Effective Health Care Program

Comparative Effectiveness Review
Number 85

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

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

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

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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 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 are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email 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 email to epc@ahrq.hhs.gov.

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

Structured Abstract

Objectives. To examine the comparative effectiveness of biologic systemic agents versus nonbiologic systemic agents or phototherapy, on an individual drug level, 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 June 2012, 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 with either an approved nonbiologic systemic agent 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 described.

Results. Five RCTs and four 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: L], Psoriasis Area and Severity Index (PASI) [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 [SOE: M] and compared with methotrexate, infliximab improved HRQoL [SOE: L], PASI [SOE: L], and PGA [SOE: L]. Compared with methotrexate, ustekinumab improved PGA [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 with treatment with 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 with either systemic nonbiolgic agents or with phototherapy on an individual drug level. Overall there is insufficient evidence to determine the comparative effectiveness of individual therapies, as compared with each other between the specified classes, with few exceptions. For the comparisons of adalimumab versus methotrexate, infliximab versus methotrexate, ustekinumab 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.

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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 clearance 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 factor (TNF)-alpha and interleukin (IL)-23].[4,5] Currently, three biologic TNF-alpha inhibitors (infliximab, etanercept, and adalimumab), and one anti-IL 12/23 agent (ustekinumab) have approval from the 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 adverse events (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 one or more of 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]

Direct comparative trials, either within or between biologic and nonbiologic classes, directly compare effectiveness.[11-13] Recently, a trial comparing 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 (RCDs) published before January 2008 that enrolled more 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 with 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 with nonbiologic systemic treatment options or phototherapy for chronic plaque psoriasis has been completed. Throughout the report we refer to three "classes" of therapy: biologics, nonbiologics, and phototherapy, which is consistent with national practice guidelines. We realize the possible heterogeneity within each class, namely the biologics, and therefore do not make between-class comparisons, rather limit comparisons with the individual drug level. Comparisons of drugs within each class was beyond the scope of this report. Please see the glossary for a listing of drugs considered within each class.

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 Figure 1 of the full report. The Key Questions[a] 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 on an individual drug level) or phototherapy when evaluating intermediate (plaque BSA measurement, PASI , 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 on an individual drug level) 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

[a] Key Question abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; 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; PGA = Physician's Global Assessment; SCr = serum creatinine; TCP = thrombocytopenia

(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 consulting 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. Another physician provided the general practitioner's perspective. Last, 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 underwent peer review and public commentary, and revisions were 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 in the full report 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 gray 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 an 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 Agency for Healthcare Quality and Research (AHRQ) Effective Health Care Program contacted the manufacturers of identified interventions and comparators for scientific information packets. The same inclusion/exclusion criteria that were applied to the database searches were applied to the packets, 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 described in Appendix A was used to search in MEDLINE®, The Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database.

Both literature searches were updated in June 2012, concurrent with the peer review process. The same inclusion and exclusion criteria were applied, and relevant literature was 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 with 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 that compared the outcome of patients taking one of the therapies of interest who were then switched to a different therapy of interest, with data available comparing patient status before and after the switch. Other observational study designs were excluded. Studies published before 1975 were excluded because 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 comparisons of results with this CER. Meta-analyses that used 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 patient 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 an indication approved by the FDA at the time of writing this report 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 with 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. Gray 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 described the association between the prespecified subgroups and outcomes—either through subgroup analysis in RCTs 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 by using recommendations from AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[15] Using a standardized tool, two reviewers independently assessed the quality of each included study and resolved disagreements through discussion. Randomized controlled trials were evaluated separately from observational studies, and each study received a quality rating of good, fair, or poor. We assessed each RCT 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 because 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 reported native measures of effect that were extracted from the included studies. Identified network meta-analyses from the second literature search were qualitatively described in respective Key Questions, although they were not included in the evaluation of strength of evidence. Last, comparisons made within this report are limited to between-class comparisons on an individual drug level, given possible heterogeneity within each class considered (see the Glossary in Appendix I in the full report for drugs within each class). Within-class comparisons were beyond the scope of this report.

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 that either was unavailable or did not permit estimation of an effect. Previously conducted meta-analyses or indirect comparisons were not included in the grading of strength of evidence.

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 were 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

Results of Literature Search

There were 472 citations identified through the database searches and four citations identified manually in our first search. 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. Upon updating the literature search in June 2012, we retrieved a total of 89 citations. After the removal of duplicates, 508 articles remained. During title and abstract review, 328 citations were excluded. Of the 180 citations remaining, 147 were excluded at the full-text level. A total of 33 citations, representing 14 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 in the full report, along with the reasons for exclusion.

The second literature search identified 19 citations that were screened at the abstract level. Upon updating the literature search in June 2012, we retrieved five additional citations. A total of 15 citations were excluded at the abstract level, and 7 citations were excluded at the full text level. One unique analysis, which was represented by two citations, was finally included.

Five RCTs (n=1,227)[13,16-19] and four observational studies (n=1,066)[20-23] directly compared either a systemic biologic agent with a systemic nonbiologic agent or phototherapy and reported at least one outcome of interest. Of the five RCTs, one was poor,[19] two were fair[16,17] and two were good quality.[13,18] Of the four observational studies, three were fair[20,21,23] and one was poor quality.[22] 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 quality[24] while the others were fair quality.[25,26] 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 quality.[27,28] Finally, we identified one network meta-analysis that used methods for indirect comparison across various therapies included in this review.[29] All included studies were available as full-text publications except for

one whose results were only available through www.clinicaltrials.gov.[19] In the full report, the baseline characteristics of included studies can be found in Appendix D, and the individual study quality assessments can be found in Appendix E.

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

Table A. 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[30] 1 OBS[23]	Adalimumab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[13] 1 OBS[23]	Adalimumab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[113] 1 OBS[23]	Adalimumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
	Patient's assessment of disease severity	1 RCT[30]	Adalimumab improves a patient's assessment of disease severity compared with methotrexate.	L
	Pain	1 RCT[30]	Adalimumab reduces a patient's pain compared with methotrexate.	L
	Pruritus	1 RCT[30]	Adalimumab reduces a patient's pruritus compared with methotrexate.	L
	Infection	1 RCT[13]	Infection rates do not differ between adalimumab and methotrexate.	L
Etanercept versus acitretin	PASI	3 RCT[17-19]	Etanercept improves a patient's PASI compared with acitretin.	M
Infliximab versus methotrexate	HRQoL	1 RCT[16]	Infliximab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[16] 1 OBS[21]	Infliximab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[16]	Infliximab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
Ustekinumab versus methotrexate	PGA	1 OBS[23]	Ustekinumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L

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.

Key Question 1

Five RCTs[13,16-19] (two good, two fair, and one poor quality) and two fair-quality observational studies[21,23] evaluated the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents. The comparisons made included adalimumab, etanercept, infliximab, and ustekinumab 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 one RCT and one observational study (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). Physician's Global Assessment (PGA), Patient Assessment of Disease Severity, pain, and pruritus were each improved in patients treated with adalimumab compared with methotrexate, each based on one RCT and one observational study (low strength of evidence). There was insufficient evidence to grade BSA, and 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 ustekinumab with methotrexate, there was insufficient evidence to grade HRQoL, and no other final health outcomes were reported. Achievement of a PGA of "clear" or "minimal" was increased in patients treated with ustekinumab compared with methotrexate, based on a single observational study (low strength of evidence). There was insufficient evidence to grade BSA and PASI and no other intermediate health outcomes were reported.

When comparing etanercept with acitretin, there was insufficient evidence to grade psychological comorbidities and patient-reported outcomes, and no other final health outcomes were reported. PASI was improved in patients treated with etanercept, compared with acitretin, based on three RCTs (moderate strength of evidence). There was insufficient evidence to evaluate BSA, PGA, joint pain, and itching, and no other intermediate outcomes were reported.

One mixed-treatment comparison that evaluated PASI 50, PASI 75, and PASI 90 suggested that the probability of achieving any of the three PASIs 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. Three observational studies (one fair and two poor quality) reported data on patients treated with adalimumab, etanercept, infliximab and ustekinumab versus narrowband-UVB and etanercept and infliximab versus PUVA. However, there was insufficient evidence to grade HRQoL, BSA, PASI, PGA, psoriatic arthritis (PsA) pain, and pruritus, and no other outcomes were reported.

Key Question 2

The literature base for the comparative safety of systemic biologic agents and systemic nonbiologic agents or phototherapy is sparse. Overall five RCTs[13,16-19] (two good, two fair, and one poor quality) and two observational studies[20,21] (both fair quality) directly compared biologics with nonbiolgics and reported at least one adverse outcome of interest. No trials or observational studies directly compared biologics with phototherapy in the evaluation of harms.

Infection rate did not differ between adalimumab and methotrexate (low strength of evidence). These data were from a single RCT conducted outside 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[13,30] evaluated the relationship between psoriasis severity, measured with the PASI, and the final health outcome HRQoL measured with the DLQI.[30]

Patients with greater PASI responses had greater improvements in DLQI over the 16-week followup. The mean DLQI change, from baseline to week 16, was significantly greater in the PASI ≥75 group (–9.5±5.8) compared with the 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) groups. The other statistically significant difference in DLQI was in patients who had PASI 50 to 75 compared with PASI <25 (p<0.001).

Two observational studies[25,27] 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 health care providers encounter several important considerations when evaluating therapeutic options in the treatment of chronic plaque psoriasis. Despite being studied in comparison with placebo, biologic systemic agents have infrequently been compared directly with nonbiologic systemic therapies or phototherapy. Our literature review yielded only five RCTs and two observational studies directly comparing systemic biologics with systemic nonbiologics and no RCTs and three observational study directly comparing systemic biologics with phototherapy. Overall, the quality of the studies was either good or fair, with a few rated with poor quality. 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 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 are shown in Table A. Although some comparisons have been rated with low or moderate strength of evidence, given the current literature base, there is insufficient evidence to determine the comparative effectiveness of systemic biologic agents, on an individual drug level, in a comparison either with systemic nonbiolgic agents or with 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, infliximab, and ustekinumab resulted in favorable outcomes when compared with individual nonbiologic agents (Table A). However, we could not determine the comparative effectiveness of these therapies with regard to final health outcomes other than HRQoL, because of a lack of evaluation in the included literature. We could not determine the comparative efficacy between other available biologics such as alefacept and systemic nonbiologic agents or between systemic biologic agents and phototherapy on any of the final or intermediate outcomes. This was because of a lack of either existing literature or direct statistical comparison between those agents.

The comparison of adalimumab with methotrexate, although based on one RCT and one observational study, had the most outcomes evaluated, although most were intermediate outcomes and all were based on low strength of evidence.[13,23] 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 considered 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 Visual Analogue Scale (VAS).[31] HRQoL improved in those treated with adalimumab, as PASI were also significantly improved as compared with methotrexate at 16 weeks, including complete clearance. Time to PASI 75 was also significantly shorter in adalimumab treated patients (28 vs. 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 with 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 (mental) and PCS (physical)—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.[31] Other intermediate outcomes, including PASI and PGA, were also improved in patients treated with infliximab, each based on low strength evidence.

Compared with methotrexate, one observational study suggested that a higher proportion of patients treated with ustekinumab had a PGA of "clear" or "minimal," based on an analysis adjusted for confounding.[23]

Compared with acitretin, three RCTs showed that etanercept improved a patient's PASI with moderate strength of evidence.[17-19] Both PASI 50 and PASI 75 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 that are clearly defined within clinical practice guidelines.[4,8,32] 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 among included studies in which harms were reported was 6 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 to be evaluated. Last, although some studies reported changes in safety parameters (such as weight) within each study arm, the arms were never compared; therefore, we could not determine whether the difference in change between the treatment groups was significant.

Based on the current literature base directly comparing biologics with nonbiologics or phototherapy, we were unable to determine comparative safety of these therapies because of a 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 whether 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 observational study, 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 that modify outcomes when comparing systemic biologics, nonbiologics, and phototherapy. Important factors in selecting appropriate therapy included baseline patient characteristics because these will directly influence the safety and efficacy of chosen agents. Another key decisional uncertainty was the disease characteristics associated with either improved or worsened 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 factors and therefore cannot be used to draw conclusions.

Based on a post hoc analysis of the randomized controlled comparative study of adalimumab versus methotrexate versus placebo in patients with psoriasis (CHAMPION) trial, data suggest that as disease severity improves, so does a patient's HRQoL. 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 improvement of less than 25 percent (-0.7±4.7). In an RCT that compared the efficacy and safety of adalimumab with placebo in patients with moderate to severe plaque psoriasis, investigators sought to correlate various measures of HRQoL to clinical outcomes.[31] DLQI was moderately correlated with PASI ($r=0.69$, $p<0.001$).[31] Data from this RCT also suggest that the minimal clinically important difference for the DLQI ranged from a change of 2.3 to 5.7.[31] Based on these data, the changes in DLQI in patients achieving a PASI 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 PASI 50, PASI 75, and PASI 90 suggested that the probability of achieving any of the three PASIs 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 seven studies that directly compared biologics with nonbiologics required patients to have moderate to severe plaque psoriasis for enrollment, and in these studies the baseline mean PASI ranged from 10.4 to 26.3. In the remaining two studies, although moderate to severe plaque psoriasis was not an explicit inclusion criterion, the mean PASI at baseline in one study was consistent with the others and ranged from 8.2 to 18.8. The second study did not report PASI at baseline. Only one of these seven studies was conducted in the United States, and therefore the overall literature may not reflect local clinical practice. The majority of patients evaluated were not naïve to psoriasis treatment. All interventions evaluated in these studies carried FDA approval at the time of the writing of this report at doses approved for chronic plaque psoriasis and are therefore relevant to treatment practice in the United States. Four of seven studies evaluated final health outcomes and were generally not sufficient in length to adequately evaluate such outcomes, with exception of HRQoL. The followup in these studies ranged from 12 to 26 weeks. Alternatively, for

intermediate outcomes, studies were sufficient in length to evaluate such outcomes, with two exceptions. One study had a short followup period, and the second had a cross-sectional design. Last, we did not consider studies long enough to accurately capture outcomes such as infection or malignancy. Otherwise, studies provided 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 for which toxicities are cumulative.

Three observational studies directly compared biologics with phototherapy in which moderate to severe plaque psoriasis was not an explicit inclusion criteria. However, the mean PASI at baseline was consistent with the other studies and ranged from 15.0 to 22.3. Therefore, the literature reflects patients with more advanced chronic plaque psoriasis and is not applicable to milder forms. Two of the three studies were conducted outside the United States, and therefore, the overall literature may not reflect local clinical practice. The majority of patients in these studies were not naïve to treatment. 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 these studies were sufficient. Only one final health outcome was evaluated, and of the intermediate outcomes, the duration of followup ranged from10.3 to 32 weeks. Adverse events were not evaluated in these studies.

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 with nonbiologic systemic agents or with phototherapy is limited. In total, only five RCTs comparing a biologic with a nonbiologic are included in this report, and no RCTs comparing a biologic with phototherapy were identified. Therefore, the most important area of future research is additional RCTs or large observational studies and registries 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 analyses using indirect comparisons may also help supplement lack of direct comparative data.

Future trials evaluating biologic versus nonbiologic systemic agents or phototherapy should be adequately powered to assess final health outcomes that are important to decisionmakers, such as mortality, major adverse cardiovascular events, and psychological outcomes. Doing so would likely require longer duration trials and larger sample sizes as compared with the current literature base. Since the longest study was 32 weeks in duration, only short-term outcome assessment was possible. Additional consideration of factors such as convenience of therapy should be weighed against these outcomes in future decisionmaking. 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 trials often were not of sufficient duration to adequately capture such risks.

Future research should be designed to determine whether 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 United States. The majority of included studies (11 of 14) were conducted in other countries, where clinical practice may not reflect practice within the United States.

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

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Acronyms/Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BSA	body surface area
CER	Comparative Effectiveness Review
DLQI	dermatology life quality index
EQ-5D	EuroQol 5-Dimension™ (test of health-related quality of life)
EQ-5D VAS	EuroQol 5-Dimension™ Visual Analogue Scale
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	health-related quality of life
IL	Interleukin
MACE	major adverse cardiovascular event
MCS	Mental Component Summary (part of SF-36)
RCT	randomized controlled trial
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary (part of SF-36)
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PUVA	psoralen plus ultraviolet A light
SCr	serum creatinine
SF-36	Short Form-36 Health Survey
TCP	thrombocytopenia
TNF	tumor necrosis factor
UVB	ultraviolet B light

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 clearance 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. The therapies with data included in this report are further described in Table 1, Table 2, and Table 3. 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 one or more of 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) and one anti-IL 12/23 agent (ustekinumab) have approval from the Food and Drug Administration (FDA) for psoriasis treatment. Although while writing this report alefacept was still on the U.S. market, this T-cell targeting agent has been voluntarily withdrawn from the U.S. market. Another T-cell targeting agent, efalizumab, 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 with 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 with 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 with nonbiologic systemic treatment options or phototherapy for chronic plaque psoriasis has been completed. Throughout the report we refer to three "classes" of therapy: biologics, nonbiologics, and phototherapy, which is consistent with national practice guidelines. We realize the possible heterogeneity within each class, namely the biologics, and therefore do not make between class comparisons rather limit comparisons with the individual drug level. Comparisons of drugs within each class were beyond the scope of this report. Please see the glossary in Appendix I for a listing of drugs considered within each class.

Table 1. FDA-approved biologic systemic therapy with identified literature in this report

Drug Name* (Brand)	Marketed by (Manufacturer)	Target of Therapy	FDA Indications
Adalimumab (Humira®)	Abbott Laboratories	TNF-α	Treatment of adults with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy when other therapies are medically less appropriate; reducing signs and symptoms, inhibition of structural damage of active arthritis and improving physical function in patients with psoriatic arthritis; reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease and improving physical function in active moderate-to-severe rheumatoid arthritis; reducing signs and symptoms in active ankylosing spondylitis; reducing signs and symptoms, inducing and maintaining clinical remission, in adult and pediatric patients with active moderate-to-severe active Crohn's disease in patients with inadequate response to conventional therapy, including intolerance and refractory response to infliximab; reducing signs and symptoms of moderate-to-severe active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older
Alefacept† (Amevive®)	AstellasPharma US, Inc.	CD2 antigen on T-lymphocytes and NK cells	Treatment of chronic moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy
Etanercept (Enbrel®)	Amgen, Inc. and Pfizer (Wyeth Pharmaceuticals Inc.)	TNF-α and TNF-β	Treatment of adults with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; reducing signs and symptoms, inhibition of structural damage of active arthritis and improving physical function in patients with psoriatic arthritis; reducing signs and symptoms of active ankylosing spondylitis; reducing signs and symptoms of active moderate-to-severe active polyarticular juvenile idiopathic arthritis; reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease, and improving physical function in active moderate-to-severe rheumatoid arthritis

Table 1. FDA-approved biologic systemic therapy with identified literature in this report (continued)

Drug Name* (Brand)	Marketed by (Manufacturer)	Target of Therapy	FDA Indications
Infliximab (Remicade®)	Centocor Ortho Biotech Inc.	TNF-α	Treatment of severe chronic plaque psoriasis in adults who are candidates for systemic therapy, and other systemic therapies are medically less appropriate; reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease and improving physical function in psoriatic arthritis; (in combination with methotrexate) reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease and improving physical function in moderate to severe active rheumatoid arthritis; reducing signs and symptoms, inducing and maintaining clinical remission in adult and pediatric patients with moderate to severe active Crohn's disease in patients with inadequate response to conventional therapy; reducing number of draining enterocutaneous, rectovaginal fistulas, maintaining fistula closure in patients with fistulizing Crohn's disease; reducing signs and symptoms in active ankylosing spondylitis; reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing and eliminating corticosteroid use in patients with moderate to severe active ulcerative colitis who have had inadequate response to conventional therapy
Ustekinumab (Stelara®)	Centocor Ortho Biotech (Cilag Ag)	IL-12 and IL-23	Treatment for moderate to severe plaque psoriasis in patients (18 years and older) who are candidates for phototherapy or systemic therapy

FDA = Food and Drug Administration; IL = interleukin; NK = natural killer; TNF = tumor necrosis factor

*Drug name is the generic formulation, if available.

†Although no longer available on the U.S. market, this drug was available at the time of writing this report.

Table 2. FDA-approved nonbiologic systemic therapy with identified literature in this report

Drug Name*	Marketed by (Manufacturer)	FDA Indications
Acitretin (Soriatane®)	Stiefel Laboratories Inc., a company of GlaxoSmithKline	Treatment of severe psoriasis
Cyclosporine, modified† (Gengraf®) (Neoral®)	Abbott Laboratories Novartis Pharmaceuticals Corp.	Treatment of adult, nonimmunocompromised patients with severe recalcitrant plaque psoriasis who have failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated or cannot be tolerated; prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants; treatment of severe active rheumatoid arthritis where disease has not adequately responded to methotrexate
Methotrexate† (Methotrexate LPF®) (Trexall®)	Hospira, Inc. Teva Pharmaceuticals USA (Barr Pharmaceuticals)	Symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy; treatment of gestational choriocarcinoma, chorioadenomadestruens, and hydatidiform mole; prophylaxis and treatment of meningeal leukemia; used alone or in combination therapy in the treatment of breast cancer, epidermoidcarcinomas of the head and neck, advanced mycosis fungoides, lung cancer, and advanced-stage non-Hodgkin's lymphomas; as combination therapy in prolongation of remission in nonmetastatic osteosarcoma; management of selected adults with severe, active rheumatoid arthritis, or children with active polyarticular juvenile rheumatoid arthritis who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full-dose nonsteroidal anti-inflammatory agents; trophoblastic neoplasms; acute lymphoblastic leukemia; meningeal leukemia; cutaneous T-cell lymphoma

FDA = Food and Drug Administration
*Drug name is the generic formulation, if available, or the developmental name as determined by the manufacturing company.
†Generic formulations commercially available.

Table 3. FDA-approved phototherapy with identified literature in this report

Modality	Description of Therapy	Example Models (Manufacturer)*	FDA Indication†
NB-UVB	Exposure to UVB radiation ranging from 311 to 313 nm	DuaLight system (TheraLight™, Inc.) 3-series Phototherapy Cabinet (Daavlin Company) MultiClear XL (Curelight Ltd.)	UVB phototherapy for psoriasis, vitiligo, atopic dermatitis, and leukoderma
PUVA	Methoxypsoralen (8-MOP®) administered orally or topically 75–120 minutes prior to exposure to UVA radiation, followed by exposure to UVA radiation ranging from 320–400 nm	8-MOP® (ICN Pharmaceuticals, Inc.) DuaLight system (TheraLight™, Inc.) 3-series Phototherapy Cabinet (Daavlin Company)	8-MOP®: For the symptomatic control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy; to be administered in conjunction with long-wave ultraviolet radiation

8-MOP = 8-methoxypsoralenFDA = Food and Drug Administration; NB-UVB = narrowband ultraviolet B light; PUVA = psoralen plus ultraviolet A light
*Listed devices are intended to represent examples of currently available products. The list is not intended to be comprehensive.
†FDA indication as listed on the 510K preapproval documentation.

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[a]

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 on an individual drug level) or phototherapy when evaluating intermediate (plaque BSA measurement, PASI, 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)]?

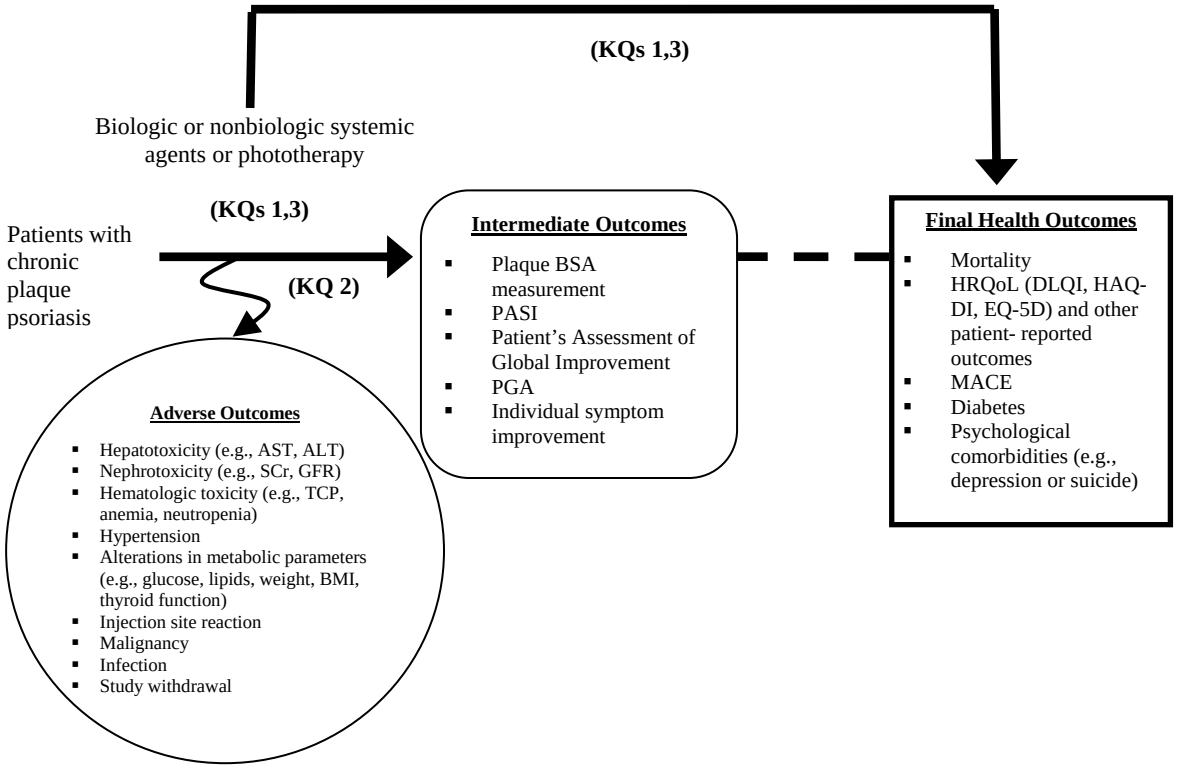
Key Question 2. In patients with chronic plaque psoriasis, what is the comparative safety of systemic biologic agents and systemic nonbiologic agents (between-class comparisons on an individual drug level) or phototherapy (hepatotoxicity [e.g., AST, ALT], nephrotoxicity [e.g., SCr, GFR], hematologic 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?

[a] Key Question abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; 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; PGA = Physician's Global Assessment; SCr = serum creatinine; TCP = thrombocytopenia

Analytic Framework

Figure 1. Analytic framework



ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimension^{TM}; GFR = glomerular filtration rate; HAQ-DI = Health Assessment Questionnaire Disability Index; HRQoL = health-related quality of life; 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 (Methods Guide) (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. Another physician provided the general practitioner's perspective. Last 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 underwent peer review and public commentary and revisions were 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 gray 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 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 gray 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 second literature search was used to systematically identify previously conducted adjusted indirect comparisons or network meta-analyses. The search strategy shown 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 were updated in June 2012, concurrent with the peer review process. The same inclusion and exclusion criteria were applied and relevant literature was 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 the 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 with 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 that 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 that 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 an indication approved by the FDA at the time of writing this report 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 with a 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. Gray 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 4). 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 4. 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 that 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. Last, comparisons made within this report are limited to between class comparisons on an individual drug level, given possible heterogeneity within each class considered (see the glossary in Appendix I for drugs within each class). Within class comparisons were beyond the scope of this report.

Grading the Strength of the Evidence

Two reviewers independently evaluated the strength of evidence for each comparison and outcome described in Key Questions 1 and 2 considered important, with disagreements resolved through discussion. Rating of the strength of evidence was conducted using recommendations from the Methods Guide.[19] 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 5). The four required domains were considered equally when grading the strength of evidence. Previously conducted meta-analyses or indirect comparisons were not included in the grading of strength of evidence.

Table 5. Strength of evidence rating definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change 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.[19] 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 were 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 list of acronyms and abbreviations list at the end of this report and in Appendix J, and a glossary of useful terms can be found in Appendix I..

Study Identification

Two literature searches were conducted as described in the Methods section. 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. Upon updating the search in June 2012, a total of 89 citations were retrieved. After the removal of duplicates, 508 articles remained. During title and abstract review, 328 citations were excluded. Of the 180 citations remaining, 147 were excluded at the full-text level. A total of 33 citations, representing 14 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 and upon updating the literature search in June 2012, five additional citations were retrieved. A total of 15 citations were excluded at the abstract level and seven 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

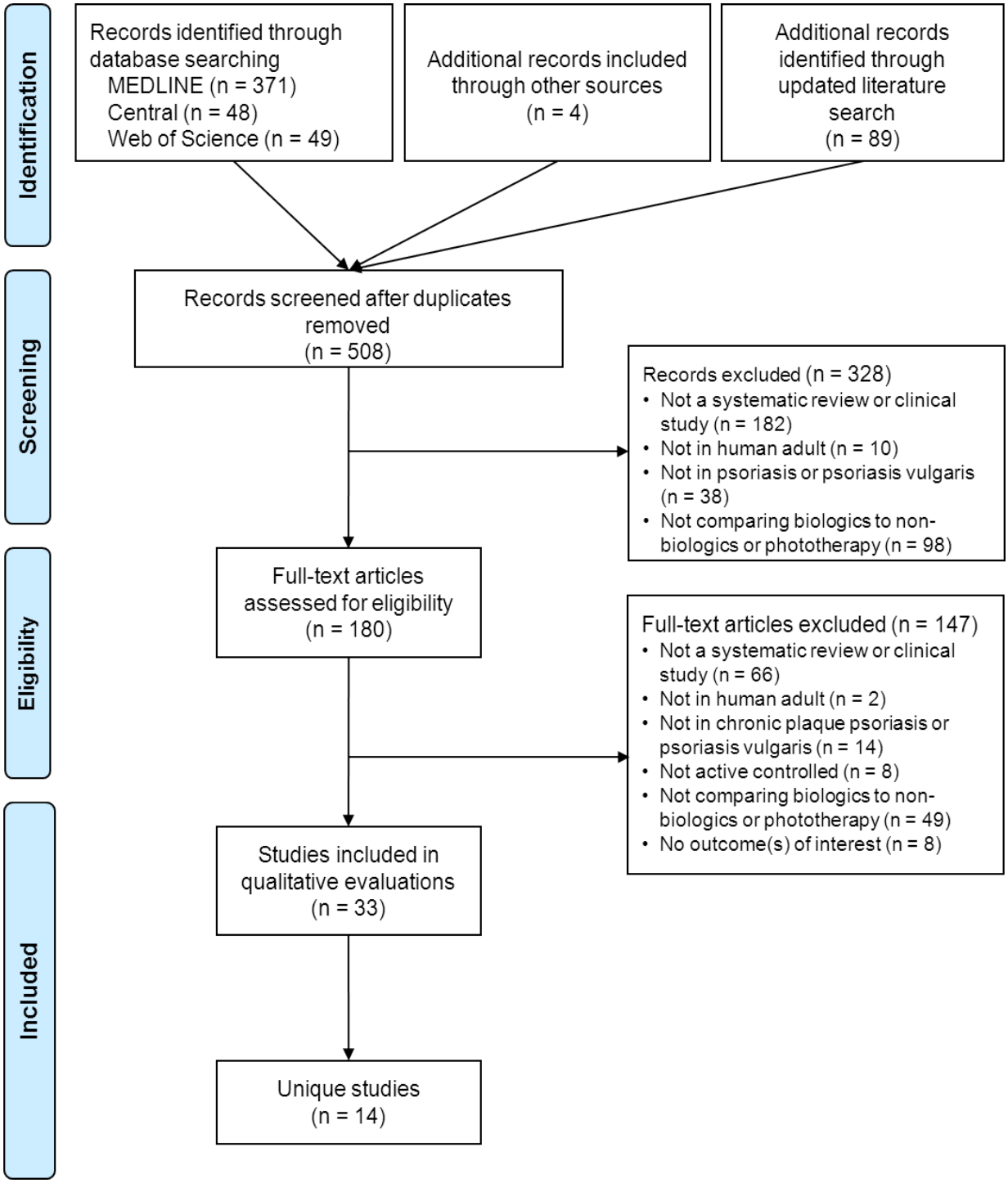
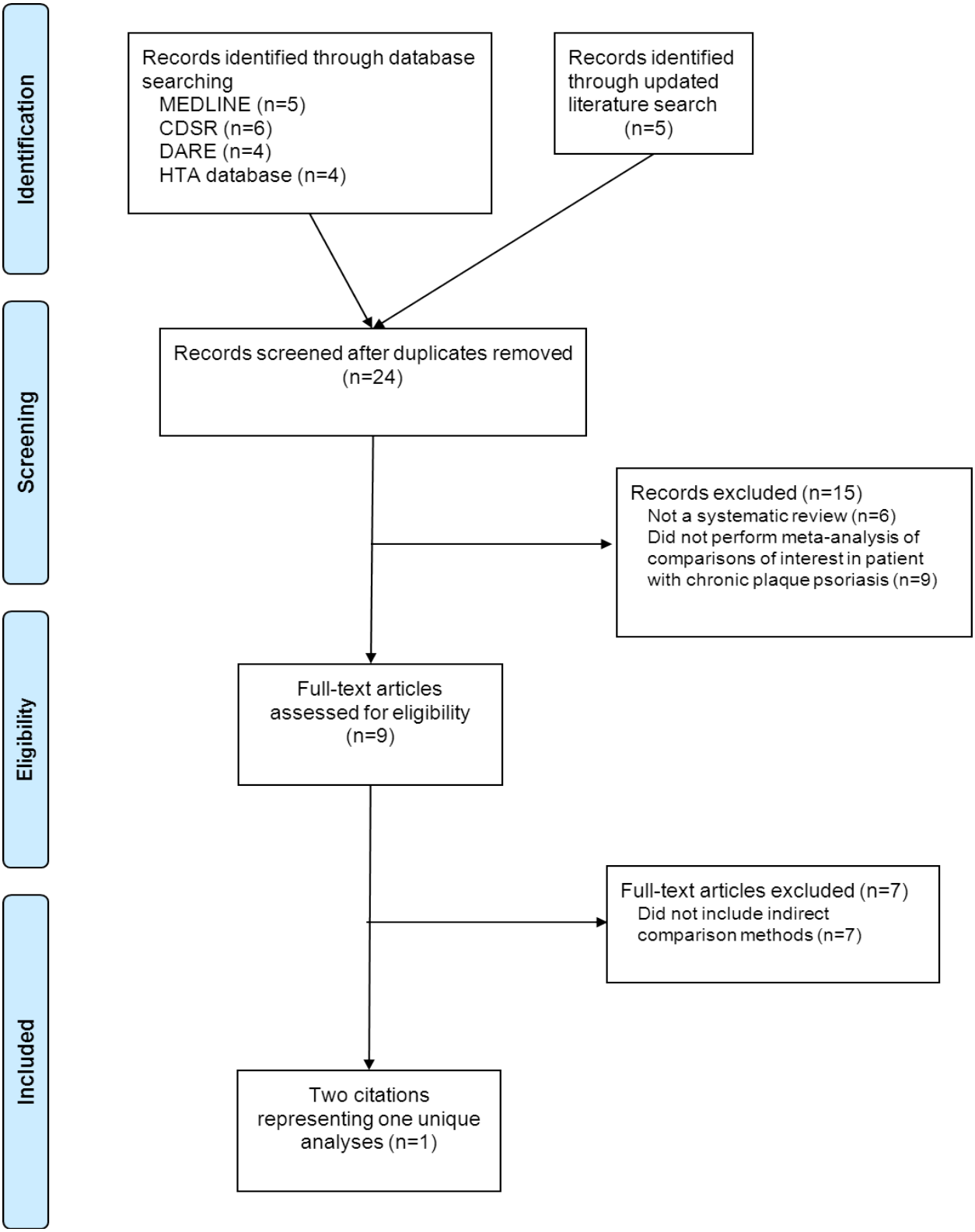


Figure 3. Inclusion and exclusion of citations in search two



CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; HTA = health technology assessment

Study Characteristics

Five randomized controlled trials (RCTs) (n=1,227)[17, 21-24] and four observational studies (n=1,066)[25-28] directly compared a systemic biologic agent with either a systemic nonbiologic agent or phototherapy and reported at least one outcome of interest. Of the five RCTs, one was poor, [24] two were fair, [21, 22] and two were good in quality.[17, 23] Of the four observational studies, three were fair in quality[25, 26, 28] and one was poor in quality. [27] Additionally, three more observational studies (n=85) evaluated the transition of patients between therapies within the biologic, nonbiologic, and phototherapy treatments. One of these studies were poor in quality [29] while the others were fair in quality.[30,31] 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.[32,33] Finally, we identified one network meta-analysis that used methods for indirect comparison across various therapies included in this review.[34] All included studies were available as full text publications except for one whose results were only available from www.clinicaltrials.gov.[24] 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 five RCTs directly compared individual biologic agents with individual nonbiolgic agents. The unique comparisons included infliximab versus methotrexate,[21] etanercept versus acitretin,[22-24] 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 2012.[24] Three trials received industry funding[17,21, 24] while two trials did not report the funding source.[22,23] The mean age of enrolled patients ranged from 38.57 to 55.3 years. Females represented between 16.7 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 D, 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 Psoriasis Area and Severity Index (PASI) ranged from 10.4 to 26.31 while the mean disease duration ranged from 17.0 to 23.5 years. The mean body surface area (BSA) ranged from 11.1 to 39.75 percent. The percentage of participants with concomitant psoriatic arthritis ranged from 0 to 21.3 percent.

Two of the four observational studies directly compared individual biologic agents with individual nonbiologic agents.[26, 28] The comparisons made included etanercept or infliximab with methotrexate[26] and adalimumab, etanercept, or ustekinumab with methotrexate.[28] The longest followup period was 24 weeks.[26] The earliest study was published in 2008[26] while the most recent was published in 2012.[28] One study received funding from the government [28] while the other study did not report the funding source.[26] The mean age of the enrolled patients ranged from 46.8 to 53.1 years. Females represented between 30.0 and 49.4 percent of the enrolled populations. Race or ethnicity was reported only in one study where Caucasians represented 85 percent of the population. [28] Mean weight and body mass index (BMI) ranged from 79.2 to 81.0 kg and 26.5 to 28.8 kg/m^2, respectively. The mean baseline PASI was reported in only one study that ranged from 8.2 to 18.8.[26] The mean disease duration ranged from 17.5 to 22.0 years. Only

one study reported concomitant psoriatic arthritis as 22.6 percent of the population and the same study also reported 25.8 percent of the population at baseline to be naïve to psoriasis therapy. [28] Mean BSA range was not reported.

Three observational studies[29-31] 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,[29] cyclosporine to alefacept,[31] methotrexate to infliximab,[21] and infliximab to methotrexate.[21] The shortest followup period was 26 weeks[17,21,30] while the longest followup was 2 years.[29] The earliest study was published in 2007[31] while the most recent was published in 2011.[21, 30] Four studies received industry funding[17,21,30,31] and one study did not report the funding source.[29] Baseline characteristics specific to the population of patients transitioned to different therapies within the two RCTs 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.[30] No other race/ethnicity percentages were reported. One study reported the mean weight as 89.5 kg while BMI data were not reported.[30] The mean baseline PASI was reported as 10.2 in one study.[30] The mean disease duration ranged from 17.0 to 22.0 years. One study reported the mean BSA as 10.9 percent.[30] The percentage of participants with concomitant psoriatic arthritis ranged from 25.0 to 41.5 percent. None of the studies reported how psoriatic arthritis was diagnosed.[17,21,29-31]

Studies Comparing Systemic Biologic Agents With Phototherapy

There were no RCTs identified that compared systemic biologic agents with phototherapy. Three observational studies directly compared individual biologic agents with phototherapies.[25, 27,28] The comparisons made included adalimumab, alefacept, etanercept, infliximab or ustekinumab versus psoralen plus ultraviolet A (PUVA); [25] adalimumab, etanercept, or ustekinumab versus narrowband-ultraviolet B (NB-UVB);[28] and infliximab or etanercept versus PUVA or NB-UVB.[27] The duration of followup period was 10.3 weeks to 12 weeks. The earliest study was published in 2011[25] while the most recent were published in 2012.[28] One study received funding from the industry[25], one from the government, [28] and one study did not report the funding source. [27] The mean age of the enrolled patients ranged from 46.2 to 55.1 years. The percentage of females ranged from 35.5 to 49.4 percent. The mean baseline PASI ranged from 15.0 to 22.3 and the mean disease duration ranged from 2 to 37 years. Race or ethnicity was reported in only one study where Caucasians represented 85 percent of the population. [28] Mean weight and BSA was not reported in any of the studies. The mean BMI was only reported in one study as 28.8 kg/m^2.[28] One study reported concomitant psoriatic arthritis as 22.6 percent of the population and also reported that 25.8 percent of the population at baseline was naïve to psoriasis therapy. [28]

One observational study (n=70) evaluated the transition of patients between biologic agents and phototherapy, evaluating the transition from NB-UVB to adalimumab.[30] 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.

Studies With Class-Level Comparisons

Two observational studies compared classes of therapy and both evaluated transitions of therapy.[32,33] The transitions evaluated included systemic nonbiologic agents to etanercept[33] and systemic nonbiologic agents or phototherapy to etanercept.[32] The followup period was 24 weeks for both studies. The earliest study was published in 2005[33] while the most recent was published in 2009.[32] One study was unfunded[32] and the other study did not report the funding source.[33] 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.[33] 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.[33] The percentage of participants with concomitant psoriatic arthritis was reported only in one study as 34.1.[33]

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.[34] 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, Patient's Assessment of Global Improvement, Physician's 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, major adverse cardiovascular events [MACE], diabetes, and psychological comorbidities [e.g., depression, suicide]}?

Key Points

- Five RCTs (two good, two fair, and one poor in quality) and two fair quality observational studies evaluated the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents.
    - The comparisons made included: adalimumab, etanercept, infliximab, and ustekinumab versus methotrexate and etanercept versus acitretin.
    - When comparing adalimumab with methotrexate:
        - HRQoL was improved in patients taking adalimumab compared with methotrexate, based on one RCT and one observation study (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 one RCT and one observational study (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).
        - There was insufficient evidence to determine the impact of adalimumab versus methotrexate on BSA and 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 ustekinumab with methotrexate:
        - There was insufficient evidence to evaluate HRQoL and no other final health outcomes were reported.
        - PGA improved in patients treated with ustekinumab compared with methotrexate, based on a single observational study (low strength of evidence).
        - There was insufficient evidence to evaluate BSA and PASI and no other intermediate health outcomes were reported.
    - When comparing etanercept with acitretin:
        - There was insufficient evidence to evaluate psychological comorbidities and patient reported outcomes and no other final health outcomes were reported.
        - PASI was improved in patients treated with etanercept compared with acitretin, based on three RCTs (moderate strength of evidence).
        - There was insufficient evidence to evaluate BSA, PGA, joint pain, and itching and no other intermediate outcomes were reported.
- One mixed-treatment comparison that evaluated PASI 50, PASI 75, and PASI 90 suggested that the probability of achieving any of the three PASIs was highest for infliximab, followed by adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care.
- No RCTs and three observational studies (one fair and two poor in quality) evaluated the comparative effectiveness of systemic biologic agents and phototherapy.

- The comparisons made included: adalimumab, etanercept, infliximab, and ustekinumab versus NB-UVB and etanercept and infliximab versus PUVA.
- There was insufficient evidence to evaluate HRQoL and no other final health outcomes were reported.
- There was insufficient evidence to evaluate BSA, PASI, PGA, psoriatic arthritis pain, and pruritus and no other intermediate outcomes were 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 were 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 E, Tables 3 and 4. Tables that display the outcomes reported within this Key Question can be found in Appendix F, Tables 5 to 11. Strength of evidence ratings as well as description of the applicability of each study can be found in Appendix G and Appendix H, Tables 12 to 48.

Outcome Evaluation

Systemic Biologic Agents Versus Systemic Nonbiologic Agents

Adalimumab Versus Methotrexate

One RCT and one observational study compared the biologic agent adalimumab versus the nonbiologic agent methotrexate. [17, 28] 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).[17,35] 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 visual analogue scale (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% CI, -10.4 to -7.8) versus -5.7 (95% CI, -6.8 to -4.5); $p<0.001$].[35] 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% CI, 16.6 to 26.3) versus 11.5 (95% 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% CI, 0.2 to 0.3) versus 0.1 (95% CI, 0.1 to 0.2); p=0.09]. At 12 weeks, adalimumab treatment resulted in greater improvement in the DLQI [-9.1 (95% CI, -10.4 to -7.8) versus -4.9 (95% CI, -5.9 to -3.8); p=not reported (NR)], the EQ-5D VAS [20.4 (95% CI, 15.3 to 25.4) versus 10.2 (95%CI, 5.3 to 15.2); p=NR], and the EQ-5D index score [0.2 (95% CI, 0.1 to 0.2) versus 0.1 (95% 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).[17,35] When compared with methotrexate, more patients who received adalimumab achieved PASI 50 (88.0 percent versus 61.8 percent, p<0.001), PASI 75 (risk difference 43.7 percent (95% CI, 30.8 to 56.7, p<0.001); 79.6 percent versus 35.5 percent, p<0.001), PASI 90 (51.9 percent versus 13.6 percent, p<0.001), and PASI 100 (16.7 percent versus 7.3 percent, p<0.04) at week 16. The median time to PAS I75 was significantly shorter in the adalimumab group compared with methotrexate (56 days versus 113 days, p<0.001) as was the median time to PASI 50 (28 days versus 84 days, p<0.001).[36] Investigators also evaluated PASI outcomes at weeks 4, 8, and 12. More patients treated with adalimumab achieved PASI 50, PASI 75, PASI 90 at all time periods evaluated (p<0.05) with significant effects observed as early as week 4, except for PASI 100. (Appendix F, Table 8) As for PASI 100, significant differences between treatment groups (p<0.05) were observed as early as 8 weeks and were maintained subsequently. (Appendix F, Table 8) The mean change in PASI 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).[35] (Appendix F, 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.[35] 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).[35]

The observational study by Gelfand et. al. evaluated one final health outcome: HRQoL. The study was rated with fair quality and 187 out of 713 (25.8 percent) patients were naïve to any psoriasis treatment. [28] The median DLQI score in patients treated with adalimumab was 2 (interquartile range of 0 to 5) and in patients treated with methotrexate was 3 (interquartile range of 1 to 5) (p=NR). When the DLQI score was analyzed as a dichotomous outcome (i.e., number of patients with response defined as no effect or a small effect of psoriasis on quality of life indicated by the DLQI score less than equal to 5), a similar proportion of patients treated with adalimumab achieved the response (78 percent; 95% CI, 70.5 to 84.3) compared with methotrexate (77.4 percent; 95% CI, 70.6 to 83.4; p=NR). [28]

This observational study also evaluated the following intermediate outcomes: BSA, PASI and PGA. [28] The median PASI in patients treated with adalimumab was 2.5 (interquartile range of 1.2 to 4.8) and in patients treated with methotrexate was 3.8 (interquartile range of 1.8 to 6.6) (p=NR). The same study also reported a median BSA percentage of 2.0 (interquartile range of 0.7 to 5.0) for patients treated with adalimumab and 3.0 (interquartile range of 1.0 to 6.0) for patients treated with methotrexate (p=NR). [28] The median PGA was 1.3 (interquartile range of 1.0 to 1.7) in patients treated with adalimumab and 1.7 (interquartile range of 1.3 to 2.0) in patients treated with methotrexate (p=NR). When the PGA was analyzed as a dichotomous outcome (i.e., number of patients with response defined as "clear" or "minimal" indicated by the PGA less than equal to 1), a significantly higher proportion of patients treated with adalimumab achieved response compared with methotrexate (adjusted relative rate of 2.15; 95% CI, 1.60 to 2.90).[28]

Transitions Between Adalimumab and Methotrexate

Two studies evaluated the transition between the biologic agent adalimumab and the nonbiologic agent methotrexate.[30,37]

The first study was a nonrandomized 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.[30] 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.[30,38] 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).[38]

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.[37] Results from this population of 95 patients were reported based on an interim analysis and included PASI. 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).[30,37] 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 improved for patients at week 16 compared with week zero (2.3 versus 10.8, p=NR), with improvements observed as early as week 2 (Appendix F, Table 8) Engauge Digitizer, Version 2.0 was used to read the reported figure to

obtain mean PASIs at all reported time periods (weeks 0, 2, 4, 8, and 16).[30] In the CHAMPION extension, PASI improved after patients transitioned to adalimumab for 24 weeks of treatment (PASI 75: 73 percent, PASI 90: 53 percent, PASI 100: 32 percent) compared with PASIs prior to treatment with adalimumab (PASI 75: 28 percent, PASI 90: 14 percent, PASI 100: 5, p=NR).[37]

In the study by Strober et al., at week 16, 61 percent of patients (95% CI, 45 to 76 percent) who switched from methotrexate to adalimumab had a PGA of "clear" or "minimal". PGA results for earlier time points (week 0, 2, 4, and 8) are available in Appendix F, Table 7.[30] 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].[30,38]

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.[31] 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 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 were 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.[31] The mean DLQI score was lower after phase I in comparison with 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.[31] 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 (7 of 11, 64 percent) and all patients remained within one category of their baseline PGA. After phase II (Week 25), the mean PGA was 4.75. During phase III, the mean PGA was 4.33 at the end of the second treatment course

and maintained through week 48 (mean PGA 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

Three RCTs compared the biologic agent etanercept with the nonbiologic agent acitretin.[22-24]

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. The third RCT (herein clinical trial 5) that was rated as having poor quality has not been published as a manuscript and the data were extracted from www.clinicaltrials.gov. [24] 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. In clinical trial 5, all patients were naïve to TNF inhibitors, efalizumab, and alefacept. The following final health outcomes were reported: psychological comorbidities (e.g. depression) and other patient-reported outcomes [i.e., Psoriasis Subject Satisfaction Questionnaire (PSSQ)].[24] In clinical trial 5, one in eighteen patients (5.6 percent) on acitretin reported depression versus none in 21 patients taking etanercept (p=NR) at 24 weeks. Although clinical trial 5 evaluated the PSSQ, the overall score was not reported.

Within the three RCTs, the following intermediate outcomes were reported: BSA, PASI, PGA, and symptom improvement [e.g. Subject Global Assessment (SGA) of psoriasis, SGA of joint pain, SGA of itching].[22-24] Two trials evaluated the affected BSA at 24 weeks. Gisondi et al. 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] In clinical trial 5, patients treated with etanercept had a greater mean change from baseline in BSA (-17.52 $\pm$ 14.91 versus -10.30 $\pm$ 18.86, p=NR) compared with patients treated with acitretin at week 24 as well as other shorter periods of follow-up (Appendix F, Table 7). All three trials evaluated PASI 50 and PASI 75. In the trial by Gisondi et al. a significantly higher proportion of patients treated with etanercept achieved PASI 50 (68 percent versus 50 percent, p=0.001) and PASI 75 (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 acitretin were seen as early as 12 weeks (p=0.001) for both PASI 50 and PASI 75 and remained significant at week 18 (p=0.001) for both outcomes (Appendix F, Table 8). In the trial by Caproni et al. the proportion of patients in the etanercept group achieving PASI 50 (87 percent versus 67 percent, p=NR) and PASI 75 (57 percent versus 27 percent, p=NR) was higher compared with acitretin.[22] The mean PASI was significantly reduced at week 12 when compared with baseline in both treatment groups.[22] The mean baseline PASI in the etanercept group was 21.54±9.09 compared with the mean PASI at week 12 of 4.61±2.75, p<0.001. The mean baseline PASI in the acitretin group was 22.25± 5.73 compared with the mean PASI at week 12 of 9.62±4.64, p<0.001. The mean PASI was significantly lower in the etanercept group compared with acitretin at week 12 (p=0.005). In clinical trial 5, the proportion of patients in the etanercept group achieving PASI 50 (71.43 percent versus 44.44 percent, p=NR) and PASI 75 (52.38 percent versus 22.22 percent, p=NR) was higher compared with acitretin at week 24 as well as other shorter periods of followup (Appendix F, Table 8). [24] The mean PASI was reduced in both treatment groups from baseline at 24 weeks as well as shorter periods of followup (Appendix F, Table 8). The mean

baseline PASI in the etanercept group was 20.83 ± 14.02 and was reduced by 12.16 ± 12.15 at week 24 (p=NR). In the acitretin group, the mean baseline PASI of 26.31 ± 13.63 was reduced by 9.62 ± 10.10 at week 24 (p=NR).

One RCT [24] evaluated the proportion of patients achieving a PGA of clear or almost clear, mean SGA of joint paint and mean SGA of itching. A higher percent of patients in the etanercept group (52.38 percent versus 44.44 percent, p=NR) achieved a PGA of clear or almost clear compared with acitretin at week 24, as well as shorter periods of followup (Appendix F, Table 7). The mean PGA was reduced from baseline in both groups. In the etanercept group, the mean baseline PGA was 3.40 ± 0.82 and decreased by 1.67 ± 1.47 at week 24 (p=NR). In the acitretin group, the mean baseline PGA of 3.50 ± 0.92 was reduced by 0.71 ± 1.37 at week 24 (p=NR). The mean PGA decreased to a greater extent in the etanercept group compared with the acitretin group at shorter periods of followup as well (Appendix F, Table 7). The change from baseline in mean SGA of psoriasis at week 24 was -1.81± 2.20 in the etanercept group versus -1.72 ± 1.93 in the acitretin group (p=NR).The mean SGA of joint pain increased in the etanercept group and decreased in the acitretin group from baseline, increasing by 0.29 ± 1.06 at week 24, from a baseline of 0.67 ± 1.43 (p=NR) in the etanercept group and decreasing by 0.61 ± 2.03 at week 24, from a baseline of 0.94 ± 1.73 (p=NR) in the acitretin group. The last intermediate outcome evaluated in clinical trial 5 was SGA of itching. In the etanercept group, the mean SGA of itching decreased by 1.19 ± 2.23 at week 24 from a baseline score of 3.33 ± 1.35 (p=NR). In the acitretin group, the mean SGA of itching decreased by 1.06 ± 1.89 at week 24, from a baseline of 3.72 ± 1.45 (p=NR)

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.[29] This study was rated as having poor quality and data about whether patients were naïve to treatment or not were 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 PASIs 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 PASIs reported at 104 weeks and continued to show comparable mean PASIs 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.

Two observational studies compared the biologic etanercept with the nonbiologic methotrexate.[26, 28] In the study by Gisondi et al., rated with fair quality, patients treated with etanercept were naïve to biologic therapy.[26] The second study by Gelfand et al., was rated with fair quality and 187 out of 713 (25.8 percent) patients were naïve to any psoriasis treatment. [28] The following final health outcome was evaluated in these studies: HRQoL (i.e. DLQI).[28]

In the study by Gelfand et al. the median DLQI score was 2 (interquartile range of 1 to 5) in patients treated with etanercept and 3 (interquartile range of 1 to 5) in patients treated with methotrexate (p=NR). When the DLQI score was analyzed as a dichotomous outcome (i.e., number of patients with response defined as no effect or a small effect of psoriasis on quality of life indicated by the DLQI score less than equal to 5), a similar proportion of patients treated with etanercept achieved the response (75.5 percent; 95% CI, 68.7 to 81.5) compared with methotrexate (77.4 percent; 95% CI, 70.6 to 83.4; p=NR).[28]

The intermediate outcomes evaluated in these observational studies include: BSA, PASI and PGA. Both studies evaluated PASI. In first study by Gisondi, the mean PASI 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 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). [26] In the second study by Gelfand et al., the median PASI was 2.9 (interquartile range of 1.8 to 4.9) in patients treated with etanercept and 3.8 (interquartile range of 1.8 to 6.6) in patients treated with methotrexate (p=NR).[28]

The study by Gelfand et al. also evaluated BSA and PGA.[28] The median BSA percentage was 2.0 (interquartile range of 0.5 to 4.5) in patients treated with etanercept and 3.0 (interquartile range of 1.0 to 6.0) in patients treated with methotrexate (p=NR). [28] The median PGA was 1.7 (interquartile range of 1.0 to 2.0) in patients treated with etanercept and 1.7 (interquartile range of 1.3 to 2.0) for patients treated with methotrexate (p=NR). When the PGA was analyzed as a dichotomous outcome (i.e., number of patients with response defined as "clear" or "minimal" indicated by the PGA less than equal to 1), a significantly higher proportion of patients treated with etanercept achieved the response compared with methotrexate (adjusted relative rate of 1.45; 95% CI, 1.06 to 1.97).[28]

Infliximab Versus Methotrexate

One RCT and one observational study directly compared the biologic agent infliximab with the nonbiologic agent methotrexate.[21,26]

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 PASI 50 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 were 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.[39] 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 with methotrexate, more patients who received infliximab achieved PASI 50 (86.8 percent versus 60.5 percent, p<0.001), PASI 75 (77.8 percent versus 41.9 percent, p<0.001), and PASI 90 (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 F, Table 8) More patients treated with infliximab achieved PASI 50 and PASI 75 at all time periods (p<0.001) compared with methotrexate with significant effects observed as soon as 2 weeks. As for PASI 90, significant differences between treatment groups (p<0.001) were observed as early as 6 weeks and were maintained subsequently. The median time to PASI 75 was shorter in infliximab treated patients compared with methotrexate [46 days (95% CI, 45 to 50) versus 127 days (95% 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 PGAs 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 PASI 50 (81

percent versus 47.9 percent, p<0.001), PASI 75 (76.8 percent versus 30.7 percent, p<0.001), and PASI 90 (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 F, Table 8). The mean percent change in PASI 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.[26] In this study by Gisondi et al., rated with fair quality, patients treated with infliximab were naïve to biologic therapy.[26] The only intermediate outcome reported was PASI. The mean PASI 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 PASIs 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.[39]

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 PASI 75 (46 of 63 patients, 73 percent) or PASI 90 (47.6 percent) compared with patient who switched to methotrexate (1 of 9 patients, 11.1 percent; no patients achieved PASI 90, p=NR). Findings were similar for PASI 75 and PASI 90 at weeks 18 and 22 as well (Appendix F, 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 F, Table 7).

Ustekinumab Versus Methotrexate

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

One observational study compared the biologic ustekinumab with the nonbiologic methotrexate.[28] In this study by Gelfand et al., rated with fair quality, 187 out of 713 (25.8 percent) patients were naïve to any psoriasis treatment.[28] This study evaluated the following final health outcome: HRQoL (i.e. DLQI).[28]

The median DLQI was 3 (interquartile range of 1 to 6) in patients treated with ustekinumab and 3 (interquartile range of 1 to 5) for patients treated with methotrexate (p=NR). When the DLQI was analyzed as a dichotomous outcome (i.e., number of patients with response defined as no effect or a small effect of psoriasis on quality of life indicated by the DLQI less than equal to 5), a similar proportion of patients treated with ustekinumab achieved response (71.2 percent;

95% CI, 59.2 to 81.4) compared with methotrexate (77.4 percent; 95% CI, 70.6 to 83.4; p=NR).[28]

This study also evaluated the following intermediate outcomes: BSA, PASI and PGA.[28] A similar median BSA percentage of 3.0 (interquartile range of 0.6 to 9.1) and 3.0 (interquartile range of 1.0 to 6.0) was reported for patients treated with ustekinumab and methotrexate, respectively (p=NR).[28] The median PASI was 4.0 (interquartile range of 1.0 to 7.9) in patients treated with ustekinumab and 3.8 (interquartile range of 1.8 to 6.6) in patients treated with methotrexate (p=NR). In addition, a similar median PGA of 1.7 (interquartile range of 1.0 to 2.1) and 1.7 (interquartile range of 1.3 to 2.0) was reported for patients treated with ustekinumab and methotrexate, respectively (p=NR). When the PGA was analyzed as a dichotomous outcome (i.e., number of patients with response defined as "clear" or "minimal" indicated by the PGA less than equal to 1), a significantly higher proportion of patients treated with ustekinumab achieved the response compared with methotrexate (adjusted relative rate of 1.57; 95% CI, 1.06 to 2.32).[28]

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.[34] RCTs evaluating adalimumab, alefacept, efalizumab, etanercept, infliximab, retinoids, methotrexate, cyclosporine, phototherapy, and combination therapy 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. Overall, the quality of this analysis was good.

A total of 22 trials (n=9,917) were included in the analysis. The authors reported a mean Jadad score of 4.3 and considered the quality of included studies high. The outcomes evaluated in this analysis were PASI 50, PASI 75, and PASI 90 and the probability of a given therapy achieving each outcome was reported (Table 6). 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 they do 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 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 than the biologic agent alefacept.

Table 6. Results from Bansback et al.

Therapy	Probability of Response PASI 50 %, (95% CI)	Probability of Response PASI 75 %, (95% CI)	Probability of Response PASI 90 %, (95% CI)
Supportive care	14 (12-16)	4 (4-5)	1 (1-1)
Etanercept 50 mg twice/wk	74 (67-80)	50 (43-58)	22 (17-28)
Efalizumab 1 mg/kg*	53 (48-59)	28 (24-34)	9 (7-12)
Infliximab 5 mg/kg	93 (91-96)	81 (75-86)	54 (47-63)
MTX 15-22.5 mg/wk	66 (51-77)	42 (27-54)	17 (9-26)
Cyclosporine 3 mg/kg/d	57 (37-73)	33 (17-49)	11 (4-21)
Adalimumab 40 mg every other wk	88 (83-93)	71 (63-79)	42 (33-52)
Alefacept 15mg IM 1/wk	34 (25-43)	15 (9-21)	4 (2-6)

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.[26,32,33] One study directly compared classes[26] while two studies observed transitions of therapy from nonbiolgics to biologics.[32,33]

One observational study by Gisondi et al., rated with fair quality, compared treatment with biologics (etanercept or infliximab) with treatment with the nonbiologic methotrexate.[26] 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 improvement in PASIat 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.[32,33] 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.[33] 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.[33] PASI was reported at weeks 0, 12, and 24. The mean PASI 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 from baseline to week 12 was 52 percent and to week 24 was 72 percent. At week 24, the number of patients with PASI 50 (12 of 15 patients, 80 percent) or PASI 75 (10 of 15 patients, 67 percent) was significantly greater compared with the number with PASI 50 (28 of 44 patients, 64 percent) or PASI 75 (19 of 44 patients, 43 percent) at 12 weeks ($p<0.05$ for both comparisons). The number of patients achieving PASI 90 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).[32] 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.[32] The mean PASI was significantly lower at 24 weeks compared with baseline (2.8±3.4 versus 16.1±7.1, $p<0.0001$) and compared with 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 PASI 50 and PASI 75, respectively. At 12 weeks, 79 of 98 patients (80.2 percent) and 43 of 98 (43.7 percent) patients achieved PASI 50 and PASI 75, respectively.

Systemic Biologic Agents Versus Phototherapy

Adalimumab Versus NB-UVB

There were no RCTs that directly compared the biological agent adalimumab with NB-UVB.

One observational study compared the biologic adalimumab with NB-UVB.[28] In this study by Gelfand et al., rated with fair quality, 187 out of 713 (25.8 percent) patients were naïve to any psoriasis treatment.[28] This study evaluated the following final health outcome: HRQoL (i.e. DLQI).[28]

The median DLQI was 2 (interquartile range of 0 to 5) for patients treated with adalimumab and 3 (interquartile range of 1 to 7) for patients treated with NB-UVB (p=NR). When the DLQI score was analyzed as a dichotomous outcome (i.e., number of patients with response defined as no effect or a small effect of psoriasis on quality of life indicated by the DLQI score less than equal to 5), a similar proportion of patients treated with adalimumab achieved the response (78.0 percent; 95% CI, 70.5 to 84.3) compared with NB-UVB (68.3 percent; 95% CI, 59.2 to 76.5; p=NR).[28]

This study also evaluated the following intermediate outcomes: BSA, PASI and PGA.[28] A lower median BSA percentage of 2.0 (interquartile range of 0.7 to 5.0) was reported in patients receiving adalimumab compared with a median BSA percentage of 3.3 (interquartile range of 1.0 to 6.5) in patients receiving NB-UVB (p=NR).[28] The median PASI was 2.5 (interquartile range of 1.2 to 4.8) in patients receiving adalimumab and 3.5 (interquartile range of 2.0 to 5.5) in patients treated with NB-UVB (p=NR). In addition, a similar median PGA of 1.3 (interquartile range of 1.0 to 1.7) and 1.7 (interquartile range of 1.0 to 2.0) was reported for patients treated with adalimumab and NB-UVB, respectively (p=NR). When the PGA was analyzed as a dichotomous outcome (i.e., number of patients with response defined as "clear" or "minimal" indicated by the PGA less than equal to 1), a higher proportion of patients treated with adalimumab achieved the response (47.7 percent; 95% CI, 39.5 to 56.0) compared with NB-UVB (27.6 percent; 95% CI, 20.0 to 36.4; p=NR).[28]

Transitions Between Adalimumab and NB-UVB Phototherapy

One nonrandomized 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.[30] Patients stopped NB-UVB phototherapy 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].[30,38] 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.[30,38] 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).[38]

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).[30] No additional intermediate health outcomes were reported for patients who transitioned from NB-UVB phototherapy to adalimumab.

The mean PASI improved at week 16 compared with 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 F, Table 8). Engauge Digitizer, Version 2.0 was used to read the reported figure to obtain values for mean PASI at all reported time periods (week 0, 2, 4, 8, and 16). At week 16, 48 percent of patients (95% CI, 29 percent to 67 percent) who transitioned from NB-UVB phototherapy to adalimumab had a PGA of “clear” or “minimal”. PGA results for earlier time periods (week 0, 2, 4, and 8) are available in Appendix F, 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].[30,38]

Etanercept Versus NB-UVB

There were no RCTs that directly compared the biologic agent etanercept with NB-UVB. Two observational studies compared the biologic etanercept with NB-UVB.[27,28] In the first study by Gelfand et al., rated with fair quality, 187 out of 713 (25.8 percent) patients were naïve to any psoriasis treatment.[28] This study evaluated the following final and intermediate health outcomes: HRQoL (i.e. DLQI), BSA, PASI and PGA. [28] The second study by Emerit et al., was rated with poor quality and subjects in the NB-UVB group were naïve to phototherapy and systemic nonbiologics.[27] The only outcome of interest reported was the intermediate outcome PASI at week 12, though subjects in the phototherapy group were also followed up at week 32.[27]

The median DLQI was 2 (interquartile range of 1 to 5) for patients treated with etanercept and 3 (interquartile range of 1 to 7) for patients treated with NB-UVB (p=NR).[28] When the DLQI score was analyzed as a dichotomous outcome (i.e., number of patients with response defined as no effect or a small effect of psoriasis on quality of life indicated by the DLQI score less than equal to 5), a higher proportion of patients treated with etanercept achieved the response (78.0

percent; 95% CI, 70.5 to 84.3) compared with NB-UVB (68.3 percent; 95% CI, 59.2 to 76.5; p=NR).[28]

The following intermediate outcomes were evaluated: BSA, PASI and PGA.[27,28] A lower median BSA percentage of 2.0 (interquartile range of 0.5 to 4.5) was reported in patients receiving etanercept compared with a median BSA percentage of 3.3 (interquartile range of 1.0 to 6.5) in patients receiving NB-UVB (p=NR).[28] The median PASI was 2.9 (interquartile range of 1.8 to 4.9) in patients treated with etanercept and 3.5 (interquartile range of 2.0 to 5.5) in patients treated with NB-UVB (p=NR).[28] In the second study by Emerit et al., there was a significant reduction in mean PASI for both groups at week 12 although there was no comparison made of the change in PASI observed between etanercept and NB-UVB.[27] In the etanercept group, PASI was reduced from 21.4 $\pm$ 6.1 at baseline to 3.7 $\pm$ 1.2 ($p<0.05$) at week 12. In the NB-UVB group, PASI was reduced from 21.3 $\pm$ 5.2 at baseline to 3.7 $\pm$ 1.2 ($p<0.05$) at week 12. [27] Subjects in the PUVA group were also examined at week 32, after discontinuation of the treatment at week 12, and the mean PASI increased to 10.8 $\pm$ 2.2 ($p<0.05$ versus week 12). [27] In addition, a similar median PGA of 1.7 (interquartile range of 1.0 to 2.0) and 1.7 (interquartile range of 1.0 to 2.0) was reported for patients treated with etanercept and NB-UVB, respectively (p=NR). When the PGA was analyzed as a dichotomous outcome (i.e., number of patients with response defined as "clear" or "minimal" indicated by the PGA less than equal to 1), a higher proportion of patients treated with etanercept achieved the response (34.2 percent; 95% CI, 27.5 to 41.4) compared with NB-UVB (27.6 percent; 95% CI, 20.0 to 36.4; p=NR).[28]

Ustekinumab Versus NB-UVB

There were no RCTs that directly compared the biologic agent ustekinumab with NB-UVB.

One observational study compared the biologic ustekinumab with NB-UVB.[28] In this study by Gelfand et al., rated with fair quality, 187 out of 713 (25.8 percent) patients were naïve to any psoriasis treatment.[28] This study evaluated the following final and intermediate health outcomes: HRQoL (i.e. DLQI), BSA, PASI and PGA.[28]

The median DLQI was 3 (interquartile range of 1 to 6) in patients treated with ustekinumab and 3 (interquartile range of 1 to 7) in patients treated with NB-UVB (p=NR). When the DLQI score was analyzed as a dichotomous outcome (i.e., number of patients with response defined as no effect or a small effect of psoriasis on quality of life indicated by the DLQI score less than equal to 5), a higher proportion of patients treated with ustekinumab achieved the response (71.2 percent; 95% CI, 59.2 to 81.4) compared with NB-UVB (68.3 percent; 95% CI, 59.2 to 76.5; p=NR).[28]

This study also evaluated the following intermediate outcomes: BSA, PASI and PGA.[28] A similar median BSA percentage of 3.0 (interquartile range of 0.6 to 9.1) and 3.3 (interquartile range of 1.0 to 6.5) were reported for patients treated with ustekinumab and NB-UVB, respectively (p=NR).[28] The median PASI was 4.0 (interquartile range of 1.0 to 7.9) in patients treated with ustekinumab and 3.5 (interquartile range of 2.0 to 5.5) in patients treated with NB-UVB (p=NR). In addition, a similar median PGA of 1.7 (interquartile range of 1.0 to 2.1) and 1.7 (interquartile range of 1.0 to 2.0) was reported for patients treated with ustekinumab and NB-UVB, respectively (p=NR). When the PGA was analyzed as a dichotomous outcome (i.e., number of patients with response defined as "clear" or "minimal" indicated by the PGA less than equal to 1), a higher proportion of patients treated with ustekinumab achieved the response (36.1 percent; 95% CI, 25.1 to 48.3) compared with patients receiving NB-UVB (27.6 percent; 95% CI, 20.0 to 36.4; p=NR).[28]

Infliximab Versus NB-UVB

There were no RCTs identified for this comparison of interest. One observational study by Emerit et al. evaluated the comparison of the biologic agent etanercept versus NB-UVB.[27] This study was rated with poor quality and subjects in the NB-UVB group were naïve to phototherapy and systemic nonbiologics.[27] The only outcome of interest reported was the intermediate outcome PASI at week 12, though subjects in the phototherapy group were also followed up at week 32.There was a significant reduction in mean PASI for both groups at week 12, although there was no comparison made of the change in PASI observed between etanercept and NB-UVB . In the infliximab group, PASI was reduced from 22.3 $\pm$ 6.5 at baseline to 2.1 $\pm$ 0.7 ($p<0.05$) at week 12. In the NB-UVB group, PASI was reduced from 21.3 $\pm$ 5.2 at baseline to 3.7 $\pm$ 1.2 ($p<0.05$) at week 12. Subjects in the NB-UVB group were also examined at week 32, after discontinuation of the treatment at week 12, and the mean PASI increased to 10.8 $\pm$ 2.2 ($p<0.05$ versus week 12).

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.[25] 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.[25] In this study, the oral portion of PUVA was either with 8-methoxypsoralen (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 were reported in the trial and are 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 clearance (6 percent versus 21 percent, p=NR), PASI 90 (22 percent versus 70 percent, p=NR), PASI 75 (56 percent versus 89 percent, p=NR), and PASI 50 (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 with PUVA but reported results by individual drug.[25] 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 that was a median duration of 10.3 weeks for the PUVA group. A lower proportion of alefacept treatment courses results in complete clearance (3 percent versus 21 percent, p=NR), PASI 90 (3 percent versus 70 percent, p=NR), PASI 75 (25 percent versus 89

percent, p=NR), and PASI 50 (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. Two observational studies evaluated the comparison of the biologic agent adalimumab versus PUVA.[25,27]

The first study by Inzinger et al. compared a variety of biologics with PUVA but reported results by individual drug.[25] 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 clearance (6 percent versus 21 percent, p=NR), PASI 90 (29 percent versus 70 percent, p=NR), PASI 75 (39 percent versus 89 percent, p=NR), and PASI 50 (84 percent versus 92 percent, p=NR) compared with PUVA therapy.

The second study by Emerit et al. was rated with poor quality and subjects in the PUVA group were naïve to phototherapy and systemic nonbiologics.[27] The only outcome of interest reported was the intermediate outcome PASI at week 12, though subjects in the phototherapy group were also followed up at week 32. There was a significant reduction in mean PASI for both groups at week 12 although there was no comparison made of the change in PASI observed between etanercept and NB-UVB. In the etanercept group, PASI was reduced from 21.4 $\pm$ 6.1 at baseline to 3.7 $\pm$ 1.2 ($p<0.05$) at week 12. In the PUVA group, PASI was reduced from 21.9 $\pm$ 6.3 at baseline to 2.2 $\pm$ 1.1 ($p<0.05$) at week 12. Subjects in the PUVA group were also examined at week 32, after discontinuation of the treatment at week 12, and the mean PASI increased to 7.3 $\pm$ 1.8 ($p<0.05$ versus week 12).

Infliximab Versus PUVA

There were no RCTs identified for this comparison of interest. Two observational studies evaluated the intermediate health outcome in this comparison of the biologic agent infliximab with PUVA.[25, 27] No data were reported for final health outcomes.

The first study by Inzinger et al. compared a variety of biologics with PUVA but reported results by individual drug.[25] 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 higher proportion of treatment courses resulted in complete clearance (29 percent versus 21 percent, p=NR), PASI 90 (71 percent versus 70 percent, p=NR), PASI 75 (100

percent versus 89 percent, p=NR), and PASI 50 (100 percent versus 92 percent, p=NR) compared with PUVA therapy.

The second study by Emerit et al. was rated with poor quality and subjects in the PUVA group were naïve to phototherapy and systemic nonbiologics.[27] The only outcome of interest reported was the intermediate outcome PASI at week 12, though subjects in the phototherapy group were also followed up at week 32. There was a significant reduction in mean PASI for both groups at week 12 although there was no comparison made of the change in PASI observed between etanercept and NB-UVB. In the infliximab group, PASI was reduced from 22.3 $\pm$ 6.5 at baseline to 2.1 $\pm$ 0.7 ($p<0.05$) at week 12. In the PUVA group, PASI was reduced from 21.9 $\pm$ 6.3 at baseline to 2.2 $\pm$ 1.1 ($p<0.05$) at week 12. Subjects in the PUVA group were also examined at week 32, after discontinuation of the treatment at week 12, and the mean PASI increased to 7.3 $\pm$ 1.8 ($p<0.05$ versus week 12).

