A New Cost-effectiveness Framework for Modeling Psoriasis Treatment

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BACKGROUND

- Biologic treatment for psoriasis is typically indicated only in moderate to severe disease and often only as the next step in the treatment sequence after failure of topical or immunosuppressive systemic treatment.
- Treatment sequencing for biologic therapies with different mechanisms of action is not yet standardized, and data addressing treatment strategies are sparse and often incomplete. However, in October 2012, the National Institute for Health and Care Excellence (NICE) issued new guidelines for the management of psoriasis, including a review for use of a second biologic drug following inadequate response to the first biologic drug.[1]
- In addition, most published economic evaluations of psoriasis treatments are based on data from randomized controlled trials that include patients with a mix of prior treatments and test a mix of treatment strategies. However, for a new product, decision makers are interested in economic evaluations that reflect specific product positioning in the treatment pathway and compare the tested treatment characteristics for the new product with a variety of treatment strategies for the current therapies that the new product might replace.
- A systematic review of treatment sequencing after the failure of a first-line biologic in cost-effectiveness models of psoriasis indicated that although treatment sequencing pathways are recommended, cost-effectiveness models of first-line biologic therapies have generally not included such pathways.[2]
- As more psoriasis treatments come to market in both new and existing drug classes, health care payers will need assistance in determining the most cost-effective regimen or sequence of regimens to control budgets.

OBJECTIVE

- To develop a cost-effectiveness modeling structure that will aid in decision making and meet the changing needs of payers by demonstrating the advantages of sequential biologic therapy in psoriasis and highlighting differentiating factors between drugs.

METHODS

- A targeted literature review was conducted to identify previously published cost-effectiveness models in moderate to severe psoriasis.
- The review focused on cost-effectiveness models to submitted to NICE as part of the manufacturer's submissions for reimbursement.

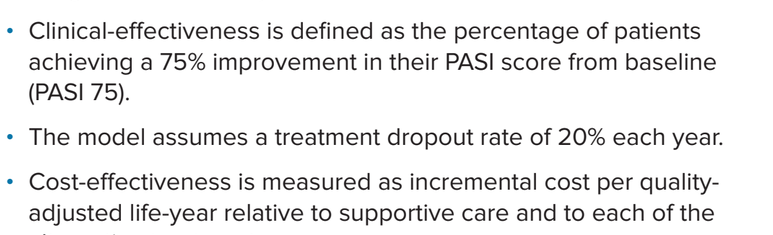
RESULTS

- The review identified four manufacturer submissions to NICE with cost-effectiveness models: etanercept and efalizumab (the York model), adalimumab, ustekinumab, and infliximab.
- We then identified publications describing these cost-effectiveness models and performed a critique from these submissions.
- Many previous models focused on one line of biologic therapy followed by standard of care.
- Psoriasis Area Severity Index (PASI) response was limited with respect to both time periods considered and the categories of response modeled.

The York Model[3]

- The York model is the most cited model in the disease of psoriasis.
- The model investigates the cost-effectiveness of etanercept and efalizumab in their licensed indications for people with moderate to severe psoriasis.
- The model seeks to identity the optimum sequence of treatments for patients based on the following:
  - Patient characteristics (medical history, renal and hepatic function, treatment history)
  - Impact of current disease
  - Willingness to accept the risk of specific side-effects
- The model uses a Markov structure (Figure 1) with an annual cycle length.
- Utility data are estimated from an analysis of data based on the three etanercept regulatory trials and the Health Outcomes Data Repository (HODaR) database, using Dermatology Life Quality Index (DLQI) data mapped to EuroQol-5 Dimensions questionnaire (EQ-5D) utility weights.
- Drug costs, laboratory costs, and hospital visit costs are included.
- Clinical-effectiveness is defined as the percentage of patients achieving a 75% improvement in their PASI score from baseline (PASI 75).
- The model assumes a treatment dropout rate of 20% each year.
- Cost-effectiveness is measured as incremental cost per quality-adjusted life-year relative to supportive care and to each of the alternative treatments.
- The most cost-effective order of treatments (treatment sequence) is determined by ranking each regimen by decreasing expected net benefit per unit time.
- Weaknesses of the model include the following:
  - No apparent consideration of heterogeneity, when pooling patient-level data from three registration trials
  - Little detail about costing of adverse events
  - No stochastic analysis of patient-level data
  - No probabilistic analysis of decision models, and no clear deterministic analysis of uncertainty

Figure 1. The York Model Structure: Markov Model of Treatment Period



Adalimumab Model[4]

- This model is based closely on the York model. Key differences include the following:
  - Sensitivity analysis includes productivity costs for nonresponders who are hospitalized.
  - The trial period lasts for between 12 and 16 weeks (16 weeks for adalimumab), and all patients in each group receive the intervention being evaluated.
  - Utility scores are calculated using the EQ-5D.

Infliximab Model[5]

- This model is based closely on the York model. Key differences include the following:
  - The trial period lasts for 10 weeks for infliximab and 12 weeks for etanercept and efalizumab, and the subsequent treatment period (average 186 weeks).
  - Responders receive two outpatient visits a year. Nonresponders receive an average of 18 outpatient visits and 21 days of inpatient care per year.

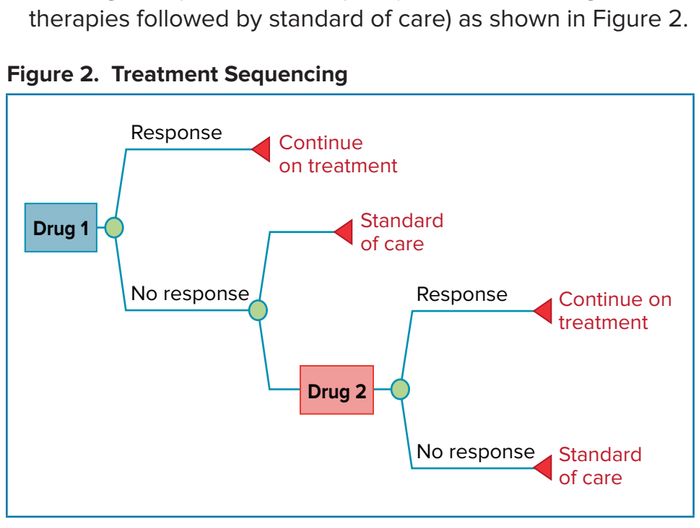
Ustekinumab Model[6]

- The model is based closely on the York model. Key differences include the following:
  - The cycle length is 3 months.
  - The trial period lasts for 16 weeks for ustekinumab and the subsequent treatment period.
  - All individuals on supportive care who have a PASI response below 75% are assumed to be nonresponders and to have one inpatient stay per year lasting 21 days.

Updated Model

- We developed a model that expanded the treatment/modeling paradigm, based on NICE recommendations, by allowing a sequence of therapies (two lines of biologic therapies followed by standard of care) as shown in Figure 2.

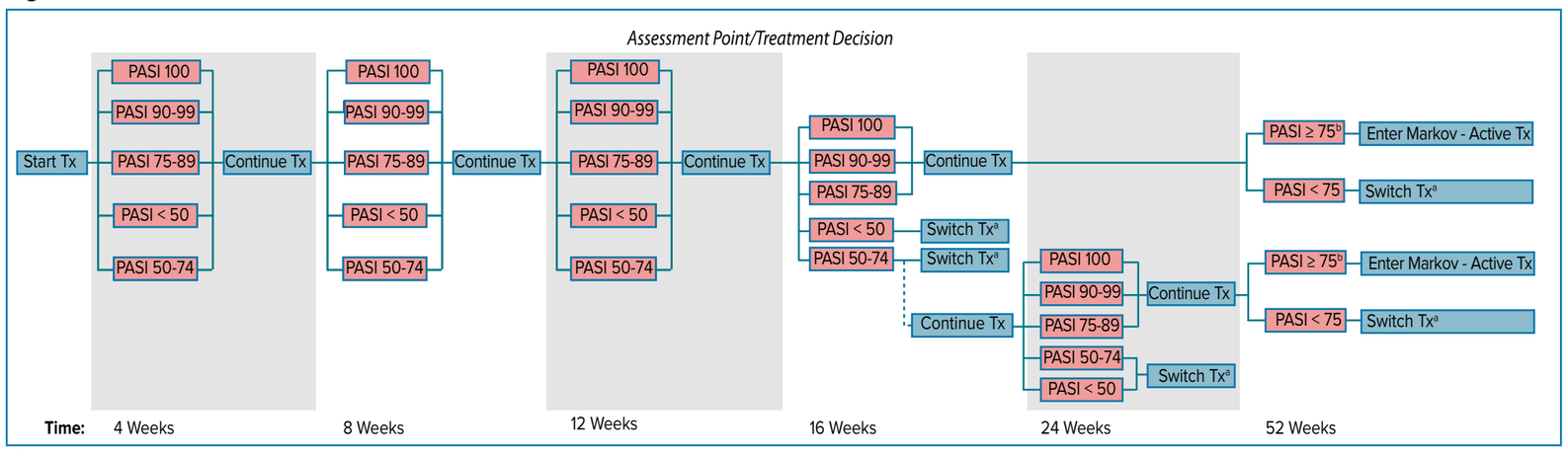
Figure 2. Treatment Sequencing



Model Structure

- A short-term decision tree allows for a clinical determination of PASI response at 12 or 16 weeks after therapy initiation. In the initial 12- or 16-week treatment period, we model the change in PASI levels over time (e.g., at 4, 8, and 12 weeks in the 16-week model) to better reflect quality of life for patients on treatments with an earlier response.
- The 16-week decision-tree model structure is shown in Figure 3.
- As new drugs allow some patients to achieve complete psoriasis clearance, a PASI 100 health state is included to better differentiate between regimens.
- Following the decision tree, patients enter a semi-Markov model with an annual cycle length (semi-Markov due to time dependent death probabilities) shown in Figure 4 to estimate long-term costs and outcomes.

Figure 3. 16-Week Decision-Tree Structure

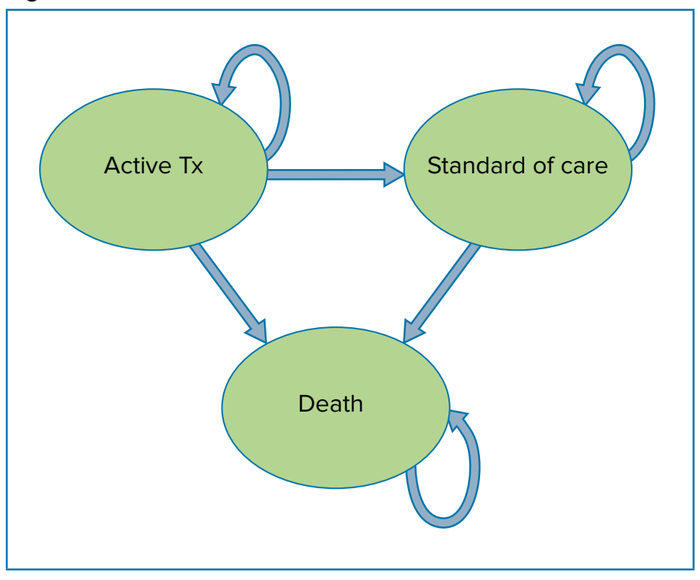


Tx = treatment.

