Draft Comparative Effectiveness Review

Number XX

Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

This information is distributed solely for the purposes of predissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the Agency for Healthcare Research and Quality. It does not represent and should not be construed to represent an Agency for Healthcare Research and Quality or Department of Health and Human Services.

Contract No. [redacted]

Prepared by: [redacted]

Investigators: [redacted]

AHRQ Publication No. xx-EHCxxx
<Month Year>

This report is based on research conducted by the <name> Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. <###-##-####>). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the 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 or actions may not be stated or implied.

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact [insert program e-mail address].

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation:

<This is the end of the page that started with the disclaimer.>

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 Children's Health Insurance Program (CHIP).

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://www.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 (http://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.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Carmen Kelly, PharmD, MPH, RPh
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Key Informants and Technical Expert Panel

<Name>
<Place>
<City>, <ST>

Peer Reviewers

<Name>
<Place>
<City>, <ST>

<Name>
<Place>
<City>, <ST>

Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis

Objectives: To examine the comparative effectiveness of biologic systemic agents versus nonbiologic systemic agents or phototherapy for treatment of chronic plaque psoriasis (CPP) and to determine patient and disease characteristics that modify outcomes of interest.

Data Sources: Medline, the Cochrane Central Register of Controlled Trials, and Web of Science from inception to September 19, 2011 with no language restrictions.

Review Methods: Randomized controlled trials (RCTs) and observational studies were included in our review if they compared treatment with Food and Drug Administration approved biologic systemic agents to either approved nonbiologic systemic agents or phototherapy in adult patients with CPP and provided data on at least one prespecified outcome. Using predefined criteria, data on study design and population, interventions, quality, and outcomes were extracted. No quantitative analyses were performed and all data were qualitatively synthesized. The strength of evidence (SOE) for individual outcome was rated, when possible, as insufficient (I), low (L), moderate (M), or high (H). The applicability of the body of evidence was determined.

Results: Four RCTs and three observational studies directly compared therapies from the specified classes. An additional five studies provided data on the transition of patients from one therapy to another. Studies generally reported short-term outcomes (median of 24 weeks) in small (<200 subjects) international patient populations. Compared with methotrexate, adalimumab improved health-related quality of life (HRQoL) [SOE: M], Psoriasis Area and Severity Index (PASI) score [SOE: L], Physician's Global Assessment (PGA) score [SOE: L], and patient's assessment of disease severity score [SOE: L], while reducing pain [SOE: L] and pruritus [SOE: L] with no effect on infection rates [SOE: L]. Compared with acitretin, etanercept improved PASI score [SOE: M] and compared with methotrexate infliximab improved HRQoL [SOE: L], PASI score [SOE: L], and PGA score [SOE: L]. Data were insufficient for any other comparisons and outcomes. Data from the post-hoc subgroup analysis of one RCT that compared treatment with adalimumab to methotrexate suggested that as disease severity improved so did a patient's HRQoL. Data were insufficient to evaluate the impact of any other patient or disease characteristics on outcomes.

Conclusions: In patients with CPP, there were limited data directly comparing systemic biologic agents to either systemic nonbiolgic agents or phototherapy. Overall there is insufficient evidence to determine the comparative effectiveness of individual therapies compared to each other between the specified classes, with few exceptions. For the comparison of adalimumab versus methotrexate, infliximab versus methotrexate, and etanercept versus acitretin, there is predominantly low strength of evidence favoring the individual biologic agent versus the nonbiologic agent. Additional trials directly comparing biologic systemic agents, systemic nonbiologic agents, and phototherapy are needed.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Objectives 3
Key Questions 3
Analytic Framework 4
Methods 5
Input from Stakeholders 5
Searching for the Evidence 5
Inclusion and Exclusion Criteria 6
Data Extraction and Data Management 6
Assessment of Methodological Quality of Included Studies 7
Data Synthesis 7
Grading the Strength of the Evidence 7
Evaluating the Applicability of the Evidence 8
Results 9
Organization of Results 9
Study Identification 9
Study Characteristics 12
Key Question 1 14
Key Points 14
Detailed Analysis 15
Key Question 2 27
Key Points 27
Detailed Analysis 27
Key Question 3 32
Key Points 33
Detailed Analysis 33
Discussion 37
Applicability 39
Research Gaps and Future Research Needs 40
Acronyms/Abbreviations 42
References 43

Tables

Table 1. Overall quality rating definitions 7
Table 2. Strength of evidence rating definitions 8
Table 3. Results from Bansback et al. 22
Table 4. Relationship between disease severity and dermatology life quality index 34
Table 5. Relationship between patient's weight and physician's global assessment 34
Table 6. The relationship between history of psoriatic arthritis and pain 35
Table 7. The relationship between prior treatment with systemic biologic agent and Psoriasis Area Severity Index 36

Table 8. Summary of findings for the comparison of systemic biologic agents versus systemic nonbiologic agents 37

Figures

Figure 1. Analytic framework 4
Figure 2. Inclusion and exclusion of citations in search one 10
Figure 3. Inclusion and exclusion of citations for search two 11

Appendixes

Appendix A. Search Strategy
Appendix B. Data Extraction Form
Appendix C. Excluded Studies from Full-Text Review
Appendix D. Baseline Characteristics for Included Studies and Trials
Appendix E. Quality and Characteristics of Included Trials and Studies
Appendix F. Evidence Tables
Appendix G. Strength of Evidence for Outcomes
Appendix H. Applicability of Individual Studies
Appendix I. Glossary
Appendix J. Abbreviations

Executive Summary

Background

Psoriasis is a common, chronic, autoimmune inflammatory skin disease affecting 2 to 3 percent of the worldwide population. The onset of psoriasis predominantly occurs early in adulthood (between the ages of 15 and 25 years) but may affect individuals at any age.[1] The course of psoriasis is marked by chronic and acute phases with a wide variety in relapse and remission rates.[2] Total health care costs of psoriasis are estimated at $11.25 billion annually.[3] This economic burden, along with the clinically relevant reductions in quality of life experienced by many patients with psoriasis, underscores the need for prompt, effective, and sustained disease management.[4,5]

Among several clinical psoriasis phenotypes, chronic plaque psoriasis is the most frequent, accounting for all but 10 percent of cases.[4-6] Chronic plaque psoriasis, also known as psoriasis vulgaris, often appears as well-demarcated, erythematous plaques covered with silvery white scales that vary in size up to several centimeters. Psoriatic skin lesions typically appear symmetrically on the scalp, trunk, and limbs (particularly on the knees and elbows) but may also affect the genitals, nails, palms, and soles of the feet.[4,5] Different parameters determine disease severity such as the degree of body surface area (BSA) involved, activity of the lesions, the location of lesions in sensitive areas, duration of disease, treatment failures, and the impact on quality of life.[2,7]

While disease localized to nonsensitive areas of skin may be managed effectively with topical agents, patients with more widespread disease often require systemic treatment.[4,5] The American Academy of Dermatology has published guidelines for the treatment of psoriasis and suggest use of either biologic or nonbiologic systemic agents or phototherapy with ultraviolet B (UVB) or with psoralen plus ultraviolet A (PUVA) therapy in patients with widespread disease.[4,8,9] Biologic therapies for psoriasis use genetically engineered drugs that target specific steps in the pathogenesis of psoriasis involving T cells and cytokines [e.g., tumor necrosis factors (TNF)-alpha and interleukin (IL)-23].[4,5] Currently, three biologic TNF-alpha inhibitors (infliximab, etanercept, and adalimumab), one T cell-targeting agent (alefacept), and one anti-IL 12/23 agent (ustekinumab) have approval from the U.S. Food and Drug Administration (FDA) for psoriasis treatment. Nonbiologic systemic therapies may be effective but can be associated with significant short-term and long-term toxicities (hepatotoxicity, nephrotoxicity, hypertension, dyslipidemia, malignancy, and teratogenicity).[8,10] Phototherapy, although considered to be one of the safer therapeutic options, requires strict compliance, and the long-term toxicity associated with it includes photocarcinogenesis.[9] Unfortunately, some patients have disease that is resistant to the above-mentioned therapies or becomes refractory to treatment. As a result, patients often report high levels of dissatisfaction with such approaches to psoriasis treatment.[4,5,8]

There are direct comparative trials either within or between biologic and nonbiologic classes directly comparing effectiveness.[11-13] Recently, a trial that compared two biologic agents concluded a difference in efficacy, suggesting heterogeneity within the class and indicating drug comparisons may be preferred over class comparisons.[11] Currently, guidelines suggest that clinicians balance individual patient characteristics with the reported adverse events and previously used treatment modalities when making therapeutic decisions.

In 2008, Schmitt and colleagues published a meta-analysis analyzing the efficacy and tolerability of biologic and nonbiologic systemic agents for moderate-to-severe plaque

psoriasis.[14] This study examined all randomized controlled trials published before January 2008 that enrolled greater than 50 patients with moderate-to-severe plaque psoriasis. Based on the results of their meta-analysis, the authors concluded that the efficacy of systemic agents approved for moderate-to-severe psoriasis likely differ considerably between biologic and nonbiologic agents, as well as within the two classes. One of the main research gaps identified in this meta-analysis was the lack of comparative effectiveness and safety data for biologic versus nonbiologic systemic treatments for moderate-to-severe plaque psoriasis. Since the completion of this systematic review, the first head-to-head trial comparing a biologic to a nonbiologic systemic treatment has been published.[13] Additionally, comparative data from nonrandomized studies likely exist, although not sought or evaluated by Schmitt and colleagues.[14] Moreover, the efficacy of phototherapy was not addressed in this meta-analysis.

To date, no comparative effectiveness review comparing the effectiveness and safety of biologic systemic to nonbiologic systemic treatment options or phototherapy for chronic plaque psoriasis has been completed.

Scope and Key Questions

The objective of this comparative effectiveness review (CER) is to examine the benefits and harms of biologic systemic agents compared with nonbiologic systemic agents or phototherapy in patients with chronic plaque psoriasis. The analytic framework is presented in the full report, Figure 1. The Key Questions addressed in this review include:

Key Question 1. In patients with chronic plaque psoriasis, what is the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy when evaluating intermediate (plaque BSA measurement, Psoriasis Area and Severity Index [PASI] score, Patient's Assessment of Global Improvement, Physician Global Assessment [PGA], and individual symptom improvement) and final health outcomes (mortality, health-related quality of life [HRQoL] [e.g., Dermatology Life Quality Index (DLQI), Health Assessment Questionnaire Disability Index (HAQ-DI), EuroQol 5 Dimension (EQ-5D)] and other patient-reported outcomes, ajor adverse cardiovascular events (MACE), diabetes, and psychological comorbidities [e.g., depression, suicide])?

Key Question 2. In patients with chronic plaque psoriasis, what is the comparative safety of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy (hepatotoxicity [e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT)], nephrotoxicity [e.g., serum creatinine (SCr), glomerular filtration rate (GFR)], hematologic toxicity [e.g., thrombocytopenia (TCP), anemia, neutropenia], hypertension, alteration in metabolic parameters [e.g., glucose, lipids, weight, body mass index (BMI), thyroid function], injection site reaction, malignancy, infection, and study withdrawal)?

Key Question 3. In patients with chronic plaque psoriasis treated with systemic biologic therapy, systemic nonbiologic therapy, or phototherapy, which patient or disease characteristics (e.g., age, gender, race, weight, smoking status, psoriasis severity, presence or absence of concomitant psoriatic arthritis, disease duration, baseline disease severity, affected BSA, disease location, number and type of previous treatments, failure of previous treatments and presence of neutralizing antibodies) affect intermediate and final outcomes?

Methods

Input from Stakeholders

The Evidence-based Practice Center drafted a topic refinement document with proposed Key Questions after consult with Key Informants. Our Key Informants included five experts in the field of psoriasis. Three physicians provided the dermatologist's perspective, one local and two national representatives. One physician provided the general practitioner's perspective. Lastly, one expert provided the perspective of the National Psoriasis Foundation as well as outcomes research. The public was invited to comment on the topic refinement document and Key Questions. After reviewing the public commentary, responses to public commentary, and proposed revisions to the Key Questions, a preliminary protocol was generated and reviewed with the Technical Expert Panel. The aforementioned Key Informants constituted our Technical Expert Panel and provided feedback on the feasibility and importance of our approach and provided their unique insight. The draft CER will undergo peer review and public commentary and revisions will be made before finalizing the report.

Literature Search Strategy

We developed two literature search strategies a priori. The first systematic literature search was used to identify studies for inclusion to answer Key Questions 1, 2 and 3. The strategy detailed in Appendix A was used to search in MEDLINE® and the Cochrane Central Register of Controlled Trials. Language restrictions were not applied. We also manually searched references from included studies and previously conducted systematic reviews, adding relevant citations to the literature base. A grey literature search for meeting abstracts was conducted in Web of Science, using the same search strategy as previously described, limiting search results to meeting proceedings. Abstracts that met inclusion criteria were paired with full text manuscripts when possible and were otherwise considered separately. For agents with a FDA-approved indication for the treatment of psoriasis, a search for completed trials with posted results was conducted on www.clinicaltrials.gov and associated FDA regulatory documents for these drugs were manually searched. Data from the clinical trial registry and FDA documents were used to supplement published manuscripts when the studies could be matched and otherwise were considered separately. The Scientific Resource Center of the AHRQ Effective Health Care Program contacted the manufacturers of identified interventions and comparators for scientific information packets. The same inclusion/exclusion criteria applied to the database searches were applied to packets that were received and relevant citations were manually added to the literature base.

The second literature search was used to systematically identify previously conducted adjusted indirect comparisons or network meta-analyses. The search strategy in Appendix A was used to search in MEDLINE®, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment database.

Both literature searches will be updated concurrently with the peer review process, and the same inclusion and exclusion criteria will be applied. Relevant literature will be incorporated into the review

Inclusion and Exclusion Criteria

Two independent investigators assessed studies for inclusion in a parallel manner based on a priori defined criteria in two-step processes. In first step, titles and abstracts were screened and studies that both investigators agreed to include were further evaluated as full text in a second step. Disagreements at either step were resolved by discussion, or when necessary, through a third investigator. Trials and observational studies that compared biologic systemic agents to either nonbiologic systemic agents or phototherapy were included. More specifically, the following observational study designs were included: cohort studies, case-control studies, and before and after studies which compared patients taking one of the therapies of interest who were then switched to a different therapy of interest with data available comparing before and after the switch. Other observational study designs were excluded. Studies published before 1975 were excluded as they were determined to be irrelevant in describing the currently available therapeutic interventions included in the CER. Systematic reviews with or without meta-analysis were included for manual reference searches as well as comparison of results with this CER. Meta-analyses which utilize methods to indirectly compare interventions of interest, including adjusted indirect comparisons or network meta-analyses, were included and summarized qualitatively for all three key questions.

To be included, the population evaluated in the study must have been adult patients (≥18 years) with chronic plaque psoriasis (or psoriasis vulgaris), or the study must have evaluated and reported data on a subgroup of adult patients with chronic plaque psoriasis. Only studies that evaluated interventions and comparators with a current indication approved by the U.S FDA were included in this CER. Studies in which patients were randomized to receive multiple therapies or were allowed to use concurrent therapies were included only if the common interventions were similar across groups compared and the final comparison was of a single biologic systemic agent with a single nonbiologic systemic agent or phototherapy. Studies with only a comparison to placebo or untreated controls were not included. Studies must have reported at least one of the prespecified outcomes (intermediate, final, or harm) to be included. Grey literature in the form of meeting abstracts, published protocols from www.clinicaltrials.gov, and FDA regulatory documents were included if they met inclusion criteria. When possible, these literature sources were matched with published studies and used as supplemental information. Otherwise, these literature sources were considered independent sources of data. Specifically for Key Question 3, data that describe the association between the prespecified subgroups and outcomes—either through subgroup analysis in randomized trials or through control of confounding in observational studies (e.g., matching or multivariate analysis)—were included.

Data Extraction and Data Management

Two reviewers used a standardized data extraction tool to independently extract data; disagreements were resolved through discussion. The following data were collected from each unique study: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, study population, intervention and comparator details, and data needed to assess intermediate and final health outcomes and harms. Authors were contacted for clarification or to provide additional data when necessary.

Quality Assessment of Individual Studies

We assessed the quality of included studies using recommendations from the *Methods Guide*.[15] Using a standardized tool, two reviewers independently assessed the quality of each included study and resolved disagreements through discussion. Randomized trials were evaluated separately from observational studies, and each study received a quality rating of good, fair or poor. We assessed each randomized trial for the following criteria: methods for randomization, allocation concealment, similarity of groups at baseline, blinding of subjects and providers, differential loss to followup, overall loss to followup, use of intention to treat, blinding of event adjudicators, methods to ascertain outcomes, and reporting of prespecified outcomes. Observational studies were evaluated for the following criteria: selection of comparison group, control for confounding, baseline differences, method to ascertain exposure, methods to ascertain outcomes, blinding of event adjudicators, differential loss to followup, overall loss to followup, and reporting of prespecified outcomes.

Data Synthesis

Data identified through the systematic review were summarized qualitatively as we determined that meta-analysis was not appropriate for several reasons. First, the literature base was very limited in quantity and there was often only one trial or study identified for any given comparison of interest. Most often, no trials were available and data evaluating comparisons of interest were observational in nature. Therefore, we qualitatively evaluated the data and report native measures of effect which were extracted from the included studies. Identified network meta-analyses from the second literature search were qualitatively described in respective Key Questions although not included in the evaluation of strength of evidence.

Strength of Evidence

Two reviewers independently evaluated the strength of evidence for each direct therapy comparison and outcome, with disagreements resolved through discussion. Rating of the strength of evidence was conducted using recommendations from the *Methods Guide*.[15] Four required domains (risk of bias, consistency, directness, and precision) were considered equally when grading the strength of evidence. The overall grade for strength of evidence for each comparison and outcome evaluated was rated and classified as high, moderate, low, or insufficient. High strength of evidence was defined as high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect. Moderate strength of evidence was defined as moderate confidence that the evidence reflects the true effect and further research may change confidence in the estimate of effect and may change the estimate. Low strength of evidence was defined as low confidence that the evidence reflects the true effect and further research is likely to change confidence in the estimate of effect and is likely to change the estimate. Insufficient evidence was defined as evidence either was unavailable or did not permit estimation of an effect.

Applicability

Two reviewers independently reviewed the applicability of the individual studies with disagreements resolved through discussion. Summarization of the applicability of evidence was completed using recommendations from the *Methods Guide*.[15] Seven domains were evaluated in assessing individual study applicability: enrolled population, enrollment eligibility criteria,

assessment of final health outcomes, adequate study duration with clinically relevant treatment modalities, assessment of adverse events, sample size, and use of intention-to-treat analysis. Data required to evaluate these domains was extracted into evidence tables. Studies that met five or more criteria were classified as effectiveness studies. These data were also reviewed to determine the overall applicability of data per outcome, describing the population and conditions to which the evidence is most applicable.

Results

A summary of findings are presented in ES-Table 1 for outcomes with strength of evidence of low, moderate or high. All comparisons between biologic systemic agents and phototherapy were rated with insufficient evidence.

ES-Table 1. Summary of findings for the comparison of systemic biologic agents versus systemic nonbiologic agents

Comparison	Outcome*	Type and Number of Studies	Conclusion	SOE
Adalimumab versus methotrexate	HRQoL	1 RCT	Adalimumab improves a patient's HRQoL compared with methotrexate	L
	PASI	1 RCT	Adalimumab improves a patient's PASI score compared with methotrexate	L
	PGA	1 RCT	Adalimumab increases the number of patients achieving a PGA score of "clear" or "minimal" compared with methotrexate	L
	Patient's assessment of disease severity	1 RCT	Adalimumab improves a patient's assessment of disease severity compared with methotrexate	L
	Pain	1 RCT	Adalimumab reduces a patient's pain compared with methotrexate	L
	Pruritus	1 RCT	Adalimumab reduces a patient's pruritus compared with methotrexate.	L
	Infection	1 RCT	Infection rates do not differ between adalimumab and methotrexate	L
Etanercept versus acitretin	PASI	2 RCT	Etanercept improves a patient's PASI score compared with acitretin	M
Infliximab versus methotrexate	HRQoL	1 RCT	Infliximab improves a patient's HRQoL compared with methotrexate	L
	PASI	1 RCT 1 OBS	Infliximab improves a patient's PASI score compared with methotrexate	L
	PGA	1 RCT	Infliximab increases the number of patients achieving a PGA score of "clear" or "minimal" compared with methotrexate	L

Abbreviations: HRQoL=health related quality of life; L=low; M=moderate; OBS=observational study; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial; SOE=strength of evidence

* Outcomes with an insufficient strength of evidence are not listed in this table

Results of Literature Search

There were 472 citations identified through the database searches and four citations identified manually in search one. One of the manual citations was from the Scientific Information Packets obtained by the Scientific Resource Center while three were from public clinical trial registries. After the removal of duplicates, 419 articles remained. During title and abstract review, 250

citations were excluded. Of the 169 citations remaining, 139 were excluded at the full-text level. A total of 30 citations, representing 11 unique studies, met our inclusion criteria for Key Questions 1, 2 and 3. The number of included citations exceeds the number of included studies because some publications evaluated the same population. In such cases we only considered the population once and did not double count data. Citations excluded at the full text level are listed in Appendix C along with the reasons for exclusion.

