Comparative Effectiveness Review
Number 85

Effective Health Care Program

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

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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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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

[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-DimensionTM; 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

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?

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

Full Report

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