[a] Patients who fail on (do not respond to) first-line biologic therapy switch to the user-defined second-line treatment. Failures from second-line treatment enter the Markov model in the standard of care health state and continue to receive standard of care until death.

[b] The PASI score distributions are used within the Active Tx health state to estimate costs and outcomes.

Figure 4. Markov Structure



Analytic Horizon

- The model calculates the clinical benefits, resource use, and costs over a range of time horizons, using an initial treatment period of 12 to 24 weeks and a subsequent maintenance phase where treatment is maintained in PASI responders (extrapolating response benefits).
- The primary analysis is conducted over a 10-year time horizon (in line with the original approach taken in York model and also with the time horizon adopted by Knight and colleagues[7] in the Swedish model for intermittent Enbrel versus Humira), which allows for the extrapolation of response benefits. This analytical approach considers the most cost-effective sequence of therapy, as opposed to recommending one specific treatment over another, and is felt to best reflect the trialing of therapies as seen in clinical practice.

Inputs

- The model follows the same general approach in assessing treatment response as seen in all previous HTA-focused economic evaluations of biologic drugs for treating psoriasis; namely, using the likelihood of achieving a predefined PASI response to separate the cohort into responders and nonresponders. In this case, the primary response in the model is defined as achieving a PASI 75 or greater response. The model also allows for an assessment of the potential clinical benefit and associated cost of extending the initial treatment duration in those patients who achieve only a partial response in the first 12 or 16 weeks of therapy. In this case, the model uses a PASI 50-74 response to define partial responders.
- Early response (4 weeks and 8 weeks) allows the model to capture the benefits of treatment that appear during the induction period.
  - Network meta-analysis of data at 4 weeks and 8 weeks is conducted for each treatment. The network meta-analysis also provides data at 12 weeks and 16 weeks.
- The model includes an option to consider a "mixed-bag" biologic treatment option to better represent clinical practice for patients who have experience failure on first- and second-line biologic therapy.
- Costs include drug costs, medical support (clinician visits and monitoring), adverse event costs, and indirect costs.
- The model has the capability to calculate the costs and cost-effectiveness with proportions of biosimilars, which are assumed to have similar efficacy to their branded counterparts but lower costs.
- The model allows user to select utility data from two separate analyses: an EQ-5D analysis, based on mixed models of EQ-5D response, and estimated utility scores based on DLQI mapping algorithms.
  - The utility weight for the active treatment state in the Markov model for each drug is calculated as a weighted average based on the drug-specific PASI distribution.
  - Between the time points PASI distributions are adjusted at the midpoint of each time. For example, baseline PASI distribution is used for 0 to 2 weeks, 4-week PASI distribution is used for 2 to 6 weeks.
- Disutilities related to standard of care are included because the trial arms included placebo, and standard of care consists of methotrexate and cyclosporine, which may have worse safety profiles. We model standard-of-care disutilities by applying a multiplier to the EQ-5D or DLQI health states based on the proportion of standard-of-care patients treated with methotrexate and cyclosporine.

Model Outcomes

- Cost-effectiveness is measured as incremental cost per quality-adjusted life-year relative to supportive care and to each of the alternative treatments (i.e., a cost-effectiveness frontier).
- Automated one-way and probabilistic sensitivity analyses are conducted.

LIMITATIONS

- Limited data on PASI efficacy following previous biologic failure are available in the clinical literature.
- Like previous analyses, PASI clearance is assumed to be stable until treatment discontinuation. Flare-ups or relapse are not modeled.
- PASI 100 data are not available for all model comparators in the mixed-treatment analysis. PASI 100 inputs are set to 0%, even though some patients may have achieved that response, and PASI 90-99 response actually represents PASI 90-100 response. PASI 90-99 and 100 inputs are reserved for the future when PASI 100 data may be available for all comparators.

CONCLUSIONS

- This new framework will help decision makers by better differentiating psoriasis treatments and determining the optimum order of biologic therapies in the psoriasis treatment pathway.

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