Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value

Condition Update
Draft Background and Scope
December 4, 2017

Background

Psoriasis is a common disease that causes itchy, red, scaly, raised lesions on the skin, most commonly on the elbows, knees, scalp, and back.[1] Psoriasis affects about 2% of the population and significantly decreases health-related quality of life, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet) or social functioning (e.g., the face).[2-4] Psoriasis is a chronic inflammatory condition that is associated with systemic diseases including psoriatic arthritis, other autoimmune diseases, metabolic syndrome, and cardiovascular disease.[5]

Cutaneous psoriasis types include plaque psoriasis, guttate psoriasis, pustular psoriasis, inverse psoriasis, nail psoriasis, and erythrodermic psoriasis. Chronic plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis. Up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis.[6]

Plaque psoriasis is caused by dysregulation of innate and adaptive immunity in genetically susceptible people.[5] This dysregulation produces an overabundance of inflammatory mediators such as tumor necrosis factor (TNF)-α and interleukins (IL)-12, 23, and 17A. Activated immune cells and inflammatory mediators lead to overgrowth, scaling, redness, and other changes in psoriatic skin.

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy. Definitions of "moderate-to-severe" plaque psoriasis vary, but generally consist of psoriasis that affects at least 3% of a patient's body surface; produces lesions that have significant redness, thickness, and scale; or significantly reduces quality of life.[7,8]

Treatments for psoriasis can be grouped within four broad categories: 1) topical therapies such as steroids, vitamin D analogues, retinoids, and calcineurin inhibitors; 2) older systemic therapies, such as cyclosporine and methotrexate; 3) phototherapy such as psoralen and ultraviolet A radiation (PUVA); and 4) biologics or "targeted immunomodulators." Clinical interest in this last category is high, as many patients with chronic plaque psoriasis do not see adequate or durable benefit from

older systemic therapies or phototherapy. Additionally, targeted immunomodulators are associated with a high financial cost, some of which is passed on to patients. Targeted immunomodulators approved, or nearing approval, for the treatment of moderate-to-severe plaque psoriasis in the United States consist of medications with activity against the following targets:

- **Anti-TNF-α agents**: adalimumab (Humira®, AbbVie Inc.), etanercept (Enbrel®, Amgen Inc.), infliximab (Remicade®, Janssen Biotech Inc., approved only for severe plaque psoriasis), certolizumab pegol (Cimzia®, UCB Inc., approved for rheumatoid arthritis, under FDA review for psoriasis)
- **Anti-IL-17A agents**: secukinumab (Cosentyx®, Novartis AG), ixekizumab (Taltz®, Eli Lilly and Co.), brodalumab (Siliq™, Ortho Dermatologics)
- **Anti-IL-12/23 agent**: ustekinumab (Stelara®, Janssen Biotech Inc.)
- **Anti-IL-23 agents**: guselkumab (Tremfya™, Janssen Biotech Inc., approved in July 2017), tildrakizumab (Sun Pharma / Merck and Co., under FDA review)
- **Phosphodiesterase (PDE-)4 agent**: apremilast (Otezla®, Celgene Corp.) Although not technically a biologic, apremilast is a novel, targeted, oral agent also approved for treatment of patients with moderate-to-severe plaque psoriasis.

Treatment of plaque psoriasis can be challenging for patients. It can be difficult to apply topical therapies, especially when the affected area involves the scalp or covers a large part of the body. Therapies can be inconvenient to use; some require multiple injections on a daily or weekly basis. Insurance plans generally mandate "step therapy," which requires patients and clinicians to first try a list of preferred medications and, only after repeated treatment failures, progress to non-preferred treatments.

Studies have found that up to half of patients are dissatisfied with psoriasis treatment.[2,9] Dissatisfaction may be due to the unpredictable effectiveness of agents, poor tolerability, lack of durable response, and lack of access to medications because of coverage restrictions or costs.[2] The newer targeted immunomodulators are generally more expensive than older medications and there are questions regarding how these costs align with the clinical value brought to patients. ICER conducted a review in 2016 to assess the comparative clinical effectiveness and value of targeted immunomodulators (biologics plus apremilast) for adults with moderate-to-severe plaque psoriasis.