The second literature search identified 19 citations which were screened at the abstract level. A total of 13 citations were excluded at the abstract level and four citations were excluded at the full text level. One unique analysis, which was represented by two citations, was finally included.

Four RCTs (n=1188)[13,16-18] and two observational studies (n=313)[19,20] directly compared either a systemic biologic agent with a systemic nonbiologic agent or phototherapy and reported at least one outcome of interest. Of the four RCTs, two were fair in quality[16,17] and two were good in quality[13,18] while the two observational studies were both fair in quality.[19,20] Additionally, three observational studies (n=85) evaluated the transition of patients between therapies within the biologic, nonbiologic, and phototherapy treatments. One of these studies was poor in quality[21] while the others were fair in quality.[22,23] Two of the RCTs also provided data regarding transitions of therapy.[13,16] Two observational studies directly compared therapies of interest but at the class level, and both were fair in quality.[24,25] Finally, we identified one network meta-analysis that used methods for indirect comparison across various therapies included in this review.[26] All included studies were available as full text publications. The baseline characteristics of included studies can be found in Appendix Table D and the individual study quality assessments can be found in Appendix Table E.

Key Question 1

Four RCTs[13,16-18] (two good and two fair quality) and one fair quality observational study[20] evaluated the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents. The comparisons made included: adalimumab, etanercept, and infliximab versus methotrexate and etanercept versus acitretin.

When comparing adalimumab with methotrexate, health-related quality of life (HRQoL) was improved in patients taking adalimumab, based on a single RCT (low strength of evidence). There was insufficient evidence to grade death and no other final health outcomes were reported. Psoriasis Area and Severity Index (PASI) was improved in patients treated with adalimumab, based on one RCT and one observational study (low strength of evidence). PGA, Patient Assessment of Disease Severity, pain, and pruritus were each improved in patients treated with adalimumab compared with methotrexate, each based on a single RCT (low strength of evidence). No other intermediate outcomes were reported.

When comparing infliximab with methotrexate, HRQoL was improved in patients taking infliximab, based on a single RCT (low strength of evidence). There was insufficient evidence to evaluate myocardial infarction and diabetes mellitus and no other final health outcomes were reported. PASI and PGA were each improved in patients treated with infliximab compared with methotrexate, based on one RCT and one observational study (low strength of evidence). No other intermediate outcomes were reported.

When comparing etanercept with acitretin, no final health outcomes were reported. PASI was improved in patients treated with etanercept compared with acitretin, based on two RCTs

(moderate strength of evidence). There was insufficient evidence to evaluate BSA and no other intermediate outcomes were reported.

One mixed-treatment comparison that evaluated PASI50, PASI75, and PASI90 suggested that the probability of achieving any of the three PASI scores was highest for infliximab, followed by adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care.

No RCTs evaluated the comparative effectiveness of systemic biologic agents and phototherapy on any outcomes. One observational study reported PASI scores in systemic biologic agent arms (i.e., adalimumab, alefacept, etanercept, infliximab) and phototherapy arms (i.e. PUVA) although did not make statistical comparisons between the groups. No final health outcomes were reported. There was insufficient evidence comparing biologics and phototherapy to evaluate PASI, the only intermediate outcome reported.

Key Question 2

The literature base for the comparative safety of systemic biologic agents and systemic nonbiologic agents or phototherapy is sparse. Overall four RCTs[13,16-18] (two good and two fair in quality) and two observational studies[19,20] (both fair in quality) directly compared biologics to nonbiolgics and reported at least one adverse outcome of interest. No trials or observational studies directly compared biologics to phototherapy in the evaluation of harms.

Infection rate did not differ between adalimumab and methotrexate (low strength of evidence). This data were from a single RCT conducted outside of the United States in patients with moderate to severe chronic plaque psoriasis naïve to TNF-alpha antagonists or methotrexate. There was insufficient evidence for other reported outcomes.

Key Question 3

A post-hoc analysis in one RCT[13,27] evaluated the relationship between psoriasis severity, measured with the PASI score, and the final health outcome HRQoL measured with the DLQI.[27] Patients with greater PASI response had greater improvements in DLQI over the 16 week followup. The mean DLQI change from baseline to week 16 was significantly greater in PASI ≥75 group (-9.5±5.8) compared with PASI 50 to 75 (-5.8±4.5, $p<0.01$), PASI 25 to 50 (-4.2±4.6, $p<0.001$), and PASI <25 (-0.7±4.7, $p<0.001$). The other statistically significant difference in DLQI was in patients who had a PASI50 to 75 compared with PASI<25 ($p<0.001$).

Two observational studies[22,24] evaluated the impact of weight on PGA, the impact of a history of PsA on plaque psoriasis or PsA pain, and the impact of prior exposure to a biologic agent on PASI. However, conclusions cannot be made from this literature base as neither study controlled for confounding factors.

Discussion

Key Findings and Strength of Evidence

Patients and healthcare providers encounter several important considerations when evaluating therapeutic options in the treatment of chronic plaque psoriasis. Despite being studied in comparison to placebo, biologic systemic agents have infrequently been compared directly with nonbiologic systemic therapies or phototherapy. Our literature review yielded only four RCTs and one observational study directly comparing systemic biologics versus systemic

nonbiologics and no RCTs and one observational study directly comparing systemic biologics and phototherapy. Overall, the quality of the studies was either good or fair. However, most often only one trial or observational study was available for a given comparison and outcome, and the majority of comparative studies were observational in nature and did not account for confounding. Together, these factors precluded the ability to statistically pool data. Therefore, a qualitative synthesis of the data was presented. A summary of the results with low, moderate, or high strength of evidence can be found in ES-Table 1. Although there are some comparisons which have been rated with low or moderate strength of evidence, given the current literature base there is insufficient evidence as a whole to determine the comparative effectiveness of systemic biologic agents compared with either systemic nonbiolgic agents or phototherapy in patients with chronic plaque psoriasis. In the evaluation of systemic biologics versus systemic nonbiologics or phototherapy for final and intermediate health outcomes (Key Question 1), the use of the biologics adalimumab, etanercept, and infliximab resulted in favorable outcomes when compared to individual nonbiologic agents (ES-Table 1). However, we could not determine the comparative effectiveness of these therapies with regard to final health outcomes other than HRQoL, due to lack of evaluation in the included literature. We could not determine the comparative efficacy between other available biologics such as ustekinumab and alefacept and systemic nonbiologic agents or between systemic biologic agents and phototherapy on any of the final or intermediate outcomes. This was due to either a lack of existing literature or a lack of direct statistical comparison between those agents.

The comparison of adalimumab with methotrexate, although based on a single RCT, had the most outcomes evaluated, although most were intermediate outcomes and all were based on low strength of evidence.[13] HRQoL was measured using both the DLQI and EQ-5D scales, with both showing favorable improvement in patients treated with adalimumab at 16 weeks. Changes seen in both treatment arms, however, can be consider clinically meaningful based on established minimally important differences of 2.3 to 5.7 for the DLQI, 0.09 to 0.22 for the EQ-5D index score, and 3.82 to 8.43 for the EQ-5D VAS.[28] It is not surprising that HRQoL improved in those treated with adalimumab, as PASI scores were also significantly improved compared with methotrexate at 16 weeks, including complete remission. Time to PASI75 was also significantly shorter in adalimumab treated patients (28 versus 84 days). Other intermediate outcomes including PGA, patient assessment of disease severity, and individual symptoms of pain and pruritus were also improved in patients treated with adalimumab.

Compared to methotrexate, one RCT showed that infliximab improved a patient's HRQoL, based on low strength of evidence. Three scales were used to measure HRQoL in this trial, DLQI, EQ-5D, and SF-36 MCS and PCS and all showed favorable improvements in the infliximab treated patients at 16 weeks. Changes seen in both treatment arms, however, can be consider clinically meaningful based on established minimally important differences as previously reported, with addition of the SF-36 in which a change of 2.5 to 3.9 in the PCS and 4 to 6 in the MCS can be considered clinically important.[28] Other intermediate outcomes including PASI and PGA were also improved in patients treated with infliximab, each based on low strength evidence.

Compared to acitretin, two RCTs showed that etanercept improved a patient's PASI score with moderate strength of evidence.[17,18] Both PASI50 and PASI75 were evaluated and showed favorable improvement in patients treated with etanercept at 12 and 24 weeks.

We evaluated systemic biologics versus systemic nonbiologics or phototherapy for safety or tolerability outcomes (Key Question 2). All three classes of therapy are associated with known

harms which are clearly defined within clinical practice guidelines.[4,8,29] Some harms, such as changes in weight or the lipid profile may surface in the shorter term while others such as malignancy and infection would require much longer followup to accurately capture the risk. Furthermore, some toxicity can be cumulative, such as hepatic toxicity associated with methotrexate or nephrotoxicity associated with cyclosporine and would also require long term followup to accurately describe. Unfortunately, the longest follow-up period amongst included studies in which harms were reported was six months, although this was a rare exception. Most studies concluded at 12 to 16 weeks, which is unlikely to be of sufficient length for all important harms evaluated.

Based on the current literature base directly comparing biologics to nonbiologics or phototherapy, we were unable to determine comparative safety of these therapies due to paucity of data and in most cases a complete lack of direct comparative data. Although one observational study reported weight changes in patients taking methotrexate, etanercept, or infliximab, between drug comparisons were not made therefore we were unable to determine if the differences within arms were significantly different across drug therapies. Of all outcomes evaluated, there was a low strength of evidence that the rate of infection was not significantly different between the biologic agent adalimumab and the nonbiolgic agent methotrexate. In this one RCT, authors stated that none of the infections were classified as serious, although further details were not specified.[13]

Key Question 3 aimed to evaluate patient and disease characteristics which modify outcomes when comparing systemic biologics, nonbiologics, and phototherapy. Important factors in selecting appropriate therapy include baseline patient characteristics as these will directly influence the safety and efficacy of chosen agents. Another key decisional uncertainty is the disease characteristics that are associated with either improved or worsen outcomes. However, there was a paucity of literature that provided insight on the relationship between patient and disease characteristics with final or intermediate health outcomes in patients treated with biologics compared with nonbiologics or phototherapy. Only one subgroup analysis from a RCT met our inclusion criteria. Two observational studies evaluated relationships between patient characteristic and outcomes although neither controlled for confounding and therefore cannot be used to draw conclusions.

Based on a post-hoc analysis of the CHAMPION trial, data suggest that as disease severity improves a patient's HRQoL improves. The mean change in DLQI at 16 weeks was greatest for patients who achieved at least a PASI improvement of 75 percent (-9.5±5.8) while the mean change in DLQI was lowest for patients who achieved a PASI score improvement of less than 25 percent (-0.7±4.7). In a RCT that compared the efficacy and safety of adalimumab versus placebo in patients with moderate to severe plaque psoriasis, investigators sought to correlate various measures of HRQoL to clinical outcomes.[28] DLQI was moderately correlated with PASI ($r=0.69$, $p<0.001$).[28] Data from this RCT also suggests that the minimal clinically important difference for the DLQI ranges from a change of 2.3 to 5.7.[28] Based on this data, the changes in DLQI in patients achieving a PASI score improvement of greater than 25 percent (-4.2 to -9.5) from the CHAMPION subgroup analysis can be considered clinically important improvements.

There were no previously conducted traditional meta-analyses identified by our literature search that addressed similar comparisons and research questions as this report. One mixed-treatment comparison that evaluated PASI50, PASI75, and PASI90 suggested that the probability of achieving any of the three PASI scores was highest for infliximab, followed by

adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care

Applicability

Our literature base is most applicable to patients with more advanced chronic plaque psoriasis and is not applicable to milder forms. Five of the six studies that directly compared biologics and nonbiologics required patients to have moderate to severe plaque psoriasis for enrollment, and in these trials the baseline mean PASI score ranged from 10.4 to 29.2. In the remaining study, although moderate to severe plaque psoriasis was not an explicit inclusion criteria, the mean PASI score at baseline was consist with the other studies and ranged from 8.2 to 18.8. None of these six studies were conducted in the United States and therefore may not reflect clinical practice. The majority of patients evaluated in these studies were not naïve to psoriasis treatment (71 percent) as only three studies clearly specified enrolled patients were naïve to psoriasis therapy. All interventions evaluated in these studies are currently approved by the FDA and were studies at doses approved for chronic plaque psoriasis, therefore are relevant to treatment practice in the United States. Only two studies evaluated final health outcomes and were generally not sufficient in length to adequately evaluate such outcomes, with exception of HRQoL. The followup in both trials was approximately 26 weeks. Alternatively, for intermediate outcomes, all but one study were of sufficient length to evaluate such outcomes. Last, we did not consider studies to be conducted long enough to accurately capture outcomes such as infection or malignancy. Otherwise, studies provide short term data about outcomes and in some cases this may not be sufficient to understand comparative safety, as is the case with methotrexate or cyclosporine where toxicities are cumulative.

One observational study directly compared biologics and phototherapy and moderate to severe plaque psoriasis was not an explicit inclusion criteria. However, the mean PASI score at baseline was consist with the other studies and ranged from 15.0 to 16.9. Therefore the literature reflects patients with more advanced chronic plaque psoriasis and is not applicable to mild forms. The study was conducted outside of the United States and therefore may not reflect clinical practice and the patients were not treatment naïve. The evaluated interventions are available for use in the United States but because phototherapy regimens are specifically tailored to patient characteristics we cannot comment whether regimens used in the study were sufficient or not. Final health outcomes and adverse events were not evaluated and the only intermediate outcome evaluated was PASI.

Research Gaps

In the treatment of chronic plaque psoriasis with biologic systemic agents, nonbiologic systemic agents and phototherapy, there are several avenues for future research. Current literature directly comparing biologic systemic agents versus nonbiologic systemic agents or phototherapy is limited. In total, only four RCTs comparing a biologic to a nonbiologic are included in this report, any no RCTs comparing a biologic to phototherapy were identified. Therefore, the most important area of future research is additional RCTs or large observational studies that directly compare individual drugs/interventions from the three classes including systemic biologic, systemic nonbiolgic, or phototherapy. If a greater number of trials are conducted, meta-analytic techniques can be used to assess direct comparisons. Presently, the literature base is too scarce to conduct such an analysis.

Future trials evaluating biologic versus nonbiologic systemic agents or phototherapy should be adequately powered to assess final health outcomes that are important to decision makers, such as mortality, MACE, and psychological outcomes. This would likely require longer duration trials and larger sample sizes compared to the current literature base. The longest trial included in this report was 26 weeks allowing for only short term outcome assessment. A similar opportunity arises with harms, as even in the current literature base harms were rarely evaluated and if they were reported the frequency was rare and often trials were not of sufficient duration to adequately capture such risks.

Future research should be designed to determine if there are specific disease or patient factors that modify intermediate, final and adverse health outcomes when comparing biologics, nonbiologics, and phototherapy. Current research is too scarce to adequately assess the impact of patient or disease factors on these outcomes. Future studies should include a population more generalizable to the US. The majority of included studies (10 of 11 studies) were conducted in other countries, where clinical practice may not reflect practice within the US.

In patients with CPP, there were limited data directly comparing systemic biologic agents to either systemic nonbiolgic agents or phototherapy. Overall there is insufficient evidence to determine the comparative effectiveness of individual therapies compared to each other between the specified classes, with few exceptions. For the comparison of adalimumab versus methotrexate, infliximab versus methotrexate, and etanercept versus acitretin, there is low strength of evidence favoring the individual biologic agent versus the nonbiologic agent.

References

1. Neimann AL, Porter SB, Gelfand JM. The epidemiology of psoriasis. Expert Rev Dermatol 2006;1:63-75.

2. Christophers E. Psoriasis – epidemiology and clinical spectrum. Clin Exp Dermatol 2001;26:314-20. PMID:11422182

3. National Psoriasis Foundation Website. About psoriasis: statistics. Available at: http://www.psoriasis.org/learn_statistics. Accessed Feb. 2, 2010. (Last accessed on April 16, 2012).

4. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826-850. PMID: 19119095

5. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol 2009;161:987-1019. PMID: 19857207

6. Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest 2004;113:1664-75. PMID: 15199399

7. Committee for Medicinal Products for Human Use (CHMP). Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. London: European Medicines Agency; Nov 2004. CHMP Publication No. CHMP/EWP/2454/02.

8. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009;61:451-85. PMID: 19493586

9. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol 2010;62:114-35. PMID: 19811850

10. Van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A, for the National Psoriasis Foundation. The psoriasis and psoriatic arthritis pocket guide: treatment algorithms and management options. Available at: http://www.psoriasis.org/NetCommunity/Document.Doc?id=354. Accessed May 27, 2011. (Last accessed April 16, 2012).

11. Griffiths CE, Strober BE, van de Kerkhof P, et al, for the ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28. PMID: 20071701.

12. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003;349:658-65. PMID: 12917302

13. Saurat JH, Stingl G, Dubertret L, et al, for the CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558-66. PMID: 18047523

14. Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 2008;158:351-9. PMID: 18627372

15. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and

Quality. April 2012. Chapters available at: www.effectivehealthcare.ahrq.gov

16. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011;165:1109-17. PMID: 21910713

17. Caproni M, Antiga E, Melani L, et al. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. J Clin Immunol 2009;29:210-214. PMID: 18763027

18. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol 2008;158:1345-1349. PMID: 18410408

19. Inzinger M, Heschl B, Weger W, et al. Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: retrospective data analysis of a patient registry**.** J Invest Dermatol 2011;165:640-5. PMID: 21564068

20. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. J Eur Acad Dermatol Venereol 2008;22:341-344. PMID: 18005022

21. Garavaglia MC, Altomare G. Etanercept therapy in patients with psoriasis and concomitant HCV infection. Int J Immunopathol Pharmacol 2010;23:965-969. PMID: 20943071

22. Strober BE, Poulin Y, Kerdel FA, et al. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. J Am Acad Dermatol 2011;64:671-681. PMID: 21414495

23. Magliocco MA, Lozano AM, Van Saders C, Schuler KW, Gottlieb AB. An open-label study to evaluate the transition of patients with chronic plaque psoriasis from cyclosporine to alefacept. J Drugs Dermatol 2007;6:424-427. PMID: 17668540

24. Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol 2009;10:319-324. PMID: 19658444

25. Costanzo A, Mazzotta A, Papoutsaki M, Nistico S, Chimenti S. Safety and efficacy study on etanercept in patients with plaque psoriasis. Br J Dermatol 2005;152:187-189. PMID: 15656833

26. Bansback N, Sizto S, Sun H, et al. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology 2009;219:209-18. PMID: 19657180

27. Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br J Dermatol 2008;158:549-557. PMID: 18047521

28. Shikiar R, Willian MK, Okun MM, Thompson CS, Revicki DA. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. Health Qual Life Outcomes 2006;4:71. PMID: 17005043

29. Kalb RE, Strober B, Weinstein g, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009 ;60:824-37. PMID: 19389524

Introduction

Background

Psoriasis is a common, chronic, autoimmune inflammatory skin disease affecting 2 to 3 percent of the worldwide population. The onset of psoriasis predominantly occurs early in adulthood (between the ages of 15 and 25 years) but may affect individuals at any age.[1] The course of psoriasis is marked by chronic and acute phases with a wide variety in relapse and remission rates.[2] Additionally, psoriasis is often associated with other comorbidities such as an inflammatory arthritis known as psoriatic arthritis, obesity, inflammatory bowel disease, diabetes, and cardiovascular disease.[2] Psoriasis has been associated with markedly elevated direct medical costs, work limitations, and productivity loss. Total health care costs of psoriasis are estimated at $11.25 billion annually.[3] This economic burden, along with the clinically relevant reductions in quality of life experienced by many patients with psoriasis, underscores the need for prompt, effective, and sustained disease management.[4,5]

Among several clinical psoriasis phenotypes, chronic plaque psoriasis is the most frequent, accounting for all but 10 percent of cases.[4-6] Chronic plaque psoriasis, also known as psoriasis vulgaris, often appears as well-demarcated, erythematous plaques covered with silvery white scales that vary in size up to several centimeters. Psoriatic skin lesions typically appear symmetrically on the scalp, trunk, and limbs (particularly on the knees and elbows) but may also affect the genitals, nails, palms, and soles of the feet.[4,5] Different parameters determine disease severity such as the degree of body surface area (BSA) involved, activity of the lesions, the location of lesions in sensitive areas, duration of disease, treatment failures, and the impact on quality of life.[2,7]

Psoriasis is a multifactorial disease with genetic and environmental factors that contribute to the dysregulation of cellular inflammation. The presence of psoriatic plaques may be triggered or exacerbated by environmental conditions, including infection, physical or psychological stress, cold weather, and medications.[4] The formation of psoriatic plaques involves the interplay of dendritic cells, T cells, antigen-presenting cells, cytokines, keratinocytes, and blood vessels. The presence of activated T cells within psoriatic plaques and the response to T cell-directed therapy suggest an immunologic nature of the disease.[8,9] Various cytokines, like tumor necrosis factor (TNF)-alpha and interleukin 23 (IL-23), are also present in psoriatic lesions.[10] Both cytokines and activated T cells promote the dysregulated growth of keratinocytes, leading to plaques of erythematous, scaly skin.

