Considerations for Assessing the Cost of Biologic Agents in the Treatment of Psoriasis

SHELDON J. RICH, RPh, PhD

ABSTRACT

OBJECTIVE: This paper will establish the rationale for developing a long-term cost model to assess the utilization and associated economics of biologic agents in the treatment of moderate-to-severe psoriasis. This information should assist with defining the total cost of drug treatment when using biologic therapy to treat psoriasis.

SUMMARY: The development of biologic therapies has effected the treatment of many chronic diseases, including psoriasis. Managed care organizations are debating the appropriate use of these injectable drugs because of the associated acquisition costs and administration requirements. Important considerations for evaluating these agents include the ability to produce off-treatment remissions, the ability to improve patients’ quality of life, and safety and tolerability profiles. A remittive therapy may be a good early treatment for these patients because it offers the chance to avoid lifelong therapy. In addition, the safety and tolerability profiles of all biologic agents are substantially improved compared with conventional systemic psoriasis treatments. However, therapy must be individualized because risks vary with each agent. Thus, these differences in the biologic agents should be considered in the assessment of the economic impact and drug utilization for biologics for patients with psoriasis.

CONCLUSION: The biologic agents currently used in the treatment of psoriasis offer patients new hope for safe and effective therapy. Comparison of these agents by managed care decision makers requires consideration of characteristics that differentiate the agents, including efficacy, duration of off-treatment response, and safety and tolerability.

KEYWORDS: Alefacept, Psoriasis, Biologic therapy, Remittive, Off-treatment response, Cost model

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Biologic therapies are changing the treatment of many chronic diseases, including psoriasis. The number of these naturally occurring molecules or modifications thereof is steadily increasing, with more than 350 agents in various stages of development. Currently, 3 biologic agents have been approved for the treatment of patients with moderate-to-severe psoriasis: alefacept, efalizumab, and etanercept. These agents target several key inflammatory mediators linked to the pathogenesis of psoriasis. As a result of their selective action, these emerging therapies promise the potential for efficacy without the toxicities associated with conventional treatments such as skin cancer from phototherapy, liver and hematologic toxicity from methotrexate, and nephrotoxicity from cyclosporine.

With the expected market penetration of these products and the influx of new products over the next several years, managed care decision makers are centering efforts on determining the appropriate use of these agents. Evaluations focus on the long-term efficacy and safety as well as the costs of biologic agents used to treat psoriasis. Many health plans have debated the use of biologic therapies since their introduction in 2003, primarily because these drugs require in-office or at-home administration and have higher acquisition costs.

Recently, several short-term cost analyses (6 to 12 months) have been presented at major dermatology meetings that provide direct cost comparisons and cost-efficacy comparisons for the biologic therapies. Because no head-to-head comparative trials are available, the analyses were based on individual clinical trial data and product labeling. This approach is limited because clinical trial data may not be reflective of what happens in clinical practice, and outcomes deemed important for regulatory approval either may be too stringent for clinical practice or may underestimate the clinical benefit. In addition, short-term cost analyses fail to consider the implications of long-term efficacy and the potential for some products to produce remissions that continue after treatment has been completed. This paper reviews key considerations for the long-term assessment of the biologic therapies.

Characteristics That Differentiate Biologic Therapies’ Remittive Versus Suppressive Mode of Action

Depending on their mechanisms of action and the clinical outcomes after treatment has been completed, psoriasis treatments can be classified as suppressive or remittive. Suppressive therapies require continuous treatment to maintain a response. Most conventional agents used in the treatment of psoriasis are suppressive, including cyclosporine, methotrexate, and retinoids. The average response duration for these treatments is approximately 1 to 2.5 months.
Suppressive agents also can be associated with disease rebound or flare on discontinuation.

Remittive therapies provide long-term management of psoriasis by controlling symptoms without the need for continuous treatment. These therapies can offer patients extended periods of time free of psoriasis and its treatment. Therapy with psoralen plus ultraviolet A (PUVA) light is associated with periods of time free of psoriasis and its treatment. Remittive therapies can offer patients extended treatment remissions, but also the potential for adverse events.

Alefacept has a dual mechanism of action that inhibits T-cell activation and induces T-cell apoptosis. The latter mechanism results in the reduction of T cells both in the peripheral circulation and in lesional skin. Alefacept-induced reductions in circulating CD4+ T-cell counts have been shown to correlate with clinical improvement in large cohorts of patients with psoriasis. However, T-cell changes in individual patients are not necessarily predictive of response. Importantly, the effects of alefacept are selective for memory T cells, which have been specifically implicated in the pathogenesis of psoriasis. As a result of this selective action, alefacept eliminates pathogenic T cells while preserving immune function.

Thus, alefacept was expected to be remittive in its effect, and phase II and III clinical studies measured the duration of response after completion of therapy. The phase II study used a subjective determination for the duration of off-treatment response by measuring the time between the last dose of alefacept and the need for retreatment in an open-label follow-up study. The time to retreatment was evaluated in patients who responded to alefacept by achieving an assessment of “clear” or “almost clear” by their physician (or Physician Global Assessment [PGA]). The median time to retreatment was 10 months, with a range of 6 to 18 months.

In subsequent phase III studies, the duration of response was defined using objective measures of disease activity, specifically the Psoriasis Area and Severity Index (PASI). Two prespecified measures for duration of response were defined as shown schematically in Figure 1. The length of time during which patients were able to maintain a 50% reduction from baseline PASI (PASI 50) was determined for 2 sets of patients: (1) patients who achieved PASI 75 at any time during the study, and (2) patients who achieved a PGA of “clear” or “almost clear” at any time during the study. The use of PASI 50 as an evaluation criterion was based on data that support achievement of PASI 50 as clinically relevant and meaningful to patients.