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.[25] 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 clearance (6 percent versus 21 percent, p=NR), PASI 90 (39 percent versus 70 percent, p=NR), PASI 75 (67 percent versus 89 percent, p=NR), and PASI 50 (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., thrombocytopenia (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 five RCTs (two good, two fair, and one poor in quality) and two observational studies (both fair in quality) directly compared biologics with nonbiolgics and reported at least one adverse outcome of interest.
    - No trials or observational studies directly compared biologics with phototherapy.

- Infection rate did not differ between adalimumab and methotrexate (low strength of evidence). These 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.

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 were 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 E, Tables 3 and 4. Tables that display the outcomes reported within this Key Question can be found in Appendix F, Tables 5 to 11. Strength of evidence ratings as well as description of the applicability of each study can be found in Appendix G and Appendix H, Tables 12 to 48.

Outcome Evaluation

Systemic Biologic Agents Versus Systemic Nonbiologic 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 aspartate aminotransferase (AST), alanine aminotransferase (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 upper limit of normal (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.[30,37] 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.[37] 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.[37]

One nonrandomized 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.[30] 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.[30] 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.[38] 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 Alefacept

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.[31] Well controlled was defined as a PGA of "mild", "almost clear" or "clear". This study was rated as having fair quality and data about whether patients were naïve to treatment were 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[31], 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 were not reported.. Although neutropenia was not reported in this study, the mean CD4+ count (a subset of white blood cells) 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

Three RCTs compared the biologic agent etanercept with the nonbiologic agent acitretin and reported data regarding harms.[22-24] 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. The third RCT (herein clinical trial 5) which was rated as having poor quality has not been published as a manuscript and the data were extracted from www.clinicaltrials.gov. [24] 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. In clinical trial 5, all patients were naïve to TNF inhibitors, efalizumab, and alefacept.

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 reports of AST toxicity in clinical trial 5, however, one patient (4.76 percent) in the etanercept group did report ALT toxicity compared with none in the acitretin group (p=NR). [24] 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 subjects in the etanercept group completed the trial (p=NR).[22,23] In clinical trial 5, four subjects (19.0 percent) withdrew from the etanercept group, while six subjects (33.3 percent) withdrew from the acitretin group (p=NR).[24] One patient in the etanercept group also reported an injection site reaction (4.76 percent) compared with none in the acitretin group (p=NR). There were no reports of hypertension or infection in either etanercept or acitretin groups in clinical trial 5 (p=NR).

Etanercept Versus Cyclosporine

No RCTs or observational studies 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.[29] This study was rated as having poor quality and data about whether patients were naïve to treatment were 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 units per L [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 with 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 with patients treated with methotrexate.[26] 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 with 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). However, statistical comparisons of weight between etanercept and methotrexate were not made. 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.[21,26] 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.[39]

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.[39] 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).[39]

One observational study by Gisondi et al., rated with fair quality, compared patients treated with the biologic agent infliximab with patients treated with the nonbiologic agent methotrexate.[26] 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).[39] No patients experienced hepatic enzyme elevation or TCP after the switch.[39] One patient (1.59 percent) was reported to have hypertension in 63 patients who transitioned from methotrexate to infliximab while no cases occurred in 9 patients who transitioned from infliximab to methotrexate (p=NR).[39] Five patients (8 percent) experienced infusion-related reactions in 63 patients who transitioned from methotrexate to infliximab. 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 63 patients who transitioned from methotrexate to infliximab while no events occurred in 9 patients who transitioned from infliximab to methotrexate (p=NR).[39]

Class Level Comparisons

Two observational studies reported data comparing biologic agents and nonbiologic agents at the class level.[26,33] One study directly compared classes[26] while the other study observed transitions of therapy from nonbiolgics to biologics.[33]

The first study by Gisondi et al., rated with fair quality, compared treatment with biologic agents (etanercept or infliximab) with the nonbiologic agent methotrexate.[26] 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.[33] 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 nonrandomized 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 2 months of therapy.[30] After stopping NB-UVB therapy for 4 to 10 days, patients were transitioned to adalimumab treatment.[30] 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 psoriatic arthritis (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.[35] Two additional observational studies were identified although neither controls for confounding and therefore are report and discussed for descriptive purposes only.[30,31]

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, and the final health outcome HRQoL measured with the DLQI (Table 7).[35] The mean DLQI change from baseline to week 16 was reported for four groups stratified by percent PASI improvement from baseline: PASI ≥75, PASI 50 to 75, PASI 25 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 PASI 50 to 75 compared with PASI<25 (p<0.001). All other comparisons were not statistically significant, although exact p-values were not reported.

Table 7. Relationship between disease severity and dermatology life quality index

Study	Characteristics	N	Followup	DLQI mean(SD)	P-values Versus PASI 50 to 75	P-values Versus PASI 25 to 50	P-values 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; p-value = probability value; SD = standard deviation; w = weeks; --- = not applicable
*Based on percentage improvement from baseline.

Weight and PGA

One nonrandomized 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.[30] 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 these 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 with 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 with 57 percent (4 out of 7) of patients weighing more than 100 kg (p=NR) (Table 8).

Table 8. 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)	---

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

History of PsA and Pain

The open label study by Strober et al.[30] 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 these 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 with patients without a history of PsA (-19.2 versus -11.6; p=NR) (Table 9). 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 with patients without a history of PsA (-47.1 versus -13.2; p=NR).

Table 9. 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)	---

MTX = methotrexate; NB-UVB = narrow-band ultraviolet B; NR = not reported; PsA = psoriatic arthritis; P-values = probability values; SD = standard deviation; VAS = visual analogue scale; 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).[32] Patients were included if they failed nonbiologic therapy (according to PASI and pain score), 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 10) 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 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 PASIs 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]. PASI 50 and PASI 75 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 PASI 50 at week 24 (p=0.013).

Table 10. The relationship between prior treatment with systemic biologic agent and Psoriasis Area Severity Index

Study	Characteristics	Followup	PASI 50 n/N (%)	PASI 75 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	---

n/N = number of patients per total population; PASI = Psoriasis Area Severity Index; SD = standard deviation; w = week; --- = not reported; p-value = probability value

*infliximab, efalizumab.

†p-value=0.013 for prior exposure to biologics versus naïve to biologics at week 24.

Discussion

Patients and health care providers encounter several important considerations when evaluating therapeutic options in the treatment of chronic plaque psoriasis. Despite being studied in comparison with placebo, biologic systemic agents have infrequently been compared directly with nonbiologic systemic therapies or phototherapy. Our literature review yielded only five randomized controlled trials (RCTs) and two observational studies directly comparing systemic biologics versus systemic nonbiologics and no RCTs and three observational study directly comparing systemic biologics and phototherapy. Overall, the quality of the studies was either good or fair, with a few rated as having poor quality. 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 11. Individual strength of evidence ratings per comparison can be found in Appendix G. None of the comparisons with phototherapies can be found in the table since there was insufficient evidence regardless of the comparison or outcome being evaluated. Although there are some comparisons that 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, on an individual drug level, in patients with chronic plaque psoriasis.

Table 11. 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[35] 1 OBS[28]	Adalimumab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[17] 1 OBS[28]	Adalimumab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[17] 1 OBS[28]	Adalimumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
	Patient's assessment of disease severity	1 RCT[35]	Adalimumab improves a patient's assessment of disease severity compared with methotrexate.	L
	Pain	1 RCT[35]	Adalimumab reduces a patient's pain compared with methotrexate.	L
	Pruritus	1 RCT[35]	Adalimumab reduces a patient's pruritus compared with methotrexate.	L
	Infection	1 RCT[17]	Infection rates do not differ between adalimumab and methotrexate.	L
Etanercept versus acitretin	PASI	3 RCT[22-24]	Etanercept improves a patient's PASI compared with acitretin.	M

Table 11. Summary of findings for the comparison of systemic biologic agents versus systemic nonbiologic agents (continued)

Comparison	Outcome*	Type and Number of Studies	Conclusion	SOE
Infliximab versus methotrexate	HRQoL	1 RCT[21]	Infliximab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[21] 1 OBS[26]	Infliximab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[21]	Infliximab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
Ustekinumab versus methotrexate	PGA	1 OBS[28]	Ustekinumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L

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, infliximab, and ustekinumab resulted in favorable outcomes when compared with individual nonbiologic agents (Table 11). However, we could not determine the comparative effectiveness of these therapies with regard to final health outcomes other than health-related quality of life (HRQoL), due to lack of evaluation in the included literature. We could not determine the comparative efficacy between other available biologics such as 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 and observational study, had the most outcomes evaluated, although most were intermediate outcomes and all were based on low strength of evidence (Table 11).[17,28] HRQoL was measured using both the dermatology life quality index (DLQI) and EuroQol 5-Dimension™ (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 considered 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 visual analogue scale (VAS).[40] It is not surprising that HRQoL improved in those treated with adalimumab, as Psoriasis Area and Severity Index (PASI) was also significantly improved compared with methotrexate at 16 weeks, including complete clearance. Time to PASI 75 was also significantly shorter in adalimumab treated patients (28 versus 84 days). Other intermediate outcomes including Physician's Global Assessment (PGA), patient assessment of disease severity, and individual symptoms of pain and pruritus were also improved in patients treated with adalimumab.

Compared with acitretin, three RCTs showed that etanercept improved a patient's PASI with moderate strength of evidence.[22-24] Both PASI 50 and PASI 75 were evaluated and showed favorable improvement in patients treated with etanercept at 24 weeks.

Compared with methotrexate, one observational study suggested that a higher proportion of patients treated with ustekinumab had a PGA of "clear" or "minimal", based on an analysis adjusted for confounding.[28]

Compared with 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 Short Form-36 Health Survey (SF-36) mental (MCS) and physical (PCS) and all showed favorable improvements in the infliximab treated patients at 16 weeks. Changes seen in both treatment arms, however, can be considered 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.[40] 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 that are clearly defined within clinical practice guidelines.[4,11,41] 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 with 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 11). 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 that 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 randomized controlled comparative study of adalimumab versus methotrexate versus placebo in patients with psoriasis (CHAMPION) trial, data suggest that as disease severity improves, so does a patient's HRQoL. 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 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.[40] DLQI was moderately correlated with PASI ($r=0.69$, $p<0.001$).[40] Data from this RCT also suggest that the minimal clinically important difference for the DLQI ranges from a change of 2.3 to 5.7.[40] Based on these data, the changes in DLQI in patients achieving a PASI 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 PASI 50, PASI 75, and PASI 90 suggested that the probability of achieving any of the three PASIs was highest for infliximab, followed by adalimumab, etanercept, methotrexate, cyclosporine, efalizumab, alefacept, and finally supportive care.[34]

Applicability

Applicability assessments for individual studies can be found in Appendix H. Our literature base is most applicable to patients with more advanced chronic plaque psoriasis and is not applicable to milder forms. Five of the seven studies that directly compared biologics and nonbiologics required patients to have moderate to severe plaque psoriasis for enrollment, and in these studies the baseline mean PASI ranged from 10.4 to 26.3. In the remaining two studies, although moderate to severe plaque psoriasis was not an explicit inclusion criterion, the mean PASI at baseline for one study was consistent with the other studies and ranged from 8.2 to 18.8 whereas the other study did not report PASI at baseline. Only one of these seven studies was conducted in the United States and therefore the overall literature may not reflect local clinical practice. The majority of patients evaluated were not naïve to psoriasis treatment. All interventions evaluated in these studies are currently approved by the Food and Drug Administration and were at doses approved for chronic plaque psoriasis, therefore are relevant to treatment practice in the U.S. Four of seven studies evaluated final health outcomes and were generally not sufficient in length to adequately evaluate such outcomes, with exception of HRQoL. The followup in these studies ranged from 12 to 26 weeks. Alternatively, for intermediate outcomes, studies were sufficient in length to evaluate such outcomes with two exceptions. One study had a short followup period and the second was cross-sectional in design. 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.

Three observational studies directly compared biologics and phototherapy where moderate to severe plaque psoriasis was not an explicit inclusion criteria. However, the mean PASI at baseline was consistent with the other studies and ranged from 15.0 to 22.3.Therefore the literature reflects patients with more advanced chronic plaque psoriasis and is not applicable to mild forms. Two of the three studies were conducted outside of the United States and therefore the overall literature may not reflect clinical practice. The majority of patient in these studies were not naïve to treatment. 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. Only one final health outcome was evaluated and of the intermediate outcomes the duration of followup ranged from10.3 to 32 weeks. Adverse events were not evaluated in these studies.

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 five RCTs comparing a biologic with a nonbiologic are included in this report, any no RCTs comparing a biologic with phototherapy were identified. Therefore, the most important area of future research is additional RCTs or large observational studies and registries 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 analyses using indirect comparisons may also help to supplement lack of direct comparative data.

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, major adverse cardiovascular events, and psychological outcomes. This would likely require longer duration trials and larger sample sizes compared with the current literature base. Since the longest study was 32 weeks in duration, only short term outcome assessment was possible. Additional consideration of factors such as convenience of therapy should be weighed against these outcomes in future decision-making. 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 U.S. The majority of included studies (11 of 14 studies) were conducted in other countries, where clinical practice may not reflect practice within the U.S.

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Acronyms/Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BSA	body surface area
CER	Comparative Effectiveness Review
CI	confidence interval
CPP	chronic plaque psoriasis
DLQI	dermatology life quality index
EQ-5D	EuroQol 5-Dimension™ (test of health-related quality of life)
EQ-5D VAS	EQ-5D visual analogue scaleFDA = Food and Drug Administration
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	health-related quality of life
IL	interleukin
Kg	kilogram
Kg/m^2	kilogram per meter squared
MACE	major adverse cardiovascular events
MCS	Mental Component Summary (part of SF-36)
NB-UVB	narrowband-ultraviolet B
NR	not reported
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary (part of SF-36)
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PSSQ	Psoriasis Subject Satisfaction Questionnaire
PUVA	psoralen plus ultraviolet A
RCT	randomized controlled trial
SCr	serum creatinine
SF-36	Short Form-36 Health Survey
SGA	Subject Global Assessment
SOE	strength of evidence
TCP	thrombocytopenia
TNF	tumor necrosis factor
ULN	upper limit of normal
UVB	ultraviolet B
5-MOP	5- methoxypsoralen
8-MOP	8-methoxypsoralen

Appendix A. Search Strategy

Search 1: MEDLINE® and Cochrane Central Register of Controlled Trials (OVID)

1. psoriasis.mp. or Psoriasis/
2. Psoriasis/ or plaque psoriasis.mp.
3. 1 or 2
4. methotrexate.mp. or Methotrexate/
5. cyclosporin.mp. or Cyclosporine/
6. cyclosporine.mp. or Cyclosporine/
7. ciclosporin.mp. or Cyclosporine/
8. calcineurin inhibitor.mp.
9. acitretin.mp. or Acitretin/
10. retinoids.mp. or Retinoids/
11. antimalarials.mp. or Antimalarials/
12. hydroxyurea.mp. or Hydroxyurea/
13. isotretinoin.mp. or Isotretinoin/
14. sulfasalazine.mp. or Sulfasalazine/
15. 6-thioguanine.mp. or Thioguanine/
16. azathioprine.mp. or Azathioprine/
17. cyclophasphamide.mp. or Cyclophosphamide/
18. mycophenolate mofetil.mp.
19. nsaid.mp. or Anti-Inflammatory Agents, Non-Steroidal/
20. antihistamine.mp. or Histamine Antagonists/
21. leflunomide.mp.
22. tacrolimus.mp. or Tacrolimus/
23. fish oil.mp. or Fish Oils/
24. ergocalciferols.mp. or Ergocalciferols/
25. bicillin l-a.mp. or Penicillin G Benzathine/
26. prednisone.mp. or Prednisone/
27. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. etanercept.mp.
29. infliximab.mp.
30. adalimumab.mp.
31. alefacept.mp.
32. ustekinumab.mp.
33. cnto 1275.mp.
34. biologics.mp.
35. biologic agents.mp.
36. monoclonal antibody.mp. or Antibodies, Monoclonal/
37. t-cell modulator.mp.
38. tumor necrosis factor inhibitor.mp.
39. briakinumab.mp.
40. ABT 874.mp.
41. voclosporin.mp.
42. ISA-247.mp.

43. CP 690,550.mp.
44. certolizumab.mp.
45. cdp870.mp.
46. daclizumab.mp.
47. erlotinib.mp.
48. abatacept.mp.
49. rituximab.mp.
50. golimumab.mp.
51. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52. psoralen.mp. or Ficusin/
53. PUVA Therapy/ or puva.mp.
54. phototherapy.mp. or Phototherapy/
55. uvb.mp.
56. uva.mp.
57. laser therapy.mp. or Laser Therapy/
58. Lasers, Excimer/ or excimer.mp.
59. goeckerman.mp.
60. ingram.mp.
61. 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62. 51 and 61
63. 3 and 62
64. 27 and 51
65. 3 and 64
66. 63 or 65

Search 2: MEDLINE®, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment database

1. randomized controlled trials/
2. controlled clinical trial.sh.
3. clinical trial/
4. randomi$ control$ trial$.tw.
5. clinical trial$.tw.
6. trial$.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. review literature/
9. meta-analysis.sh.
10. meta-analy$.tw.
11. metaanaly$.tw.
12. (meta adj analy$).tw.
13. 8 or 9 or 10 or 11 or 12
14. (indirect adj2 comparison$).tw.
15. (indirect adj2 evaluat$).tw.
16. (indirectly adj2 compar$).tw.
17. bayesian.tw.
18. (mixed treatment adj compar$).tw.

19. (mixed treatment adj evaluat$).tw.
20. MTC.tw.
21. 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 and 13
23. 21 and 22
24. psoriasis.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tx, kw, sh, ct]
25. psoriasis/
26. chronic psoriasis.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tx, kw, sh, ct]
27. 24 or 25 or 26
28. 23 and 27
29. remove duplicates from 28

Appendix B. Data Extraction Form

Study Identification

Unique ID:	**First author's name, publication year:**	**Study acronym (if applicable):**	**Publication format**: ☐ Full text manuscript ☐ Abstract ☐ Other (specify):

Funding Source (specify): ☐ Industry ☐ Government/Foundation ☐ Academia ☐ Other/NR	**Conflicts of interest reported?** Y ☐ Not reported ☐	**Geographic location and setting:**	**Number of Centers:**	**Total N randomized (N randomized in arms we use):**

Study Design and Quality Characteristics

(Select either RCT or observational and complete corresponding section, if you answer N report why)

☐ **Randomized controlled trial** ☐ **Before and after study**	
Were the groups similar baseline in terms of baseline characteristics? Y ☐ N ☐ Not reported ☐	**Were outcomes assessed using a valid methodology and criteria?** Y ☐ N ☐ Partially ☐ Not reported ☐
Were subjects and providers blind to intervention status of participants? Y ☐ N ☐ Partially ☐ Not reported ☐	**Were outcome assessors blind to intervention status?** Y ☐ N ☐ Partially ☐ Not reported ☐
Randomization technique described:	**Outcome assessment described (Who and How):**
Was intention to treat analysis used? **Y** ☐ **N** ☐	
Were methods used for randomization adequate? Y ☐ N ☐ Partially ☐ Not reported ☐	**Was incomplete data adequately addressed?** Y ☐ N ☐ Not reported ☐
Was allocation concealment adequate? Y ☐ N ☐ Partially ☐ Not reported ☐	

Was the differential loss to followup between groups <10%? Y ☐ N ☐		**Was the overall loss to followup <20%?** Y ☐ N ☐	
Duration of followup (longest):		**Follow-up % for the primary outcome:** Intervention Comparator	
Overall quality score (use protocol for criteria): good ☐ fair ☐ poor ☐			
☐ **Controlled observational study (specify design in detail):** ❑ **Case-control** ❑**Cohort** ☐ **Other (specify)**			
Unbiased selection of cohort: Y ☐ N ☐ NR ☐	**Selection minimizes baseline differences:** Y ☐ N ☐ NR ☐	**Blinded outcome assessment:** Y ☐ N ☐ Partially ☐ NR ☐	**Outcome assessment described:**
Sample size calculated: Y ☐ N ☐ NR ☐	**Adequate description of cohort:** Y ☐ N ☐ Partially ☐ NR ☐	**Validated method to ascertain exposure (CC):** Y ☐ N ☐ Partially ☐ NR ☐	**Validated method to ascertain outcomes:** Y ☐ N ☐ Partially ☐ NR ☐
Adequate follow-up period: Y ☐ N ☐ Partially ☐ NR ☐	**ITT for cohort:** Y ☐ N ☐ Partially ☐ NR ☐	**Adequate analysis to control for confounding:** Y ☐ N ☐ Partially ☐ NR ☐	**Covariates/potential confounders adjusted for:**
Selection of comparison group: Y ☐ N ☐ NR ☐	**Differential loss to follow-up <10%:** Y ☐ N ☐ NR ☐	**Overall loss to follow-up <20%:** Y ☐ N ☐ NR ☐	**Reporting of specified outcomes:** Y ☐ N ☐
Overall quality score (use protocol for criteria): good ☐ fair ☐ poor ☐			

METHODS

Patient Population

Inclusion criteria:	**Exclusion criteria:**
Disease location:	
Definition of cohort:	
Case:	**Control**:

Study Interventions

☐ Biologic systemic agent versus nonbiologic systemic agent
☐ Biologic systemic agent versus phototherapy
☐ Class comparisons

*Multiple therapies will only be included if the common interventions are similar across groups compared and the final comparison is of a single biologic systemic agent with a single nonbiologic systemic agent *or* phototherapy.

Intervention 1	**Intervention 2**	**Intervention 3**	**Intervention 4**
Pharmacologic Class:	**Pharmacologic Class:**	**Phototherapy:**	**Pharmacologic Class:**
Drug name:	Drug name:	Name:	Drug name:
Dose:	Dose:	Description of the regimen (exact):	Dose:
Route:	Route:		Route:
Frequency:	Frequency:		Frequency:
Timing of first dose:	Timing of first dose:		Timing of first dose:
Duration of therapy (no. days):	Duration of therapy (no. days):	Duration of therapy (no. days):	Duration of therapy (no. days):
Other (drug holiday, regimen details):	Other (drug holiday, regimen details):	Other (drug holiday, regimen details):	Other (drug holiday, regimen details):
Concurrent medications:		Concurrent topical agents:	

Characteristic	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Comments
Number of participants (N)					
Age, years (mean±SD, median IQR)					
Female n/N (%)					
Race n/N (%) • White					
• Black					
• Asian					
• Other					
Hispanic					
Weight, kg (mean ± SD, range)					
BMI (mean ± SD, range)					
Smoker n/N (%)					
Obesity n/N (%)					
Lipids (mean ± SD) • LDL					
• HDL					
• Total Cholesterol					
• TG					
HRQoL(mean ± SD) • DLQI					
• HAQ-DI					
• EQ-5D IS					
• EQ-5D VAS					

Baseline disease severity • PASI (mean ± SD, range) • %					
• BSA (%)					
• PGA (%) Moderate					
Moderate to severe					
Very severe					
Concomitant psoriatic arthritis n/N (%)					
Disease duration, years (mean ± SD, range)					
Neutralizing antibodies n/N (%)					
Naïve to psoriasis therapy (specify) n/N (%)					
No. patients previously treated n/N (%)					
No. previous treatments • 0					
• 1					
• 2-3					
• >3					
Previous treatment failure n/N (%)					
Compliance (mean ± SD)					
Dose (mean ± SD)					

Final health Outcomes						
Outcome	**Definition**	**Time point**	**Intervention 1**	**Intervention 2**	**Summary estimate**	**Variances**
Total Mortality n/N (%)						
• DLQI						
• HAQ-DI						
• EQ-5D						
• EQ-5D						
MACE						
Diabetes n/N (%)						
Psychological comorbidities • Depression n/N (%)						
• Suicide n/N (%)						

Intermediate Health Outcomes						
Outcome	**Definition**	**Time point**	**Intervention 1**	**Intervention 2**	**Summary Estimate**	**Variances**
BSA (mean ± SD, range)						
PASI (mean ± SD)						
PASI						

Intermediate Health Outcomes						
Outcome	**Definition**	**Time point**	**Intervention 1**	**Intervention 2**	**Summary Estimate**	**Variances**
PASI n/N (%) • PASI 50						
• PASI 75						
• PASI 90						
• PASI 100						
Physician's Global Assessment (PGA) "clear" or "minimal"						

Intermediate Health Outcomes						
Outcome	**Definition**	**Time point**	**Intervention 1**	**Intervention 2**	**Summary Estimate**	**Variances**
Mean Physician's Global Assessment (PGA)						
Symptom Improvement n/N (%)						
Patient's assessment of global improvement (PaGA)						

Adverse Outcomes						
Outcome	**Definition**	**Time point**	**Intervention 1**	**Intervention 2**	**Summary Estimate**	**Variances**
Hepatotoxicity • AST n/N (%)						
• ALT n/N (%)						
Nephrotoxicity • SCr or GFR						
Hematologic Toxicity • Thrombocytopenia n/N (%)						
• Anemia n/N (%)						
• Neutropenia n/N (%)						

Adverse Outcomes						
Outcome	**Definition**	**Time point**	**Intervention 1**	**Intervention 2**	**Summary Estimate**	**Variances**
Hypertension n/N (%)						
Metabolic alterations • Glucose (mean ± SD)						
• HDL (mean ± SD)						
• LDL (mean ± SD)						
• Total Cholesterol (mean ± SD)						
• TG (mean ± SD)						
• BMI (mean ± SD)						
• Thyroid function n/N (%)						
Injection site reaction n/N (%)						
Malignancy						
Infections n/N (%)						
Study Withdrawal n/N (%)						
Study Withdrawal due to study drug n/N (%)						

Does this trial or study have sub group analysis looking at 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 or presence of neutralizing antibodies? ☐ Yes ☐ No If yes, report data:

Does this trial or study have information that might be used to answer?
KQ1? ☐ Yes ☐ No Class comparisons? ☐ Yes

KQ2? ☐ Yes ☐ No Class comparisons? ☐ Yes
KQ3? ☐ Yes ☐ No Class comparisons? ☐ Yes
If yes, please print a copy of the article and put into the correct pile for KQ1, 2 or 3.

Appendix C. Excluded Studies From Full-Text Review

Table 1. Excluded studies at the full text level from primary search

Excluded because citation was not a full text systematic review, study or trial (n=66)
Ahmad K, McDonnell TJ, Rogers S. Does prior treatment with fumaric acid esters predispose to tuberculosis in patients on etanercept? Clin Exp Dermatol 2007;32:329.
Amital H, Ingber A, Rubinow A. Infliximab-induced remission of extensive plaque psoriasis. Isr med Assoc J 2003;5:827-28.
Balato N, Gallo L, Gaudiello F, et al. Transient and reversible thrombocytopenia in a psoriatic patient treated with etanercept. J Dermatolog Treat 2010;21:117-18.
Bansal C, Leonardi C, Van Voorhees AS. Persistent CD4+ T cell depression following combination alefacept and methotrexate therapy. Int J Dermatol 2008;47:1204-06.
Barland C, Kerdel FA. Addition of low-dose methotrexate to infliximab in the treatment of a patient with severe, recalcitrant pustular psoriasis. Arch Dermatol 2003;139:949-50.
Belinchon J, Lucas A, Mataix J, Perez-Crespo M, Silvestre J, Betlloch I. Therapy-resistant psoriasis treated with adalimumab and concomitant narrow band ultraviolet B phototherapy with clearing of psoriasis. J Eur Acad Dermatol Venereol 2007;21:22.
Berns MW, McCullough JL. Porphyrin sensitized phototherapy. Arch Dermatol 1986;122:871-74.
Boulinguez S. [News on psoriasis from the 2010 Dermatology Days in Paris] Ann Dermatol Venereol 2011;138(Suppl 1):H1.
Carrascosa J M, Soria X, Ferrandiz C. Effective management of a psoriatic flare with narrowband UVB phototherapy during efalizumab therapy without discontinuing treatment. J Eur Acad Dermatol Venereol 2007;21:828-29.
Dalaker M, Bonesronning JH. [Treatment of severe psoriasis with anti-TNF-alpha-antibody and methotrexate]. Tidsskr Nor Laegeforen 2003;123:1070-71.
Daulat S, Detweiler JG, Pandya AG. Development of pemphigus vulgaris in a patient with psoriasis treated with etanercept. J Eur Acad Dermatol Venereol 2009;23:483-84.
Davison SC, Bunker CB, Basarab T. Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. Br J Dermatol 2002;147:831-32.
Dawe RS. Using 'number needed to treat' to express the magnitudes of benefit of ultraviolet B phototherapy and of antitumour necrosis factor-alpha therapies for psoriasis. Br J Dermatol 2010;162:456-57.
Drijkoningen M, De Wolf-Peeters C, Roelandts R, et al. A morphological and immunohistochemical study of phytophotodermatitis-like bullae induced by PUVA. Photodermatol 1986;3:199-201.
Dubin DB, Tanner W, Ellis R. Biologics for psoriasis. Nat Rev Drug Discov 2003;2:855-56.
Egnatios G, Warthan MM, Pariser R, et al. Pustular psoriasis following treatment of rheumatoid arthritis with TNF-alpha inhibitors. J Drugs Dermatol 2008;7:975-77.
Elewski BE. Infliximab for the treatment of severe pustular psoriasis. J Am Acad Dermatol 2002;47:796-97.
Fiala K, Schierl M, Breier F, et al. Transient paresis of the right recurrent laryngeal nerve after treatment with etanercept for plaque-type psoriasis. Eur J Dermatol 2010;20:818-19.
Gonzalo-Garijo MA, Perez-Calderon R, de Argila Fernandez-Duran D. Severe generalized exanthema due to etanercept given for severe plaque psoriasis. Ann Allergy Asthma Immunol 2008;100:621-22.
Gonzalo-Garijo M A, Rodriguez-Nevado I, Perez-Calderon R, et al. Severe cutaneous reaction and fever due to adalimumab. Ann Allergy Asthma Immunol 2010;105:490-91.
Heikkila H, Ranki A, Cajanus S,et al. Infliximab combined with methotrexate as long-term treatment for erythrodermic psoriasis. Arch Dermatol 2005;141:1607-10.
Honigsmann H. Comparison of psoralen plus ultraviolet A therapy and biologics in moderate to severe chronic plaque psoriasis. Br J Dermatol 2011;165:455-56.
Jackle R. [Vitamin D3 analogs, oral fumaric acid, TNF-alpha antibodies. New hope for patients with psoriasis]. MMW Fortschr Med 2001;143:4-8.
Jaiswal R, Darabi K, Bechtel M, Zirwas M, Hostetler S. Spontaneous epidural abscess and subsequent quadriplegia in a psoriasis patient treated with etanercept and methotrexate. J Am Acad Dermatol 2009;60:AB170.
Katz KA. Psoriasis Area and Severity Index 50 as an endpoint in psoriasis trials: an unconvincing proposal. J Am Acad Dermatol 2005;53:547-51.
Kerner M, Rozenman D, Ziv M. Combination therapy with cyclosporine A and an anti-TNF alpha agent (adalimumab) in the treatment of severe psoriasis. J Am Acad Dermatol 2011;64:AB161.
Kincaid L. Psoriasis: TNF-alpha inhibitors and beyond. Drug Discov Today 2005;10:884-86.
Kluger N, Girard C, Guillot B, et al. Efficiency and safety of etanercept after acute hepatitis induced by infliximab for psoriasis. Acta Derm Venereol 2009;89:332-34.
Lee MR, Cooper AJ. Use of infliximab in the treatment of psoriasis. Australas J Dermatol 2004;45:193-95.

Leonardi C. Rebound in patients abruptly discontinued from etanercept. J Am Acad Dermatol 2005;52:P193.

Lima HC, Kubo E, Rosas F, Santamaria JR, Moraes L. Combining biologics and cyclosporine for psoriasis treatment. J Am Acad Dermatol 2009;60:AB179.

Lucas A, Belinchon I, Perez-Crespo M, et al. Successful response to narrow-band UVB in a patient undergoing concomitant treatment with adalimumab for psoriasis. Australas J Dermatol 2008;49:173-74.

McCluggage LK, Hussar DA. New drugs: Ustekinumab, tocilizumab, and telavancin hydrochloride. J Am Pharm Assoc 2010;50:324-27.

Menter A. Goeckerman therapy versus biologics in the treatment of psoriasis. J Am Acad Dermatol 2010;62:516-17.

Mocciaro F, Renna S, Orlando A, et al. Severe cutaneous psoriasis after certolizumab pegol treatment: report of a case. Am J Gastroenterol 2009;104:2867-68.

Mrowietz U, Barth J, Boehncke WH, et al. [Therapy of psoriasis vulgaris and psoriatic arthritis with etanercept]. J Deutschen Dermatologischen Gesellschaft 2005;3:470-72.

Naidoo P, Rambiritch V. Voclosporin (ISA247) for plaque psoriasis. Lancet 2008;372:888-89.

Nakagomi D, Harada K, Yagasaki A, et al. Psoriasiform eruption associated with alopecia areata during infliximab therapy. Clin Exp Dermatol 2009;34:923-24.

Naldi L. The search for effective and safe disease control in psoriasis. Lancet2008;371:1311-12.

Nallamothu PG, Nallamothu BK, Lim HW. Etanercept in patients with moderate to severe psoriasis who fail methotrexate: a cost-effectiveness analysis. J Invest Dermatol 2004;122:378.

Nijsten T, Spuls PI. Adalimumab may be better or no worse than methotrexate in the treatment of psoriasis. Br J Dermatol 2008;159:257-58.

Nikkels AF, Pierard GE. Etanercept and recalcitrant acrodermatitis continua of Hallopeau. J Drugs Dermatol 2006;5:705-06.

Olivieri I, D'Angelo S, Leccese P, et al. Worsening of psoriasis with rituximab therapy. Clin Exp Rheumatol 2010;28:926.

Ozdemir M, Mevlitoglu I, Balevi A. Acitretin narrow-band TL-01 phototherapy but not etanercept treatment improves a localized inflammatory linear verrucous epidermal naevus with concomitant psoriasis. J Eur Acad Dermatol Venereol 2009;23:1453-54.

Papadavid E, Makris M, Dalamaga M, et al. Recall injection-site reactions to etanercept in a patient with psoriasis. Clin Exp Dermatol 2009;34:414-15.

Pereira TM, Vieira AP, Fernandes JC, et al. Anti-TNF-alpha therapy in childhood pustular psoriasis. Dermatology 2006;213:350-52.

Rallis E, Verros CD. Ustekinumab treats psoriasis refractory to seven conventional and biologic therapies. Dermatol Online J 2011;17:14.

Rallis E, Verros CD. Ustekinumab treats psoriasis refractory to seven conventional and biologic therapies. Dermatol Online J 2011;17:14.

Renner R, Colsman A, Sticherling M. ILVEN: is it psoriasis? Debate based on successful treatment with etanercept. Acta Derm Venereol 2008;88:631-32.

Rokhsar C, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. J Am Acad Dermatol 2006;54:361-62.

Strober BE. Successful treatment of psoriasis and psoriatic arthritis with etanercept and methotrexate in a patient newly unresponsive to infliximab. J Am Acad Dermatol 2004;50:P570.

Strober BE. Successful treatment of psoriasis and psoriatic arthritis with etanercept and methotrexate in a patient newly unresponsive to infliximab. Arch Dermatol 2004;140:366.

Tan E, Grattan C. Non-Hodgkin's T-cell lymphoma in a patient with erythrodermic pustular psoriasis treated with infliximab, cyclosporine, and methotrexate. J Am Acad Dermatol 2006;54:AB204.

Taniguchi Y, Kumon Y, Shimamura Y, et al. Rapidly progressive destructive arthritis in psoriatic arthritis sine psoriasis: do bone resorption marker levels predict outcome of bone destruction in psoriatic arthritis? Mod Rheumatol 2011;21:106-108.

Thielen AM, Barde C, Saurat JH. Infliximab- and methotrexate-resistant rebound of psoriasis after discontinuation of efalizumab (Raptiva). Br J Dermatol 2006;155:846-47.

Toledo Alberola F, Ballester Nortes I, Belinchon Romero I, Betlloch Mas I, Cuesta Montero L. Concomitant treatment with adalimumab and narrowband UVB for severe plaque psoriasis: Report of three cases. J Am Acad Dermatol 2011;642:AB162.

Tun TT, Dewitt CA, Stone SP. The combination of alefacept and acitretin for the treatment of chronic plaque psoriasis. J Am Acad Dermatol 2006;54:AB225.

Tuxen AJ, Yong MK, Street AC, et al. Disseminated cryptococcal infection in a patient with severe psoriasis treated with efalizumab, methotrexate and ciclosporin. Br J Dermatol 2007;157:1067-68.

Ventura F, Gomes J, Duarte Mda L, et al. Efficacy and safety of etanercept in patients with psoriasis and hepatitis C. Eur J Dermatol 2010;20:808-09.

Warren RB, Brown BC, Carmichael AJ, et al. Long-term control of recalcitrant psoriasis with combination infliximab and methotrexate. Clin Exp Dermatol 2009;34:415-16.

Yamauchi P, Lowe N. Cessation of cyclosporine therapy by treatment with etanercept in patients with severe psoriasis. J Am Acad Dermatol 2005;52:P1.
Yamauchi PS, Lowe NJ. Cessation of cyclosporine therapy by treatment with etanercept in patients with severe psoriasis. J Am Acad Dermatol 2006;54:S135-38.
Yamauchi P, Lowe N, Koo S. Etanercept therapy allows tapering of methotrexate and sustained clinical responses in patients with moderate to severe psoriasis. J Am Acad Dermatol 2005;52:P185.
Yamauchi PS, Lowe NJ, Gindi V. Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol 2006;54:S121-22.
Yang YS, Haw CR, Lee EJ, Cho HR, Kim NI. Severe psoriasis in identical twin treated with etanercept and low-dose cyclosporine. J Am Acad Dermatol 2009;60:AB178.
No authors listed. [Aldalimumab in psoriatic arthritis and as the initial therapy in rheumatoid arthritis]. Krankenpfl J 2005;43:244.

Excluded because the population was not human adults (n=2)
Moore A, Wright E, Ostrowski L, Moore T. Etanercept and narrowband UVB combination therapy for plaque-type psoriasis shortens onset of action in both adults and children. J Am Acad Dermatol 2006;54:AB217.
Sasson M, Stiller MJ, Shupack JL, et al. Antibody titers to an oxidized thymidine moiety are altered by systemic pharmacotherapy and by ultraviolet B phototherapy. Arch Dermatol Res 1993;285:227-29.

Excluded because the population was not patients with chronic plaque psoriasis or psoriasis vulgaris (n=14)
Bose F, Raeli L, Garutti C, et al. Dual role of anti-TNF therapy: enhancement of TCR-mediated T cell activation in peripheral blood and inhibition of inflammation in target tissues. Clin Immunol 2011;139:164-76.
Cassano N, Loconsole F, Amoruso A, et al. Infliximab monotherapy for refractory psoriasis: preliminary results. Int J Immunopathol Pharmacol 2004;17:373-80.
Dai WW, Moore AY. Combination regimen of acitretin and adalimumab for moderate to severe psoriasis. J Am Acad Dermatol 2010;62:AB132.
Kamili QU, Miner A, Hapa A, et al. Infliximab treatment for psoriasis in 120 patients on therapy for a minimum of one year: a review. J Drugs Dermatol 2011;10:539-44.
Mease PJ. Cytokine blockers in psoriatic arthritis. Ann Rheum Dis 2001;60:37-40.
Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264-72.
Moore A, Wright E, Slay D, Castillo A. Alefacept and low-dose acitretin therapy for inverse psoriasis and palmar/plantar psoriasis shortens onset of action. J Am Acad Dermatol 2006;54:AB211.
Ogilvie AL, Antoni C, Dechant C, et al. Treatment of psoriatic arthritis with antitumour necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. Br J Dermatol 2001;144:587-89.
Salvarani C, Cantini F, Olivieri I, et al. Efficacy of infliximab in resistant psoriatic arthritis. Arthritis Rheum 2003;49:541-45.
Sánchez-Regaña M, Sola-Ortigosa J, Alsina-Gibert M, et al. Nail psoriasis: a retrospective study on the effectiveness of systemic treatments (classical and biological therapy). J Eur Acad Dermatol Venereol. 2011;25:579-86.
Saraceno R, Schipani C, Mazzotta A, et al. Effect of anti-tumor necrosis factor-alpha therapies on body mass index in patients with psoriasis. Pharmacol Res 2008;57:290-95.
Spuls PI, Hadi S, Rivera L, et al. Retrospective analysis of the treatment of psoriasis of the palms and soles. J Dermatolog Treat 2003;14:21-25.
Worlicek C, Kaufmann R, Thaci D. Combination Therapy of Etanercept and Acitretin in Treatment-Resistant Palmoplantar pustular Psoriasis in the Long-Term Control. J Dtsch Dermatol Ges 2011;9:221.

Excluded because the study was not controlled or a before and after study (n=8)
de Miguel R, el-Azhary R. Efficacy, safety, and cost of Goeckerman therapy compared with biologics in the treatment of moderate to severe psoriasis. Int J Dermatol 2009;48:653-58.
Kircik L, Elmets C, Menter A, Koo J. Utilization of narrow-band UVB light therapy and etanercept for the treatment of psoriasis (UNITE): Characteristics of PASI responders. J Am Acad Dermatol 2007;56:AB5.
Landells I, Searles G, Bissonnette R, et al. Efficacy outcomes in patients using alefacept in the AWARE study. J Cutan Med Surg 2009;13:S122-30.
Martin B, Sanchez-Carazo JL, Perez-Ferriols A, et al. [Clinical experience with etanercept in the treatment of psoriasis]. Actas Dermosifiliogr 2008;99:540-45.
Marzo-Ortega H, McGonagle D, Rhodes LA, et al. Efficacy of infliximab on MRI-determined bone oedema in psoriatic arthritis. Ann Rheum Dis 2007;66:778-81.
Moore A, Slay D, Wright E, Moore T. Alefacept and narrowband UVB combination therapy for psoriasis shortens onset of action. J Am Acad Dermatol 2006;54:AB212.

Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367:29-35.

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Table 2. Excluded studies at the full text level for search two

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Appendix D. Baseline Characteristics for Included Studies and Trials

Table 3. Baseline characteristics of included studies

Study, Year	Group	N	Age (y) mean(SD)	Female n/N (%)	Race/ethnic group n/N (%)	Wt (kg) mean(SD)	BMI (kg/m^2) mean(SD)	PASI mean(SD)	BSA (%) mean(SD)	Disease duration (y) mean(SD)	Psoriatic arthritis n/N (%)
CT5, 2012	Etanercept	21	38.57 (9.53)	5/21 (23.8)	---	---	---	20.83 (14.02)	32.98 (20.21)	---	---
	Acitretin	18	42.39 (11.95)	3/18 (16.7)	---	---	---	26.31 (13.63)	39.75 (22.96)	---	---
Gelfand, 2012	Adalimumab	152	48.6 (15.5)*	352/713 (49.4)*	W:606/713(85.0)*	---	28.8 (25.3-33.0) *†	---	---	19 (8-29) *‡	161/713 (22.6)*
	Etanercept	191	---	---	---	---	---	---	---	---	---
	Ustekinumab	73	---	---	---	---	---	---	---	---	---
	MTX	174	---	---	---	---	---	---	---	---	---
	NB-UVB	123	---	---	---	---	---	---	---	---	---
Barker, 2011	Infliximab	653	44.1 (18-78) §	215/653 (32.9)	W:636/653(97.3)	84.5(18.6)	28.0(5.8)	21.4(8.0)‖	31.9(16.5)‖	18.8(11.6)	118/653 (18.1)
	MTX	215	41.9 (18-69) §	67/215 (31.2)	W:211/215(98.1)	83.8(18.2)	27.7(5.0)	21.1(7.6)	31.0(15.0)	17.0(10.3)	36/215 (16.7)
Emerit, 2011	Etanercept	10	55.1 (13.8) ¶	18/40 (45) ¶	---	---	---	21.4(6.1)	---	(2-37) ¶**	---
	Infliximab	10	---	---	---	---	---	22.3(6.5)	---	---	---
	PUVA	10	---	---	---	---	---	21.9(6.3)	---	---	---
	NB-UVB	10	---	---	---	---	---	21.3(5.2)	---	---	---
Inzinger, 2011††	Biologics‡‡	130 §§	46.2(11.8)	61/172 (35.5)‖‖	---	---	---	16.9(7.3)	---	22.9(10.5)	---
	PUVA	118 §§	48.5(15.7)		---	---	---	15.0(4.0)	---	23.4(11.9)	---
Strober, 2011	MTX to adalimumab	41	47.4(13.1)	13/41 (31.7)	W:39/41(95.1)	89.5(17.5)	---	10.2(5.5)	10.9(7.3)	19.8(13.5)	17/41 (41.5)
	NBUVB to adalimumab	29	45.7(14.6)	13/29 (44.8)	W:25/29(86.2)	86.0(17.8)	---	12.8(5.7)	14.5(12.6)	23.0(14.1)	7/29 (24.1)
Garavaglia, 2010	CyA to etanercept	4	58.3(12.2)	1/4 (25.0)	---	---	---	---	---	17.0(12.0)	1/4 (25.0)
Caproni, 2009	Etanercept	30	NR (28-67) ¶¶	17/30 (56.7)	---	---	---	21.5(9.1)	---	---	0/30 (0)
	Acitretin	30	NR (31-65) ¶¶	19/30 (63.3)	---	---	---	22.3(5.7)	---	---	0/30 (0)

Study, Year	Group	N	Age (y) mean(SD)	Female n/N (%)	Race/ethnic group n/N (%)	Wt (kg) mean(SD)	BMI (kg/m^2) mean(SD)	PASI mean(SD)	BSA (%) mean(SD)	Disease duration (y) mean(SD)	Psoriatic arthritis n/N (%)
Mazzotta, 2009††	Nonbiologics or phototherapy to etanercept***	98	---	---	---	---	---	16.1(7.1)	---	---	---
Gisondi, 2008a	Etanercept	22	55.3(10.9)	10/22 (45.4)	---	79.5(9.4)	27.3(6.0)	11.0(4.6)	12.6(6.3)	23.5(10.9)	0/22 (0)
	Acitretin	20	55.0(11.3)	8/20 (40.0)	---	78.4(10.3)	27.2(3.1)	10.4(5.3)	11.1(7.3)	18.8(16.6)	0/20 (0)
Gisondi, 2008b	Etanercept	58	50.2(11.1)	19/58 (32.7)	---	80.1(16.2)	27.6(5.0)	18.8(7.4)	---	22.0(12.9)	0/58 (0)
	Infliximab	40	46.8(11.2)	12/40 (30.0)	---	79.2(15.2)	26.5(3.5)	17.7(7.3)	---	17.5(13.4)	0/40 (0)
	MTX	43	53.1(12.7)	17/43 (39.5)	---	81.0(12.6)	27.4(3.6)	8.2(3.1)	---	18.6(12.0)	0/43 (0)
Saurat, 2008	Adalimumab	108	42.9(12.6)	38/108 (35.2)	W:98/103(95.1) B:2/103(1.9) A:3/103(2.9) O:0/103(0) H:11/103(10.7)	81.7(20.0)	---	20.2(7.5)	33.6(19.9)	17.9(10.1)	23/108 (21.3)
	MTX	110	41.6(12.0)	37/110 (33.6)	W:103/108(95.4) B:1/108(0.9) A:4/108(3.7) O:0/108(0) H:9/108(8.3)	83.1(17.5)	---	19.4(7.4)	32.4(20.6)	18.9(10.2)	19/110 (17.3)
	MTX to adalimumab	95	---	---	---	---	---	---	---	---	---
Magliocco, 2007	CyA to alefacept	11	45 (25-65) †	---	---	---	---	---	---	22(7-32) ¶	---
Costanzo, 2005††	Nonbiologics to etanercept†††	44	41.2(NR)	16/44 (36.4)	---	---	---	15.6(NR)	21.7(NR)	15.5(NR)	15/44 (34.1)

Table note: A=asian; B=black; BMI=body mass index; BSA=body surface area; CyA=cyclosporine; d=day(s); H=hispanic; kg=kilogram(s); m=meter(s); MTX=methotrexate; N=total population; NBUVB=narrowband ultraviolet B; NR=not reported; O=other; PASI=Psoriasis Area and Severity Index; PUVA=psoralen plus ultraviolet A; SD=standard deviation; W=white; Wt=weight; y=year(s); ---=not reported

* Total population, n=713
† Mean(IQR)
‡ Median(IQR)
§ Mean(range)
|| n=650
¶ Total population, n=40
** Range

†† Baseline characteristics reported by drug class, not individual agent
‡‡ Adalimumab, alefacept, etanercept, infliximab, ustekinumab
§§ Number corresponds to treatment courses, not patients
|||| Total population, n=172
¶¶ Median(range)
*** CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA
††† CyA, corticosteroids, MTX, retinoids

Appendix E. Quality and Characteristics of Included Trials and Studies

Table 4. Characteristics and quality assessment of included studies

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
CT5, 2012	Publication type: ClinicalTrials.gov results Study design: RCT Geographic location: Korea Funding: Industry Conflict of interest reported? NR Number of centers: 10 Randomization and allocation concealment: NR Outcome assessment: NR Total number randomized: 60 (39)	Inclusion criteria: Patients 18y and older with active, moderate to severe psoriasis defined by the following criteria: clinically stable, plaque psoriasis involving more than 10% body surface area (BSA) or PASI 10; in the opinion of the investigator, failure, intolerance, contraindication or not a candidate for the following: Methotrexate (MTX), cyclosporine, and PUVA therapy; negative urine pregnancy test before the first dose of study drug in all female patients Exclusion criteria: Evidence of skin conditions other than psoriasis that would interfere with evaluations of the effect of study medication on psoriasis; any rheumatologic disease such as rheumatoid arthritis, psoriatic arthritis, gout, systemic lupus erythematous, systemic vasculitis, scleroderma and polymyositis, or associated syndromes; prior exposure to TNF inhibitors including etanercept; prior exposure to efalizumab and alefacept also prohibited Intervention 1: Etanercept at a dose of 50mg SC twice weekly for 12 weeks followed by 25mg twice weekly for 12 weeks Intervention 2: Acitretin at a dose of 10mg BID SC for 24 weeks	Duration of followup: 24 weeks Followup: Etanercept 80.95% Acitretin 66.7% Final outcomes: Psychological comorbidities (depression) Intermediate outcomes: BSA, PASI, PGA, PaGA (SGA of psoriasis), individual symptom improvement (SGA of joint pain, SGA of itching) Adverse events: Hepatotoxicity (AST, ALT), hypertension, injection site reaction, infection, study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? No 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to intervention status? NR 5. Were the methods used for randomization adequate? NR 6. Were methods for allocation concealment adequate? NR 7. Was incomplete outcome data adequately addressed? NR 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? No 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Poor

