Cost-Effectiveness of Biologic Agents in Psoriasis: Modeling Analysis Plan

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Approach

Biological agents approved for the treatment of plaque psoriasis can be divided into three categories: Tumor Necrosis Factor (TNF) inhibitors, Interleukin (IL)-17A inhibitors, and IL-12/23 inhibitors. This analysis seeks to establish the cost-effectiveness of several agents representing these classes in addition to the single phosphodiesterase-4 inhibitor approved for treatment of psoriasis. The benefits and costs of treatment with these agents will be modelled in Microsoft Excel using a Markov model. The draft approach proposed below may be modified based on external and internal feedback.

Key model choices and assumptions

- The population in this model represents adults with moderate to severe plaque psoriasis who have not responded adequately to phototherapy and are taking a biologic agent for psoriasis for the first time.
- The estimated effectiveness of each drug will be gathered from a network meta-analysis of published trials and unpublished data from manufacturers. Effectiveness will be measured via the PASI score. Four groups of patients will be defined by their PASI scores: 90 to 100; 75 to 89; 50 to 74; and less than 50. A PASI score of 75 or greater is considered adequate response; a PASI score between 50 and 74 is considered partial response.
- Cycle length will be determined in part by the results of the network meta-analysis, which will also take note of the times at which clinical endpoints were assessed in the various trials. Cycle length will also be chosen based on the ability to accommodate the dosing frequencies in each drug's initiation and maintenance phases.
- Each group will have a per-cycle probability of discontinuation or treatment failure, which can be unique to each drug. After discontinuation, the patient may proceed to either a second-line biologic or to best supportive care.
- The effectiveness of the second-line biologic agent will not be disambiguated for each possible combination of first- and second-line agents. Rather, 2nd-line biologic effectiveness will represent the estimated average probability of response for all agents in this analysis when used as second-line therapy.
- Health state utilities will be assigned to each PASI score category, regardless of the drug that is being modeled. These utilities will be ascertained by literature review or obtained from preference data gathered in trials.
- Patients in each health state may transition to death. A differential probability of death may be assigned to individuals with uncontrolled psoriasis relative to those with controlled psoriasis if adequate evidence indicates that treatment of the disease reduces risk of death.
- Once supportive care is initiated, no further biologics will be modeled.
- Adverse events will not affect utility directly unless supportive evidence is provided, and will incur costs.
- This analysis will be conducted from the payer perspective. Therefore, the cost of a given treatment will comprise the cost of the drug itself, clinic visits, any labs that are needed for monitoring the therapy, and the treatment of any adverse events that may occur. Productivity costs will be considered in a scenario analysis is sufficient supporting data are available.
- A ten-year and potentially lifetime time horizon will be used, with mean patient age at initiation of therapy linked to mean age in the trials included in the network meta-analysis.
- Costs and outcomes will be discounted at a rate of 3% per year.

Population

- Base case: adults with moderate to severe plaque psoriasis who have failed phototherapy but have not taken a prior biologic agent for psoriasis
- Potential scenario analysis, data dependent: Patients who have previously received a biologic agent for psoriasis

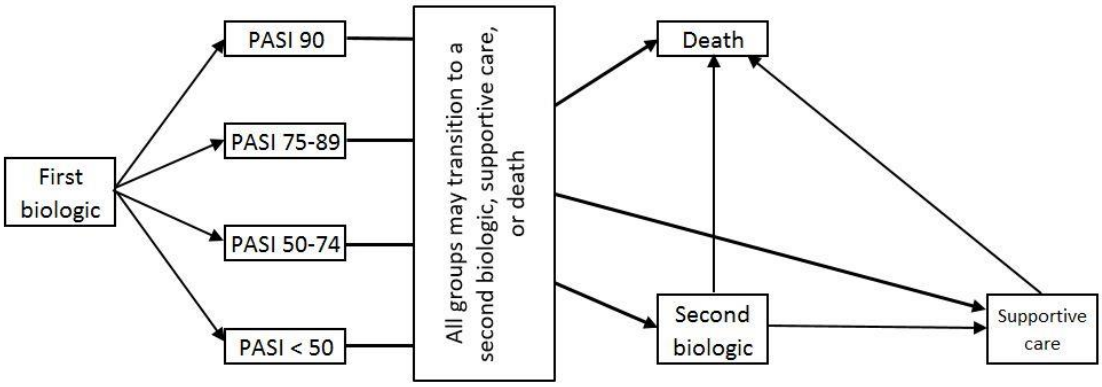
Interventions

The following interventions included in the model were chosen from the list of FDA-approved biologic agents for plaque psoriasis as well as by consultation with experts:

- TNF inhibitors
  - adalimumab (Humira®)
  - etanercept (Enbrel®)
  - infliximab (Remicade®)
- IL-17A inhibitors
  - secukinumab (Cosentyx®)
  - ixekizumab (Taltz®)
  - brodalumab (investigational)
- IL-12/23 inhibitor
  - ustekinumab (Stelara®)
- Phosphodiesterase-4 inhibitor
  - apremilast (Otezla®)

Model structure

Figure 1: Draft model schematic



The model will be a Markov model based on the York model that was established for use in NICE evaluations of anti-psoriasis drugs.[Woolacott et al, 2006] While the York model uses weighted averages of utility among all clinical responders, the proposed model makes these health states explicit, as well as adding in states for death and a second-line biologic.

In the base-case, the population enters the model upon the administration of the first-line biologic. Their distribution into different response groups will be based on the results of the network meta-analysis being conducted on the drugs' trials. Once in a response grouping, there will be no potential to transition between PASI scores, either upward or downward. Rather, each group will have a probability

of transitioning out of the health state indicating their response to the first biologic, either due to treatment failure or discontinuation for any other reason. At that point, patients may start a second biologic agent or begin supportive care. Users of a second-line biologic again have a probability of discontinuing each cycle, at which point they would initiate supportive care. All states have some probability of death.

Clinical inputs

Treatment effectiveness will be incorporated using response by PASI category (90 to 100; 75 to 89; 50 to 74; and less than 50) as derived from a network meta-analysis of relevant clinical trials. All-cause discontinuation rates for each drug will be included by PASI score as feasible. Adverse event rates will be derived from clinical trial publications and drug prescribing information.

Information on the probability of clinical response to biologic agents among those who have previously used biologics will be used to estimate the likelihood of response to the unspecified second-line biologic. The probability of death for patients with controlled and uncontrolled psoriasis will be used in the model as well, provided that there is adequate evidence to support differential rates of mortality.

Drug costs

Treatment specific costs are determined by multiplying the cost per dose by the frequency of dosing, then adding in the sum of costs associated with treating adverse events, and lab and clinic costs associated with therapeutic drug monitoring.

Table: Dosing parameters during maintenance therapy

Drug	Intiation	Maintenance	Cost / Unit	Annual clinic visits	Labs
Adalimumab	80mg once	40mg Q2wks (1 wk after 1st dose)			
Etanercept	50mg 2x/wk through wk 12	50mg QW			
Infliximab	5mg/kg at wks 0, 2, and 6	5mg/kg Q8wks			
Secukinumab	300mg QW through wk 4	300mg Q2wks			
Ixekizumab	160mg Q2wks through wk 12	80mg Q4wks			
Brodalumab	TBD	TBD			
Ustekinumab	45mg at wks 0 and 4	45mg Q12wks			
Apremilast	Increase of 10mg per day over 5 days	30mg BID			

Utilities

This analysis will base its utilities on the results of a literature search and/or preference data from trials. Previous published cost-effectiveness analyses of drugs treating psoriasis have linked PASI score categories to the DLQI and then mapped DLQI scores to EQ5D scores to derive utility scores. The utilities used in this model will be the same for each PASI score regardless of drug.

Table 6: Utility-assigned health states

Health state
PASI 90
PASI 75-89
PASI 50-74
PASI <50
Clinical response to second-line biologic
Supportive care

Other inputs

Mean age at initiation of therapy will be informed by the mean patient age in trials found by the meta-analysis. Probability of death by age will be provided by the standard US life table for patients who have well-controlled psoriasis, with the hazard rate being modified for patients with uncontrolled psoriasis if evidence dictates that this distinction is justified.

Model outcomes

The main outputs of the model will be direct costs of psoriasis treatment and quality-adjusted life years (QALYs). The model will also produce incremental cost-effectiveness ratios (ICER) as dictated by the cost-effectiveness frontier.

Sensitivity analyses

A one-way sensitivity analysis ("tornado diagram") will be produced in order to show which parameters have the greatest influence on the results of the base case. A probabilistic sensitivity analysis (PSA) will be conducted and cost-effectiveness acceptability curves for all interventions generated.

A scenario analysis will test the role of productivity improvement in the value of anti-psoriasis treatments, if sufficient supporting evidence is available, by adopting a limited societal perspective. The model will be altered to allow cost offsets by gains in productivity brought about by reduced severity of disease.