While disease localized to nonsensitive areas of skin may be managed effectively with topical agents (emollients, analogs of vitamins A and D, and corticosteroids), patients with more widespread disease often require systemic treatment due to the extent of BSA involvement, as well as the adverse impact on quality of life and activities of daily living.[4,5] Therapeutic options for more widespread disease include systemic treatment with biologic agents, nonbiologic agents, and phototherapy. Nonbiologic systemic therapies may be effective but can be associated with significant short-term and long-term toxicities (hepatotoxicty, nephrotoxicity, hypertension, dyslipidemia, malignancy, and teratogenicity).[11,12] Phototherapy, although considered to be one of the safer therapeutic options, requires strict compliance, and the long-term toxicity associated with it includes photocarcinogenesis.[13] Unfortunately, some patients have disease that is resistant to the above-mentioned therapies or becomes refractory to treatment. As a result, patients often report high levels of dissatisfaction with such approaches to psoriasis treatment.[4,5,11]

Biologic therapies for psoriasis use genetically engineered drugs that target specific steps involving T cells and cytokines (e.g., TNF-alpha and IL-23), which are important in the pathogenesis of psoriasis.[4,5] Currently, three biologic TNF-alpha inhibitors (infliximab, etanercept, and adalimumab), one T cell-targeting agent (alefacept), and one anti-IL 12/23 agent (ustekinumab) have approval from the U.S. Food and Drug Administration (FDA) for psoriasis treatment. Another T cell-targeting agent, efalizumab (Raptiva®), was withdrawn from the U.S. market due to its potential risk of causing progressive multifocal leukoencephalopathy. Other biologic agents with similar mechanisms of action have FDA marketing approval, albeit not for the treatment of chronic plaque psoriasis (e.g., certolizumab pegol, golimumab, abatacept). While biologic treatments may represent a treatment option with fewer adverse effects, there are concerns about their higher costs versus nonbiologic systemic therapies. The estimated annual per-patient cost of biologic treatment ranges from $18,000 to $42,000 (based on the average wholesale price).[14] This cost is in comparison to methotrexate, the most commonly prescribed nonbiologic systemic treatment for psoriasis worldwide, which costs approximately $1,200 per year.[14]

The American Academy of Dermatology has published guidelines for the treatment of psoriasis.[4,11,13] As stated above, topical agents, or even targeted phototherapy, are effective therapies for limited disease. When treating patients for more extensive disease, there are no clear guidelines established for selecting first-line therapy, albeit the presence of concomitant psoriatic arthritis is an important determinant of treatment choice (often a TNF-alpha inhibitor with or without methotrexate).[4] For patients with widespread disease, guidelines suggest therapy with either biologic or nonbiologic systemic agents or phototherapy with ultraviolet B (UVB) or with psoralen plus ultraviolet A (PUVA) therapy.[4] There are few direct comparative trials either within or between biologic and nonbiologic classes directly comparing effectiveness.[15,-17] Recently, a trial that compared two biologic agents concluded a difference in efficacy, suggesting heterogeneity within the class and indicating drug comparisons may be preferred over class comparisons.[15] Currently, guidelines suggest that clinicians balance individual patient characteristics with the reported adverse events and previously used treatment modalities when making therapeutic decisions.

In 2008, Schmitt and colleagues published a meta-analysis analyzing the efficacy and tolerability of biologic and nonbiologic systemic agents for moderate-to-severe plaque psoriasis.[18] This study examined all randomized controlled trials published before January 2008 that enrolled greater than 50 patients with moderate-to-severe plaque psoriasis. Based on the results of their meta-analysis, the authors concluded that the efficacy of systemic agents approved for moderate-to-severe psoriasis likely differ considerably between biologic and nonbiologic agents, as well as within the two classes. One of the main research gaps identified in this meta-analysis was the lack of comparative effectiveness and safety data for biologic versus nonbiologic systemic treatments for moderate-to-severe plaque psoriasis. Since the completion of this systematic review, the first head-to-head trial comparing a biologic to a nonbiologic systemic treatment has been published.[17] Additionally, comparative data from nonrandomized studies likely exist, although not sought or evaluated by Schmitt and colleagues.[18] Moreover, the efficacy of phototherapy was not addressed in this meta-analysis.

To date, no comparative effectiveness review comparing the effectiveness and safety of biologic systemic to nonbiologic systemic treatment options or phototherapy for chronic plaque psoriasis has been completed.

Objectives

To perform a comparative effectiveness review examining the benefits and harms of biologic systemic agents compared with nonbiologic systemic agents or phototherapy in patients with chronic plaque psoriasis. The analytic framework is presented in Figure 1.

Key Questions

Key Question 1. In patients with chronic plaque psoriasis, what is the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy when evaluating intermediate (plaque BSA measurement, PASI score, Patient's Assessment of Global Improvement, PGA, and individual symptom improvement) and final health outcomes (mortality, HRQoL [e.g., DLQI, HAQ-DI, EQ-5D] and other patient-reported outcomes, MACE, diabetes, and psychological comorbidities [e.g., depression, suicide])?

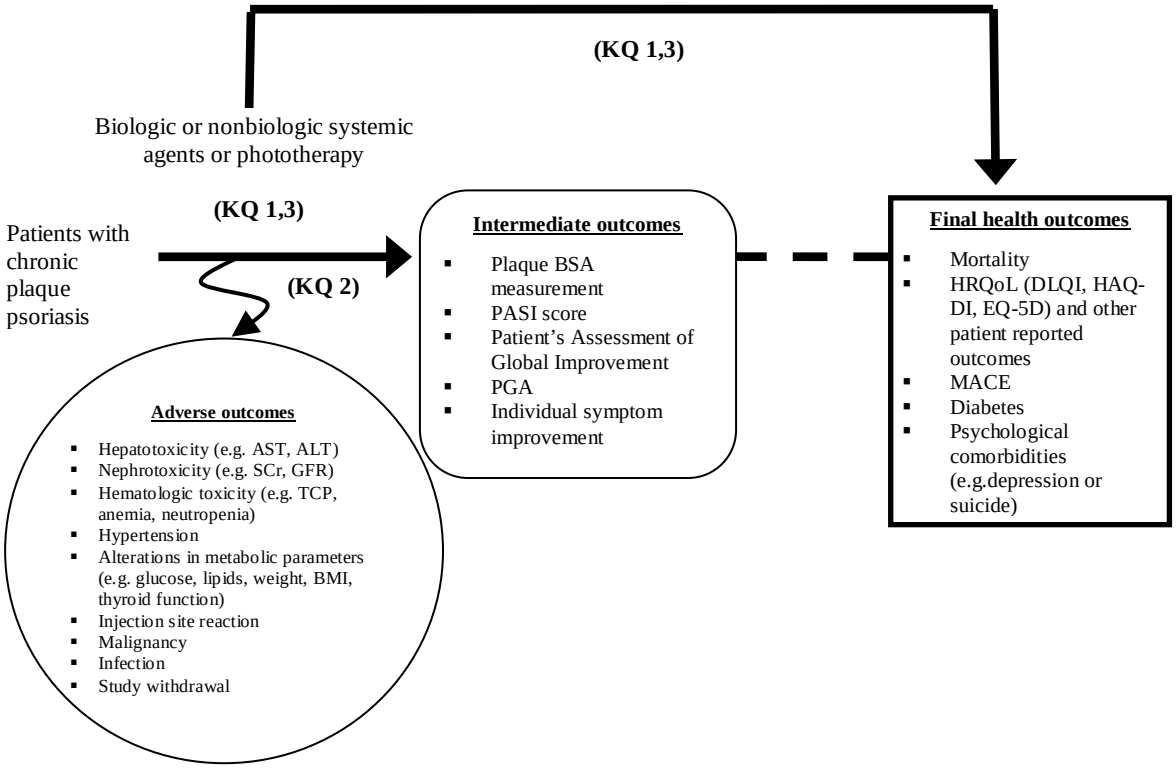
Key Question 2. In patients with chronic plaque psoriasis, what is the comparative safety of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy (hepatotoxicity [e.g., AST, ALT], nephrotoxicity [e.g., SCr, GFR], hematologic toxicity [e.g., TCP, anemia, neutropenia], hypertension, alteration in metabolic parameters [e.g., glucose, lipids, weight, BMI, thyroid function], injection site reaction, malignancy, infection, and study withdrawal)?

Key Question 3. In patients with chronic plaque psoriasis treated with systemic biologic therapy, systemic nonbiologic therapy, or phototherapy, which patient or disease characteristics (e.g., age, gender, race, weight, smoking status, psoriasis severity, presence or absence of concomitant psoriatic arthritis, disease duration, baseline disease severity, affected BSA, disease location, number and type of previous treatments, failure of previous treatments and presence of neutralizing antibodies) affect intermediate and final outcomes?

Key Question abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; BSA=body surface area; DLQI= Dermatology Life Quality Index; EQ-5D= EuroQol 5 Dimension; GFR=glomerular filtration rate; HAQ-DI=Health Assessment Questionnaire Disability Index; HRQoL= health-related quality of life; MACE=major adverse cardiovascular event; PASI=Psoriasis Area and Severity Index; SCr=serum creatinine; TCP=thrombocytopenia

Analytic Framework

Figure 1. Analytic framework



Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; BSA=body surface area; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol; GFR=glomerular filtration rate; HAQ-DI = Health Assessment Questionnaire Disability Index; HRQoL=health-related qualityoflife; KQ=key question; MACE=major adverse cardiovascular events; PASI= Psoriasis Area and Severity Index; PGA=physician's global assessment; SCr=serum creatinine; TCP=thrombocytopenia

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Guide for Effectiveness and Comparative Effectiveness Reviews*, hereafter referred to as *Methods Guide* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm) . The main sections in this chapter reflect the elements of the protocol established for the CER.

Input from Stakeholders

The Evidence-based Practice Center drafted a topic refinement document with proposed Key Questions after consult with Key Informants. Our Key Informants included five experts in the field of psoriasis. Three physicians provided the dermatologist's perspective, one local and two national representatives. One physician provided the general practitioner's perspective. Lastly, one expert provided the perspective of the National Psoriasis Foundation as well as outcomes research. The public was invited to comment on the topic refinement document and Key Questions. After reviewing the public commentary, responses to public commentary, and proposed revisions to the Key Questions, a preliminary protocol was generated and reviewed with the Technical Expert Panel. The aforementioned Key Informants constituted our Technical Expert Panel and provided feedback on the feasibility and importance of our approach and provided their unique insight. The draft CER will undergo peer review and public commentary and revisions will be made before finalizing the report.

Searching for the Evidence

We developed two literature search strategies a priori.. The first systematic literature search was used to identify studies for inclusion to answer Key Questions 1, 2 and 3. The strategy detailed in Appendix A was used to search in MEDLINE® and the Cochrane Central Register of Controlled Trials. Language restrictions were not applied. A manual search of references from included studies and previously conducted systematic reviews was also conducted. Relevant citations were manually added to the literature base. A grey literature search for meeting abstracts was conducted in Web of Science, using the same search strategy as previously described, limiting search results to meeting proceedings. Abstracts that met inclusion criteria were paired with full text manuscripts when possible and were otherwise considered separately. For agents with a U.S Food and Drug Administration (FDA)-approved indication for the treatment of psoriasis, a search for completed trials with posted results was conducted on www.clinicaltrials.gov and associated FDA regulatory documents for these drugs were manually searched. Data from grey literature search were used identify addition literature and to supplement published manuscripts identified in the database search when the studies could be matched. The Scientific Resource Center of the AHRQ Effective Health Care Program contacted the manufacturers of identified interventions and comparators for scientific information packets. The same inclusion/exclusion criteria applied to the database searches were applied to packets that were received. Relevant citations were manually added to the literature base. The literature search will be updated concurrently with the peer review process, and the same inclusion and exclusion criteria will be applied as described previously. Relevant literature will be incorporated into the review.

The second literature search was used to systematically identify previously conducted adjusted indirect comparisons or network meta-analyses. The search strategy in Appendix A was

used to search in MEDLINE®, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment database.

Inclusion and Exclusion Criteria

Two independent investigators assessed studies for inclusion in a parallel manner based on a priori defined criteria in two-step processes. In first step, titles and abstracts were screened and studies that both investigators agreed to include were further evaluated as full text in a second step. Disagreements at either step were resolved by discussion, or when necessary, through a third investigator. Trials and observational studies that compared biologic systemic agents to either nonbiologic systemic agents or phototherapy were included. More specifically, the following observational study designs were included: cohort studies, case-control studies, and before and after studies which compared patients taking one of the therapies of interest who were then switched to a different therapy of interest with data available comparing before and after the switch. Other observational study designs were excluded. Studies published before 1975 were excluded as they were determined to be irrelevant in describing the currently available therapeutic interventions included in the CER. Systematic reviews with or without meta-analysis were included for manual reference searches as well as comparison of results with this CER. Meta-analyses which utilize methods to indirectly compare interventions of interest, including adjusted indirect comparisons or network meta-analyses, were included and summarized qualitatively for all three key questions.

To be included, the population evaluated in the study must have been adult patients (≥18 years) with chronic plaque psoriasis (or psoriasis vulgaris), or the study must have evaluated and reported data on a subgroup of adult patients with chronic plaque psoriasis. Only studies that evaluated interventions and comparators with a current indication approved by the U.S. FDA were included in this CER. Studies in which patients were randomized to receive multiple therapies or were allowed to use concurrent therapies were included only if the common interventions were similar across groups compared and the final comparison was of a single biologic systemic agent with a single nonbiologic systemic agent or phototherapy. Studies with only a comparison to placebo or untreated controls were not included. Studies must have reported at least one of the prespecified outcomes (intermediate, final, or harm) to be included. Grey literature in the form of meeting abstracts, published protocols from www.clinicaltrials.gov, and FDA regulatory documents were included if they met inclusion criteria. When possible, these literature sources were matched with published studies and used as supplemental information. Otherwise, these literature sources were considered independent sources of data. Specifically for Key Question 3, data that describe the association between the prespecified subgroups and outcomes—either through subgroup analysis in randomized trials or through control of confounding in observational studies (e.g., matching or multivariate analysis)—were included.

Data Extraction and Data Management

Two reviewers used a standardized data extraction tool to independently extract data; disagreements were resolved through discussion (Appendix. B). The following data were collected from each unique study: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, study population (inclusion and exclusion criteria, geographic location, intervention, length of study, and duration of patient followup), patient baseline characteristics (including whether the patient is naïve to biologic

therapy or not), intervention and comparator regimen in detail (name, strength, dose, frequency, route of administration, duration of therapy, if a drug holiday was allowed, and details regarding the regimen), use of concurrent standard medical therapies, data needed to assess intermediate and final health outcomes and harms, outcome definitions, and data reported for subgroups of interest defined in Key Question 3. Authors were contacted for clarification or to provide additional data when necessary.

Assessment of Methodological Quality of Included Studies

We assessed the quality of included studies using recommendations from the *Methods Guide*).[19] Using a standardized tool, two reviewers independently assessed the quality of each included study and resolved disagreements through discussion. Randomized trials were evaluated separately from observational studies, and each study received a quality rating of good, fair or poor (Table 1). We assess each randomized trial for the following criteria: methods for randomization, allocation concealment, similarity of groups at baseline, blinding of subjects and providers, differential loss to followup, overall loss to followup, use of intention to treat, blinding of event adjudicators, methods to ascertain outcomes, and reporting of prespecified outcomes. Observational studies were evaluated for the following criteria: selection of comparison group, control for confounding, baseline differences, method to ascertain exposure, methods to ascertain outcomes, blinding of event adjudicators, differential loss to followup, overall loss to followup, and reporting of prespecified outcomes.

Table 1. Overall quality rating definitions

Grade	Definition
Good	Confidence that the study results are valid. Study reporting is adequate to judge that no major or minor sources of bias are likely to influence results. The study meets the majority of prespecified criteria.
Fair	Some confidence that the study results are valid. The study is susceptible to some bias and the problems are not sufficient to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor	Low confidence that the study results are valid. The study has significant flaws that imply biases of various types that may invalidate the results. The biases may arise from serious errors in conduct, analysis or reporting, large amounts of missing information, or discrepancies in reporting.

Data Synthesis

Data identified through the systematic review were summarized qualitatively as we determined that meta-analysis was not appropriate for several reasons. First, the literature base was very limited in quantity and there was often only one trial or study identified for any given comparison of interest. Most often, no trials were available and data evaluating comparisons of interest were observational in nature. Therefore, we qualitatively evaluated the data and report native measures of effect which were extracted from the included studies. Identified network meta-analyses from the second literature search were qualitatively described in respective Key Questions although not included in the evaluation of strength of evidence.

Grading the Strength of the Evidence

Two reviewers independently evaluated the strength of evidence for each comparison and outcome described in KQs 1 and 2considered important, with disagreements resolved through discussion. Rating of the strength of evidence was conducted using recommendations from the

Methods Guide.[20] This system uses four required domains: risk of bias, consistency, directness, and precision. Additional optional domains were not applied.

Risk of bias is the degree to which the included studies, for a given outcome or comparison, have a high likelihood of adequate protection against bias. Risk of bias was ranked as high, medium, or low using the quality assessments of the individual trials included for the given outcome and comparison. Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. We assessed whether or not the effect sizes from multiple sources were on the same side of unity, whether the range of effect sizes was narrow, and the degree of statistical heterogeneity. Consistency was rated as either consistent or inconsistent. When only one study was available, consistency could not be judged and was rated as not applicable. Directness refers to whether the evidence linked the compared interventions directly with health outcomes and compared two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence was required to link interventions to the most important health outcomes. We ranked outcomes as either direct or indirect. Precision refers to the degree of certainty surrounding the effect estimate with respect to a given outcome. 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 (e.g., both clinically important superiority and inferiority), a circumstance that will preclude a conclusion. We rated the effect estimate of each outcome as either precise or imprecise. The overall grade for strength of evidence for each comparison and outcome evaluated was rated and classified as high, moderate, low, or insufficient (Table 2). The four required domains were considered equally when grading the strength of evidence.

Table 2. Strength of evidence rating definitions

Grade	Definition
High	There is 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 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 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.

Evaluating the Applicability of the Evidence

Two reviewers independently reviewed the applicability of the individual studies with disagreements resolved through discussion. Summarization of the applicability of evidence was completed using recommendations from the *Methods Guide*. Seven domains were evaluated in assessing individual study applicability: enrolled population, enrollment eligibility criteria, assessment of final health outcomes, adequate study duration with clinically relevant treatment modalities, assessment of adverse events, sample size, and use of intention-to-treat analysis. Data required to evaluate these domains was extracted into evidence tables. Studies that met five or more criteria were classified as effectiveness studies. These data were also reviewed to determine the overall applicability of data per outcome, describing the population and conditions to which the evidence is most applicable.