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Gelfand, 2012	Publication type: Full text Study design: Observational, Cohort study Geographic location: United States Funding: Government/Foundation Conflict of interest reported? NR Number of centers: 10 Outcome assessment: Patient data collected prospectively at a single, regularly scheduled clinic appointment with no followup where trained study coordinators collected data using standardized case report forms Confounders adjusted for: The incidence rates of acute MI by treatment group, adjusted for age, sex and comorbid diagnoses of depression, hypertension, hyperlipidemia and diabetes, were compared using a Cox proportional hazards regression model Total number randomized: 713 (713)	Inclusion criteria: Patients who met at least 1 of the following criteria: were currently receiving a biologic, oral systemic, or phototherapy prescribed by the dermatologist or physician assistant for psoriasis; were candidates for systemic therapy as defined by a history of 5% or more BSA involvement as documented in the medical record; or were previously treated with a biologic, oral systemic, or phototherapy for psoriasis; patients new to the practice became eligible for study inclusion only at their next regularly scheduled visit subsequent to the initial appointment Exclusion criteria: Patients who were not currently receiving systemic or phototherapy for psoriasis, who were receiving more than 1 systemic or phototherapy at the time of their visit, and whose primary indication was a variant of psoriasis other than plaque (eg, guttate, palmar plantar) Intervention 1: adalimumab† Intervention 2: etanercept† Intervention 3: ustekinumab† Intervention 4: methotrexate† Intervention 5: NBUVB†	Duration of followup: NA Followup: NA Final outcomes: DLQI Intermediate outcomes: BSA, PASI, PGA Adverse events: NR	1. Was the selection of cohorts unbiased? Yes 2. Were the groups selected to minimize baseline differences? Yes 3. Was the description of the cohort adequate? Yes 4. Was the selection of a comparison group adequate? Yes 5. Was the sample size calculated? No 6. Were outcome assessments blinded? No 7. Were outcomes assessed using a valid methodology? Yes 8. Was intention to treat analysis used? NR 9. Was adequate control for confounding used in the analysis? Yes 10. Was the differential loss to followup between the compared groups < 10%? Yes 11. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Barker, 2011 RESTORE1	Publication type: Full text, manuscript before edit, clinical trial registry Study design: RCT with optional transition period Geographic location: Europe Funding: Industry Conflict of interest reported? Yes Number of centers: 106 Randomization and allocation concealment: At each eligible subject's baseline visit, study centers phoned the Interactive Voice Response System (IVRS; Quintiles, Morrisville, North Carolina, USA) for randomization. IVRS assigned a patient randomization number. Patients were randomized 3:1 to receive infliximab:MTX Outcome assessment: Patients were assessed for clinical response at all visits. Total number randomized: 868 (868)	Inclusion criteria: Patients 18y to 75y diagnosed with moderate to severe plaque psoriasis for ≥6 months prior to screening, candidates for phototherapy or systemic treatment, and BSA ≥10% involvement and PASI ≥12 Exclusion criteria: Previous treatment with MTX, or with a biologic or TNF antagonist within 3 months of baseline; diagnosis of CHF, history of chronic or recurrent infectious disease, or serious infection, or had been hospitalized or received IV antibiotics for infection within past 2 months; opportunistic infection within past 6 months; history or signs/ symptoms of lymphoproliferative disease; active or history of malignancy Intervention 1: Infliximab 5mg/kg IV infusion at weeks 0, 2, 6, 14, 22 Intervention 2: MTX 15mg PO per week for 22 weeks	Duration of followup: 26 weeks Followup: Infliximab 100% MTX 100% Final outcomes: HRQoL (DLQI, EQ-5D), SF36 Intermediate outcomes: PASI, PGA, individual symptom improvement (pruritus) Adverse events: Hepatotoxicity (LFT abnormalities), injection site reaction, malignancy, infection, study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to intervention status? NR 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Emerit, 2011	Publication type: Full text Study design: Observational, Cohort study Geographic location: Europe Funding: NR Conflict of interest reported? NR Number of centers: 1 Total number randomized: 40 (40)	Inclusion criteria: NR Exclusion criteria: Patients presenting other skin diseases, diabetes, inflammatory or infectious diseases, cardiovascular, hepatic or renal disease Intervention 1: Etanercept 25mg SC twice a week Intervention 2: Infliximab 5mg/kg IV infusion over a period of 2-4 hours, additional perfusions at the same dose were administered 2 and 6 weeks later and continued every 8 weeks Intervention 3: 8-MOP (0.6mg/kg body weight) plus UVA irradiation (initial dose of 2-3J/cm^2, where the dose increased by 0.5J/cm^2 in every session until a maximum dose of 10J/cm^2 was reached) three times a week Intervention 4: NBUVB (initial dose of 0.2-0.3J/cm^2, where the dose increased by 0.1J/cm^2 until a maximum dose of 2.5J/cm^2 was reached) three times a week	Duration of followup: 32 weeks Followup: Etanercept 100% Infliximab 100% PUVA100% NBUVA 100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: NR	1. Was the selection of cohorts unbiased? No 2. Were the groups selected to minimize baseline differences? NR 3. Was the description of the cohort adequate? NR 4. Was the selection of a comparison group adequate? Yes 5. Was the sample size calculated? NR 6. Were outcome assessments blinded? NR 7. Were outcomes assessed using a valid methodology? Yes 8. Was intention to treat analysis used? NR 9. Was adequate control for confounding used in the analysis? NR 10. Was the differential loss to followup between the compared groups < 10%? Yes 11. Was the overall loss to followup< 20%? Yes Overall quality rating: Poor

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Inzinger, 2011	Publication type: Full text, Abstract Study design: Observational, Cohort study Geographic location: Austria Funding: Industry Conflict of interest reported? Yes Number of centers: 1 Outcome assessment: Data on patient characteristics and clinical PASI reduction categories were extracted from the electronic databank of the Psoriasis Registry, Graz Confounders adjusted for: As patients underwent more than one treatment cycle, scores from individual treatments were not independent and the test had to be adapted Total number studied: 248 (199) ‡	Inclusion criteria: Patients ≥18y with chronic plaque psoriasis treated with oral PUVA and/or at least one course of a biologic agent Exclusion criteria: NR Definition of cohort: Patients with psoriasis treated regularly with PUVA vs. biologics under daily life conditions outside of clinical trials between January 2003 and February 2010 Intervention 1: Biologics (adalimumab; alefacept; etanercept; infliximab; ustekinumab; standard therapy for all except median dose of etanercept 25mg SC twice a week) Intervention 2: 8-MOP plus UVA 2 to 4 times per week for a minimum of 3 months	Duration of followup: Biologics 12 weeks PUVA 8-MOP 10.3 weeks (median) Followup: Biologics§100% Phototherapy|| 100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: NR	1. Was the selection of cohorts unbiased? Yes 2. Were the groups selected to minimize baseline differences? Yes 3. Was the description of the cohort adequate? Yes 4. Was the selection of a comparison group adequate? Yes 5. Was the sample size calculated? NR 6. Were outcome assessments blinded? NR 7. Were outcomes assessed using a valid methodology? Yes 8. Was intention to treat analysis used? Yes 9. Was adequate control for confounding used in the analysis? Partially 10. Was the differential loss to followup between the compared groups < 10%? Yes 11. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Strober, 2011	Publication type: Full text, Abstract, ClinicalTrials.gov results Study design: Observational, Cohort study Geographic location: United States and Canada Funding: Industry Conflict of interest reported? Yes Number of centers: 24 Outcome assessment: PGA, PASI, DLQI and a VAS for plaque psoriasis and PsA pain were measured at each visit Total number studied: 152 (70)	Inclusion criteria: Age ≥18y; chronic plaque psoriasis ≥6 months; suboptimal response to prior therapy with etanercept, MTX, or NBUVB phototherapy; patients achieving a PGA of "mild" or worse after ≥4 months MTX therapy or a PGA of "moderate" or worse after ≥2 months NBUVB therapy at screening; patients with latent TB were permitted if prophylactic treatment was initiated before administration of study drug; women of childbearing potential were required to use contraception Exclusion criteria: Prior treamtment with adalimumab or natalizumab; concurrent active skin diseases or infections; history of neuologic symptoms suggestive of CNS demyelinating disease; history of cancer or lymphoproliferative disease other than successfully treated nonmelanoma skin cancer or localized carcinoma in situ of the cervix Definition of cohort: Patients enrolled between December 28, 2008 and April 14, 2009 Interventions: Patients failing MTX or NBUVB were transitioned to adalimumab 80mg SC at week 0, then 40mg SC every other week for weeks 1 to 15, after washout period of 4-10 days	Duration of followup: 70 days after end of adalimumab treatment (16 weeks + 70 days) Followup: MTX transitioned to adalimumab 100% NBUVB transitioned to adalimumab 100% Final outcomes: Mortality, HRQoL (DLQI) Intermediate outcomes: PASI, PGA, Individual symptom improvement (Pain involving Psoriatic Plaques and/or PsA, Psoriasis-related Pruritus Assessment) Adverse events: Metabolic alterations (TG), injection site reaction, malignancy, infection, study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to intervention status? NR 5. Were the methods used for randomization adequate? NA 6. Were methods for allocation concealment adequate? NA 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? No 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Garavaglia, 2010	Publication type: Full text Study design: Observational, Cohort study Geographic location: Italy Funding: NR Conflict of interest reported? NR Number of centers: 1 Outcome assessment: AST, ALT, viral load and PASI were monitored at 3-month intervals from the start of treatment up to two years after the initiation of etanercept therapy Total number studied: 5 (4)	Inclusion criteria: Diagnosis of psoriasis and/or psoriatic arthritis; positive HCV status as determined by serological testing for anti-HCV antibodies; active etanercept therapy Exclusion criteria: NR Definition of cohort: Patients attending the dermatology service of the Istituto Galeazzi, Milan, between 2007 and 2009 Intervention: Patients previously treated with CyA (dose/route/frequency NR) were treated with etanercept 50mg per week	Duration of followup: 2 years Followup: CyA transitioned to etanercept100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: Hepatotoxicity (AST, ALT)	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? NA 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to intervention status? NR 5. Were the methods used for randomization adequate? NA 6. Were methods for allocation concealment adequate? NA 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Poor

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Caproni, 2009	Publication type: Full text, Abstract Study design: RCT Geographic location: Italy Funding: NR Conflict of interest reported? NR Number of centers: NR Randomization and allocation concealment: Patients randomly assigned to one of the two groups, etanercept or acitretin Outcome assessment: At the baseline and at the end of the treatment, a blind clinical assessment by calculating PASI was made, and blood samples were taken to evaluate IL-17, IL-22 and IL-23 levels Total number randomized: 60 (60)	Inclusion criteria: Moderate to severe plaque-type psoriasis without joint involvement defined as BSA ≥10% involvement and PASI ≥ 10 Exclusion criteria: Patients treated in the previous month with any topical or systemic psoriasis therapy; history or risk of serious infection, lymphoproliferative disease or active or latent TB Intervention 1: Etanercept 50mg twice a week for 12 weeks Intervention 2: Acitretin 0.4mg/kg/d for 12 weeks	Duration of followup: 12 weeks Followup: Etanercept 100% Acitretin 100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: Study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? NR 4. Were outcome assessors blind to intervention status? Yes 5. Were the methods used for randomization adequate? NR 6. Were methods for allocation concealment adequate? NR 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Mazzotta, 2009	Publication type: Full text Study design: Observational-class level data only, Cohort study Geographic location: Italy Funding: Not funded Conflict of interest reported? Yes Number of centers: 1 Outcome assessment: Clinical and laboratory evaluations were performed at baseline (week 0) and after 12 and 24 weeks of treatment Confounders adjusted for: NA Total number randomized: 234 (124)	Inclusion criteria: Patients 18 – 80y affected by moderate to severe plaque-type psoriasis or psoriatic arthritis who had had an unsatisfactory clinical response or resistance to traditional or biologic systemic treatments Exclusion criteria: Subjects with co-morbid conditions that were contraindications to anti-TNF treatment Definition of cohort: Patients were recruited from an academic dermatology outpatient clinic, during the period from May 2004 to April 2005 Intervention: Nonbiologics (CyA, retinoids, corticosteroids, MTX, fumaric acid esters) or phototherapy (PUVA) transitioned to etanercept 50mg SC twice weekly for 12 weeks then reduced to 25mg SC twice weekly for 12 weeks	Duration of followup: 24 weeks Followup: Nonbiologics or phototherapy transitioned to etanercept¶ 100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: NR	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? NA 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? NA 4. Were outcome assessors blind to intervention status? NR 5. Were the methods used for randomization adequate? NA 6. Were methods for allocation concealment adequate? NA 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Gisondi, 2008a	Publication type: Full text, Abstract Study design: RCT Geographic location: Italy Funding: NR Conflict of interest reported? NR Number of centers: 1 Randomization and allocation concealment: Randomization was performed with the use of computer-generated random numbers and block size of four patients Outcome assessment: The PASI assessor was blinded concerning the group allocation of the patient Total number randomized: 60 (42)	Inclusion criteria: Patient ≥18y with active, stable moderate to severe plaque psoriasis Exclusion criteria: Diagnosis of PsA or other type of psoriasis (gutatte, erythrodermic, or pustular); active or chronic infections(HIV, HBV, HCV, latent TB); previous or active malignancies except for skin carcinomas; severe hematological, renal and hepatic disorders that could contraindicate acitretin and⁄or etanercept; severe CHF; demyelinating diseases; fertile women; elevation of serum cholesterol > 4.90 mmol/ L (220 mg/dL) and serum triglycerides > 1.70 mmol/ L (180 mg/dL); previous treatment with biologics; and receipt of phototherapy or any systemic or topical therapy for psoriasis within the previous 4 weeks. Intervention 1: Etanercept 25mg SC twice weekly Intervention 2: Acitretin 0.4mg/kg/d PO	Duration of followup: 24 weeks Followup: Etanercept 100% Acitretin 100% Final outcomes: NR Intermediate outcomes: BSA, PASI Adverse events: Hepatotoxicity (AST and ALT), metabolic alterations (TC, TG), study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Partially 4. Were outcome assessors blind to intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Good

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Gisondi, 2008b	Publication type: Full text Study design: Observational, Cohort study Geographic location: Italy Funding: NR Conflict of interest reported? NR Number of centers: 1 Outcome assessment: All subjects were visited by a dermatologist who registered demographical, biometrical and the other relevant data on a case report form. Relevant data collected included age, gender, weight, height, body mass index (BMI), age of psoriasis onset, type and severity of psoriasis and concomitant medications Confounders adjusted for: NR Total number studied: 141 (141)	Inclusion criteria: Patients with diagnosis of chronic plaque psoriasis according to clinical criteria; resistant or intolerant to MTX Exclusion criteria: Patients with psoriatic arthritis diagnosed according to the CASPAR criteria Definition of cohort: Patients consecutively admitted to the outpatient clinics of the University Hospital of Verona were involved. The source population of the study was people living in city of Verona or in the neighborhood Intervention 1: Etanercept 25mg SC twice a week for 6 months Intervention 2: Infliximab 5mg/kg IV at week 0, 2, 6 and every 8 weeks for 6 months Intervention 3: MTX 15mg IM once a week for 6 months	Duration of followup: 6 months Followup: Etanercept 100% Infliximab 100% MTX 100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: Metabolic alterations (TC, TG, BMI, weight)	1. Was the selection of cohorts unbiased? Yes 2. Were the groups selected to minimize baseline differences? Yes 3. Was the description of the cohort adequate? Yes 4. Was the selection of a comparison group adequate? Yes 5. Was the sample size calculated? NR 6. Were outcome assessments blinded? NR 7. Were outcomes assessed using a valid methodology? Yes 8. Was intention to treat analysis used? Yes 9. Was adequate control for confounding used in the analysis? NR 10. Was the differential loss to followup between the compared groups < 10%? Yes 11. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Saurat, 2008 CHAMPION	Publication type: Full text, abstract Study design: RCT with OLE Geographic location: Europe and Canada Funding: Industry Conflict of interest reported? Yes Number of centers: 28 Randomization and allocation concealment: Randomized through a central computer-generated scheme stratified by center, with block sizes of four. Patient numbers were centrally assigned by an interactive voice-response system in consecutive order in a 2:2:1 ratio (Adalimumab:MTX:placebo) Outcome assessment: A qualified investigator from each site performed clinical efficacy assessments at each study visit and remained throughout the study, if possible Total number randomized: 271 (218)	Inclusion criteria: Age ≥18y; moderate to severe psoriasis defined as BSA ≥10% involvement and PASI ≥ 10; plaque psoriasis ≥1 year; stable ≥2 months; candidates for systemic therapy or phototherapy with active psoriasis despite topical treatments; naïve to both TNF-antagonists and MTX; patients with latent TB were permitted if prophylactic treatment was initiated before administration of study drug; all men and women of childbearing potential were required to use contraception; patients must have been willing to self-administer SC injections or have a qualified person administer them Exclusion criteria: A history of clinically significant hematological, renal or liver disease ⁄abnormal laboratory values; history of demyelinating disease, cancer, or other lymphoproliferative disease (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and⁄or localized carcinoma in situ of the cervix); immunocompromised patients RCT intervention 1: Adalimumab 80mg SC at week 0, then 40mg SC every other week for weeks 1 to 15 RCT intervention 2: MTX 7.5mg PO weekly, increased as needed and tolerated to 25mg weekly** OLE study: Patients on MTX were transitioned to adalimumab 40mg SC every other week	Duration of followup: 70 days after last treatment (16 weeks + 70 days) Followup: Adalimumab100% MTX 100% OLE 100% Final outcomes: Mortality, HRQoL (DLQI, EQ-5D) Intermediate outcomes: PASI, PGA, Patient's Assessment of Global improvement, Individual symptom improvement (Pain Involving Psoriatic Plaques and/or PsA, Psoriasis-related Pruritus Assessment) Adverse events: Hepatotoxicity (AST, ALT), infection, study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants?Yes 4. Were outcome assessors blind to intervention status?Yes 5. Were the methods used for randomization adequate?Yes 6. Were methods for allocation concealment adequate?Yes 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Good

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Magliocco, 2007	Publication type: Full text, Abstract Study design: Observational, Cohort study Geographic location: United States Funding: Industry Conflict of interest reported? Yes Number of centers: 1 Outcome assessment: Efficacy assessments included PGA and the DLQI, which were measured monthly during the study. Safety assessments included monthly hematology and blood chemistry assessments while patients were on cyclosporine, CD4+ T cell monitoring weekly during alefacept treatment and monthly during the observation periods in phases II and III , and adverse event monitoring throughout the study Total number studied: 12 (11)	Inclusion criteria: Patients 18 to 80y with chronic plaque psoriasis well-controlled on cyclosporine (defined as PGA of "mild', "almost clear", or "clear"), and a need or desire to transition to alefacept therapy; required to have CD4+ T cell counts >400 cells/mm at time of enrollment Exclusion criteria: Pregnant or lactating; active infection (with the exception of common colds); history of HIV, HBV, HCV, heart disease, or liver disease Disease location: NR Intervention: Patients were transitioned to alefacept following three phases. Phase I (wk 1 to 12): Alefacept 15 mg IM once weekly plus CyA taper Phase II (wk 13 to 24): Neither alefacept nor CyA and only topical agents and UVB were permitted Phase III (wk 25 to 48): Alefacept 15 mg IM once weekly for the first 12 weeks then observation during the second 12 weeks where only UVB and topical therapies were permitted	Duration of followup: 48 weeks Followup: CyA transitioned to alefacept 54.5% Final outcomes: HRQoL (DLQI) Intermediate outcomes: PGA Adverse events: Malignancy, infection, study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? NA 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to intervention status? NR 5. Were the methods used for randomization adequate? NA 6. Were methods for allocation concealment adequate? NA 7. Was incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%? NA 10. Was the overall loss to followup< 20%? No Overall quality rating: Fair

Study, year	Trial characteristics	Population and interventions	Followup* and outcomes of interest (Timing)	Quality assessment
Costanzo, 2005	Publication type: Full text Study design: Observational, class level data only, Cohort study Geographic location: Italy Funding: NR Conflict of interest reported? NR Number of centers: NR Outcome assessment: Clinical and laboratory assessments were done at screening, at baseline and every 4 weeks thereafter Total number randomized: 44 (44)	Inclusion criteria: Patients 18 to 75y with chronic plaque psoriasis or psoriatic arthritis, PASI >10, and had failed at least one systemic therapy for lack of efficacy or adverse events Exclusion criteria: NR Disease location: NR Intervention 1: Systemic corticosteroids, CyA, MTX or retinoids transitioned to etanercept 25mg SC twice weekly	Duration of followup: 24 weeks Followup: Nonbiologics transitioned to etanercept†† 100% Final outcomes: NR Intermediate outcomes: PASI Adverse events: Hematologic toxicity, injection site reaction, infection, study withdrawal	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? NA 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to intervention status? No 5. Were the methods used for randomization adequate? NA 6. Were methods for allocation concealment adequate? NA 7. Was incomplete outcome data adequately addressed? NR 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups < 10%?Yes 10. Was the overall loss to followup< 20%? Yes Overall quality rating: Fair

Abbreviations: 8-MOP=8-methoxypsoralen; ALT=alanine aminotransferase;AST=aspartate aminotransferase; BMI=body mass index; BSA=body surface area; CHF=congestive heart failure; CNS=central nervous system; CyA=cyclosporin; d=day(s); dL=deciliter(s); DLQI=Dermatology Life Quality Index; EQ-5D=EuroQOL 5D; h=hour(s); HBV= hepatitis B virus; HCV= hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=heatlh related quality of life; IL=interleukin; IM=intramuscular; IV=intravenous;kg=kilogram(s); L=liter;mg=milligram(s); mm=millimeter(s); mmol=millimol(s); MTX=methotrexate; NA=not applicable; NBUVA=narrowband ultraviolet A; NBUVB=narrowband ultraviolet B;NR=not reported; NS=not specified; OLE=open label extension; PASI=Psoriasis Area and Severity Index; PaGA=Patients Assessment of Global Improvement; PGA=Physician's Global Assessment; PO=by mouth; PsA=psoriatic arthritis; PUVA=psoralen plus ultraviolet A; QD=daily; RCT=randomized controlled trial; SC=subcutaneous; SGA=Subjects Global Assessment; TB=tuberculosis; TC=total cholesterol; TG=triglycerides; TNF=tumor necrosis factor; UVA=ultraviolet A; VAS=visual analog scale; vs.=versus; w=week(s); y=year(s)

* Duration of followup is reported as the original study's longest reported followup for outcomes of interest and followup percent is reported for the study's pre-specified primary outcome

† The dosage and frequencies, duration of therapy without interruption (median (IQR), month), and the use of topical prescription drug in past week (median (IQR), day), respectively, of the following treatments with adalimumab, etanercept, ustekinumab, methotrexate, and NBUVB are as follows: adalimumab 40 mg every 2 week (86.8%), 80 mg every 2 week (0.7%), 40 mg once/week (11.2%), other (1.3%), 11.0 (3.0-16.8), 2 (0-6); etanercept 50 mg every 2 week (4.7%), 25 mg once/week (3.1%), 50 mg once/week (49.7%), 25 mg twice/week (3.1%), 50 mg twice/week (36.1%), other (2.6%), 12.0 (6.0-36.0), 1 (0-4); ustekinumab 45 mg/kg every 3 month (56.2%), 90 mg/kg every 3 month (35.6%), other (5.5%), 4.0 (2.0-6.0), 0 (0-4); methotrexate 7.5 mg/week (1.7%), 7.5-15 mg (62.6%), 17.5-25 mg (27.6%), 30 mg (5.2%), other (2.9%), 10.5 (4.0-24.0), 2 (0-7); NBUVB 3 treatments in past 4 week (5.7%), 3-5 treatments in past 4 week (23.6%), 6-8 treatments in past 4 week (31.7%), 9-11 treatments in past 4 week (28.5%), ≥12 treatments in past 4 week (10.6%), 1.8 (1.0-4.0), 4 (1-7).
‡ Total number of treatment courses
§ Adalimumab, alefacept, etanercept, infliximab, ustekinumab
|| PUVA
¶ CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA
** Oral methotrexate was administered as a single weekly dose and was initiated at 7.5 mg per week at week 0, increased to 10 mg per week at week 2, and increased to 15 mg per week at week 4 for all patients. At week 8 onward, patients who achieved at least a 50% reduction in Psoriasis Area and Severity Index (PASI 50) response maintained their current dosages (15 mg per week maximum) for the duration of the study. However, at week 8, patients who did not achieve a PASI 50 response had their dosage increased to 20 mg per week. By week 12, only patients not achieving a PASI 50 response and who had a < PASI 50 response at week 8 underwent further dosage increase to 25 mg per week for the duration of the study. Patients who achieved ≥ PASI 50 responses at week 12 maintained their current dosages (20 mg per week maximum) for the duration of the study. Oral medication dosages were also adjusted to alanine aminotransferase, aspartate aminotransferase, serum creatinine and blood cell count between week 2 and week 15, if necessary, and could be withheld or reduced at any time, as deemed appropriate by the safety assessors
†† CyA, corticosteroids, MTX, retinoids

Appendix F. Evidence Tables

Table 5. Final health outcomes (1)