Rationale for Condition Update

Since the publication of the report in 2016, two new drugs have been approved. One of the drugs, brodalumab, was included in our 2016 review, while the second drug, guselkumab was not. In addition, two drugs, certolizumab pegol and tildrakizumab, may be approved for this indication before mid-2018, when this report update will be discussed at a public meeting. In addition, both

guselkumab and tildrakizumab, which specifically target IL-23, represent novel treatment approaches for plaque psoriasis.

New evidence has also emerged for many of the treatments originally assessed. As such, ICER has decided to revisit its 2016 report in a "Condition Update" for adults with moderate-to-severe plaque psoriasis. This effort will entail gathering evidence on the new treatments that have emerged, and incorporating new evidence on the treatments included in the original assessment. We expect to integrate these new data in updated syntheses of the clinical evidence as well as our evaluations of long-term cost-effectiveness and budgetary impact.

Key Findings of 2016 Review

The 2016 review focused on all of the agents listed above except certolizumab pegol, tildrakizumab, and guselkumab for the treatment of moderate-to-severe plaque psoriasis, and was deliberated on at the November 18, 2016 public meeting of the New England Comparative Effectiveness Public Advisory Council.[10] At that time, findings from placebo-controlled trials indicated a substantial net health benefit of all therapies as compared to placebo. Between-agent comparisons were completed using a combination of direct and indirect evidence, including head-to-head trials and a network meta-analysis. Overall, the ICER review concluded that agents targeted against IL-17a produced better outcomes than the older, anti-tumor necrosis factor (TNF) drugs. Overall, all agents offered added benefits for patients for whom topical and non-targeted systemic therapies have proven unsuccessful. Beyond effectiveness and safety of targeted immunomodulators, the method of administration, frequency of dosing during maintenance, and rapidity of effect were considered important factors by a variety of stakeholders.

The economic analyses resulted in incremental cost-effectiveness ratios across all agents that were well-aligned with commonly-accepted thresholds for cost-effectiveness (range: $89,610 – $129,904 per quality-adjusted life year). The potential budget impact of two newer agents – ixekizumab (approved in March 2016) and brodalumab (not approved at the time of the initial report) – was calculated and neither agent was expected to pose a challenge to health system budgets. It was estimated that the additional overall costs for treatment with immunomodulatory drugs are reasonably aligned with the added benefits they provide to patients. Considering this alignment of cost and benefit, the final report recommended that purchasers and insurers should consider limiting or abolishing "step therapy" approaches to coverage for targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis.

Report Aims

The objective of this Condition Update is to assess the comparative clinical effectiveness and value of new targeted immunomodulators for moderate-to-severe plaque psoriasis, including guselkumab, tildrakizumab, and certolizumab pegol. In addition, this update will incorporate any

new evidence generated with respect to the populations and outcomes of interest for the agents evaluated in the original 2016 review.