Results

Organization of Results

In the result chapter, we first describe the literature identification process along with the inclusion and exclusion of studies. The characteristics of the included studies follows and is organized into four sections that correspond to the comparisons of interest: systemic biologics versus systemic nonbiolgics, systemic biologics versus phototherapy, studies providing only class level comparisons, and included network meta-analyses. After the general characteristics are presented, we organize the remainder of the results by Key Question. A complete list of abbreviations can be found in the Abbreviations list at the end of this report and a glossary of useful terms can be found in Appendix I and J.

Study Identification

Two literature searches were conducted as described in the Methods chapter. The first literature search was conducted to identify relevant literature to answer Key Questions 1, 2 and 3. As delineated in Figure 2, there were 472 citations identified through the database searches and four citations identified manually. One of the manual citations was from the Scientific Information Packets obtained by the Scientific Resource Center while three were from public clinical trial registries. After the removal of duplicates, 419 articles remained. During title and abstract review, 250 citations were excluded. Of the 169 citations remaining, 139 were excluded at the full-text level. A total of 30 citations, representing 11 unique studies, met our inclusion criteria for key questions 1, 2 and 3. The number of included citations exceeds the number of included studies because some publications evaluated the same population. In such cases we only considered the population once and did not double count data. Citations excluded at the full text level are listed in Appendix C along with the reasons for exclusion.

The second literature search was used to specifically identify systematic reviews with meta-analysis that implemented methods to indirectly compare systemic biologic agents with systemic nonbiologic agents or phototherapy. The original literature search identified 19 citations which were screened at the abstract level. A total of 13 citations were excluded at the abstract level and four citations were excluded at the full text level. One unique analysis, which was represented by two citations, was finally included (Figure 3).

Figure 2. Inclusion and exclusion of citations in search one

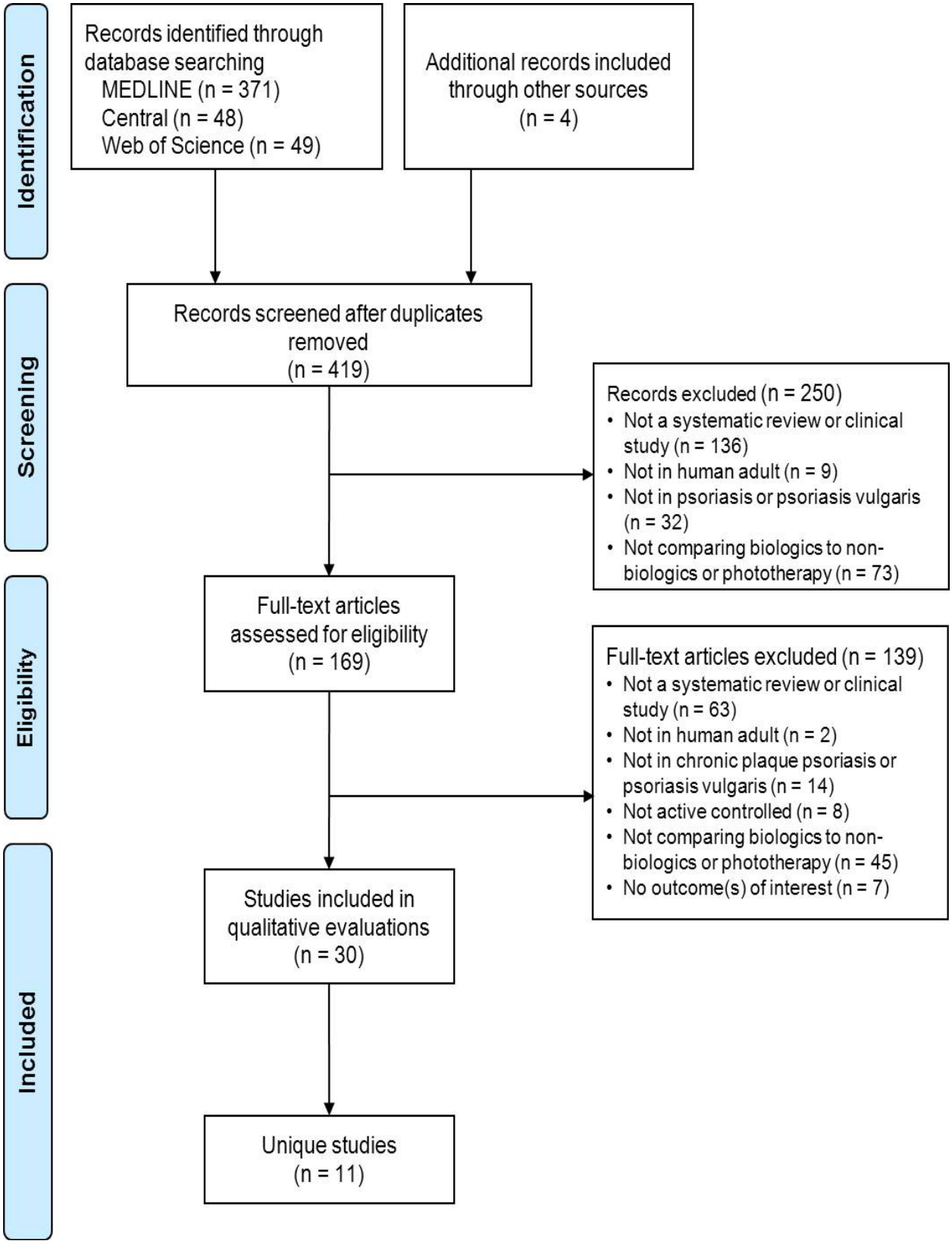
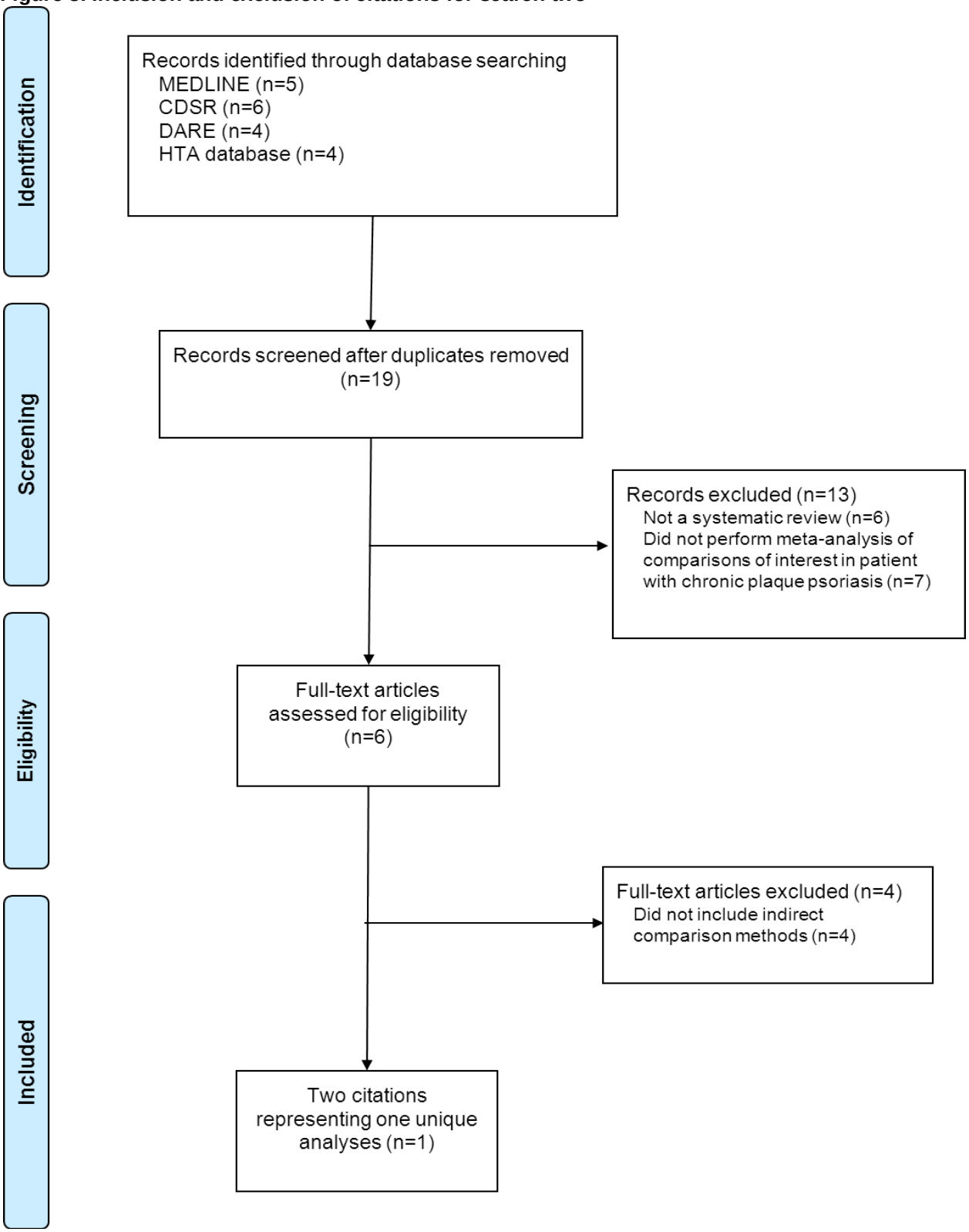


Figure 3. Inclusion and exclusion of citations for search two



Abbreviations: CDSR= Cochrane databse of systematic reviews; DARE=database of abstracts of reviews of effects; HTA=health technology assessment

Study Characteristics

Four RCTs (n=1188)[17,21-23] and two observational studies (n=313)[24,25] directly compared either a systemic biologic agent with a systemic nonbiologic agent or phototherapy and reported at least one outcome of interest. Of the four RCTs, two were fair in quality[21,22] and two were good in quality,[17,23] while the two observational studies were all fair in quality.[24,25] Additionally, three observational studies (n=85) evaluated the transition of patients between therapies within the biologic, nonbiologic, and phototherapy treatments. One of these studies was poor in quality[26] while the others were fair in quality.[27,28] Two of the RCTs also provided data regarding transitions of therapy.[17,21] Two observational studies directly compared therapies of interest but at the class level, and both were fair in quality.[29,30] Finally, we identified one network meta-analysis that used methods for indirect comparison across various therapies included in this review.[31] All included studies were available as full text publications. The baseline characteristics of included studies can be found in Appendix D and the individual study quality assessments can be found in Appendix E.

Studies comparing systemic biologic agents with systemic nonbiologic agents

All four RCTs directly compared individual biologic agents with individual nonbiolgic agents. The unique comparisons included infliximab versus methotrexate,[21] etanercept versus acitretin,[22,23] and adalimumab versus methotrexate.[17] The shortest followup was 12 weeks[22] while the longest followup was 26 weeks.[17,21] The earliest trial was published in 2008[17,23] while the most recent was published in 2011.[21] Two trials received industry funding[17,21] while two trials did not report the funding source.[22,23] The mean age of enrolled patients ranged from 41.6 to 55.3 years. Females represented between 31.2 and 63.3 percent of the enrolled populations. Only two trials reported race/ethnicity of the enrolled population, in which Caucasians represented more than 95 percent of the populations in both trials, with other groups representing a minority of the studied populations (Appendix Table 3).[17,21] The mean weight ranged from 78.4 to 84.5 kg while the mean BMI ranged from 27.2 to 28.0 kg/m^2. The mean baseline PASI ranged from 10.4 to 22.3 while the mean disease duration ranged from 17.0 to 23.5 years. The mean BSA ranged from 11.1 to 33.6 percent. The percentage of participants with concomitant psoriatic arthritis ranged from 0 to 21.3 percent.

One of the two observational studies directly compared individual biologic agents with individual nonbiologic agents.[25] The comparisons made included etanercept or infliximab with methotrexate.[25] The followup period was 24 weeks and the study was published in 2008. The study did not report the funding source. The mean age of the enrolled patients ranged from 46.8 to 53.1 years. Females represented between 30.0 and 39.5 percent of the enrolled populations. Race or ethnicity was not reported. Mean weight and BMI ranged from 79.2 to 81.0 kg and 26.5 to 27.6 kg/m^2, respectively. The mean baseline PASI ranged from 8.2 to 18.8. The mean disease duration ranged from 17.5 to 22.0 years and no patients had concomitant psoriatic arthritis. Mean BSA range was not reported.

Three observational studies[26-28] along with data from two RCTs[17,21] evaluated the transition of patients between biologic agents and nonbiologic agents. The transitions evaluated included methotrexate to adalimumab,[17,21] cyclosporine to etanercept,[26] cyclosporine to alefacept,[28] methotrexate to infliximab,[21] and infliximab to methotrexate.[21] The shortest followup period was 26 weeks[17,21,27] while the longest followup was 2 years.[26] The earliest study was published in

2007[28] while the most recent was published in 2011.[17,21] Four studies received industry funding[17,21,27,28] and one study did not report the funding source.[26] Baseline characteristics specific to the population of patients transitioned to different therapies within the two RCT were not reported. According to the baseline characteristics of the three observational studies, the mean age of the enrolled patients ranged from 45.0 to 58.3 years. Females represented between 25.0 and 31.7 percent of the enrolled populations. One study reported 95.1 percent of patients were Caucasian.[27] No other race/ethnicity percentages were reported. One study reported the mean weight as 89.5 kg while BMI data was not reported.[27] Mean baseline PASI was reported as 10.2 in one study.[27] The mean disease duration ranged from 17.0 to 22.0 years. One study reported the mean BSA as 10.9 percent.[27] The percentage of participants with concomitant psoriatic arthritis ranged from 25.0 to 41.5 percent.

Studies comparing systemic biologic agents with phototherapy

There were no RCTs identified that compared systemic biologic agents with phototherapy. One observational study directly compared individual biologic agents with phototherapies.[24] The comparisons made included adalimumab, alefacept, etanercept, infliximab or ustekinumab versus PUVA.[24] The duration of followup period was 10.3 weeks to 12 weeks and the study was published in 2011. The study received funding from industry. The mean age of the enrolled patients ranged from 46.2 to 48.5 years. The percentage of females was 35.5 percent. The mean baseline PASI ranged from 15.0 to 16.9 and the mean disease duration ranged from 22.9 to 23.4 years. Race or ethnicity, weight, BMI, and BSA were not reported in this study. The percentage of participants with concomitant psoriatic arthritis was not reported.

One observational study evaluated the transition of patients between biologic agents and phototherapy, evaluating the transition from NB-UVB to adalimumab.[27] The study was published in 2011 and received funding from industry. The followup period was 26 weeks. The mean age of enrolled patients was 45.7 years. Females and Caucasians represented 44.8 and 86.2 percent of the enrolled population, respectively. The mean weight was 86.0 kg while the mean BMI was not reported. The mean baseline PASI was 12.8 while the mean disease duration was 23.0 years. The mean BSA was reported as 14.5 percent. The percentage of participants with concomitant psoriatic arthritis was 24.1 percent.

Studies with class level comparisons

Two observational studies compared classes of therapy and both evaluated transitions of therapy.[29,30] The transitions evaluated included systemic nonbiologic agents to etanercept[30] and systemic nonbiologic agents or phototherapy to etanercept.[29] The followup period was 24 weeks for both studies. The earliest study was published in 2005[30] while the most recent was published in 2009.[29] One study was unfunded[29] and the other study did not report the funding source.[30] The mean age of the enrolled patients and percent of females was only reported in one study as 41.2 years and 36.4 percent, respectively.[30] Race/ethnic groups, weight, and BMI were not reported in either study. The mean baseline PASI ranged from 15.6 to 16.1. Only one study reported disease duration and mean BSA as 15.5 years and 21.7 percent, respectively.[30] The percentage of participants with concomitant psoriatic arthritis was reported only in one study as 34.1.[30]

Network Meta-analyses

One systematic review by Bansback et al. evaluated the comparative efficacy of various treatments for chronic plaque psoriasis using a Bayesian model to conduct a mixed-treatment comparison.[31] RCTs evaluating systemic biologic and systemic nonbiologic therapy or phototherapy in patients with moderate to severe psoriasis were included. Additionally, for a therapy to be included, either a direct or indirect link to placebo was required. Because of this, acitretin and phototherapy were excluded because no link to placebo was identified in the literature.

Key Question 1

In patients with chronic plaque psoriasis, what is the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy when evaluating intermediate (plaque BSA measurement, PASI score, Patient's Assessment of Global Improvement, PGA, and individual symptom improvement) and final health outcomes (mortality, HRQoL [e.g., DLQI, HAQ-DI, EQ-5D] and other patient-reported outcomes, MACE, diabetes, and psychological comorbidities [e.g., depression, suicide])?

Key Points

- Four RCTs (two good and two fair in quality) and one fair quality observational study evaluated the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents.
    - The comparisons made included: adalimumab, etanercept, and infliximab versus methotrexate and etanercept versus acitretin.
    - When comparing adalimumab with methotrexate:
        - HRQoL was improved in patients taking adalimumab compared with methotrexate, based on a single RCT (low strength of evidence).
        - There was insufficient evidence to grade death and no other final health outcomes were reported.
        - PASI was improved in patients treated with adalimumab compared with methotrexate, based on one RCT and one observational study (low strength of evidence).
        - PGA was improved in patients treated with adalimumab compared with methotrexate, based on a single RCT(low strength of evidence).
        - Patient Assessment of Disease Severity, pain, and pruritus were each improved in patients treated with adalimumab compared with methotrexate, each based on a single RCT (low strength of evidence).
        - No other intermediate outcomes were reported.
    - When comparing infliximab with methotrexate:
        - HRQoL was improved in patients taking infliximab compared with methotrexate, based on a single RCT (low strength of evidence).
        - There was insufficient evidence to evaluate myocardial infarction and diabetes mellitus and no other final health outcomes were reported.
        - PASI was improved in patients treated with infliximab compared with methotrexate, based on one RCT and one observational study (low strength of evidence).

        - PGA improved in patients treated with infliximab compared with methotrexate, based on a single RCT (low strength of evidence).
        - No other intermediate outcomes were reported.
    - When comparing etanercept with acitretin:
        - No final health outcomes were reported.
        - PASI was improved in patients treated with etanercept compared with acitretin, based on two RCTs (moderate strength of evidence).
        - There was insufficient evidence to evaluate BSA and no other intermediate outcomes were reported.
- One mixed-treatment comparison that evaluated PASI50, PASI75, and PASI90 suggested that the probability of achieving any of the three PASI scores was highest for infliximab, followed by adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care.
- No RCTs evaluated the comparative effectiveness of systemic biologic agents and phototherapy on any outcomes. One observational study reported PASI scores in systemic biologic agent arms (i.e., adalimumab, alefacept, etanercept, infliximab) and phototherapy arms (i.e. PUVA) although did not make statistical comparisons between the groups.
    - No final health outcomes were reported.
    - There was insufficient evidence comparing biologics and phototherapy to evaluate PASI, the only intermediate outcome reported.

Detailed Analysis

Key Question 1 is organized by the comparisons of interest. Systemic biologic agents versus systemic nonbiologic agents are presented first followed by the comparison of systemic biologic agents versus phototherapy. Within each comparison of interest, we present data from direct comparisons first and describe data for final health outcomes followed by intermediate outcomes. Data from RCTs are presented first followed by observational study data. If data describing the transition from one therapy to another was identified, a subsection describing transition data follows the direct comparative data. At the end of the Key Question, data based class comparisons and indirect comparisons are summarized.

The individual study characteristics for all studies included in this Key Question along with their quality assessments can be found in Appendix Tables 3 and 4. Tables which display the outcomes reported within this Key Question can be found in Appendix Tables 5 to 11. Strength of evidence ratings as well as description of the applicability of each study can be found in Appendix Tables 12 to 38.

Outcome Evaluation

Systemic Biologic Agents versus Systemic Nonbiologic Agents

Adalimumab versus methotrexate

One RCT directly compared the biologic agent adalimumab versus the nonbiologic agent methotrexate.[17] The Efficacy and safety results from the randomized controlled comparative study of adalimumab versus methotrexate versus placebo in patients with psoriasis (CHAMPION) trial was the only source of data from a RCT for this comparison.[17] This trial was rated with good quality and all patients were naïve to both tumor necrosis factor (TNF)-

antagonists and methotrexate. A secondary analysis of the CHAMPION population by Revicki et al. was published with additional outcomes and supplemented data from the CHAMPION trial itself. The following final health outcomes were reported: mortality and HRQoL (e.g., DLQI, EQ-5D).[17,32] No additional final health outcomes were reported for the comparison of adalimumab with methotrexate.

