Comparative Clinical Effectiveness of Treatment Options for Moderate-to-Severe Plaque Psoriasis

Research Protocol

July 25, 2016

Institute for Clinical and Economic Review

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Background, Objectives, and Research Questions

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, the 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 patients' 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 4 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:

- ***TNF-α:*** adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®)
- ***IL-17A:*** secukinumab (Cosentyx®), ixekizumab (Taltz®), brodalumab (investigational)
- ***IL-12/23:*** ustekinumab (Stelara®)
- ***Phosphodiesterase (PDE)-4:*** apremilast (Otezla®) Although not technically a biologic, apremilast is a novel, targeted, oral agent also approved for treatment of patients with moderate-to-severe plaque psoriasis.

[Note: Certolizumab pegol (Cimzia®) and golimumab (Simponi®, Simponi ARIA) are anti-TNF agents that have been approved for the treatment of psoriatic arthritis, but not 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.[3,9] 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.[3] 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.

Overview

This project will evaluate the health and economic outcomes of targeted immunomodulators (biologics plus apremilast) for adults with moderate-to-severe plaque psoriasis. The proposed scope for these assessments is described below using 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 http://icer-review.org/wp-content/uploads/2016/02/Slides-on-value-frameworkfor-website-v4-13-16.pdf).

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[10]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair*: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor*: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

PICOTS Inclusion Criteria

All search algorithms for the systematic literature review will be generated utilizing PICOTS related elements: Patient, Interventions, Comparisons, Outcomes, Timing, and Setting.

Population

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.

Interventions

The interventions of interest are the targeted immunomodulators (biologics and apremilast) all but one of which have been approved for the treatment of moderate-to-severe plaque psoriasis:

- ***Anti-TNF-α agents:*** adalimumab, etanercept, infliximab (approved only for severe plaque psoriasis)
- ***Anti IL-17A agents:*** secukinumab, ixekizumab, brodalumab (not yet approved)
- ***Anti IL-12/23 agent:*** ustekinumab
- ***Anti PDE-4 agent:*** apremilast

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. 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.[3,11] Standard trial outcomes are generally not used or feasible to employ in actual clinical practice. 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): 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
- Symptom control
- Treatment tolerability

We will develop evidence tables for each selected study and results will be summarized in a qualitative fashion; meta-analysis will be used to quantitatively summarize outcomes for the therapies of interest. We will perform a network meta-analysis for PASI scores and consider network meta-analysis to combine direct and indirect evidence of effectiveness as available data permit.

Timing

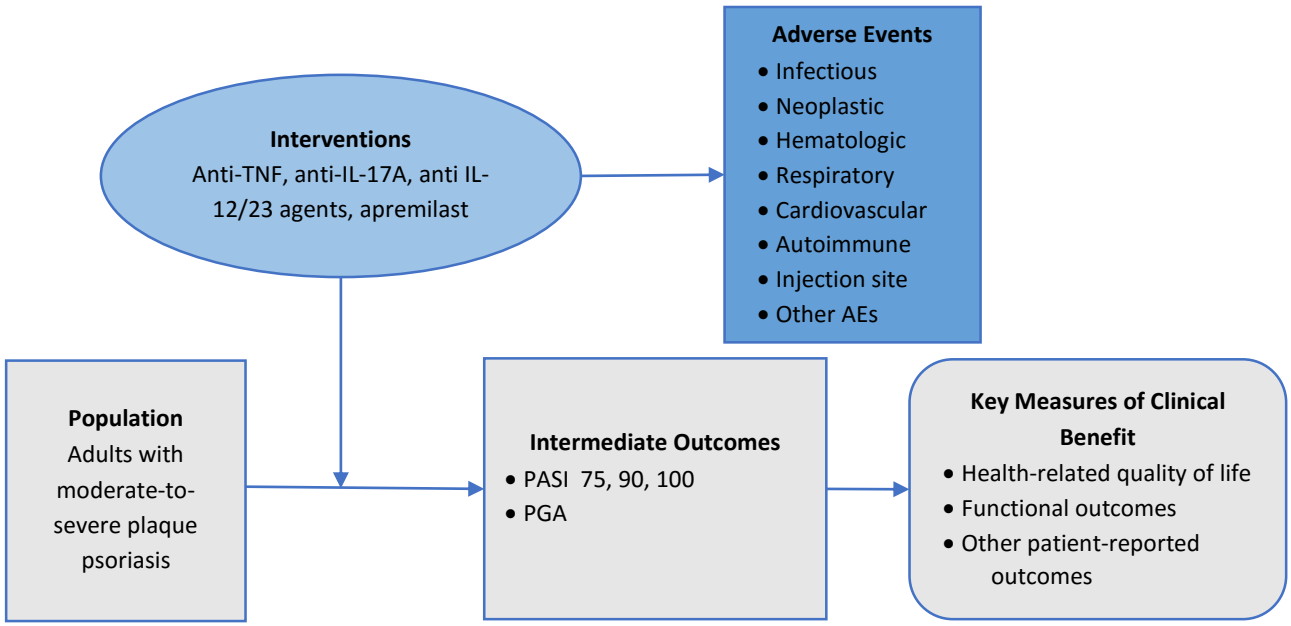
Evidence on intervention effectiveness and harms will be derived from studies of any duration. Because psoriasis is a chronic condition with no cure, we are particularly interested in evidence of durability of response to medications, as well as long-term safety.