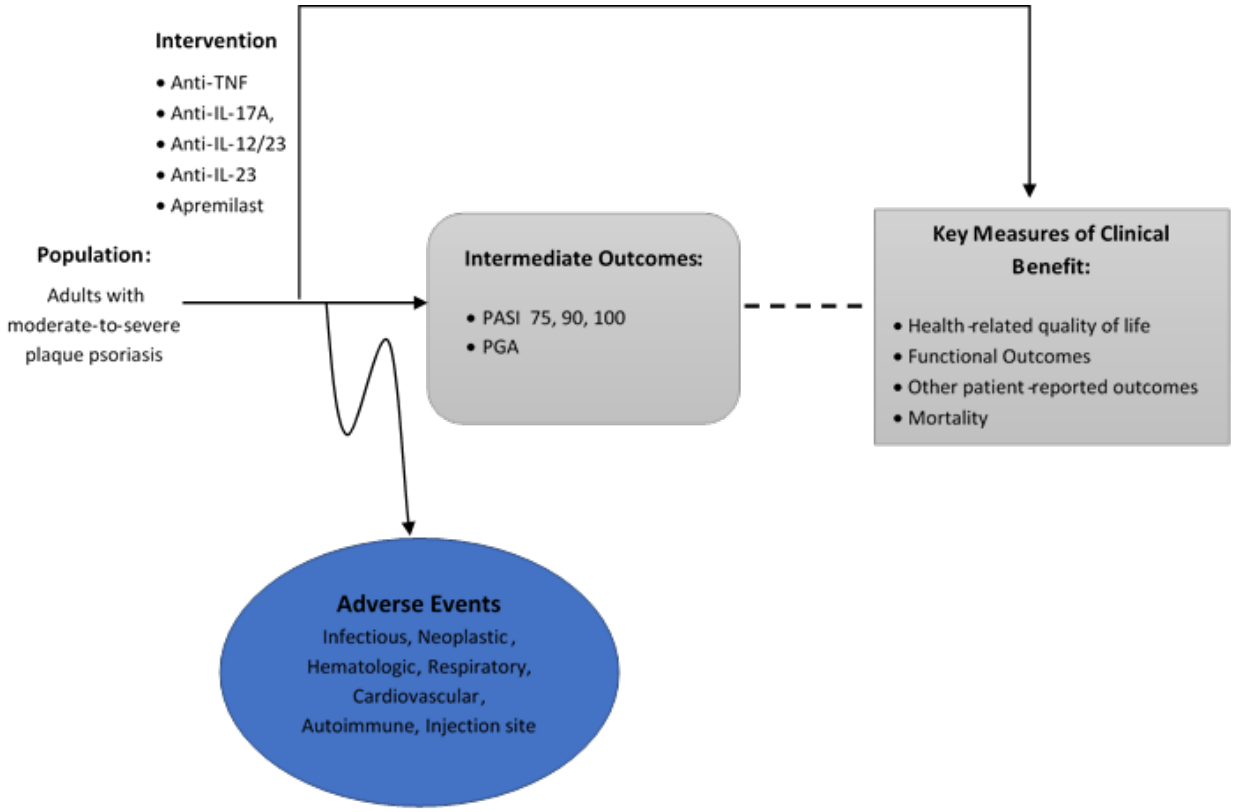
Scope of the Assessment

The proposed scope for this update will generally follow the approach used in 2016, described below. The update will use the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated as necessary. We will not restrict studies according to study duration or study setting; however, we will limit our review to those that capture the key outcomes of interest. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The general analytic framework for assessment of anti-plaque psoriasis medications is depicted in Figure 1 below.

Figure 1. Analytic Framework: Management of Moderate-to-Severe Chronic Plaque Psoriasis



PASI = psoriasis area severity index; PGA = physician global assessment

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., PASI 75, 90, and 100), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[11]

Populations

The population of focus for this review is adults with moderate-to-severe chronic plaque psoriasis. Although not a focus of the review, we will not exclude patient populations with other concomitant psoriasis types or psoriatic arthritis, and will evaluate psoriasis outcomes in these subgroups if data are available. Additionally, we will attempt to distinguish outcomes for patients who have and have not been previously treated with a targeted immunomodulator.

Sub-group analyses conducted in the 2016 report will be updated: patients with concomitant psoriatic arthritis, patients who had previous used biologic therapy, and results from Asian studies. Other sub-group analyses, such as those based on other co-morbidities, may be conducted, data permitting.

Interventions

The interventions of interest are the targeted immunomodulators (biologics and apremilast) approved or expected to be approved, by July 2018 for the treatment of moderate-to-severe plaque psoriasis:

- **Anti-TNF-α agents**: adalimumab, etanercept, infliximab, certolizumab pegol (not yet approved for psoriasis)
- **Anti-IL-17A agents**: secukinumab, ixekizumab, brodalumab
- **Anti-IL-12/23 agent**: ustekinumab
- **Anti-IL-23 agents**: guselkumab (approved in 2017), tildrakizumab (not yet approved)
- **Anti-PDE-4 agent**: apremilast

We note that several biosimilar agents are FDA-approved for the treatment of plaque psoriasis. We will include information on biosimilars if clinical studies have been conducted in the target population that focus on the outcomes of interest. Studies focused only on bioequivalence (e.g., pharmacokinetics, pharmacodynamics) of biosimilar and originator products will not be considered.

Comparators

Wherever possible, we will evaluate head-to-head trials of these interventions. Other comparators may include placebo or other active treatments not listed above.

Outcomes

This review will examine key clinical outcomes, including outcomes common to plaque psoriasis trials (a list of outcomes is included on the next page). Discussions with patients, patient groups, clinicians, industry, and publications from academic research groups indicate that people with psoriasis have symptoms and burdens that are not well-captured by standard trial outcomes.[2,12] We will examine available data for evidence about the comparative effectiveness of targeted immunomodulators in affecting domains such as itch, scaling, pain, quality of life, work productivity, and satisfaction with treatment.

Clinical Trial and Study Outcomes

- Psoriasis Area and Severity Index (PASI): 50, 75, 90, 100
- Physician Global Assessment (PGA)
- Treatment-related adverse events

Patient-Reported Outcomes

- Dermatology Life Quality Index (DLQI)
- Other measures of health-related quality of life
- Psoriasis Symptom Inventory {PSI)
- Symptom control
- Treatment tolerability

We will update the evidence tables with data from the newly selected studies and results will be summarized in a qualitative fashion. Network meta-analysis to combine direct and indirect evidence on PASI 75 scores will be updated. As available data permits, we will perform a network meta-analysis for PASI 90 & PASI 100.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration. Because psoriasis is a chronic condition with no cure, we are particularly interested in evidence of durability of response to medications, as well as long-term safety.

Settings

Plaque psoriasis is generally treated in outpatient and/or clinic settings, which will be the focus of our review.

Economic Models Focusing on Comparative Value

As a complement to the evidence review, we will use the Markov model developed for our 2016 report to assess the cost-effectiveness of the regimens of interest, updated to include certolizumab pegol, guselkumab, and tildrakizumab, as well as any new data on the regimens evaluated in the 2016 report. The model structure was based in part on previously developed economic models assessing treatments for psoriasis.[13] As before, the analysis will be conducted from a health system perspective over a 10-year time horizon, and will focus attention on regimens most likely to be used for adults with moderate-to-severe chronic plaque psoriasis who have failed topical and/or phototherapy. We will evaluate a lifetime time horizon in a scenario analysis.

Proposed regimens will be the same as those evaluated in the clinical effectiveness analyses.

Effectiveness will be estimated based on network meta-analyses of randomized controlled trial data on PASI response.

As in our 2016 report, key model inputs will include disease-specific measures such as the PASI, symptom improvement, treatment-related adverse events, health-related quality of life, and systemic manifestations, as feasible. Costs will include those of current and subsequent treatment, management of adverse events, and ongoing care. If sufficient data are available, the model will incorporate effects on productivity as a scenario analysis. Results will be expressed in terms of the marginal cost per QALY gained and cost per PASI 90 attainment. Cost per life-year gained is not relevant here due to the lack of mortality effects from psoriasis treatment.

In separate analyses, we will explore the potential health system budgetary impact of each new treatment (certolizumab pegol, tildrakizumab, and guselkumab) over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the Markov model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected using targeted immunomodulators for plaque psoriasis (e.g., reduced use of topical or systemic therapies), as these will be captured in the economic model. Rather, we are seeking services used in the treatment of plaque psoriasis beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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