In the CHAMPION trial, there were no deaths in either group at 70 days after the last treatment. Two measures of HRQoL were evaluated in the study by Revicki et al., the DLQI and the EQ-5D (both the index score and the VAS). At week 16, the DLQI and the EQ-5D VAS demonstrated a favorable result in the adalimumab group compared with methotrexate. The mean change in DLQI from baseline was significantly greater in the adalimumab group compared with methotrexate group at week 16 [-9.1 (95 percent CI -10.4 to -7.8) versus -5.7 (95 percent CI -6.8 to -4.5); p<0.001].[32] There was significant difference in the mean change in the EQ-5D VAS from baseline to 16 weeks in the adalimumab group compared with methotrexate [21.4 (95 percent CI 16.6 to 26.3) versus 11.5 (95 percent CI 6.5 to 16.5); p<0.001]. However, there was no significant difference in the mean change in EQ-5D index score from baseline to week 16 in the adalimumab group compared with methotrexate [0.2 (95 percent CI 0.2 to 0.3) versus 0.1 (95 percent CI 0.1 to 0.2); p=0.09]. At 12 weeks, adalimumab treatment resulted in greater improvement in the DLQI [-9.1 (95 percent CI -10.4 to -7.8) versus -4.9 (95 percent CI -5.9 to -3.8); p=NR], the EQ-5D VAS [20.4 (95 percent CI 15.3 to 25.4) versus 10.2 (95 percent CI 5.3 to 15.2); p=NR], and the EQ-5D index score [0.2 (95 percent CI 0.1 to 0.2) versus 0.1 (95 percent CI 0.1 to 0.2); p=NR) compared with methotrexate.

CHAMPION and the secondary analysis by Revicki et al. evaluated the following intermediate health outcomes: PASI, PGA, Patient's Global Assessment of disease Severity, and individual symptom improvement (i.e., VAS for plaque psoriasis and psoriatic arthritis pain, psoriasis-related pruritus assessment).[17,32] When compared to methotrexate, more patients who received adalimumab achieved PASI50 (88.0 percent versus 61.8 percent, p<0.001), PASI75 (risk difference 43.7 percent (95 percent CI 30.8 to 56.7, p<0.001); 79.6 percent versus 35.5 percent, p<0.001), PASI90 (51.9 percent versus 13.6 percent, p<0.001), and PASI100 (16.7 percent versus 7.3 percent, p<0.04) at week 16. The median time to PASI75 was significantly shorter in the adalimumab group compared with methotrexate (56 days versus 113 days, p<0.001) as was the median time to PASI50 (28 days versus 84 days, p<0.001).[33] Investigators also evaluated PASI outcomes at weeks 4, 8, and 12. More patients treated with adalimumab achieved PASI50, PASI75, PASI90 at all time periods evaluated (p<0.05) with significant effects observed as early as week 4, except for PASI100. (Appendix Table 8) As for PASI100, significant differences between treatment groups (p<0.05) were observed as early as 8 weeks and were maintained subsequently. (Appendix Table 8) The mean change in PASI score from baseline was significantly greater in the adalimumab group compared with the methotrexate group at week 16 (-16.7±8.8 versus -10.9±8.3, p<0.001).

There was a significantly greater number of patients with a score of "clear" or "minimal" using the PGA tool in the adalimumab group compared with methotrexate at 16 weeks (73.1 percent versus 30.0 percent, p<0.001) as well as earlier time points (weeks 4, 8, and 12).[32] (Appendix Table 7) At week 16, the adalimumab group demonstrated significant improvements from baseline compared with methotrexate in the Patient's Global Assessment of disease severity and in the individual symptoms of pain and pruritus.[32] The mean change in Patient's Global Assessment of disease severity from baseline was significantly greater in the adalimumab group compared with methotrexate at week 16 (-1.6 versus -1.2, p<0.001). The mean change in VAS

for plaque psoriasis and psoriatic arthritis pain from baseline was significantly greater in the adalimumab group compared with methotrexate at week 16 (-24.2 versus -11.1, p<0.001). The mean change in psoriasis-related pruritus from baseline was significantly greater in the adalimumab group compared with the methotrexate at week 16 (-5.0 versus -3.5, p<0.001).[32]

Transitions between adalimumab and methotrexate

Two studies evaluated the transition between the biologic agent adalimumab and the nonbiologic agent methotrexate.[27,34]

The first study was a non-randomized open-label study by Strober et al. Patients who had a suboptimal response to methotrexate, defined as a PGA of "mild" or worse after at least four months of methotrexate therapy were evaluated. Patients stopped methotrexate four to 10 days prior to transitioning to adalimumab treatment.[27] This study was rated as having fair quality and all patients were naïve to adalimumab and natalizumab although being naïve to other therapies was not reported. The following final health outcomes were reported: mortality, HRQoL (e.g., DLQI), and impact on activities of daily living (e.g., work time missed, overall work impairment, impairment while working, and activity impairment due to psoriasis). No additional final health outcomes were reported for patients who transitioned from methotrexate to adalimumab.

In this study by Strober et al., there were no deaths reported through week 16. The mean DLQI improved from baseline to weeks 4 and 16 [(-7.0±7.45, p=NR) and (-4.8±5.89, p=NR), respectively]. Corresponding standard deviations were not reported in the original publication but were reported separately in the results available on www.clinicaltrials.gov. Measures of the impact of psoriasis on activities of daily living were also reported in the results available on www.clinicaltrials.gov.[27,35] At week 16, patients showed improvement in the mean percent change of overall work impairment due to psoriasis (-4.0±28.1 percent, p=NR), impairment while working due to psoriasis (-5.5±30.3 percent, p=NR), and activity impairment due to psoriasis (-13.3±33.1 percent, p=NR). However, there was no improvement in the mean percent change in work time missed due to psoriasis (0.7 ± 3.43 percent, p=NR).[35]

Two studies evaluated intermediate outcomes. The first being the study by Strober et al. and the second was an open-label extension of the CHAMPION trial. In the open-label extension, methotrexate treated patients who completed the original 16-week trial were allowed to transition to treatment with adalimumab.[34] Results from this population of 95 patients were reported based on an interim analysis and included PASI response. In these two studies, the following intermediate health outcomes were evaluated: PASI, PGA, and individual symptom improvement (i.e., VAS for plaque psoriasis and psoriatic arthritis pain and psoriasis-related pruritus assessment).[27,34] No additional intermediate health outcomes were reported for patients who transitioned from methotrexate to adalimumab.

In the study by Strober et al., the mean PASI score improved for patients at week 16 compared to week zero (2.3 versus 10.8, p=NR), with improvements observed as early as week 2 (Appendix Table 8) Engauge Digitizer, Version 2.0 was used to read the reported figure to obtain mean PASI scores at all reported time periods (weeks 0, 2, 4, 8, and 16).[27] In the CHAMPION extension, PASI response rates improved after patients transitioned to adalimumab for 24 weeks of treatment (PASI75: 73 percent, PASI90: 53 percent, PASI100: 32 percent) compared with PASI scores prior to treatment with adalimumab (PASI75: 28 percent, PASI90: 14 percent, PASI100: 5, p=NR).[34]

In the study by Strober et al., at week 16, 61 percent of patients (95 percent CI 45 to 76 percent) who switched from methotrexate to adalimumab had a PGA score of "clear" or

"minimal". PGA results for earlier time points (week 0, 2, 4, and 8) are available in Appendix Table 7.[27] Two measures of individual symptom improvement (i.e., VAS for plaque psoriasis and psoriatic arthritis pain and psoriasis-related pruritus assessment) were assessed through week 16. Both symptoms, pain and pruritus, improved at week 16 from baseline [(-14.7±24.4, p=NR) and (-2.9±3.9, p=NR), respectively].[27,35]

Alefacept versus cyclosporine

No RCTs or observational studies directly compared the biologic agent alefacept with the nonbiologic agent cyclosporine.

Transitions from cyclosporine to alefacept

One study by Magliocco et al. evaluated patients who were well-controlled on cyclosporine therapy with a need or desire to switch to alefacept therapy.[28] Possible reasons in which a patient necessitated a switch from cyclosporine may have included adverse events, cumulative toxicity, or dose limits for cyclosporine. Well-controlled was defined as a PGA score of "mild (5)", "almost clear (6)" or "clear (7)". This study was rated as having fair quality and data about whether patients were naïve to treatment was not reported. The study consisted of three phases over 48 weeks to determine if psoriasis control could be maintained while transitioning patients from cyclosporine to alefacept. In phase I (12 weeks), patients received alefacept for 12 weeks and were being tapered off of cyclosporine in weeks 5 through 12. In phase 2 (12 weeks), patients did not receive alefacept or cyclosporine but were allowed to use topical agents and UVB phototherapy. In phase III (24 weeks), patients were treated with alefacept for 12 weeks followed by additional 12 weeks of observation, in which topical and UVB therapy was permitted. Topical therapy was used by three patients (25 percent) in phase II and in phase III. UVB therapy was used by one patient (8 percent) in phase III. Twelve patients began this study and completed phase I, three patients dropped out during phase II, and 2 patients dropped out during phase III. Therefore, six patients (50 percent) completed the 48 week study.

One measure of HRQoL, the DLQI, was evaluated throughout the course of this study. The mean DLQI score was lower after phase I in comparison to the baseline mean (1.09 versus 3.18, p=NR) and increased to a value higher than baseline at the end of phase II (4.88 versus 3.18, p=NR). After the second treatment course administered during phase III, the mean DLQI value was 3.14 (p=NR), and then increased slightly to 3.83 at the end of the observation period during phase III (48 weeks). Authors concluded that the quality of life was improved or maintained in all patients during phase I and that no significant changes in quality of life were observed in patients who completed the study. No additional final health outcomes were reported.

One intermediate outcome, the PGA, was measured in this study. At baseline, 11 of 12 patients had a PGA of "mild (5)" and one patient had a PGA of "moderate to severe (2)". After phase I, the majority of patients maintained the same PGA score (7 of 11, 64 percent) and all patients remained within one category of their baseline PGA score. After phase II (Week 25), the mean PGA score was 4.75. During phase III, the mean PGA score was 4.33 at the end of the second treatment course and maintained through week 48 (mean PGA score of 4.33). Authors concluded that the PGA remained stable during phase I and response to alefacept was maintained during the observation period in the majority of patients. No additional intermediate health outcomes were reported.

Etanercept versus acitretin

Two RCTs compared the biologic agent etanercept with the nonbiologic agent acitretin.[22,23]

The first RCT by Caproni et al. was rated as having fair quality while the second trial by Gisondi et al. was rated as having good quality. In the trial by Caproni et al. the percent of treatment naïve patients was not reported and individuals were allowed into the trial as long as treatment with either topical or systemic therapy was greater than one month prior to enrollment. In the trial by Gisondi et al. all patients were naïve to biologic therapy as prior use was an exclusion criterion. Patients were allowed into the trial as long as treatment with either topical, systemic, or phototherapy was greater than four weeks prior to enrollment.

No final health outcomes were reported for the comparison of etanercept with acitretin. Within the two RCTs, the following intermediate outcomes were reported: BSA and PASI.. One trial, by Gisonidi et al., evaluated the affected BSA at 24 weeks and found that patients treated with etanercept had a greater percentage of BSA improvement (80 percent) compared with patients treated with acitretin (45.8 percent, p=NR).[23] Both trials evaluated PASI50 and PASI75 scores. In the trial by Gisondi et al. a significantly higher proportion of patients treated with etanercept achieved PASI50 (68 percent versus 50 percent, p=0.001) and PASI75 (45 percent versus 30 percent, p=0.001) compared with acitretin at week 24, the longest duration of followup for this outcome.[23] Statistically significant differences between etanercept and aceitretin were seen as early as 12 weeks (p=0.001) for both PASI50 and PASI75 and remained significant at week 18 (p=0.001) for both outcomes (Appendix Table 8). In the trial by Caproni et al. the proportion of patients in the etanercept group achieving PASI50 (87 percent versus 67 percent, p=NR) and PASI75 (57 percent versus 27 percent, p=NR) was higher compared with acitretin.[22] The mean PASI score was significantly reduced at week 12 when compared with baseline in both treatment groups.[22] The mean baseline PASI score in the etanercept group was 21.54±9.09 compared with the mean PASI score at week 12 of 4.61±2.75, p<0.001. The mean baseline PASI score in the acitretin group was 22.25± 5.73 compared with the mean PASI score at week 12 of 9.62±4.64, p<0.001. The mean PASI score was significantly lower in the etanercept group compared with acitretin at week 12 (p=0.005).

Etanercept versus cyclosporine

There were no RCTs or observational studies that directly compared the biologic agent etanercept with the nonbiologic agent cyclosporine.

Transitions from cyclosporine to etanercept

One observational study by Garavaglia et al. evaluated patients with hepatitis C virus who had been previously treated with cyclosporine and were currently receiving etanercept treatment.[26] This study was rated as having poor quality and data about whether patients were naïve to treatment or not was not reported. PASI was the only intermediate health outcome reported at baseline, 3, 6, 12, 18, and 24 months and no final health outcomes were reported. All four patients who switched from cyclosporine to etanercept therapy showed an improvement in mean PASI scores at week 52 (22.5, 23.8, 22.4, and 27.3 at baseline versus 5.6, 3.7, 0, and 8.4 at week 52, p=NR). Two of the four patients had PASI scores reported at 104 weeks and continued to show comparable mean PASI scores as in week 52 (0 and 8.3 at week 104 versus 5.6 and 8.4 at week 52, p=NR).

Etanercept versus methotrexate

There were no RCTs that directly compared the biologic agent etanercept with the nonbiologic agent methotrexate.

One observational study compared the biologic etanercept with the nonbiologic methotrexate. In this study by Gisondi et al., rated with fair quality, patients treated with etanercept were naïve to biologic therapy.[25] No final health outcomes were evaluated in this study and the only intermediate outcome reported was PASI. The mean PASI score significantly decreased from baseline to 6 months in the etanercept (18.8±7.4 versus 4.8±4.7, p=0.0001) and in the methotrexate groups (8.2±3.1 versus 4.3±6, p=0.0002), although between group comparisons were not made. The mean percent reduction in PASI scores was statistically significant within each group: 74.5 percent in the etanercept group (p=0.0001 versus baseline) and 47.1 percent in the methotrexate group (p=0.0002 versus baseline).

Infliximab versus methotrexate

One RCT and one observational study directly compared the biologic agent infliximab with the nonbiologic agent methotrexate.[21,25]

The RCT by Barker et al., rated with fair quality, compared the biologic agent infliximab with the nonbiologic agent methotrexate.[21] Patients enrolled in this trial were naïve to methotrexate therapy and were not treated with any systemic biologic agents within 3months of baseline. Therapy with topical agents or systemic therapies that could affect PASI were discontinued two and four weeks, respectively, prior to the start of the study.

In this RCT, patients were followed for 26 weeks, although at week 16, patients who did not achieve PASI50 or who were intolerant to assigned therapy could switch from assigned therapy to the other intervention.[21] After week 16, patients were evaluated in the groups in which they were taking therapy, not in the groups in which they were originally randomized. Additionally, patients who switched therapy were considered PASI nonresponders at week 26. A total of 29 percent of patients originally randomized to receive methotrexate switched to infliximab at week 16 whereas only one percent of patients randomized to infliximab switched to methotrexate at week 16. Therefore, for all final and intermediate health outcomes, we report the 16 week followup as the maximal duration of followup when possible. When alternate time periods are reported, an explanation accompanies the results.

This trial evaluated the following final health outcomes: HRQoL, myocardial infarction (a component of MACE), and diabetes mellitus.[21] No additional final health outcomes were reported for the comparison of infliximab with methotrexate and no observational data was available for final health outcomes. Three measures of HRQoL were evaluated, the DLQI, the EQ-5D, and the mental (MCS) and physical (PCS) components of the SF-36.[21] At 16 weeks, all scales demonstrated a favorable result in the infliximab treated patients compared with methotrexate. The mean change in DLQI at 16 weeks from baseline was significantly greater in the infliximab group compared with methotrexate (-11.6 versus -8.95, p<0.001). The mean EQ-5D score was significantly greater in the infliximab group compared with methotrexate (0.86 versus 0.84, p<0.05). Differences between infliximab and methotrexate were statistically significant in the change in DLQI (-11.4 versus -7.9, p<0.001) and in the mean EQ-5D score (0.86 versus 0.81, p<0.05) as early as 10 weeks, the first time period in which these outcomes were evaluated. The mean change in the PCS of the SF-36 was significantly greater in the infliximab group compared with the methotrexate group (5.53 versus 3.76, p<0.002) at 16 weeks. The mean change in the PCS was also significantly greater in the infliximab group at 10 weeks compared with methotrexate (5.15 versus 3.00, p<0.001). The mean change in the MCS was significantly greater in the infliximab group at week 10 compared with methotrexate (7.94 versus 5.63, p<0.041), while results at week 16 were not reported.

Myocardial infarction and diabetes mellitus were not reported in the original publication[21] although data were reported on www.clinicaltrials.gov for all patients who did not switch therapy through week 26 including data through week 16 for patients who did switch therapy.[36] One case of myocardial infarction was reported in the methotrexate group (0.47 percent) while no cases occurred in the infliximab group (p=NR). One case of diabetes was reported in the infliximab group (0.15 percent) while no cases occurred in the methotrexate group (p=NR).

The RCT by Barker et al. evaluated the following intermediate health outcomes: PASI and PGA.[21] No other intermediate health outcomes were evaluated for the comparison of infliximab with methotrexate. When compared to methotrexate, more patients who received infliximab achieved PASI50 (86.8 percent versus 60.5 percent, p<0.001), PASI75 (77.8 percent versus 41.9 percent, p<0.001), and PASI90 (54.4 percent versus 19.1 percent, p<0.001) at 16 weeks. Investigators also evaluated these PASI outcomes at weeks 2, 6, 10 and 14. (Appendix Table 8) More patients treated with infliximab achieved PASI50 and PASI75 at all time periods (p<0.001) compared with methotrexate with significant effects observed as soon as 2 weeks. As for PASI90, significant differences between treatment groups (p<0.001) were observed as early as 6 weeks and were maintained subsequently. The median time to PASI75 was shorter in infliximab treated patients compared with methotrexate [46 days (95 percent CI 45 to 50) versus 127 days (95 percent CI 113 to 154); p<0.0001]. Authors reported that the mean change in PASI from baseline was significantly greater (p<0.001) in the infliximab group compared with methotrexate at all time periods evaluated (weeks 2, 6, 10, 14, p<0.001) although the magnitude of effect was not reported. PGA was evaluated at 16 weeks and there was a significantly greater number of patients with PGA scores of "cleared" or "minimal" in the infliximab treated group compared with methotrexate (76 percent versus 38 percent, p<0.001). No other intermediate outcomes were reported in patients as randomized.

In this RCT, patients were followed for 26 weeks, although outcomes reported at weeks 18, 22, and 26 consider patients who switched therapy at week 16 nonresponders.[21] At week 26, the mean change in DLQI from baseline was significantly greater in the infliximab group compared with methotrexate (-11.3 versus -9.14, p<0.004. At week 26, the mean EQ-5D score was significantly greater in the infliximab group compared with methotrexate (0.86 versus 0.81, p<0.05). At week 26, a greater number of patients in the infliximab group achieved PASI50 (81 percent versus 47.9 percent, p<0.001), PASI75 (76.8 percent versus 30.7 percent, p<0.001), and PASI90 (51 percent versus 14.9 percent, p<0.001). Findings were similar for these outcomes at weeks 18 and 22, where infliximab had a significantly greater number of patients achieving PASI improvement compared with methotrexate (Appendix Table 8). The mean percent change in PASI score from baseline to week 26 was also greater in the infliximab group compared with methotrexate (85 percent versus 54 percent, p<0.001). Authors reported that the mean change in PASI from baseline was significantly greater (p<0.001) in the infliximab group compared with methotrexate at weeks 18 and 22 as well, although the magnitude of effect was not reported.

One observational study compared the biologic infliximab with the nonbiologic methotrexate.[25] In this study by Gisondi et al., rated with fair quality, patients treated with infliximab were naïve to biologic therapy.[25] The only intermediate outcome reported was PASI. The mean PASI score significantly decreased from baseline to 6 months in the infliximab (17.7±7.3 versus 2.1±3.2, p=0.0001) and in the methotrexate groups (8.2±3.1 versus 4.3±6, p=0.0002), although between group comparisons were not made. The percent reduction of mean PASI scores was statistically significant within each group: 88.8 percent in the infliximab group

(p=0.0001 versus baseline) and 47.1 percent in the methotrexate group (p=0.0002 versus baseline).