In both phase III studies of alefacept, the median duration of response exceeded 7 months, regardless of the definition of response. Some patients who have received additional courses of alefacept have reported longer durations of response, up to 24 months. These data are unique to alefacept. Efalizumab and etanercept are clearly suppressive in their mode of action and require continuous therapy to maintain a response. Alefacept’s remittive action suggests that it is a good early treatment for patients with moderate-to-severe psoriasis, offering time free of the disease and its treatment.

**Treatment Selection**

Typically, drug utilization and cost analyses are based on a stepwise treatment approach. However, treatment algorithms for moderate-to-severe psoriasis are difficult to create because of the potential risks of treatment and the unpredictable nature of disease progression. The placement of a particular drug in a given patient’s therapeutic options must be individualized for risk. For example, a patient with congestive heart failure is not a good candidate for methotrexate or etanercept, whereas a patient with a history of liver disease or alcohol abuse is not a good candidate for methotrexate or retinoids. In addition to these medical contraindications, personal factors must be considered, such as the frequency of dosing and office visits, convenience of and expected compliance with administration, and cost.

Although no comparative trials exist for the biologic agents, differences are evident among the products. These differences can significantly influence therapy selection and its administration frequency and subsequent cost (Table 1). The need for continuous therapy versus intermittent therapy could substantially impact cost, particularly for a chronic and incurable disease such as psoriasis. Not only is actual drug administration reduced with an intermittent therapy that provides off-treatment remissions, but also the potential for adverse events...
is reduced because patients are not continuously receiving medication. The associated frequency and cost of adverse events are other factors in the overall cost of care for patients receiving biologic therapy for psoriasis.

Safety and Tolerability

Safety and tolerance profiles of the various biologic therapies are substantially improved compared with generalized immunosuppressants used to treat psoriasis, such as methotrexate and cyclosporine.3 However, safety warnings also exist for the various approved biologic therapies. Because the biologic agents affect the immune system, they all have warnings about the risk of serious infection and malignancy (Table 1). Key differences in safety warnings include the following: etanercept has a warning about serious infections, including tuberculosis24; efalizumab has warnings about thrombocytopenia and worsening of psoriasis on discontinuation of treatment25; and alefacept is associated with decreased CD4+ T-cell counts, requiring routine patient monitoring.25

Designing a Cost Model

An approach for comparing the costs of the approved biologic therapies and quantifying the potential cost savings associated with off-treatment remissions would be to investigate the costs for achieving symptom-free and side effect–free days in patients with psoriasis. Key elements for such an analysis would include side effect/adverse event frequencies, duration of therapy, and total cost of care, inclusive of concomitant therapies. The objective would be to capture the cost per day of remission with no side effects for each therapy and compare the costs of maintaining a remission for patients with psoriasis for up to 2 years.

A basic equation for such a model is as follows:

\[
\text{Cost of care}/\text{Side effect–free days in remission} = \text{Cost per side effect–free remission day}
\]

Cost of care includes the costs of product acquisition for all therapies (including systemic agents used concomitantly), delivery, and monitoring (including T-cell counts, platelet counts, liver function tests, and purified protein derivative tests for tuberculosis, as appropriate) for all patients started on treatment over periods of 12, 18, and 24 months. The duration of observation is another key variable because it examines the long-term costs for this chronic disease. Side effect–free days in remission represent the total number of days achieved by all patients with symptoms in “adequate control” or “remission” and also without side effects of treatment for each of the 3 observation periods. Cost per side effect–free remission day represents the output of the equation.

Using clinical trial data, the total number of days that patients are free of symptoms and have no side effects could be estimated. The goals of this approach would be to differentiate biologic therapies regarding efficacy and duration of off-treatment response, examine the economic impact of side effects/adverse events; and investigate the costs associated with individual products for up to 2 years. Using these key attributes of the various products, this type of analysis could identify an agent with lower overall costs because it possesses several key characteristics, including a low incidence of side effects; good tolerability; compliance, such that patients achieve clinically meaningful responses; and a long duration of symptom control without the need for new or additional treatments.

DISCLOSURES

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REFERENCES


TABLE 1

<table>
<thead>
<tr>
<th>Characteristics of Biologic Agents Used in the Treatment of Moderate-to-Severe Psoriasis</th>
<th>Alefacept</th>
<th>Efalizumab</th>
<th>Etanercept</th>
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<tr>
<td>Approval status for psoriasis</td>
<td>Approved January 2003</td>
<td>Approved December 2003</td>
<td>Approved May 2004</td>
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<td>Route of administration</td>
<td>Intramuscular</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
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<tr>
<td>Remittive (R) suppressive (S) action</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Expected number of doses per year</td>
<td>12–24</td>
<td>52</td>
<td>128</td>
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<tr>
<td>Contraindications/warnings</td>
<td>Lymphopenia, malignancy, serious infection</td>
<td>Serious infection, malignancy, thrombocytopenia, worsening of psoriasis after discontinuation</td>
<td>Serious infection/sepsis, demyelinating diseases, seizure, transverse myelitis, optic neuritis, pancreatitis, lymphoma</td>
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<tr>
<td>Patient monitoring</td>
<td>CD4+ T cells</td>
<td>Platelets</td>
<td>PPD* (tuberculosis)</td>
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</table>

* PPD = purified protein derivative.


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