup analyses or used subgroups as the study population; the strength of evidence is therefore low and results have to be interpreted cautiously. In severe stage of disease for RA, those with moderate RA improved in DAS28 and HAQ scores, but the severe group had greater gains from baseline scores for DAS28.[137] For MTX, the odds for major clinical improvement dropped slightly as age increased in all clinical trial patients; age did not affect MTX efficacy or the rate of side effects.[286] Safety profiles of concomitant therapies (i.e., antidiabetics, antihypertensives or statin therapies) with anakinra were investigated in one trial and revealed no greater harms.[287] RA patients with high risk comorbidities taking anakinra experienced no increase in serious adverse events or overall infectious events.[288] A Medicare database analysis concluded that biologics neither decreased nor increased cardiovascular risks in the elderly.[189] This same study also found that risks for cardiovascular events increased with oral glucocorticoids and cytotoxic immunosuppressive agents.[189] For those with renal impairment, a direct relationship was found with MTX toxicity, where adverse effects from toxicity increased with the greater renal impairment.[286]

Future Research

We have identified several areas needing further research to help clinicians and researchers arrive at stronger conclusions on the comparative efficacy, effectiveness, quality of life, and harms of medications for RA.

Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) applicability of combination strategies and biologic DMARD therapy in community practice, and (3) timing of initiation of therapies. The results of our MTC found greater improvement in disease activity for etanercept and CTZ than for some other biologic DMARDs. However, the strength of evidence was low, and head-to-head studies are needed to confirm or refute these results. Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases.

Timing of initiation of therapies needs to be addressed, including whether aggressive early treatment in RA influences the course and prognosis beneficially. Adequately powered, long-term RCTs must examine different treatment strategies with and without corticosteroids, oral DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in this population. These trials should be conducted over multiple years to guarantee that results provide a relevant assessment of the long-term prognosis of RA under different treatment strategies. Such trials would also provide insight about whether the long-term benefits of any combination of drugs outweigh the adverse effects.

Given that available long-term data indicate high discontinuation rates for drugs used to treat RA, having backup regimens is crucial. Additional well-conducted research is needed to assess the comparative efficacy and safety of oral DMARDs in patients who currently do not qualify for a treatment with a biologic DMARD. Also still unclear is whether newer oral DMARDs such as leflunomide have a better, long-term adverse events profile than older oral DMARDs such as MTX. Additionally, although combination strategies with oral DMARDs with or without corticosteroids appear more effective, further research examining *which* combination strategy is more effective would be beneficial for medical treatment decisionmaking.

Moreover, head-to-head RCTs need to establish the comparative effectiveness and safety of biologic DMARDs. Currently, evidence from systematic reviews, placebo-controlled trials, and observational studies does not allow us to draw any firm conclusions for the head-to-head comparisons between biologic DMARDs (i.e. those with greater than low strength of evidence). Biologic DMARDs differ substantially in the route and frequency of administration, which can influence the choice of a biologic agent by patients and physicians. Establishing the comparative effectiveness and safety of biologic DMARDs, therefore, is helpful for balanced, informed decisionmaking.

The risk of rare but serious adverse events such as malignancies, serious infections, demyelinations, severe infusion reactions, or congestive heart failure must be established in well-conducted observational studies, such as large cohort or case-control studies. The balance of risks and benefits of biologic DMARDs can be determined reliably only if good long-term data on such harms are available.

In general, all future studies have to ensure a high rate of applicability to patients seen in community practices. Future research has to establish the comparative effectiveness, health-related quality of life, and safety of all therapies, but especially biologic DMARDs, in settings

that reflect daily clinical care and take into account factors such as varying adherence due to administration schedules, costs, and adverse events. The current evidence indicates that severity of disease and population characteristics may differ substantially between the highly selected populations enrolled in efficacy trials and those treated in daily clinical practice. Future trials must plan subgroup analyses in older patients or patients with comorbidities a priori.

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