Transitions between infliximab and methotrexate

In the trial by Barker et al, patients who did not respond to or were intolerant to randomized therapy were given the option of switching therapies from infliximab to methotrexate and vice-a-versa after week 16.[21] A total of 9 patients (1 percent) randomized to infliximab switched to methotrexate and 63 patients (29 percent) randomized to methotrexate switched in infliximab.[21]

In terms of final health outcomes, no myocardial infarctions or cases of diabetes mellitus occurred in any of the patients that switched therapy at 16 weeks.[36]

PASI and PGA were intermediate outcomes evaluated in the transition populations.[21] At week 26, a greater proportion of patients that switched to infliximab from methotrexate achieved PASI75 (46 of 63 patients, 73 percent) or PASI90 (47.6 percent) compared with patient who switched to methotrexate (1 of 9 patients, 11.1 percent; no patients achieved PASI90, p=NR). Findings were similar for PASI75 and PASI90 at weeks 18 and 22 as well (Appendix Table 8). Similarly, a greater proportion of patients achieved "clear" or "minimal" on the PGA in the infliximab group (47 of 63, 75 percent) compared with the methotrexate group (2 of 9, 22 percent, p=NR) at week 26. Weeks 18 and 22 demonstrated a similar trend (Appendix Table 7).

Indirect comparisons

One systematic review by Bansback et al. evaluated the comparative efficacy of various treatments for chronic plaque psoriasis using a Bayesian mixed-treatment comparison.[31] RCTs evaluating biologic and nonbiologic systemic therapy or phototherapy in patients with moderate to severe psoriasis were included. Additionally, for a therapy to be included, either a direct or indirect link to placebo was required. Because of this, acitretin and phototherapy were excluded because no link to placebo was identified in the literature. The outcomes evaluated in this analysis were PASI50, PASI75, and PASI90 and the probability of a given therapy achieving each outcome was reported (Table 3). Although relative risks were also reported, they were relative to placebo treatment and estimates of direct drug comparisons were not reported. Regardless of the PASI outcome evaluated, infliximab had the highest probability of achieving the outcome followed by adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care. Of note, efalizumab data are not included in our report as it does not carry a current FDA indication. Overall, the three biologic agents that comprise the TNF-alpha blocker class (i.e., infliximab, adalimumab, and etanercept) individually had higher probabilities of achieving a given PASI response than either of the nonbiologic systemic agents (i.e, methotrexate and cyclosporine) included in the analysis. The nonbiologics individually had higher probabilities of achieving a given PASI response than the biologic agent alefacept.

Table 3. Results from Bansback et al.

Therapy	Probability of Response PASI50 %, (95% CI)	Probability of Response PASI75 %, (95% CI)	Probability of Response PASI90 %, (95% CI)
Supportive care	14 (12-16)	4 (4-5)	1 (1-1)
Etanercept 50mg twice weekly	74 (67-80)	50 (43-58)	22 (17-28)
Efalizumab 1mg/kg*	53 (48-59)	28 (24-34)	9 (7-12)
Infliximab 5mg/kg	93 (91-96)	81 (75-86)	54 (47-63)
MTX 15-22.5mg/wk	66 (51-77)	42 (27-54)	17 (9-26)
Cyclosporine 3mg/kg/d	57 (37-73)	33 (17-49)	11 (4-21)

Therapy	Probability of Response PASI50 %, (95% CI)	Probability of Response PASI75 %, (95% CI)	Probability of Response PASI90 %, (95% CI)
Adalimumab 40mg every other wk	88 (83-93)	71 (63-79)	42 (33-52)
Alefacept 15mg IM weekly	34 (25-43)	15 (9-21)	4 (2-6)

Abbreviations: CI=confidence interval; d=day(s); IM=intramuscular; kg=kilogram(s); mg=milligram(s); MTX=methotrexate; PASI=Psoriasis Area and Severity Index; wk=week(s)
*Efalizumab (not our comparison of interest) administered every 8 weeks following doses at 0, 2, and 6 weeks

Class level comparisons

Three observational studies reported data comparing biologic agents with nonbiologic agents at the class level.[25,29,30] One study directly compared classes[25] while two studies observed transitions of therapy from nonbiolgics to biologics.[29,30]

One observational study by Gisondi et al., rated with fair quality, compared treatment with biologics (etanercept or infliximab) to treatment with the nonbiologic methotrexate.[25] Patients treated with biologics were naïve to biologic therapy. No final health outcomes were evaluated in this study and the only intermediate outcome reported was PASI. The mean PASI improvement at 6 months was significantly lower in the methotrexate (47.6 percent) group compared with etanercept (74.5 percent) or infliximab (88.8 percent) collectively (p-value for comparison of methotrexate versus etanercept or infliximab=0.0004).

Transitions between biologics and nonbiologics

Two observational studies evaluated the transition between biologics and nonbiologics.[29,30] No studies evaluated final health outcomes in this comparison of interest. The first study by Costanzo et al., rated with fair quality, was an open-label compassionate use study in which patients who failed or had adverse events to at least one nonbiologic systemic agent (systemic corticosteroids, cyclosporine, methotrexate, and/or retinoids) in the past were treated with etanercept.[30] The majority of patients had also been previously treated with topical steroids (75 percent, 33 out of 44 patients) The interim results of this study were reported where all patients (44 patients) had data at week 12 and 15 patients (34.1 percent) had data at week 24. No final health outcomes were evaluated.

One intermediate outcome, PASI, was measured in this study.[30] PASI score was reported at weeks 0, 12, and 24. The mean PASI score at baseline was 15.6 and decreased to 7.5 and 4.3 at weeks 12 and 24, respectively (p=NR). Corresponding percent improvement in the mean PASI score from baseline to week 12 was 52 percent and to week 24 was 72 percent. At week 24, the number of patients with PASI50 (12 of 15 patients, 80 percent) or PASI75 (10 of 15 patients, 67 percent) was significantly greater compared to the number with PASI50 (28 of 44 patients, 64 percent) or PASI75 (19 of 44 patients, 43 percent) at 12 weeks ($p<0.05$ for both comparisons). The number of patients achieving PASI90 was higher at 24 weeks (6 of 15 patients, 40 percent) compared with 12 weeks (4 of 44 patients, 9 percent, p=NR).

The second study by Mazzotta et al., rated with fair quality, also observed treatment of patients with etanercept who had previously been treated with nonbiologic systemic agents or phototherapy (cyclosporine, corticosteroids, fumaric acid esters, methotrexate, retinoids, and PUVA).[29] Patients were included if they failed nonbiologic therapy (according to PASI and pain scores), had an adverse event to nonbiologic therapy, or were noncompliant with nonbiologic treatment. The percentage of patients in each of these categories was not reported by the study.

Most patients (98 of 124, 79 percent) were naïve to systemic biologics. No final health outcomes were evaluated.

One intermediate outcome, PASI, was measured in this study.[29] The mean PASI score was significantly lower at 24 weeks compared to baseline (2.8±3.4 versus 16.1±7.1, p<0.0001) and compared to 12 weeks (2.8±3.4 versus 4.9±4.0, p<0.0001). At 24 weeks, 88 of 98 patients (89.9 percent) and 74 of 98 (75.3 percent) patients achieved PASI50 and PASI75, respectively. At 12 weeks, 79 of 98 patients (80.2 percent) and 43 of 98 (43.7 percent) patients achieved PASI50 and PASI75, respectively.

Biologic Systemic Agents versus Phototherapy

Adalimumab versus NB-UVB

There were no RCTs or observational studies identified for this comparison of interest.

Transitions between adalimumab and NV-UVB phototherapy

One non-randomized open-label study by Strober et al. evaluated patients who had a suboptimal response to NB-UVB phototherapy, defined as a PGA of "moderate" or worse after at least two months of therapy.[27] Patients stopped NB-UVB therapy four to 10 days prior to transitioning to adalimumab treatment. This study was rated as having fair quality. All patients were naïve to adalimumab and natalizumab, and whether patients were naïve to other therapies was not reported. The following final health outcomes were evaluated: mortality, HRQoL (e.g., DLQI), and impact of psoriasis on activities of daily living (e.g., work time missed, overall work impairment, impairment while working, and activity impairment due to psoriasis). No additional final health outcomes were reported for patients who transitioned from NB-UVB to adalimumab.

In this study, there were no deaths reported through week 16. The mean change in DLQI from baseline to weeks 4 and 16 improved [(-5.2±5.45, p=NR) and (-6.5±6.44, p=NR), respectively].[27,35] Corresponding standard deviations were not reported in the original publication but were reported separately in the results available on www.clinicaltrials.gov. Measures of the impact of psoriasis on activities of daily living were reported in the results available on www.clinicaltrials.gov.[27,35] At week 16, patients showed improvement in the mean percent change of overall work impairment due to psoriasis (-6.4±19.8 percent, p=NR), impairment while working due to psoriasis (-8.0±19.4 percent, p=NR), and activity impairment due to psoriasis (-12.2± 25.6 percent, p=NR). However, there was no improvement in the mean percent work time missed due to psoriasis (1.3 ± 4.8 percent, p=NR).[35]

This study also evaluated the following intermediate health outcomes: PASI, PGA, and individual symptom improvement (i.e., VAS for plaque psoriasis and psoriatic arthritis pain and psoriasis-related pruritus assessment).[27] No additional intermediate health outcomes were reported for patients who transitioned from NB-UVB phototherapy to adalimumab.

The mean PASI score improved at week 16 compared to week 0 in patients who switched from NB-UVB phototherapy to adalimumab (3.6 versus 12.4, p-NR) with improvements observed as early as week 2 (Appendix Table 8). Engauge Digitizer, Version 2.0 was used to read the reported figure to obtain values for mean PASI score at all reported time periods (week 0, 2, 4, 8, and 16). At week 16, 48 percent of patients (95 percent CI 29 percent to 67 percent) who transitioned from NB-UVB phototherapy to adalimumab had a PGA score of "clear" or "minimal". PGA results for earlier time periods (week 0, 2, 4, and 8) are available in Appendix Table 7.

Two measures of individual symptom improvement (i.e., VAS for plaque psoriasis and psoriatic arthritis pain and psoriasis-related pruritus assessment) were assessed through week 16. Both symptoms, pain and pruritus, improved at week 16 from baseline [(-21.4±30.0, p=NR) and (-3.0±2.96 p=NR), respectively].[27,35]

Adalimumab versus PUVA

There were no RCTs identified for this comparison of interest. One observational study evaluated the comparison of the biologic agent adalimumab versus PUVA.[24] No studies evaluated final health outcomes in this comparison of interest.

The study by Inzinger et al. compared a variety of biologics to PUVA but reported results by individual drug.[24] In this study, the oral portion of PUVA was either with 8-MOP or 5-MOP. Only the 8-MOP data were considered since 5-MOP is not FDA approved. This study was rated with fair quality and patients were not naïve to treatment since inclusion was based on having treatment with oral PUVA and/or at least one course of biologics. Some patients in this study also received treatment with the nonbiologic acitretin although data excluding these patients was reported in the trial and is presented here. Additionally, results of this study were reported in terms of treatment course, not patients. The only outcome reported in this trial was the intermediate outcome PASI, at week 12 for biologics and at the end of PUVA therapy (median 10.3 weeks) for the PUVA group. A lower proportion of adalimumab treatment courses resulted in complete remission (6 percent versus 21 percent, p=NR), PASI90 (22 percent versus 70 percent, p=NR), PASI75 (56 percent versus 89 percent, p=NR), and PASI50 (72 percent versus 92 percent, p=NR) when compared with PUVA therapy.

Alefacept versus PUVA

There were no RCTs identified for this comparison of interest. No studies evaluated final health outcomes in this comparison of interest. One observational study by Inzinger et al. compared a variety of biologics to PUVA but reported results by individual drug.[24] In this study, the oral portion of PUVA was either with 8-MOP or 5-MOP and only the 8-MOP data were considered since 5-MOP is not FDA approved. This study was rated with fair quality and patients were not naïve to treatment since inclusion was based on having treatment with oral PUVA and/or at least one course of biologics. Some patients in this study also received treatment with the nonbiologic acitretin. Data were reported excluding those patients and is presented here. Additionally, results were reported in terms of treatment course, not patients. One outcome was reported in this study, the intermediate outcome PASI, at week 12 for biologics and at the end of PUVA therapy which was a median duration of 10.3 weeks for the PUVA group. A lower proportion of alefacept treatment courses results in complete remission (3 percent versus 21 percent, p=NR), PASI90 (3 percent versus 70 percent, p=NR), PASI75 (25 percent versus 89 percent, p=NR), and PASI50 (63 percent versus 92 percent, p=NR) compared with PUVA therapy.

Etanercept versus PUVA

There were no RCTs identified for this comparison of interest. No studies evaluated final health outcomes in this comparison of interest. One observational study evaluated the comparison of the biologic agent adalimumab versus PUVA.[24]

The study by Inzinger et al. compared a variety of biologics to PUVA but reported results by individual drug.[24] In this study, the oral portion of PUVA was either with 8-MOP or 5-MOP and only the 8-MOP data were considered since 5-MOP is not FDA approved. This study was rated

with fair quality and patients were not naïve to treatment since inclusion was based on having treatment with oral PUVA and/or at least one course of biologics. Some patients in this study also received treatment with the nonbiologic acitretin. Data were reported excluding those patients and are presented here. Additionally, results were reported in terms of treatment course, not patients. One outcome was reported in this study, the intermediate outcome PASI, at week 12 for biologics and at the end of PUVA therapy which was a median duration of 10.3 weeks for the PUVA group. A lower proportion of treatment courses with etanercept resulted in complete remission (6 percent versus 21 percent, p=NR), PASI90 (29 percent versus 70 percent, p=NR), PASI75 (39 percent versus 89 percent, p=NR), and PASI50 (84 percent versus 92 percent, p=NR) compared with PUVA therapy.

Infliximab versus PUVA

There were no RCTs identified for this comparison of interest. No studies evaluated final health outcomes in this comparison of interest. One observational study evaluated the intermediate health outcome in this comparison of the biologic agent adalimumab with PUVA.[24]

The study by Inzinger et al. compared a variety of biologics to PUVA but reported results by individual drug.[24] In this study, the oral portion of PUVA was either with 8-MOP or 5-MOP and only the 8-MOP data was considered since 5-MOP is not FDA approved. This study was rated with fair quality and patients were not naïve to treatment since inclusion was based on having treatment with oral PUVA and/or at least one course of biologics. Some patients in this study also received treatment with the nonbiologic acitretin. Data were reported excluding those patients and are presented here. Additionally, results were reported in terms of treatment course, not patients. One outcome was reported in this study, the intermediate outcome PASI, at week 12 for biologics and at the end of PUVA therapy which was a median duration of 10.3 weeks for the PUVA group. A higher proportion of treatment courses resulted in complete remission (29 percent versus 21 percent, p=NR), PASI90 (71 percent versus 70 percent, p=NR), PASI75 (100 percent versus 89 percent, p=NR), and PASI50 (100 percent versus 92 percent, p=NR) compared with PUVA therapy.

Ustekinumab versus PUVA

There were no RCTs identified for this comparison of interest. No studies evaluated final health outcomes in this comparison of interest. One observational study by Inzinger et al. compared a variety of biologics to PUVA but reported results by individual drug.[24] In this study, the oral portion of PUVA was either with 8-MOP or 5-MOP and only the 8-MOP data were considered since 5-MOP is not FDA approved. This study was rated with fair quality and patients were not naïve to treatment since inclusion was based on having treatment with oral PUVA and/or at least one course of biologics. Some patients in this study also received treatment with the nonbiologic acitretin. Data were reported excluding those patients and are presented here. Additionally, results were reported in terms of treatment course, not patients. One outcome was reported in this study, the intermediate outcome PASI, at week 12 for biologics and at the end of PUVA therapy which was a median duration of 10.3 weeks for the PUVA group. A lower proportion of ustekinumab treatment courses resulted in complete remission (6 percent versus 21 percent, p=NR), PASI90 (39 percent versus 70 percent, p=NR), PASI75 (67 percent versus 89 percent, p=NR), and PASI50 (89 percent versus 92 percent, p=NR) compared with PUVA therapy.

Key Question 2

In patients with chronic plaque psoriasis, what is the comparative safety of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy (hepatotoxicity [e.g., AST, ALT], nephrotoxicity [e.g., SCr, GFR], hematologic toxicity [e.g., TCP, anemia, neutropenia], hypertension, alteration in metabolic parameters [e.g., glucose, lipids, weight, BMI, thyroid function], injection site reaction, malignancy, infection, and study withdrawal)?

Key Points

- The literature base for the comparative safety of systemic biologic agents and systemic nonbiologic agents or phototherapy is sparse.
    - Overall four RCTs (two good and two fair in quality) and two observational studies (both fair in quality) directly compared biologics to nonbiolgics and reported at least one adverse outcome of interest.
    - No trials or observational studies directly compared biologics to phototherapy.
- Infection rate did not differ between adalimumab and methotrexate (low strength of evidence). This data was from a single RCT conducted outside of the United States in patients with moderate to severe chronic plaque psoriasis naïve to TNF-alpha antagonists or methotrexate.
- There was insufficient evidence for other reported outcomes.

Detailed Analysis

Key Question 2 is organized by the comparisons of interest. Biologics versus nonbiologics are presented first followed by the comparison of biologics versus phototherapy. Within each comparison of interest, we present data from direct comparisons first. Data from RCTs are presented first followed by observational study data. If data describing the transition from one therapy to another was identified, a subsection describing transition data follows the direct comparative data. At the end of the Key Question, data based on class level comparisons are summarized. There were no data based on indirect comparison meta-analyses identified for this Key Question.

The individual study characteristics for all studies included in this Key Question along with their quality assessments can be found in Appendix Table 3 and 4. Tables which display the outcomes reported within this Key Question can be found in Appendix Tables 5 to 11. Strength of evidence ratings as well as description of the applicability of each study can be found in Appendix Tables 12 to 38.

Outcome Evaluation

Biologic Systemic Agents versus Nonbiologic Systemic Agents

Adalimumab versus methotrexate

The “CHAMPION” trial was the only source of data directly comparing the biologic agent adalimumab with the nonbiologic agent methotrexate.[17] This trial was rated with good quality and all patients were naïve to both TNF-antagonists and methotrexate. Harms were reported up to 70 days after the last treatment.[17] The harms reported in this trial include AST, ALT, infection,

and study withdrawal. No additional harm outcomes were reported for the comparison of adalimumab with methotrexate.

More patients in the methotrexate group compared with adalimumab had AST elevation [2 (1.8 percent) versus 0 (0 percent), p=NR] or ALT elevation [4 (3.6 percent) versus 0 (0 percent), p=NR], with elevation defined as > 2.5 times the ULN. The difference in infection rate was reported to be not significant and infection was observed in 51 patients (47.7 percent) receiving adalimumab and 46 patients (41.8 percent) receiving methotrexate. No infections were considered serious. Four patients (3.7 percent) and six patients (5.5 percent) withdrew from the adalimumab treated group and the methotrexate treated group, respectively (p=NR).

Transitions between adalimumab and methotrexate

Two studies evaluated the transition of patients between the biologic agent adalimumab and the nonbiologic agent methotrexate.[27,34] The CHAMPION trial included an open-label extension study in which methotrexate treated patients who completed a 16-week study period were allowed to switch to treatment with adalimumab.[34] Results from this population of 95 patients were reported based on an interim analysis and no serious infections occurred during the 24 weeks of adalimumab treatment.[34]

One non-randomized open-label study by Strober et al. evaluated patients who had a suboptimal response to methotrexate, defined as a PGA of "mild" or worse after a minimum of four weeks of therapy.[27] Patients stopped methotrexate for four to 10 days and then transitioned to adalimumab treatment. The following harm outcomes were evaluated: injection site reaction, malignancy, infection, and study withdrawal. No additional harm outcomes were reported for patients who transitioned from methotrexate to adalimumab. Throughout week 26, there were no malignancies reported.[27] Thirteen patients (31.7 percent) had an infectious adverse event, none of which were classified as serious infections. Two patients (4.8 percent) experienced injection site reaction, as reported in the results found on www.clinicaltrials.gov.[35] Two patients (4.9 percent) withdrew from the study.

Alefacept versus cyclosporine

No RCTs or observational studies directly compared the biologic agent alefacept with the nonbiologic agent cyclosporine.

Transitions from cyclosporine to etanercept

There were no RCTs identified for this comparison of interest. One open-label study by Magliocco et al. evaluated patients who were well controlled on cyclosporine therapy with a need or desire to switch to alefacept therapy.[28] Well controlled was defined as a PGA score of "mild", "almost clear" or "clear". This study was rated as having fair quality and data about whether patients were naïve to treatment was not reported. The study consisted of three phases over 48 weeks to determine if psoriasis control could be maintained while transitioning patients from cyclosporine to alefacept. In phase I (12 weeks) patients received alefacept for 12 weeks and were tapered off of cyclosporine in weeks 5 through 12. In phase 2 (12 weeks), patients did not receive alefacept or cyclosporine but were allowed to use topical agents and UVB phototherapy. In phase III (24 weeks), patients were treated with alefacept for 12 weeks followed by 12 weeks of observation, with topical and UVB therapy permitted during the 12 week observation period. Topical therapy was used by 3 patients (37 percent) in phase II and in phase III. UVB therapy was used by one patient (8 percent) in phase III. Twelve patients began this

study and completed phase I, three patients dropped out during phase II, and 2 patients dropped out during phase III. Therefore, six patients completed the 48 week study.

During this study, authors report that there were no cases of serious infection, opportunistic infection, or malignancies, and that no remarkable changes were observed in renal or hepatic function. However, data to represent the direction or magnitude of changes in these laboratory parameters was not reported. CD4+ T cells were monitored during this study. Although neutropenia was not reported in this study, the mean CD4+ count was provided. At baseline, the mean cell count was 856 cells/mm^3 which decreased to 706 cells/mm^3 after phase I. After phase II, the mean cell count increased to 804 cells/mm^3. After the second course of treatment during phase II, the mean CD4+ T cell count was at the lowest value of 464 cells/mm^3 but increased after the observation period in phase III to a mean of 872 cells/mm^3. One patient had two doses of alefacept withheld during phase III due to CD4+ T cell counts lower than 250 cells/mm^3. In both instances CD4+ counts resolved and therapy resumed the following week. Three patients (27.3 percent) dropped out during phase II, and 2 patients dropped out during phase III (18.2 percent), leaving six patients (50 percent) who completed the 48 week study.

Etanercept versus acitretin

Two RCTs compared the biologic agent etanercept with the nonbiologic agent acitretin and reported data regarding harms.[22,23] The trial by Caproni et al. was rated as having fair quality while the trial by Gisondi et al. was rated as having good quality. In the trial by Caproni et al. the percent of treatment naïve patients was not reported and individuals were allowed into the trial as long as treatment with either topical or systemic therapy was greater than one month prior to enrollment. In the trial by Gisondi et al. all patients were naïve to biologic therapy as prior use was an exclusion criterion. Patients were allowed into the trial as long as treatment with either topical, systemic, or phototherapy was greater than four weeks prior to enrollment.

The trial by Gisondi et al. evaluated AST, ALT, and total cholesterol at weeks 6, 12, and 24 and reported that there were no significant alterations in any of these laboratory parameters found at any of the time points evaluated.[23] No other data were reported in the trial, such as the direction or magnitude of any observed changes. There were no study withdrawals in the trial by Caproni et al. although in the trial by Gisondi et al., four subjects (20 percent) withdrew from the acitretin group, while all subject in the etanercept group completed the trial (p=NR).[22,23]

Etanercept versus cyclosporine

No RCTs or observational studies directly compared the biologic agent etanercept to the nonbiologic agent cyclosporine.

Transitions from cyclosporine to etanercept

One observational study by Garavaglia et al. evaluated patients with hepatitis C virus who had been previously treated with cyclosporine and were currently receiving etanercept treatment.[26] This study was rated as having poor quality and data about whether patients were naïve to treatment was not reported. AST and ALT values were the only adverse outcomes reported, at baseline, 3, 6, 12, 18, and 24 months. Authors concluded that in all four patients who had previously been treated with cyclosporine, AST (65 U/L, 36 U/L, 47 U/L, and 38 U/L at baseline versus 35 U/L, 36 U/L, 32 U/L, and 52 U/L at week 52, p=NR) and ALT remained unchanged at week 52 (63 U/L, 49 U/L , 54 U/L, and 44 U/L at baseline versus 29 U/L, 41 U/L, 42 U/L, and 73 U/L at week 52, p=NR). Two of the four patients had measured AST and ALT levels up to 104 weeks. Levels remained unchanged in one patient but increased in the second

patient compared to baseline (38 U/L at baseline versus 73 U/L at week 104 for AST and 44 U/L at baseline versus 75 U/L at week 104, p=NR).

Etanercept versus methotrexate

One observational study by Gisondi et al., rated with fair quality, compared patients treated with etanercept to patients treated with methotrexate.[25] Patients treated with etanercept were naïve to biologic therapy. The harms reported in this study included total cholesterol, weight, and BMI. There was no statistically significant difference in mean total cholesterol comparing baseline to 6 month values in the etanercept (233±15.1 versus 235±17.3, p=0.5) or methotrexate (234±16.8 versus 236±18.1, p=0.4) groups. Patients treated with etanercept gained an average of 1.5±2.7 kg over 6 months which was a significant change from baseline (p=0.0002). Patients treated with methotrexate did not experience a significant change in mean body weight from baseline (-0.6±1.4, p=0.4). The amount of weight loss or gain was also categorized for each treatment group as the number of patient who lost weight, did not vary in weight, gained 1 to 3 kg, or gained 4 to 10 kg. In the etanercept group, six patients (10.3 percent) lost weight, 15 (25.8 percent) did not vary in weight, 24 (41.3 percent) gained 1 to 3 kg, and 13 (22.4 percent) gained 4 to 10 kg. In the methotrexate group, eight patients (18.6 percent) lost weight, 32 (74.4 percent) did not vary in weight, three (6.9 percent) gained 1 to 3 kg, and no patients gained 4 to 10 kg. Statistical comparisons between treatment groups were not made. Lastly, the mean BMI increased significantly in the etanercept group (0.5±0.5, p=0.01) and did not change significantly in the methotrexate group (-0.2±0.5, p=0.06) over 6 months.

Infliximab versus methotrexate

One RCT and one observational study directly compared the biologic agent infliximab with the nonbiologic agent methotrexate.[21,25] One RCT, rated with fair quality, compared the biologic agent infliximab with the nonbiologic agent methotrexate.[21] Patients enrolled in this trial were naïve to methotrexate therapy and were allowed in the trial if treatment with biologics was greater than three months prior. Therapy with topical agents or systemic therapies that could affect PASI were discontinued two and four weeks, respectively, prior to the start of the study.

All harms outcomes evaluated in the original trial were reported at week 26 including all patients who received at least one dose of study drug and excluding all events that occurred on or after treatment switch at week 16.[21] Data were available on www.clinicaltrials.gov for patients who switched therapy at week 16 and we present results separately for this transition population below.[36]

Hepatic enzymes increased in two patients receiving infliximab (0.31 percent) and one patient receiving methotrexate (0.47 percent, p=NR).[21] TCP was reported in one patient receiving infliximab (0.15 percent) and none receiving methotrexate (p=NR).[21] Hypertension did not occur in either group. Infusion related reactions occurred in 2.6 percent of infliximab treated patients. Under the category of lymphoproliferative disorders or malignancy, one case, specifically basal cell carcinoma, occurred in a patient treated with infliximab (0.2 percent) and no cases were observed in the methotrexate group (P=NR).[21] Serious infections were reported and defined as tuberculosis, opportunistic infections such as *pneumocystis jiroveci* pneumonia, listeriosis, atypical mycobacteria, histoplasmosis, salmonellosis and serious viral infections. Ten cases occurred in the infliximab group (1.5 percent) while 4 cases occurred in the methotrexate group (1.9 percent, p=NR). Study withdrawals were higher in the methotrexate group (40.9 percent) compared with the infliximab group (17.2 percent, p=NR).[21]

Additional infectious outcomes through week 26 were reported in the results posted on www.clinicaltrials.gov.[36] A variety of infections were reported including bacterial arthritis, febrile infection, Lyme disease, streptococcal pharyngitis, pneumonia, pulmonary tuberculosis, staphylococcal infection, and viral infection. Of these infections the following cases occurred in the infliximab group: one case of Lyme disease (0.15 percent), one case of streptococcal pharyngitis (0.15 percent), two cases of pneumonia (0.31 percent), one case of pulmonary tuberculosis (0.15 percent), and one viral infection (0.15 percent). The following cases occurred in the methotrexate group: one case of febrile infection (0.47 percent). Hepatic enzyme elevation (not further defined) was also reported in the results on www.clinicaltrials.gov. Two patients in the infliximab group (0.31 percent) and one patient in the methotrexate group (0.47 percent) had hepatic enzyme elevation (p=NR).[36]

One observational study by Gisondi et al., rated with fair quality, compared patients treated with the biologic agent infliximab to patients treated with the nonbiologic agent methotrexate.[25] Patients treated with infliximab were naïve to biologic therapy. The harms reported in this study included total cholesterol, weight, and BMI. There was no statistically significant difference in mean total cholesterol levels comparing baseline with 6 month values in the infliximab (235.5±14.2 versus 237±16.9, p=0.6) or methotrexate (234±16.8 versus 236±18.1, p=0.4) groups. Patients treated with infliximab gained an average of 2.5±3.3 kg over 6 months which was a significant change from baseline (p=0.0004). Patients treated with methotrexate did not experience a significant change in mean body weight from baseline (-0.6±1.4, p=0.4). The amount of weight loss or gain was also categorized for each treatment group as the number of patient who lost weight, did not vary in weight, gained 1 to 3 kg, or gained 4 to 10 kg. In the infliximab group, three patients (7.5 percent) lost weight, seven (17.5 percent) did not vary in weight, 19 (47.5 percent) gained 1 to 3 kg, and 11 (27.5 percent) gained 4 to 10 kg. In the methotrexate group, eight patients (18.6 percent) lost weight, 32 (74.4 percent) did not vary in weight, three (6.9 percent) gained 1 to 3 kg, and no patients gained 4 to 10 kg. Statistical comparisons between treatment groups were not made. Lastly, the mean BMI increased significantly in the infliximab group (0.8±1, p=0.003) but did not change significantly in the methotrexate group (-0.2±0.5, p=0.06) over 6 months.

Transitions between infliximab and methotrexate

The trial by Barker allowed patients to switch therapy at 16 weeks, as previously described. Adverse events for this population were reported in the results posted on www.clinicaltrials.gov for the period of time after the therapy switch (weeks 16 to 26).[36] No patients experienced hepatic enzyme elevation or TCP after the switch.[36] One patient was reported to have hypertension in the methotrexate group (1.59 percent) while no cases occurred in the infliximab group (p=NR).[36] Five patients (8 percent) experienced infusion-related reactions in the infliximab group. A variety of infections were reported including bacterial arthritis, febrile infection, Lyme disease, streptococcal pharyngitis, pneumonia, pulmonary tuberculosis, staphylococcal infection, and viral infection. Of all of these infections, one case of bacterial arthritis (1.59 percent) and one case of staphylococcal infection (1 percent) occurred in the methotrexate group while no events occurred in the infliximab group (p=NR).[36]

Class level comparisons

Two observational studies reported data comparing biologic agents and nonbiologic agents at the class level.[25,30] One study directly compared classes[25] while the other study observed transitions of therapy from nonbiolgics to biologics.[30]

The first study by Gisondi et al., rated with fair quality, compared treatment with biologic agents (etanercept or infliximab) with the nonbiologic agent methotrexate.[25] Patients treated with biologics were naïve to biologic therapy. Authors concluded that in patients exposed to infliximab or etanercept, the risk of weight gain of greater than 5 kg was 4.3 times higher compared with patients exposed to methotrexate, with differences in body weight variations reaching statistical significance.

Transitions between biologics and nonbiologics

The study by Costanzo et al., rated with fair quality, was an open-label compassionate use study in which patients who failed or had adverse events to at least one nonbiologic systemic agent (systemic corticosteroids, cyclosporine, methotrexate, and/or retinoids) in the past were treated with etanercept.[30] The majority of patients had also been previously treated with topical steroids (75 percent, 33 out of 44 patients) The interim results of this study were reported where all patients (44 patients) had data at week 12 and 15 patients (34.1 percent) had data at week 24. No final health outcomes were evaluated. One patient (2.3 percent) developed TCP at week 8 of therapy. There were no cases of tuberculosis, opportunistic infections, or clinically significant viral infections during the study (24 weeks). Two patients (4.5 percent) experienced injection site reactions at week 2. Four patients (9 percent) withdrew from the study and all were related to adverse effects.

Biologic Systemic Agents versus Phototherapy

Adalimumab versus NB-UVB phototherapy

No RCTs or observational studies directly compared the biologic agent adalimumab with NB-UVB phototherapy.

Transitions between adalimumab and NB-UVB phototherapy

One non-randomized open-label study by Strober et al. evaluated patients who had a suboptimal response to NB-UVB phototherapy, defined as a PGA score of “moderate” or worse after at least 2 months of therapy. After stopping NB-UVB therapy for 4 to 10 days, patients were transitioned to adalimumab treatment.[27] The following harm outcomes were evaluated: injection site reaction, malignancy, infection, and study withdrawal. No additional harm outcomes were reported for patients who transitioned from NB-UVB phototherapy to adalimumab. Throughout week 26, there were no cases of injection site reactions or malignancies reported. Seven patients (24.1 percent) had an infectious adverse event and one patient (3.4 percent) experienced infection which was defined as serious. Five patients (17.2 percent) withdrew from the study.

Key Question 3

In patients with chronic plaque psoriasis treated with systemic biologic therapy, systemic nonbiologic therapy, or phototherapy, which patient or disease characteristics (e.g., age, gender, race, weight, smoking status, psoriasis severity, presence or absence of concomitant psoriatic arthritis, disease duration, baseline disease severity, affected BSA, disease location, number and type of previous treatments, failure of previous treatments and presence of neutralizing antibodies) affect intermediate and final outcomes?

Key Points

- One post-hoc subgroup analysis of the CHAMPION RCT met inclusion criteria for Key Question 3. Two additional observational studies were identified although neither controlled for confounding and therefore were reported and discussed for descriptive purposes only.
- Data from the post-hoc subgroup analysis of CHAMPION, a trial that compared treatment with the biologic agent adalimumab with the nonbiologic agent methotrexate, suggested that as disease severity improves (measured with PASI), so did a patient's HRQoL (measured with the DLQI).
- Two observational studies evaluated the impact of weight on PGA, the impact of a history of PsA on plaque psoriasis or PsA pain, and the impact of prior exposure to a biologic agent on PASI. Conclusions cannot be made from this literature base as neither study controlled for confounding factors.

Detailed Analysis

Outcome Evaluation

This key question is organized by the patient/disease characteristic and health outcome that is being described. One post-hoc subgroup analysis of the CHAMPION RCT met inclusion criteria for Key Question 3.[32] Two additional observational studies were identified although neither controls for confounding and therefore are report and discussed for descriptive purposes only.[27,28]

Psoriasis disease severity and HRQoL

The CHAMPION RCT by Saurat et al, compared the biologic agent adalimumab with the nonbiologic agent methotrexate.[17] A post-hoc analysis of the CHAMPION population evaluated the relationship between psoriasis severity, measured with the PASI score, and the final health outcome HRQoL measured with the DLQI (Table 4).[32] The mean DLQI change from baseline to week 16 was reported for four groups stratified by percent PASI improvement from baseline: PASI ≥75, PASI50 to 75, PASI25 to 50, and PASI< 25. Patients with greater PASI response had greater improvements in DLQI over the 16 week followup. The mean DLQI change from baseline to week 16 was significantly greater in PASI ≥75 group (-9.5±5.8) compared with PASI 50 to 75 (-5.8±4.5, $p<0.01$), PASI 25 to 50 (-4.2±4.6, $p<0.001$), and PASI <25 (-0.7±4.7, $p<0.001$) (Table 4). The other statistically significant difference in DLQI was in patients who had a PASI50 to 75 compared with PASI<25 ($p<0.001$). All other comparisons were not statistically significant, although exact p-values were not reported.

Table 4. Relationship between disease severity and dermatology life quality index

Study	Characteristics	N	Followup	DLQI mean(SD)	P-values		
					versus PASI50 to 75	versus PASI25 to 50	versus PASI <25
Saurat, 2008	PASI ≥75*	131	16w	-9.5(5.8)	<0.01	<0.001	<0.001
	PASI 50 to 75*	44	16w	-5.8(4.5)	---	NS	<0.001
	PASI 25 to 50*	25	16w	-4.2(4.6)	NS	---	NS
	PASI <25*	49	16w	-0.7(4.7)	<0.001	NS	---

DLQI=dermatology life quality index; N=number of patients; NS=not significant; PASI=Psoriasis Area Severity Index ; SD=standard deviation; w=weeks; ---=not applicable
*Based on percentage improvement from baseline

Weight and PGA

One non-randomized open-label study by Strober et al. evaluated patients who had a suboptimal response to methotrexate or NB-UVB and were transitioned to adalimumab. Suboptimal response to methotrexate was defined as a PGA of "mild" or worse after at least four months of methotrexate therapy. Suboptimal response to NB-UVB was defined as a PGA of "moderate" or worse after at least two months of NB-UVB therapy.[27] The relationship between patient's weight and the intermediate outcome PGA was reported in this study based on a subgroup analysis, although methods to control for confounding were not used and therefore conclusions based on this data cannot be made.

Patients were stratified into two subgroups: patients weighting 100 kg or less and patients weighting more than 100 kg. For patients who transitioned from methotrexate to adalimumab, 67 percent (20 out of 30) of patients weighting 100 kg or less achieved a PGA of "clear" or "minimal at week 16 compared to 45 percent (5 out of 11) of patients weighing more than 100 kg (p=NR). For patients who transitioned from NB-UVB to adalimumab, 45 percent (10 out of 22) of patients weighting 100 kg or less achieved a PGA of "clear" or "minimal at week 16 compared to 57 percent (4 out of 7) of patients weighing more than 100 kg (p=NR) (Table 5).

Table 5. Relationship between patient's weight and physician's global assessment

Study	Population	Characteristics	Followup	PGA* n/N (%)	P-values
Strober, 2011	MTX transitioned to adalimumab	weight ≤100kg	16w	20/30 (66.7)	---
		weight >100kg	16w	5/11 (45.5)	---
	NB-UVB transitioned to adalimumab	weight ≤100kg	16w	10/22 (45.5)	---
		weight >100kg	16w	4/7 (57.1)	---

Table Note: kg=kilograms; MTX=methotrexate; NB-UVB=narrow-band ultraviolet B; n/N=number of patients per total population; PGA=physician's global assessment; w=weeks; ---=not reported
*Number of patients achieving a PGA score of "clear" or "minimal"

History of PsA and pain

The open label study by Strober et al.[27] also evaluated the relationship between the presence of concomitant PsA and the intermediate outcome VAS for plaque psoriasis and PsA pain. However, methods to control for confounding were not used and therefore conclusions based on this data cannot be made. Patients were stratified into two groups: patients with a history of PsA and patients without a history of PsA. For patients who transitioned from methotrexate to adalimumab, the improvement in VAS for plaque psoriasis and PsA pain was greater in patients with a history of PsA compared to patients without a history of PsA (-19.2 versus -11.6; p=NR) (Table 6). For patients who transitioned from NB-UVB to adalimumab, the improvement in VAS

for plaque psoriasis and PsA pain was greater in patients with a history of PsA compared to patients without a history of PsA (-47.1 versus -13.2; p=NR).

Table 6. The relationship between history of psoriatic arthritis and pain

Study	Population	Characteristics	Followup	Pain* mean(SD)	P-values
Strober, 2011	MTX transitioned to adalimumab	No history of PsA	16w	-11.6(NR)	---
		History of PsA	16w	-19.2(NR)	---
	NB-UVB transitioned to adalimumab	No history of PsA	16w	-13.2(NR)	---
		History of PsA	16w	-47.1(NR)	---

Table Note: MTX=methotrexate; NB-UVB=narrow-band ultraviolet B; NR=not reported; PsA=psoriatic arthritis; SD=standard deviation; w=weeks; ---=not reported

* Mean (SD) change from baseline in VAS for pain involving psoriatic plaques and/or PsA

Type of previous treatments and PASI

One observational study by Mazzotta et al. evaluated patients currently being treated with etanercept who had previously been treated with nonbiologic systemic agents or phototherapy (cyclosporine, corticosteroids, fumaric acid esters, methotrexate, retinoids, and PUVA).[29] Patients were included if they failed nonbiologic therapy (according to PASI and pain scores), had an adverse event to nonbiologic therapy, or were noncompliant with nonbiologic treatment. The percentage of patients in each of these categories was not reported by the study. Most patients (98 of 124, 79 percent) were naïve to systemic biologics.

This study evaluated the relationship between being naïve to systemic biologic therapy and the intermediate outcome PASI (Table 7) in a univariate analysis. No methods were used to control for confounding therefore conclusions cannot be made based on these data. In both subgroups, there was a statistically significant improvement in the mean PASI score from baseline to week 12 and week 24 ($p<0.0001$ for all comparisons). However, the difference between week 12 and 24 was only statistically significant in the subgroup of patients who were naïve to biologics ($p<0.0001$). There were no statistically significant differences in mean PASI scores at baseline, week 12, and week 24 when patients naïve to biologic treatment were compared with patients who were not naïve to biologic treatment [(16.1 versus 14.5 at baseline), (4.9 versus 5.4 at week 12), and (2.8 versus 4.0 at week 24); p=NR]. PASI50 and PASI75 were not statistically significant at weeks 12 and 24 when comparing patients naïve to biologic treatment with patients who were not naïve to biologic treatment (p=NR), with the exception of PASI50 at week 24 (p=0.013).

Table 7. The relationship between prior treatment with systemic biologic agent and Psoriasis Area Severity Index

Study	Characteristics	Followup	PASI50 n/N (%)	PASI75 n/N (%)	PASI mean(SD)	P-Values		
						Mean PASI versus baseline	Mean PASI versus week 12	Mean PASI versus week 24
Mazzotta, 2009	Naïve to biologics*	12w	79/98 (80.2)	43/98 (43.7)	4.9(4.0)	<0.0001	---	<0.0001
	Prior exposure to biologics*	12w	18/26 (69.2)	8/26 (30.8)	5.4(3.8)	<0.0001	---	0.4113
	Naïve to biologics*	24w	88/98† (89.9)	74/98 (75.3)	2.8(3.4)	<0.0001	<0.0001	---
	Prior exposure to biologics*	24w	18/26† (69.6)	17/26 (65.2)	4.0(4.5)	<0.0001	0.4113	---

Table Note: n/N=number of patients per total population; PASI=Psoriasis Area Severity Index; SD=standard deviation; w=week
* Infliximab, efalizumab
† p-value=0.013 for prior exposure to biologics versus naïve to biologics at week 24

Discussion

Patients and healthcare providers encounter several important considerations when evaluating therapeutic options in the treatment of chronic plaque psoriasis. Despite being studied in comparison to placebo, biologic systemic agents have infrequently been compared directly with non-biologic systemic therapies or phototherapy. Our literature review yielded only four RCTs and one observational study directly comparing systemic biologics versus systemic nonbiologics and no RCTs and one observational study directly comparing systemic biologics and phototherapy. Overall, the quality of the studies was either good or fair. However, most often only one trial or observational study was available for a given comparison and outcome, and the majority of comparative studies were observational in nature and did not account for confounding. Together, these factors precluded the ability to statistically pool data. Therefore, a qualitative synthesis of the data was presented. A summary of the results with low, moderate, or high strength of evidence can be found in Table 8. Given the current literature base, there is insufficient evidence to determine the comparative effectiveness of systemic biologic agents compared with either systemic nonbiolgic agents or phototherapy in patients with chronic plaque psoriasis.

Table 8. Summary of findings for the comparison of systemic biologic agents versus systemic nonbiologic agents

Comparison	Outcome*	Type and Number of Studies	Conclusion	SOE
Adalimumab versus methotrexate	HRQoL	1 RCT	Adalimumab improves a patient's HRQoL compared with methotrexate	L
	PASI	1 RCT	Adalimumab improves a patient's PASI score compared with methotrexate	L
	PGA	1 RCT	Adalimumab increases the number of patients achieving a PGA score of "clear" or "minimal" compared with methotrexate	L
	Patient's assessment of disease severity	1 RCT	Adalimumab improves a patient's assessment of disease severity compared with methotrexate	L
	Pain	1 RCT	Adalimumab reduces a patient's pain compared with methotrexate	L
	Pruritus	1 RCT	Adalimumab reduces a patient's pruritus compared with methotrexate.	L
	Infection	1 RCT	Infection rates do not differ between adalimumab and methotrexate	L
Etanercept versus acitretin	PASI	2 RCT	Etanercept improves a patient's PASI score compared with acitretin	M
Infliximab versus methotrexate	HRQoL	1 RCT	Infliximab improves a patient's HRQoL compared with methotrexate	L
	PASI	1 RCT 1 OBS	Infliximab improves a patient's PASI score compared with methotrexate	L
	PGA	1 RCT	Infliximab increases the number of patients achieving a PGA score of "clear" or "minimal" compared with methotrexate	L

Abbreviations: HRQoL=health related quality of life; L=low; M=moderate; OBS=observational study; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial; SOE=strength of evidence

* Outcomes with an insufficient strength of evidence are not listed in this table

In the evaluation of systemic biologics versus systemic nonbiologics or phototherapy for final and intermediate health outcomes (Key question 1), the use of the biologics adalimumab, etanercept, and infliximab resulted in favorable outcomes when compared to individual nonbiologic agents (Table 8). However, we could not determine the comparative effectiveness of these therapies with regard to final health outcomes other than HRQoL, due to lack of evaluation in the included literature. We could not determine the comparative efficacy between other available biologics such as ustekinumab and alefacept and systemic nonbiologic agents or between systemic biologic agents and phototherapy on any of the final or intermediate outcomes. This was due to either a lack of existing literature or a lack of direct statistical comparison between those agents.

The comparison of adalimumab with methotrexate, although based on a single RCT, had the most outcomes evaluated, although most were intermediate outcomes and all were based on low strength of evidence (Table 8).[17] HRQoL was measured using both the DLQI and EQ-5D scales, with both showing favorable improvement in patients treated with adalimumab at 16 weeks. Changes seen in both treatment arms, however, can be consider clinically meaningful based on established minimally important differences of 2.3 to 5.7 for the DLQI, 0.09 to 0.22 for the EQ-5D index score, and 3.82 to 8.43 for the EQ-5D VAS.[37] It is not surprising that HRQoL improved in those treated with adalimumab, as PASI scores were also significantly improved compared with methotrexate at 16 weeks, including complete remission. Time to PASI75 was also significantly shorter in adalimumab treated patients (28 versus 84 days). Other intermediate outcomes including PGA, patient assessment of disease severity, and individual symptoms of pain and pruritus were also improved in patients treated with adalimumab.

Compared to acitretin, two RCTs showed that etanercept improved a patient's PASI score with moderate strength of evidence.[22,23] Both PASI50 and PASI75 were evaluated and showed favorable improvement in patients treated with etanercept at 24 weeks.

Compared to methotrexate, one RCT showed that infliximab improved a patient's HRQoL, based on low strength of evidence. Three scales were used to measure HRQoL in this trial, DLQI, EQ-5D, and SF-36 MCS and PCS and all showed favorable improvements in the infliximab treated patients at 16 weeks. Changes seen in both treatment arms, however, can be consider clinically meaningful based on established minimally important differences as previously reported, with addition of the SF-36 in which a change of 2.5 to 3.9 in the PCS and 4 to 6 in the MCS can be considered clinically important.[37] Other intermediate outcomes including PASI and PGA were also improved in patients treated with infliximab, each based on low strength evidence.

We evaluated systemic biologics versus systemic nonbiologics or phototherapy for safety or tolerability outcomes (Key question 2). All three classes of therapy are associated with known harms which are clearly defined within clinical practice guidelines.[4,11,38] Some harms, such as changes in weight or the lipid profile may surface in the shorter term while others such as malignancy and infection would require much longer followup to accurately capture the risk. Furthermore, some toxicity can be cumulative, such as hepatic toxicity associated with methotrexate or nephrotoxicity associated with cyclosporine and would also require long term followup to accurately describe. Unfortunately, the longest followup period amongst included studies in which harms were reported was six months, although this was a rare exception. Most studies concluded at 12 to 16 weeks, which is unlikely to be of sufficient length for all important harms evaluated.

Based on the current literature base directly comparing biologics to nonbiologics or phototherapy, we were unable to determine comparative safety of these therapies due to paucity of data and in most cases a complete lack of direct comparative data. Although one observational study reported weight changes in patients taking methotrexate, etanercept, or infliximab, between drug comparisons were not made therefore we were unable to determine if the differences within arms were significantly different across drug therapies. Of all outcomes evaluated, there was a low strength of evidence that the rate of infection was not significantly different between the biologic agent adalimumab and the nonbiolgic agent methotrexate (Table 8). In this one RCT, authors stated that none of the infections were classified as serious, although further details were not specified.[17]

Key question 3 aimed to evaluate patient and disease characteristics which modify outcomes when comparing systemic biologics, nonbiologics, and phototherapy. Important factors in selecting appropriate therapy include baseline patient characteristics as these will directly influence the safety and efficacy of chosen agents. Another key decisional uncertainty is the disease characteristics that are associated with either improved or worsen outcomes. However, there was a paucity of literature that provided insight on the relationship between patient and disease characteristics with final or intermediate health outcomes in patients treated with biologics compared with nonbiologics or phototherapy. Only one subgroup analysis from a RCT met our inclusion criteria. Two observational studies evaluated relationships between patient characteristic and outcomes although neither controlled for confounding and therefore cannot be used to draw conclusions.

Based on a post-hoc analysis of the CHAMPION trial, data suggests that as disease severity improves a patient's HRQoL improves. The mean change in DLQI at 16 weeks was greatest for patients who achieved at least a PASI improvement of 75 percent (-9.5±5.8) while the mean change in DLQI was lowest for patients who achieved a PASI score improvement of less than 25 percent (-0.7±4.7). In a RCT that compared the efficacy and safety of adalimumab versus placebo in patients with moderate to severe plaque psoriasis, investigators sought to correlate various measures of HRQoL to clinical outcomes.[37] DLQI was moderately correlated with PASI ($r=0.69$, $p<0.001$).[37] Data from this RCT also suggests that the minimal clinically important difference for the DLQI ranges from a change of 2.3 to 5.7.[37] Based on this data, the changes in DLQI in patients achieving a PASI score improvement of greater than 25 percent (-4.2 to -9.5) from the CHAMPION subgroup analysis can be considered clinically important improvements.

There were no previously conducted traditional meta-analyses identified by our literature search that addressed similar comparisons and research questions as this report. One mixed-treatment comparison that evaluated PASI50, PASI75, and PASI90 suggested that the probability of achieving any of the three PASI scores was highest for infliximab, followed by adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care.

Applicability

Our literature base is most applicable to patients with more advanced chronic plaque psoriasis and is not applicable to milder forms. Five of the six studies that directly compared biologics and nonbiologics required patients to have moderate to severe plaque psoriasis for enrollment, and in these trials the baseline mean PASI score ranged from 10.4 to 29.2. In the remaining study, although moderate to severe plaque psoriasis was not an explicit inclusion criteria, the mean PASI score at baseline was consist with the other studies and ranged from 8.2

to 18.8. None of these six studies were conducted in the United States and therefore may not reflect clinical practice. The majority of patients evaluated in these studies were not naïve to psoriasis treatment (71 percent) as only three studies clearly specified enrolled patients were naïve to psoriasis therapy. All interventions evaluated in these studies are currently approved by the FDA and were studies at does approved for chronic plaque psoriasis, therefore are relevant to treatment practice in the United States. Only two studies evaluated final health outcomes and were generally not sufficient in length to adequately evaluate such outcomes, with exception of HRQoL. The followup in both trials was approximately 26 weeks. Alternatively, for intermediate outcomes, all but one study were of sufficient length to evaluate such outcomes. Last, we did not consider studies long enough to accurately capture outcomes such as infection or malignancy. Otherwise, studies provide short term data about outcomes and in some cases this may not be sufficient to understand comparative safety, as is the case with methotrexate or cyclosporine where toxicities are cumulative.

One observational study directly compared biologics and phototherapy and moderate to severe plaque psoriasis was not an explicit inclusion criteria. However, the mean PASI score at baseline was consist with the other studies and ranged from 15.0 to 16.9. Therefore the literature reflects patients with more advanced chronic plaque psoriasis and is not applicable to mild forms. The study was conducted outside of the United States and therefore may not reflect clinical practice and the patients were not treatment naïve. The evaluated interventions are available for use in the United States but because phototherapy regimens are specifically tailored to patient characteristics we cannot comment whether regimens used in the study were sufficient or not. Final health outcomes and adverse events were not evaluated and the only intermediate outcome evaluated was PASI.

Research Gaps and Future Research Needs

In the treatment of chronic plaque psoriasis with biologic systemic agents, nonbiologic systemic agents and phototherapy, there are several avenues for future research. Current literature directly comparing biologic systemic agents versus nonbiologic systemic agents or phototherapy is limited. In total, only four RCTs comparing a biologic to a nonbiologic are included in this report, any no RCTs comparing a biologic to phototherapy were identified. Therefore, the most important area of future research is additional RCTs or large observational studies that directly compare individual drugs/interventions from the three treatment modalities including systemic biologic, systemic nonbiolgic, or phototherapy. If a greater number of trials are conducted, meta-analytic techniques can be used to assess direct comparisons. Presently, the literature base is too scarce to conduct such an analysis.

Future trials evaluating biologic versus nonbiologic systemic agents or phototherapy should be adequately powered to assess final health outcomes that are important to decision makers, such as mortality, MACE, and psychological outcomes. This would likely require longer duration trials and larger sample sizes compared to the current literature base. The longest trial included in this report was 26 weeks allowing for only short term outcome assessment. A similar opportunity arises with harms, as even in the current literature base harms were rarely evaluated and if they were reported the frequency was rare and often trials were not of sufficient duration to adequately capture such risks.

Future research should be designed to determine if there are specific disease or patient factors that modify intermediate, final and adverse health outcomes when comparing biologics, nonbiologics, and phototherapy. Current research is too scarce to adequately assess the impact of

patient or disease factors on these outcomes. Future studies should include a population more generalizable to the US. The majority of included studies (10 of 11 studies) were conducted in other countries, where clinical practice may not reflect practice within the US.

Acronyms/Abbreviations

ALT = aspartate aminotransferase
AST= alanine aminotransferase
BMI=body mass index
BSA = body surface area
CI = confidence interval
DLQI = dermatology life quality index
EQ-5D = EuroQol^{TM}-5 Dimension
Kg = kilogram
Kg/m^2=kilogram per meter squared
HRQoL = health-related quality of life
MACE = major adverse cardiovascular events
NB-UVB = narrowband-ultraviolet B
NR = not reported
RCT = randomized controlled trial
PASI = Psoriasis Area and Severity Index
PGA = Physician's Global Assessment
PsA = psoriatic arthritis
PUVA = psoralen plus ultraviolet A
SCr = serum creatinine
SF-36 = Short Form-36 Health Survey
TCP = thrombocytopenia
TNF = tumor necrosis factor
ULN = upper limit of normal
VAS = visual analogue scale
8-MOP = 8-methoxypsoralen

References

1. Neimann AL, Porter SB, Gelfand JM. The epidemiology of psoriasis. Expert Rev Dermatol 2006;1:63-75.

2. Christophers E. Psoriasis – epidemiology and clinical spectrum. Clin Exp Dermatol 2001;26:314-20. PMID:11422182

3. National Psoriasis Foundation Website. About psoriasis: statistics. Available at: http://www.psoriasis.org/learn_statistics. Accessed Feb. 2, 2010. (Last accessed on April 16, 2012).

4. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826-850. PMID: 19119095

5. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol 2009;161:987-1019. PMID: 19857207

6. Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest 2004;113:1664-75. PMID: 15199399

7. Committee for Medicinal Products for Human Use (CHMP). Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. London: European Medicines Agency; Nov 2004. CHMP Publication No. CHMP/EWP/2454/02.

8. Panayi GS. Immunology of psoriasis and psoriatic arthritis. Baillieres Clin Rheumatol 1994;8:419-27. PMID: 8076395

9. Chang JC, Smith LR, Froning KJ, et al. Persistence of T-cell clones in psoriatic lesions. Arch Dermatol 1997;133:703-8. PMID: 9197823

10. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-90. PMID: 10972371

11. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009;61:451-85. PMID: 19493586

12. Van Voorhees A, Feldman SR, Koo JYM, Lebwohl MG, Menter A, for the National Psoriasis Foundation. The psoriasis and psoriatic arthritis pocket guide: treatment algorithms and management options. Available at: http://www.psoriasis.org/NetCommunity/Document.Doc?id=354. Accessed May 27, 2011. (Last accessed April 16, 2012).

13. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol 2010;62:114-35. PMID: 19811850

14. Beyer V, Wolverton SE. Recent trends in systemic psoriasis treatment costs. Arch Dermatol 2010;146:46-54. PMID: 20083692

15. Griffiths CE, Strober BE, van de Kerkhof P, et al, for the ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28. PMID: 20071701.

16. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003;349:658-65. PMID: 12917302

17. Saurat JH, Stingl G, Dubertret L, et al, for the CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with

psoriasis (CHAMPION). Br J Dermatol 2008;158:558-66. PMID: 18047523

18. Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 2008;158:351-9. PMID: 18627372

19. Assessing the risk of bias of individual studies when comparing medical interventions. Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectives Reviews. Draft Publication. Available at: Available at http://effectivehealthcare.ahrq.gov/

20. Owens D, Lohr K, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions: AHRQ and the effective health care program. J Clin Epidemiol 2010;63:513-23. PMID: 19595577

21. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011;165:1109-17. PMID: 21910713

22. Caproni M, Antiga E, Melani L, et al. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. J Clin Immunol 2009;29:210-214. PMID: 18763027

23. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol 2008;158:1345-1349. PMID: 18410408

24. Inzinger M, Heschl B, Weger W, et al. Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: retrospective data analysis of a patient registry**.** J Invest Dermatol 2011;165:640-5. PMID: 21564068

25. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. J Eur Acad Dermatol Venereol 2008;22:341-344. PMID: 18005022

26. Garavaglia MC, Altomare G. Etanercept therapy in patients with psoriasis and concomitant HCV infection. Int J Immunopathol Pharmacol 2010;23:965-969. PMID: 20943071

27. Strober BE, Poulin Y, Kerdel FA, et al. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. J Am Acad Dermatol 2011;64:671-681. PMID: 21414495

28. Magliocco MA, Lozano AM, Van Saders C, Schuler KW, Gottlieb AB. An open-label study to evaluate the transition of patients with chronic plaque psoriasis from cyclosporine to alefacept. J Drugs Dermatol 2007;6:424-427. PMID: 17668540

29. Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol 2009;10:319-324. PMID: 19658444

30. Costanzo A, Mazzotta A, Papoutsaki M, Nistico S, Chimenti S. Safety and efficacy study on etanercept in patients with plaque psoriasis. Br J Dermatol 2005;152:187-189. PMID: 15656833

31. Bansback N, Sizto S, Sun H, et al. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology 2009;219:209-18. PMID: 19657180

32. Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque

psoriasis. Br J Dermatol 2008;158:549-557. PMID: 18047521

33. Saurat JH, Langley R, Sting G, Mcllrait M. Adalimumab treatment is associated with more rapid improvement in psoriasis versus methotrexate and versus placebo: results from the CHAMPION study. Br J Dermatol 2007;157:S1-S9.

34. Mrowietz U, Gu Y, Okun, M, Luger T. Methotrexate-treated psoriasis patients transitioning to adalimumab: Efficacy and safety outcomes. J Am Acad Dermatol 2008 Feb;AB120, P2609.

35. Open Label Study of Adalimumab in Subjects Who Have a Sub-optimal Response to Systemic Therapy or Phototherapy. Available at: http://clinicaltrials.gov/ct2/show/NCT00566722. Accessed Apr. 16, 2012.

36. The Effects of Infliximab Versus Methotrexate in the Treatment of Moderate to Severe Psoriasis. Available at: http://clinicaltrials.gov/ct2/show/NCT00251641. Accessed Apr. 16, 2012.

37. Shikiar R, Willian MK, Okun MM, Thompson CS, Revicki DA. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. Health Qual Life Outcomes 2006;4:71. PMID: 17005043

38. Kalb RE, Strober B, Weinstein g, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009 ;60:824-37. PMID: 19389524