Study, year	Study group	Followup	Total mortality n/N	MACE n/N	Diabetes n/N	Psychological comorbidities* n/N
CT5, 2012	Etanercept	24w	---	---	---	0/21†
	Acitretin	24w	---	---	---	1/18†
Gelfand, 2012	MTX	---	---	---	---	---
	Adalimumab	---	---	---	---	---
	Etanercept	---	---	---	---	---
	Ustekinumab	---	---	---	---	---
	NB-UVB	---	---	---	---	---
Barker, 2011	Infliximab	10w	---	---	---	---
		16w	---	---	---	---
		26w‡	---	0/649§	1/649	---
	MTX	10w	---	---	---	---
		16w	---	---	---	---
		26w‡	---	1/211§	0/211	---
	Infliximab transitioned to MTX	26w	---	0/9§	0/9	---
	MTX transitioned to infliximab	26w	---	0/63§	0/63	---
Inzinger, 2011	Adalimumab	---	---	---	---	---
	Alefacept	---	---	---	---	---
	Etanercept	---	---	---	---	---
	Infliximab	---	---	---	---	---
	Ustekinumab	---	---	---	---	---
	PUVA	---	---	---	---	---
Strober, 2011	MTX transitioned to adalimumab	4w	---	---	---	---
		16w	0/41	---	---	---
	NB-UVB transitioned to adalimumab	4w	---	---	---	---
		16w	0/29	---	---	---
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---
Caproni, 2009	Etanercept	---	---	---	---	---
	Acitretin	---	---	---	---	---
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept‖	---	---	---	---	---
Gisondi, 2008a	Etanercept	---	---	---	---	---

Study, year	Study group	Followup	Total mortality n/N	MACE n/N	Diabetes n/N	Psychological comorbidities* n/N
	Acitretin	---	---	---	---	---
Gisondi, 2008b	Etanercept	---	---	---	---	---
	Infliximab	---	---	---	---	---
	MTX	---	---	---	---	---
Saurat, 2008	Adalimumab	12w	---	---	---	---
		16w	---	---	---	---
		70d¶	0/107	---	---	---
	MTX	12w	---	---	---	---
		16w	---	---	---	---
		70d¶	0/110	---	---	---
	MTX transitioned to adalimumab	---	---	---	---	---
Magliocco, 2007	CyA transitioned to alefacept	13w	---	---	---	---
		25w	---	---	---	---
		37w	---	---	---	---
		48w	---	---	---	---
Costanzo, 2005	Nonbiologics transitioned to etanercept**	---	---	---	---	---

Abbreviations: CyA=cyclosporine; d=day(s); MACE=major adverse cardiovascular event; MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; PUVA=psoralen plus ultraviolet A; w=week(s); ---=not reported

* Includes depression or suicide

† Depression

‡ Includes events through week 16 for patients who switched treatments and through week 26 for others who did not

§ Myocardial infarction

|| CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA

¶ 70 days after last treatment

** CyA, corticosteroids, MTX, retinoids

Table 6. Final health outcomes (2)

Study, year	Study group	Followup	DLQI* mean(SD)	HAQ-DI mean(SD)	EQ-5D† mean(SD)	SF-36 mean(SD)	Other reported outcomes
CT5	Etanercept	2w	---	---	---	---	---
		4w	---	---	---	---	---
		8w	---	---	---	---	---
		12w	---	---	---	---	---
		18w	---	---	---	---	---
		24w	---	---	---	---	---
	Acitretin	2w	---	---	---	---	---
		4w	---	---	---	---	---
		8w	---	---	---	---	---
		12w	---	---	---	---	---
		18w	---	---	---	---	---
		24w	---	---	---	---	---
Gelfand, 2012	MTX	NR	3(1-5)‡	---	---	---	---
	Adalimumab	NR	2(0-5)‡	---	---	---	---
	Etanercept	NR	2(1-5)‡	---	---	---	---
	Ustekinumab	NR	3(1-6)‡	---	---	---	---
	NB-UVB	NR	3(1-7)‡				
Barker, 2011	Infliximab	10w	-11.4(NR)	---	0.86(NR)	5.15(NR)‖, 7.94(NR)¶	---
		16w	-11.6(NR)	---	0.86(NR)	5.53(NR)‖	---
		26w§	-11.3(NR)	---	0.86(NR)	---	---
	MTX	10w	-7.9(NR)	---	0.81(NR)	3.00(NR)‖, 5.63(NR)¶	---
		16w	-8.95(NR)	---	0.84(NR)	3.76(NR)‖	---
		26w§	-9.14(NR)	---	0.81(NR)	---	---
	Infliximab transitioned to MTX	---	---	---	---	---	---
	MTX transitioned to infliximab	---	---	---	---	---	---
Inzinger, 2011	Adalimumab	---	---	---	---	---	---
	Alefacept	---	---	---	---	---	---
	Etanercept	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---
	Ustekinumab	---	---	---	---	---	---
	PUVA	---	---	---	---	---	---
Strober, 2011	MTX transitioned to adalimumab	4w	-4.8(5.89)	---	---	---	---
		16w	-7.0(7.45)	---	---	---	0.7(3.4)** -4.0(28.1)†† -5.5(30.3)‡‡ -13.3(33.1)§§

Study, year	Study group	Followup	DLQI* mean(SD)	HAQ-DI mean(SD)	EQ-5D† mean(SD)	SF-36 mean(SD)	Other reported outcomes
	NB-UVB	4w	-5.2(5.45)	---	---	---	---
	transitioned to adalimumab	16w	-6.5(6.44)	---	---	---	1.3(4.8)** -6.4(19.8)†† -8.0(19.4)‡‡ -12.2(25.6)§§
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---	---
Caproni, 2009	Etanercept	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept‖‖	---	---	---	---	---	---
Gisondi, 2008a	Etanercept	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---
Gisondi, 2008b	Etanercept	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---
	MTX	---	---	---	---	---	---
Saurat, 2008	Adalimumab	12w	-9.1(-10.4, -7.8)***	---	IS: 0.2(0.1, 0.2)*** VAS: 20.4(15.3, 25.4)***	---	---
		16w	-9.1(-10.4, -7.8)***	---	IS: 0.2(0.2, 0.3)*** VAS: 21.4(16.6, 26.3)***	---	---
		70d¶¶	---	---	---	---	---
	MTX	12w	-4.9(-5.9, -3.8)***	---	IS: 0.1(0.1, 0.2)*** VAS: 10.2(5.3, 15.2)***	---	---
		16w	-5.7(-6.8, -4.5)***	---	IS: 0.1(0.1, 0.2)*** VAS: 11.5(6.5, 16.5)***	---	---
		70d¶¶	---	---	---	---	---
	MTX transitioned to adalimumab	---	---	---	---	---	---
Magliocco, 2007	CyA transitioned to alefacept	0w	3.18(NR)†††	---	---	---	---
		13w	1.09(NR)†††	---	---	---	---
		25w	4.88(NR)†††	---	---	---	---
		37w	3.14(NR)†††	---	---	---	---
		48w	3.83(NR)†††				
Costanzo, 2005	Nonbiologics transitioned to etanercept‡‡‡	---	---	---	---	---	---

Abbreviations: CyA=cyclosporine; d=day(s); DLQI=Dermatology Life Quality Index; EQ-5D=EuroQol-5D; HAQ-DI= Health Assessment Questionnaire Disability Index; IS=index score; MACE=major adverse cardiovascular event; MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; NR=not reported; PUVA=psoralen plus ultraviolet A; SD=standard deviation; SF-36=Short form-36; VAS=visual analogue scale; w=week(s); ---=not reported

* Mean(SD) change from baseline, unless otherwise noted
† Mean(SD) composite score, unless otherwise noted
‡ Median (IQR) DLQI
§ Includes patients who switched treatments at week 16 as nonresponders
|| Mean(SD) change from baseline in Physical Component Score of SF-36
¶ Mean(SD) change from baseline in Mental Component Score of SF-36
** Mean(SD) change from baseline in percent work time missed due to psoriasis
†† Mean(SD) change from baseline in percent overall work impairment due to psoriasis
‡‡ Mean(SD) change from baseline in percent impairment while working due to psoriasis
§§ Mean(SD) change from baseline in percent activity impairment due to psoriasis
|||| CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA
¶¶ 70 days after last treatment
*** Mean(95% confidence interval) change from baseline
††† Mean(SD) DLQI
‡‡‡ CyA, corticosteroids, MTX, retinoids

Table 7. Intermediate health outcomes (1)

Study, year	Study group	Followup	BSA mean(SD)	PGA* n/N	Patient's Assessment of Global Improvement mean(SD)	Symptom improvement		
						Pruritus	Pain	Other
CT5, 2012	Etanercept	2w	-2.64(6.69)†	0/21	-0.90(1.58)‡	-0.67(1.59)§	0.00(0.71)||	
		4w	-7.36(10.89)†	4/21	-1.86(1.28)‡	-1.52(1.33)§	0.29(1.19)||	
		8w	-12.67(13.17)†	6/21	-2.29(1.79)‡	-1.86(2.06)§	0.19(0.81)||	
		12w	-15.43(14.90)†	9/21	-2.67(1.56)‡	-2.10(2.07)§	0.00(0.63)||	
		18w	-16.57(14.70)†	7/21	-2.57(1.99)‡	-1.81(2.06)§	-0.05(0.67)||	
		24w	-17.52(14.91)†	11/21	-1.81(2.20)‡	-1.19(2.23)§	0.29(1.06)||	
	Acitretin	2w	-0.36(5.54)†	1/18	-0.72(1.02)‡	-0.39(1.29)§	-0.44(1.10)||	
		4w	-0.75(7.66)†	2/18	-0.83(1.04)‡	-0.39(2.03)§	-0.72(1.81)||	
		8w	-5.14(16.96)†	1/18	-1.67(1.71)‡	-1.28(1.71)§	-0.56(1.72)||	
		12w	-5.08(11.89)†	1/18	-1.61(1.72)‡	-1.22(1.73)§	-0.44(2.36)||	
		18w	-9.25(16.72)†	3/18	-1.83(1.76)‡	-1.17(1.62)§	-0.44(1.85)||	
		24w	-10.30(18.86)†	8/18	-1.72(1.93)‡	-1.06(1.89)§	-0.61(2.03)||	
Gelfand, 2012	MTX	---	3.0(1.0 to 6.0)¶	1.7(1.3 to 2.0)¶	---	---	---	---
	Adalimumab	---	2.0(0.7 to 5.0)¶	1.3(1.0 to 1.7)¶	---	---	---	---
	Etanercept	---	2.0(0.5 to 4.5)¶	1.7(1.0 to 2.0)¶	---	---	---	---
	Ustekinumab	---	3.0(0.6 to 9.1)¶	1.7(1.0 to 2.1)¶	---	---	---	---
	NB-UVB	---	3.3(1.0 to 6.5)¶	1.7(1.0 to 2.0)¶	---	---	---	---
Barker, 2011	Infliximab	16w	---	496/653	---	---	---	---
		26w**	---	477/653	---	---	---	---
	MTX	16w	---	82/215	---	---	---	---
		26w**	---	60/215	---	---	---	---
	Infliximab	18w	---	0/9	---	---	---	---
	transitioned to	22w	---	1/9	---	---	---	---
	MTX	26w	---	2/9	---	---	---	---
	MTX	18w	---	19/63	---	---	---	---
	transitioned to	22w	---	45/63	---	---	---	---
	infliximab	26w	---	47/63	---	---	---	---
Inzinger, 2011	Adalimumab	---	---	---	---	---	---	---
	Alefacept	---	---	---	---	---	---	---
	Etanercept	---	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---	---
	Ustekinumab	---	---	---	---	---	---	---
	PUVA	---	---	---	---	---	---	---

Study, year	Study group	Followup	BSA mean(SD)	PGA* n/N	Patient's Assessment of Global Improvement mean(SD)	Symptom improvement		
						Pruritus	Pain	Other
Strober, 2011	MTX transitioned to adalimumab	0w	---	1/41	---	---	---	---
		2w	---	0/41	---	---	---	---
		4w	---	13/41	---	---	---	---
		8w	---	22/41	---	---	---	---
		16w	---	25/41 61% (95%CI 45 to 76)††	---	-2.9(3.9)‡‡	-14.7(24.4)§§	
	NB-UVB transitioned to adalimumab	0w	---	0/29	---	---	---	---
		2w	---	3/29	---	---	---	---
		4w	---	6/29	---	---	---	---
		8w	---	13/29	---	---	---	---
		16w	---	14/29 48% (95%CI 29 to 67)††	---	-3.0(2.96)‡‡	-21.4(30.0)§§	
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---	---	---
Caproni, 2009	Etanercept	---	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---	---
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept‖‖	---	---	---	---	---	---	---
Gisondi, 2008a	Etanercept	24w	-80.0%¶¶	---	---	---	---	---
	Acitretin	24w	-45.8%¶¶	---	---	---	---	---
Gisondi, 2008b	Etanercept	---	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---	---
	MTX	---	---	---	---	---	---	---
Saurat, 2008	Adalimumab	4w	---	17/108	---	---	---	---
		8w	---	52/108	---	---	---	---
		12w	---	72/108	---	---	---	---
		16w	---	79/108	-1.6(NR)§	-5.0(NR)	-24.2(NR)	---
	MTX	4w	---	4/110	---	---	---	---
		8w	---	10/110	---	---	---	---
		12w	---	24/110	---	---	---	---
		16w	---	33/110	-1.2(NR)§	-3.5(NR)	-11.1(NR)	---

Study, year	Study group	Followup	BSA mean(SD)	PGA* n/N	Patient's Assessment of Global Improvement mean(SD)	Symptom improvement		
						Pruritus	Pain	Other
	MTX transitioned to adalimumab	---	---	---	---	---	---	---
Magliocco, 2007	CyA transitioned to alefacept	13w	---	---	---	---	---	---
		25w	---	4.75(NR)***	---	---	---	---
		37w	---	4.33(NR)***	---	---	---	---
		48w	---	4.33(NR)***	---	---	---	---
Costanzo, 2005	Nonbiologics transitioned to etanercept†††	---	---	---	---	---	---	---

Abbreviations: BSA=body surface area; CI=confidence interval; CyA=cyclosporine; MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; NR=not reported; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; PUVA=psoralen plus ultraviolet A; SD=standard deviation; VAS=visual analog scale; w=week(s); ---=not reported

* Number of patients achieving a PGA score of "clear" or "minimal", unless otherwise noted

† Mean(SD) change from baseline

‡ Mean(SD) change from baseline in SGA of psoriasis

§ Mean(SD) change from baseline in SGA of itching

|| Mean(SD) change from baseline is SGA of joint pain

¶ Median (IQR)

** Includes patients who switched treatments at week 16 as nonresponders

†† 95%CI reported as percentage of respective population

‡‡ Mean(SD) change from baseline in Psoriasis-related Pruritus Assessment

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

|||| CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA

¶¶ Mean percentage change from baseline

*** Mean(SD) PGA

††† CyA, corticosteroids, MTX, retinoids

Table 8. Intermediate health outcomes (2)

Study, year	Study group	Followup	PASI50 n/N	PASI75 n/N	PASI90 n/N	PASI100 n/N	PASI mean(SD)
CT5, 2012	Etanercept	2w	1/21	---	---	---	-5.38(7.13)*
		4w	10/21	---	---	---	-9.98(10.64)*
		8w	15/21	---	---	---	-11.11(10.89)*
		12w	16/21	---	---	---	-11.97(11.63)*
		18w	16/21	---	---	---	-12.13(11.67)*
		24w	15/21	11/21	---	---	-12.16(12.15)*
	Acitretin	2w	0/18	---	---	---	-3.17(5.60)*
		4w	2/18	---	---	---	-4.06(5.68)*
		8w	5/18	---	---	---	-6.84(9.57)*
		12w	4/18	---	---	---	-6.71(6.81)*
		18w	7/18	---	---	---	-8.77(8.54)*
		24w	8/18	4/18	---	---	-9.62(10.10)*
Gelfand, 2012	MTX	---	---	---	---	---	3.8(1.8 to 6.6)†
	Adalimumab	---	---	---	--	---	2.5(1.2 to 4.8)†
	Etanercept	---	---	---	---	---	2.9(1.8 to 4.9)†
	Ustekinumab	---	---	---	---	---	4.0(1.0 to 7.9)†
	NB-UVB	---	---	---	---	---	3.5(2.0 to 5.5)†
Barker, 2011	Infliximab	2w	247/653	59/653	11/653	---	---
		6w	535/653	365/653	150/653	---	---
		10w	579/653	487/653	291/653	---	---
		14w	562/653	473/653	310/653	---	---
		16w	567/653	508/653	356/653	---	---
		18w‡	543/653	488/653	349/653	---	---
		22w‡	530/653	473/653	306/653	---	
		26w‡	529/653	502/653	333/653	---	-85%§
	MTX	2w	19/215	1/215	0/215	---	---
		6w	80/215	31/215	6/215	---	---
		10w	118/215	58/215	19/215	---	---
		14w	131/215	85/215	37/215	---	---
		16w	130/215	90/215	41/215	---	---
		18w‡	120/215	85/215	39/215	---	---
		22w‡	118/215	82/215	39/215	---	---
		26w‡	103/215	66/215	32/215	---	-54%§
	Infliximab transitioned to MTX	18w	---	0/9	0/9	---	---
		22w	---	1/9	0/9	---	---
		26w	---	1/9	0/9	---	---
	MTX transitioned to infliximab	18w	---	15/63	5/63	---	---
		22w	---	38/63	17/63	---	---
		26w	---	46/63	30/63	---	---

Study, year	Study group	Followup	PASI50 n/N	PASI75 n/N	PASI90 n/N	PASI100 n/N	PASI mean(SD)
Emerit, 2011	Etanercept	0w	---	---	---	---	21.4(6.1)
		12w	---	---	---	---	3.7(1.2)
		32w	---	---	---	---	---
	Infliximab	0w	---	---	---	---	22.3(6.5)
		12w	---	---	---	---	2.1(0.7)
		32w	---	---	---	---	---
	PUVA	0w	---	---	---	---	21.9(6.3)
		12w	---	---	---	---	2.2(1.1)
		32w	---	---	---	---	7.3(1.8)
	NB-UVB	0w	---	---	---	---	21.3(5.2)
		12w	---	---	---	---	3.7(1.2)
		32w	---	---	---	---	10.8(2.2)
Inzinger, 2011‖	Adalimumab	12w	13/18	10/18	4/18	1/18	---
	Alefacept	12w	20/32	8/32	1/32	1/32	---
	Etanercept	12w	32/38	15/38	11/38	2/38	---
	Infliximab	12w	7/7	7/7	5/7	2/7	---
	Ustekinumab	12w	16/18	12/18	7/18	1/18	---
	PUVA	10.3w¶	65/71	63/71	50/71	15/71	---
Strober, 2011	MTX transitioned to adalimumab	0w	---	---	---	---	10.8(NR)
		2w	---	---	---	---	6.9(NR)
		4w	---	---	---	---	5.4(NR)
		8w	---	---	---	---	3.4(NR)
		16w	---	---	---	---	2.3(NR)
	NB-UVB transitioned to adalimumab	0w	---	---	---	---	12.4(NR)
		2w	---	---	---	---	9.1(NR)
		4w	---	---	---	---	6.7(NR)
		8w	---	---	---	---	4.1(NR)
		16w	---	---	---	---	3.6(NR)
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---	---
Caproni, 2009	Etanercept	12w	26/30	17/30	---	---	4.61(2.75)
	Acitretin	12w	20/30	8/30	---	---	9.62(4.64)
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept**	12w	79/98	43/98	---	---	4.9(4.0)
		24w	88/98	74/98	---	---	2.8(3.4)
Gisondi, 2008a	Etanercept	6w	6/22	2/22	---	---	---
		12w	9/22	5/22	---	---	---
		18w	11/22	8/22	---	---	---
		24w	15/22	10/22	---	---	---

Study, year	Study group	Followup	PASI50 n/N	PASI75 n/N	PASI90 n/N	PASI100 n/N	PASI mean(SD)
	Acitretin	6w	2/20	1/20	---	---	---
		12w	4/20	2/20	---	---	---
		18w	7/20	2/20	---	---	---
		24w	10/20	6/20	---	---	---
Gisondi, 2008b	Etanercept	24w	---	---	---	---	4.8(4.7) -74.5%§
	Infliximab	24w	---	---	---	---	2.1(3.2) -88.8%§
	MTX	24w	---	---	---	---	4.3(6.0) -47.1%§
Saurat, 2008	Adalimumab	2w	---	5/108	---	---	---
		4w	73/108	25/108	7/108	1/108	---
		8w	88/108	67/108	29/108	9/108	---
		12w	98/108	83/108	52/108	12/108	---
		16w	95/108	86/108	56/108	18/108	-16.7(8.8)*
	MTX	2w	---	0/110	---	---	---
		4w	17/110	3/110	1/110	1/110	---
		8w	42/110	10/110	3/110	0/110	---
		12w	60/110	27/110	10/110	1/110	---
		16w	68/110	39/110	15/110	8/110	-10.9(8.3)*
	MTX transitioned to adalimumab	0w	---	26/95	13/95	5/95	---
		24w	---	70/95	50/95	30/95	---
Magliocco, 2007	CyA transitioned to alefacept	---	---	---	---	---	---
Costanzo, 2005	Nonbiologics transitioned to etanercept††	12w	28/44	19/44	4/44	---	7.5(NR) -52%§
		24w	12/15	10/15	6/15	---	4.3(NR) -72%§

Abbreviations: CyA=cyclosporine; MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; NR=not reported; PASI=Psoriasis Area and Severity Index; PUVA=psoralen plus ultraviolet A; w=week(s); ---=not reported

* Mean(SD) change from baseline

† Median (IQR)

‡ Includes patients who switched treatments at week 16 as nonresponders

§ Mean percentage change from baseline

|| Results reported out of treatment courses, not patients. Patients could have more than one treatment course

¶ End of phototherapy treatment, median 10.3w

** Nonbiologics included CyA, corticosteroids, MTX, retinoids

†† Nonbiologics included CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA

Table 9. Adverse outcomes (1)

Study, year	Study group	Followup	Hepatotoxicity n/N		Nephrotoxicity n/N		Hematologic toxicity n/N		
			AST	ALT	SCr	GFR	TCP	Anemia	Neutropenia
CT5, 2012	Etanercept	---	0/21	1/21	---	---	---	---	---
	Acitretin	---	0/18	0/18	---	---	---	---	---
Barker, 2011	Infliximab	26w*	2/649†	---	---	---	1/649	---	---
	MTX	26w*	1/211†	---	---	---	0/211	---	---
	Infliximab transitioned to MTX	26w	0/9†	---	---	---	0/9	---	---
	MTX transitioned to infliximab	26w	0/63†	---	---	---	0/63	---	---
Inzinger, 2011	Adalimumab	---	---	---	---	---	---	---	---
	Alefacept	---	---	---	---	---	---	---	---
	Etanercept	---	---	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---	---	---
	Ustekinumab	---	---	---	---	---	---	---	---
	PUVA	---	---	---	---	---	---	---	---
Strober, 2011	MTX transitioned to adalimumab	---	---	---	---	---	---	---	---
	NB-UVB transitioned to adalimumab	---	---	---	---	---	---	---	---
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---	---	---	---
Caproni, 2009	Etanercept	---	---	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---	---	---
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept‡	---	---	---	---	---	---	---	---
Gisondi, 2008a	Etanercept	---	---	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---	---	---
Gisondi, 2008b	Etanercept	---	---	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---	---	---
	MTX	---	---	---	---	---	---	---	---
Saurat, 2008	Adalimumab	70d§	0/107‖	0/107‖	---	---	---	---	---
	MTX	70d§	2/110‖	4/110‖	---	---	---	---	---

Study, year	Study group	Followup	Hepatotoxicity n/N		Nephrotoxicity n/N		Hematologic toxicity n/N		
			AST	ALT	SCr	GFR	TCP	Anemia	Neutropenia
	MTX transitioned to adalimumab	---	---	---	---	---	---	---	---
Magliocco, 2007	CyA transitioned to alefacept	---	---	---	---	---	---	---	---
Costanzo, 2005	Nonbiologics transitioned to etanercept¶	2w	---	---	---	---	---	---	---
		8w	---	---	---	---	1/44	---	---
		12w	---	---	---	---	---	---	---

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CyA=cyclosporine; d=day(s); GFR=glomerular filtration rate; MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; PUVA=psoralen plus ultraviolet A; SCr=serum creatinine; TCP=thrombocytopenia; w=week(s); ---=not reported

* Includes events through week 16 for patients who switched treatments and through week 26 for others who did not

† Hepatic enzyme increases

‡ CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA

§ 70 days after last treatment

|| Level greater than 2.5 times upper limit of normal

¶ CyA, corticosteroids, MTX, retinoids

Table 10. Adverse outcomes (2)

Study, year	Study group	Followup	Hypertension n/N	Metabolic alterations n/N				
				Glucose	Lipids	Weight	BMI	Thyroid function
CT5, 2012	Etanercept	---	0/21	---	---	---	---	---
	Acitretin	---	0/18	---	---	---	---	---
Barker, 2011	Infliximab	26w*	0/649	---	---	---	---	---
	MTX	26w*	0/211	---	---	---	---	---
	Infliximab transitioned to MTX	26w	0/9	---	---	---	---	---
	MTX transitioned to infliximab	26w	1/63	---	---	---	---	---
Inzinger, 2011	Adalimumab	---	---	---	---	---	---	---
	Alefacept	---	---	---	---	---	---	---
	Etanercept	---	---	---	---	---	---	---
	Infliximab	---	---	---	---	---	---	---
	Ustekinumab	---	---	---	---	---	---	---
	PUVA	---	---	---	---	---	---	---
Strober, 2011	MTX transitioned to adalimumab	---	---	---	---	---	---	---
	NB-UVB transitioned to adalimumab	---	---	---	---	---	---	---
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---	---	---
Caproni, 2009	Etanercept	---	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---	---
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept†	---	---	---	---	---	---	---
Gisondi, 2008a	Etanercept	---	---	---	---	---	---	---
	Acitretin	---	---	---	---	---	---	---
Gisondi, 2008b	Etanercept	24w	---	---	235(17.3)‡	1.5(2.7)§	0.5(0.5)‖	---
	Infliximab	24w	---	---	237(16.9)‡	2.5(3.3)§	0.8(1.0)‖	---
	MTX	24w	---	---	236(18.1)‡	-0.6(1.4)§	-0.2(0.5)‖	---
Saurat, 2008	Adalimumab	---	---	---	---	---	---	---

Study, year	Study group	Followup	Hypertension n/N	Metabolic alterations n/N				
				Glucose	Lipids	Weight	BMI	Thyroid function
	MTX	---	---	---	---	---	---	---
	MTX transitioned to adalimumab	---	---	---	---	---	---	---
Magliocco, 2007	CyA transitioned to alefacept	---	---	---	---	---	---	---
Costanzo, 2005	Nonbiologics transitioned to etanercept¶	---	---	---	---	---	---	---

Abbreviations: BMI=body mass index; CyA=cyclosporine; d=day(s); MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; PUVA=psoralen plus ultraviolet A; w=week(s); ---=not reported

* Includes events through week 16 for patients who switched treatments and through week 26 for others who did not

† CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA

‡ Mean(SD) total cholesterol level

§ Mean(SD) body weight (kg) change from baseline

|| Mean(SD) BMI change from baseline

¶ CyA, corticosteroids, MTX, retinoids

Table 11. Adverse outcomes (3)

Study, year	Study group	Followup	Injection site reaction n/N	Malignancy n/N	Infections n/N	Study withdrawal n/N
CT5, 2012	Etanercept	---	1/21	---	0/21	4/21
	Acitretin	---	0/18	---	0/18	6/18
Barker, 2011	Infliximab	26w*	17/649†	1/649‡	10/649§	112/653
	MTX	26w*	0/211†	0/211‡	4/211§	88/215
	Infliximab transitioned to MTX	26w	0/9†	0/9	0/9‖	---
	MTX transitioned to infliximab	26w	5/63†	0/63	1/63‖	---
Inzinger, 2011	Adalimumab	---	---	---	---	---
	Alefacept	---	---	---	---	---
	Etanercept	---	---	---	---	---
	Infliximab	---	---	---	---	---
	Ustekinumab	---	---	---	---	---
	PUVA	---	---	---	---	---
Strober, 2011	MTX transitioned to adalimumab	70d¶	2/41	0/41	13/41** 0/41††	2/41
	NB-UVB transitioned to adalimumab	70d¶	0/29	0/29	7/29** 1/29††	5/29
Garavaglia, 2010	CyA transitioned to etanercept	---	---	---	---	---
Caproni, 2009	Etanercept	12w	---	---	---	0/30
	Acitretin	12w	---	---	---	0/30
Mazzotta, 2009	Nonbiologics or phototherapy transitioned to etanercept‡‡	---	---	---	---	---
Gisondi, 2008a	Etanercept	6w	---	---	---	0/22
		12w	---	---	---	---
		24w	---	---	---	---
	Acitretin	6w	---	---	---	4/20
		12w	---	---	---	---
		24w	---	---	---	---
Gisondi, 2008b	Etanercept	---	---	---	---	---
	Infliximab	---	---	---	---	---
	MTX	---	---	---	---	---
Saurat, 2008	Adalimumab	70d¶	---	---	51/107** 0/107††	4/108
	MTX	70d¶	---	---	46/110** 0/110††	6/110
	MTX transitioned to adalimumab	---	---	---	---	---
Magliocco, 2007	CyA transitioned to alefacept	---	---	0/11	0/11	5/11

Study, year	Study group	Followup	Injection site reaction n/N	Malignancy n/N	Infections n/N	Study withdrawal n/N
Costanzo, 2005	Nonbiologics transitioned to etanercept§§	2w	2/44	---	---	4/44
		8w	---	---	---	---
		12w	---	---	0/44§	---

Abbreviations: CyA=cyclosporine; d=day(s); MTX=methotrexate; n/N=number of patients per total population; NB-UVB=narrowband ultraviolet B; PUVA=psoralen plus ultraviolet A; w=week(s); ---=not reported
* Includes events through week 16 for patients who switched treatments and through week 26 for others who did not
† Infusion related reaction
‡ Basal cell carcinoma
§ Includes tuberculosis, opportunistic infections and serious viral infections
|| Includes bacterial arthritis and staphylococcal infection
¶ 70 days after last treatment
** Any infection
†† Any serious infection
‡‡ CyA, corticosteroids, fumaric acid esters, MTX, retinoids, PUVA
§§ CyA, corticosteroids, MTX, retinoids

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Appendix G. Strength of Evidence for Outcomes

Table 12. Strength of evidence for final health outcomes comparing adalimumab with methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (1)	Low risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (1)	Low risk of bias	NA	Direct	Precise	Low
	Observational (1)	Medium risk of bias	NA	Direct	NA	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 13. Strength of evidence for intermediate health outcomes comparing adalimumab with methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PASI	RCT (1)	Low risk of bias	NA	Direct	NA	Low
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (1)	Low risk of bias	NA	Direct	NA	Low
	Observational (1)	Medium risk of bias	NA	Direct	Precise	
Patient assessment of disease	RCT (1)	Low risk of bias	NA	Direct	NA	Low
	Observational (0)	---	---	---	---	
Individual symptoms-pain	RCT (1)	Low risk of bias	NA	Direct	NA	Low
	Observational (0)	---		---	---	
Individual symptoms-puritus	RCT (1)	Low risk of bias	NA	Direct	NA	Low
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 14. Strength of evidence for final health outcomes comparing etanercept versus acitretin

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (1)	High risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 15. Strength of evidence for intermediate health outcomes comparing etanercept versus acitretin

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (2)	Medium risk of bias	Consistent	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (3)	Medium risk of bias	Consistent	Direct	NA	Moderate
	Observational (0)	---	---	---	---	
PGA	RCT (1)	High risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (1)	High risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms-joint pain	RCT (1)	High risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms-itching	RCT (1)	High risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 16. Strength of evidence for final health outcomes comparing etanercept versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 17. Strength of evidence for intermediate health outcomes comparing etanercept versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	High risk of bias	NA	Direct	NA	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (2)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	High risk of bias	NA	Direct	NA	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 18. Strength of evidence for final health outcomes comparing infliximab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (0)	---	---	---	---	
HRQoL	RCT (1)	Medium risk of bias	NA	Direct	NA	Low
	Observational (0)	---	---	---	---	
MACE	RCT (1)	Medium risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (1)	Medium risk of bias	NA	Direct	NA	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 19. Strength of evidence for intermediate health outcomes comparing infliximab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (1)	Medium risk of bias	NA	Direct	NA	Low
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (1)	Medium risk of bias	NA	Direct	NA	Low
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 20. Strength of evidence for final health outcomes comparing ustekinumab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (1)	Medium risk of bias	NA	Direct	NA	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 21. Strength of evidence for intermediate health outcomes comparing ustekinumab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Low
	Observational (1)	Medium risk of bias	NA	Direct	NA	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 22. Strength of evidence for final health outcomes comparing adalimumab with psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 23. Strength of evidence for intermediate health outcomes comparing adalimumab with psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 24. Strength of evidence for final health outcomes comparing adalimumab with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 25. Strength of evidence for intermediate health outcomes comparing adalimumab with narrow band ultaviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

Table 26. Strength of evidence for final health outcomes comparing etanercept with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 27. Strength of evidence for intermediate health outcomes comparing etanercept with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (2)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

Table 28. Strength of evidence for final health outcomes comparing ustekinumab with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
MACE	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 29. Strength of evidence for intermediate health outcomes comparing ustekinumab with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

Table 30. Strength of evidence for final health outcomes comparing infliximab with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 31. Strength of evidence for intermediate health outcomes comparing infliximab with narrow band ultraviolet B

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	High risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

Table 32. Strength of evidence for final health outcomes comparing alefacept with psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 33. Strength of evidence for intermediate health outcomes comparing alefacept with psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 34. Strength of evidence for final health outcomes comparing etanercept with psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 35. Strength of evidence for intermediate health outcomes comparing etanercept with psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (2)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 36. Strength of evidence for final health outcomes comparing infliximab versus psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 37. Strength of evidence for intermediate health outcomes comparing infliximab versus psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (2)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 38. Strength of evidence for final health outcomes comparing ustekinumab versus psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Mortality	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
HRQoL	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
MACE	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Diabetes	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Psychological Comorbidities	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

HRQoL= health-related quality of ligr; MACE=major cardiovascular events; NA=not applicable; RCT=randomized controlled trials

Table 39. Strength of evidence for intermediate health outcomes comparing ustekinumab versus psoralen plus ultaviolet A

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
Plaque BSA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
PASI	RCT (0)	---	---	---	---	Insufficient
	Observational (1)	Medium risk of bias	NA	Direct	NA	
PGA	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Patient assessment of disease	RCT (0)	---	---	---	---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precisions	Strength of Evidence
	Observational (0)	---	---	---	---	
Individual symptoms	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 40. Strength of evidence for harms comparing adalimumab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (1) Observational (0)	Low risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Nephrotoxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Hematologic toxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Hypertension	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Alterations in metabolic parameters	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Injection site reaction	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Malignancy	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Infection	RCT (1) Observational (0)	Low risk of bias ---	NA ---	Direct ---	NA ---	Low
Study withdrawal	RCT (1) Observational (0)	Low risk of bias ---	NA ---	Direct ---	NA ---	Insufficient

NA=not applicable; RCT=randomized cotnrolled trial

Table 41. Strength of evidence for harms comparing alefacept versus cyclosporine

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Nephrotoxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Hematologic toxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Hypertension	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Alterations in metabolic parameters	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Injection site reaction	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Malignancy	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Infection	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Study withdrawal	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 42. Strength of evidence for harms comparing etanercept versus acitretin

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (2) Observational (0)	Low risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Nephrotoxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Hematologic toxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Hypertension	RCT (1) Observational (0)	High risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Alterations in metabolic parameters	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Injection site reaction	RCT (1) Observational (0)	High risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Malignancy	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Infection	RCT (1) Observational (0)	High risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Study withdrawal	RCT (3) Observational (0)	High risk of bias ---	Inconsistent ---	Direct ---	NA ---	Insufficient

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 43. Strength of evidence for harms comparing etanercept versus cyclosporine

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Nephrotoxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Hematologic toxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Hypertension	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Alterations in metabolic parameters	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Injection site reaction	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Malignancy	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Infection	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Study withdrawal	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 44. Strength of evidence for harms comparing etanercept versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Nephrotoxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Hematologic toxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Hypertension	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Total cholesterol	RCT (0) Observational (1)	--- Medium risk of bias	--- NA	--- Direct	--- NA	Insufficient
Weight and BMI	RCT (0) Observational (1)	--- Medium risk of bias	--- NA	--- Direct	--- NA	Insufficient
Injection site reaction	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Malignancy	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Infection	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Study withdrawal	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 45. Strength of evidence for harms comparing infliximab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Nephrotoxicity	RCT (0) Observational (0)	--- ---	--- ---	--- ---	--- ---	Insufficient
Thrombocytopenia	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Hypertension	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Total cholesterol	RCT (0) Observational (1)	--- Medium risk of bias	--- NA	--- Direct	--- NA	Insufficient
Weight and BMI	RCT (0) Observational (1)	--- Medium risk of bias	--- NA	--- Direct	--- NA	Insufficient
Injection site reaction	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Malignancy	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Infection	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient
Study withdrawal	RCT (1) Observational (0)	Medium risk of bias ---	NA ---	Direct ---	NA ---	Insufficient

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Table 46. Strength of evidence for harms comparing infliximab versus methotrexate

Outcome	Study design and number	Risk of bias	Consistency	Directness	Precision	Strength of Evidence
Hepatotoxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Nephrotoxicity	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Thrombocytopenia	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Hypertension	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Total cholesterol	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Weight and BMI	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Injection site reaction	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Malignancy	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Infection	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	
Study withdrawal	RCT (0)	---	---	---	---	Insufficient
	Observational (0)	---	---	---	---	

BSA=body surface area; NA=not applicable; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment; RCT=randomized controlled trial

Appendix H. Applicability of Individual Studies

Table 47. Evaluation of applicability for individual randomized controlled trials

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
CT5, 2012	Study Designation: Efficacy study Composite Score: 4of 7	1. Assessed final health outcomes 2. Adequate study duration with clinically relevant treatments 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	• High male to female ratio (M: 79.5% F: 20.5%) • More stringent eligibility criteria • Duration of followup for final health outcomes (Psychological outcomes – 24 weeks) • Duration of followup for adverse health outcomes (AST, ALT, HTN, Injection site reaction, Infections – NR) • Conducted in Korea
Barker, 2011	Study Designation: Effectiveness study Composite Score: 6 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate study duration with clinically relevant treatments 4. Assessed adverse outcomes 5. Adequate sample size 6. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Duration of followup for final health outcomes (MACE, diabetes – 26 weeks) • Duration of followup for adverse outcomes (malignancy, infections – 26 weeks) • Conducted in Europe
Caproni, 2009	Study Designation: Efficacy study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed adverse outcomes 3. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Did not assess final health outcomes • Duration of followup for intermediate health outcomes (PASI – 12 weeks) • Inadequate sample size • Conducted in Italy
Gisondi, 2008a	Study Designation: Efficacy study Composite Score: 4 of 7	1. Enrolled primary care population 2. Adequate study duration with clinically relevant treatments 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Did not assess final health outcomes • Inadequate sample size • Conducted in Italy

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Saurat, 2008	Study Designation: Effectiveness study Composite Score: 6 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate study duration with clinically relevant treatments 4. Assessed adverse outcomes 5. Adequate sample size 6. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Duration of followup for final health outcomes (mortality – 70 days after last treatments) • Duration of followup for adverse events (infections – 70 days after last followup) • Conducted in Europe and Canada

Table 48. Evaluation of applicability for individual observational studies

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Gelfand, 2012	Study Designation: Efficacy study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate sample size	Population, Intervention, Outcomes	• More stringent eligibility criteria • Duration of followup for final health outcomes (DLQI – NR) • Duration of followup for intermediate outcomes (PASI, BSA, PGA, PaGA – NR) • Did not report adverse events • Did not use intention-to-treat analysis
Emerit, 2011	Study Designation: Efficacy study Composite Score: 3 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Adequate study duration with clinically relevant treatments	Population, Outcomes, Setting	• Did not report final health outcomes • Did not report adverse events • Inadequate sample size • Did not use intention-to-treat analysis • Conducted in Europe
Inzinger, 2011	Study Designation: Efficacy study Composite Score: 3 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis	Intervention, Outcomes, Setting	• Did not report final health outcomes • Duration of followup for intermediate outcomes (PASI – 12 weeks) • Did not report adverse events • Inadequate sample size • Conducted in Austria
Strober, 2011	Study Designation: Effectiveness study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate study duration with clinically relevant treatments 4. Assessed adverse outcomes 5. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Duration of followup for final health outcomes (mortality – 16 weeks) • Duration of followup for adverse events (malignancy, infections – 16 weeks) • Inadequate sample size • Multicenter study with the US included

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Garavaglia, 2010	Study Designation: Efficacy study Composite Score: 2 of 7	1. Assessed adverse outcomes 2. Used intention-to-treat analysis	Population, Intervention, Outcomes, Setting	• High male to female ratio (M: 75%, F: 25%) • More stringent eligibility criteria • Did not assess final health outcomes • Duration of followup for intermediate health outcomes (PASI – 12 weeks) • Inadequate sample size • Conducted in Italy
Mazzotta, 2009	Study Designation: Efficacy study Composite Score: 3 of 7	1. Enrolled primary care population 2. Adequate study duration with clinically relevant treatments 3. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Did not assess final health outcomes • Did not assess adverse events • Inadequate sample size • Conducted in Italy
Gisondi, 2008b	Study Designation: Efficacy study Composite Score: 4 of 7	1. Enrolled primary care population 2. Adequate study duration with clinically relevant treatments 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Intervention, Outcomes, Setting	• More stringent eligibility criteria • Did not assess final health outcomes • Inadequate sample size • Conducted in Italy
Magliocco, 2007	Study Designation: Efficacy study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Adequate study duration with clinically relevant treatments 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes	• Male to female ratio not reported • More stringent eligibility criteria • Duration of followup for adverse events (malignancy, infection – NR) • Inadequate sample size
Costanzo, 2005	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Adequate study duration with clinically relevant treatments 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	• More stringent eligibility criteria • Did not assess final health outcomes • Duration of followup for adverse events (infection – 12 weeks) • Inadequate sample size • Conducted in Italy

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSA=body surface area; DLQI=Dermatology Life Quality Index; F=female(s); HTN=hypertension; M=male(s); MACE=major adverse cardiovascular event; NR=not reported; PaGA=Patient's Assessment of Global Improvement; PASI=Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; US=United States

Appendix I. Glossary

Biologic: Adalimumab, alefacept, etanercept, infliximab, and ustekinumab.
Body mass index (BMI): A measure of body fat based on height and weight that applies to adult men and women. There are four categories including underweight (≤18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥30).
Body surface area (BSA): Estimation of BSA affected by psoriasis may be done by using hand area representing approximately 1% of total body surface.
Confidence Intervals (CIs): The range within which the 'true' value (e.g. size of effect of an intervention) would be expected to lie if sampling could be repeated a large number of times (e.g. 95% or 99%).
Dermatology Life Quality Index (**DLQI):** A 10-item dermatology-specific validated questionnaire which assesses the health related quality of life of patients suffering from a particular skin condition. All questions refer to "over the past week". Scores range from 0 (no effect at all on patient's life) to 30 (extremely large effect on patient's life). A 5-point reduction is considered clinically relevant.
EuroQoL-5D (EQ-5D): A standardized instrument for use as a measure of health outcomes; it is utilized in a wide variety of disease states. EQ-5D utility index is scaled between 0 (dead) and 1 (optimal health).
Glomerular filtration rate (**GFR):** A measure of the overall index of kidney function where the normal GFR varies according to age, sex, and body size, and declines with age.
Health Assessment Questionnaire (HAQ): An assessment of patient-oriented outcomes based on five dimensions including disability, pain, medication effects, costs of care, and mortality. There are two HAQ versions including the Full HAQ, which assesses all of the five dimensions, and the Short HAQ, which contains only the HAQ disability index (HAQ-DI) and the HAQ's patient global and pain visual analog scales (VAS).
Health Assessment Questionnaire Disability Index (**HAQ-DI):** A 20 question, eight category assessement of a paitent's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. Patient responses are based on a scale from zero, representing no disability, to three, corresponding to complete disability.
Health-Related Quality-of-Life (HRQoL): A person or cohort's perceived physical and mental health over time. Often assesed in chronic plaque psoriasis evaluations using the Dertmatology Life Quality Index (DLQI), 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36) or other disease-specific or general measures.
Intention to treat (ITT): One in which all of the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.
Major adverse cardiac events (MACE): Psoriasis, an inflammatory skin disease, if severe, has been observed to be a risk factor for cardiovascular disease; however, the degree of the association with MACE, such as myocardial infarction, stroke and cardiovascular death, has not been defined.
Meta-Analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.
Neutralizing antibodies: A phenomenon observed with prolonged therapy of TNF-alpha inhibitors, including infliximab (Remicade), adalimumab (Humira), and etanercept (Enbrel), which may lead to the development of autoantibodies that counteract the TNF-alpha antagonist activity of the drugs and reduces efficacy.

Nonbiologic: Acitretin, cyclosporine, and methotrexate.
Patient's Assessment of Global Improvement: A measure of patient's impression of how well his/her disease is controlled. The score ranges from 0 (complete disease control) to 3 (uncontrolled disease).
Percent activity impairment due to psoriasis: Percent impairment in regular activities was evaluated using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP), a 6-item questionnaire that measures effect of psoriasis on daily activity impairment, number of hours worked and the number of hours missed from work. Scores range from 0% to 100%. A decrease in percent impairment indicates improvement.
Percent impairment while working due to psoriasis: Percent impairment while working was evaluated using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP), a 6-item questionnaire that measures effect of psoriasis on daily activity impairment, number of hours worked and the number of hours missed from work. Scores range from 0% to 100%. A decrease in percent impairment indicates improvement.
Percent overall work impairment due to psoriasis: Percent overall work impairment was evaluated using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP), a 6-item questionnaire that measures effect of psoriasis on daily activity impairment, number of hours worked and the number of hours missed from work. Scores range from 0% to 100%. A decrease in percent overall work impairment indicates improvement.
Percent work time missed due to psoriasis: Percent work time missed due to psoriasis was evaluated using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP), a 6-item questionnaire that measures effect of psoriasis on daily activity impairment, number of hours worked and the number of hours missed from work. Scores range from 0% to 100%. A decrease in percent work time missed indicates improvement.
Physician's Global Assessment (PGA): A 6-point scale used to measure the severity of a patient's disease relative to baseline condition by a dermatologist. Overall lesions are graded for induration, erythema, and scaling. The score ranges from 0=clear (no plaque elevation; no scaling; erythema=hyperpigmentation, pigmented macules, diffuse faint pink or red coloration) to 5=very severe (plaque elevation=very marked; scaling=very coarse; erythema=very severe). A 7-point scale also available with 7 being clear and 6 almost clear, 5 mild, 4 mild to moderate, 3 moderate, 2 moderately severe and 1 being severe psoriasis.
Plaque psoriasis: The most common form of psoriasis, also known as psoriasis vulgaris, recognized by red, raised lesions covered by silvery scales. About 80% of patients with psoriasis have this type.
Psoriasis Area and Severity Index (PASI): A clincal assessment of the severity and extend of disease based on body surface area involvement, erythema, induration, and scaling. The PASI score is commonly used to assess efficacy of psoriasis treatments. The score ranges from 0 (no disease) to 72 (maximal disease). An improvement of 50%, 75%, 90%, 100% from baseline corresponds to PASI 50, PASI 75, PASI 90, and PASI 100, respectively. An improvement of 75% from baseline (PASI 75) is commonly used as a dichotomous cut-off for efficacy in most trials.
Psoriatic Arthritis: Rheumatoid factor-negative inflammatory arthritis associated with psoriasis. This disease is characterised by stiffness, pain, and swelling in the joints, especially of the hands and feet. It affects about 23% of people with psoriasis. Early diagnosis and treatment can help inhibit the progression of joint deterioration.

Psoriasis-related Pruritus Assessment: A scale for evaluating pruritus-related to psoriasis over the previous week; values range from 0 (no itching) to 10 (severe itching). A decrease in score indicates an improvement in pruritus.
Psoriasis Subject Satisfaction Questionnaire (PSSQ): An 18-item psoriasis-specific questionnaire which assesses patients' satifisfaction. The change from baseline in PSSQ was determined by week X minus baseline, where larger scores indicate improvement.
Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a non-exposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.
Subject Global Assessment (SGA): A 6-point scale used to measure the severity of a patient's disease relative to baseline condition by the subject; values range from 0 (good) to 5 (severe). A decrease in score indicates improvement.
Sensitivity Analyses: A 'what if' analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.
Standard Deviations (SDs): A measure of the variability of a data set.
Thrombocytopenia: A condition where there is an abnormally low amount of platelets (<50,000 platelets/microliter), components of the blood that assist in clotting, which may lead to abnormal bleeding. Normal human platelet count ranges from 150,000 to 450,000 platelets per microliter of blood.
Tumor necrosis factor (TNF): One of the cytokines, or messengers, known to be fundamental to the disease process that underlies psoriasis. It often plays a key role in the onset and the continuation of skin inflammation.
TNF-alpha inhibitors: Agents that bind to and neutralize the effects of TNF-alpha, a pro-inflammatory cytokine, by preventing its binding to receptors. FDA-approved agents for use in plaque psoriasis include infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira).
Variance: A measure of the variation shown by a set of observations, defined by the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of observations.
Visual analogue scale (VAS): Direct rating where raters are asked to place a mark at a point between two anchor states appearing at either end of the line. It is used as a method of valuing health states.
Visual analogue scale (VAS) for plaque psoriasis and psoriatic arthritis pain: A scale for evaluating pain due to plaque psoriasis and psoriatic arthritis during the previous week; values range from 0 (no pain) to 100 (pain as bad as it could be). A decrease in score indicates an improvement in pain.

Appendix J. 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 5-Dimension ^{TM}
Kg	kilogram
Kg/m^2	ilogram 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
PSSQ	Psoriasis Subject Satisfaction Questionnaire
PUVA	psoralen plus ultraviolet A
SCr	serum creatinine
SF-36	Short Form-36 Health Survey
SGA	Subject Global Assessment
TCP	thrombocytopenia
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analogue scale
8-MOP	8-methoxypsoralen