Settings

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

Analytic Framework

The proposed analytic framework for this project is depicted below.



Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on targeted immunotherapies for moderate-to-severe plaque psoriasis will follow established best methods.[12] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English-language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. The search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below. We will also include abstracts from conference proceedings in the literature search. In order to supplement the above searches and ensure optimal and complete literature retrieval, we will perform a manual check of the references of recent relevant reviews and meta-analyses.

We will not conduct a *de novo* search for the anti-TNF agents. Rather, data from the key comparative studies not captured in the initial survey of the literature will be abstracted from recently published high-quality systematic reviews. These data will be summarized descriptively, and pooled estimates of

treatment effect may be incorporated into our quantitative synthesis of the evidence, depending on the comparability of trial populations and outcome measures.

Table 1: Search Strategy of Medline 1996 to Present with Daily Update, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled

1	Psoriasis/	16220
2	psoria$.ti,ab.	24352
3	(secukinumab or cosentyx).ti,ab.	222
4	(ustekinumab or stelara).ti,ab.	649
5	(ixekizumab or taltz).ti,ab.	64
6	brodalumab.ti,ab.	77
7	(apremilast or otezla).ti,ab.	179
8	1 or 2	26043
9	3 or 4 or 5 or 6 or 7	1094
10	8 and 9	861
11	limit 10 to english language	824
12	limit 11 to humans	824
13	(guideline or practice guideline or letter or editorial or news or case reports or clinical	1931126
14	12 not 13	700
15	remove duplicates from 14	601
Date of Search: June 28, 2016		

Table 2: Search Strategy of Embase on June 28, 2016

#20	#19 AND [humans]/lim	1017
#19	#18 NOT 'case report' NOT 'case study'	1124
#18	#15 NOT #16 NOT #17	1184
#17	#15 AND [humans]/lim AND [animals]/lim	32
#16	#15 AND [animals]/lim	40
#15	#13 NOT #14	1224
#14	#12 AND [medline]/lim	413
#13	#12 AND [english]/lim	1622
#12	#10 NOT #11	1683
#11	#3 AND #9 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR	122
#10	#3 AND #9	1805
#9	#4 OR #5 OR #6 OR #7 OR #8	2235
#8	'brodalumab':ab,ti	127
#7	'apremilast':ab,ti OR 'otezla':ab,ti	331
#6	'ixekizumab':ab,ti OR 'taltz':ab,ti	156
#5	'ustekinumab':ab,ti OR 'stelara':ab,ti	1454
#4	'secukinumab':ab,ti OR 'cosentyx':ab,ti	399
#3	#1 OR #2	58457
#2	psorias*:ab,ti OR psoriat*:ab,ti	57572
#1	'psoriasis vulgaris'	8040

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will screen the titles and abstracts of all publications identified through electronic searches according to the inclusion and exclusion criteria defined by the PICOTS elements; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

For the systematic literature review, the data extraction will be performed in the following steps:

1. Two reviewers will extract information from the full articles.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Information from the accepted studies will be entered into data extraction forms.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, multiple assessments of publication bias will be performed. We will first scan the ClinicalTrials.gov site to identify studies completed more than 2 years ago which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies, in order to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables, and synthesized qualitatively in the text of the report. An evidence table shell is presented in Appendix B.

In addition, quantitative indirect comparisons using Bayesian network meta-analysis (NMA) will be considered where possible. Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points will be used to assess model fit under multiple alternative assumptions. Given the large number of comparisons to be made among psoriasis treatments, and the expectation of at least some degree of heterogeneity in

patient populations and/or study design, there is a general preference for a random-effects approach. However, the number of single-study connections in any feasible network may limit the best approach to use of a fixed-effects model (to preserve statistically-significant effects observed in trials) and selected subgroup analyses (to address heterogeneity). As previously mentioned, we will examine pooled estimates from recently published high-quality systematic reviews of the anti-TNF agents for all available comparisons to ensure a comprehensive network.

Quantitative analyses will focus attention on the effects of the regimens of interest on PASI scores, and will be conducted using the NetMetaXL tool (http://www.netmetaxl.com/), a publicly-available and validated Excel-based tool for specifying and analyzing Bayesian indirect comparisons in a WinBUGS environment. For these outcomes, adjusted hazard ratios from the randomized trials will be log-transformed and entered into the spreadsheet, and 95% confidence intervals will be used to specify variance estimates (i.e., standard errors). A total of 40,000 iterations each will be used for both "burn-in" (for model convergence) and model (for model results) simulations.

References

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[13] Additional explanation of each item can be found in Liberati et al. 2009.[14]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms