Case Study 1. Impact of Route of Administration, Distribution Channels, and Need for Cotherapy on Overall Cost: Rheumatoid Arthritis

A case study in rheumatoid arthritis (RA) was selected to demonstrate how differences in drug distribution channels, route of administration, and the need for cotherapy can impact the overall cost of therapy. The second case demonstrates the need for tight control of drug utilization when a biologic agent offers only marginal incremental clinical benefit over existing options but at a substantial increase in cost. The third case provides an example of the relationship between increased efficacy and the cost of therapy, and the fourth case demonstrates that PA criteria can be flexible with respect to drug coverage when clear therapeutic differences have not been demonstrated among drugs.

CONCLUSION: As more biologic agents become available, it is critical that pharmacy decision makers critically evaluate these innovative new therapies by using the best available evidence to determine the products that provide the greatest clinical and economic value.

KEYWORDS: Biologic agents, Drug utilization guidelines, Managed care

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>A Comparison of Anti-TNF Agents Approved for the Treatment of Rheumatoid Arthritis*</th>
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<tbody>
<tr>
<td>Type</td>
<td>Etanercept (ENBREL)</td>
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<tr>
<td>Construct</td>
<td>Soluble receptor</td>
</tr>
<tr>
<td>Half-life</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Fixes complement</td>
<td>Yes</td>
</tr>
<tr>
<td>Lyses cells</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosage</td>
<td>50 mg every week</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Injection/infusion-related adverse reactions</td>
<td>Injection site reaction: 34%</td>
</tr>
<tr>
<td>Indications</td>
<td>RA, JRA, PSA, AS</td>
</tr>
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</table>

TNF = tumor necrosis factor; RA = rheumatoid arthritis; JRA = juvenile rheumatoid arthritis; PSA = psoriatic arthritis; AS = ankylosing spondylitis.

Adapted from:
* These agents are not currently approved for the treatment of psoriasis. Recommended monitoring, if any, is not yet known.
Injectable Biologic Case Studies

for age- and gender-matched controls. A diagnosis of RA is also associated with a substantial loss of income and a reduced work capacity. Yelin estimated that 50% of RA patients cannot function in their jobs within 10 years of the onset of the disease.

When Health Net of Arizona created its original RA prior-authorization (PA) criteria, only etanercept and infliximab were available for use. Currently there are 3 biotechnology agents approved for the treatment of RA (Table 1). At the time the RA prior-authorization criteria were developed, much of the data currently available that describes the durability of response for etanercept and infliximab and their effects on radiographic progression were not yet published. Additionally, because direct comparative trials that identified differences in clinical outcomes were also not available at the time, a decision was made to consider the drugs therapeutically equivalent. Coverage decisions for the 2 products centered on 3 main issues: dosing, administration, and the need for cotherapy. The PA criteria required a prescriber to provide evidence that one drug was superior to the other if coverage of the nonpreferred agent was requested.

Etanercept offered fixed dosing of 25 mg twice weekly versus the variable dosing of 3 mg/kg to 10 mg/kg every 8 weeks associated with infliximab therapy. Etanercept was self-administered via subcutaneous injection while infliximab required administration via intravenous infusion. Etanercept was distributed through the retail pharmacy network, allowing for quantity restrictions to be placed on the drug at the claims processor level. This distribution method also allowed for the collection of a drug copayment. Infliximab, on the other hand, was reimbursed through the medical claims system, making limitations on covered doses and frequency of dosing difficult. This situation was addressed by granting the pharmacy department access to the medical claims authorization and payment system, allowing limitations to be placed both on dose and frequency.

To arrive at a dollar amount that represented the total cost to provide each therapy, the acquisition cost of etanercept was compared with the acquisition cost of infliximab plus the administration costs and the physician professional fees incurred by the need for intravenous delivery. Acquisition costs for etanercept were controlled through the retail pharmacy network. While infliximab could be supplied to requesting physicians by the Health Net of Arizona contracted specialty injectable pharmacy at a slight discount, several fee-for-service physician specialists refused to participate in the specialty pharmacy program. These physicians purchased the drug through other vendors and were reimbursed by the health plan at significantly higher rates than those paid to our specialty pharmacy, increasing the overall cost of infliximab therapy. Physicians administering infliximab also charged professional fees for drug infusion and office visits. Several hospital-based infusion centers had contracts allowing charges 2 to 3 times in excess of the average wholesale price and an infusion fee. The required coadministration of methotrexate was added to the estimated costs of infliximab therapy as were anticipated costs for the potential need to treat infusion-related side effects.

Based on a review of dosing, frequency, route of administration, and need for cotherapy, PA criteria were developed that required that patients fail nonbiotechnology (e.g., traditional) disease-modifying antirheumatic drug therapy before the initiation of biologic therapy. Etanercept was identified as the preferred biotechnology agent because of its fixed 25 mg dose, fixed twice-weekly dosing interval, subcutaneous route of administration, lack of mandated methotrexate cotherapy, availability through retail community pharmacies, and billing through the pharmacy claims system. Strict dose and frequency limits were placed on both etanercept and infliximab. The limits on etanercept were enforced through authorization of monthly quantity limits. Limits on infliximab were initially difficult to enforce primarily because the drug was billed and reimbursed through medical claims. When possible, infliximab was supplied directly to physicians through a specialty injectable pharmacy provider that billed Health Net directly at a discounted rate. To avoid the excessive costs associated with hospital-based infusion clinics, urgent care centers were contracted to infuse infliximab for a fixed infusion rate.

The results of a retrospective, 12-month drug utilization review (DUR) in 647 patients over 12 years who received either etanercept or infliximab demonstrated that dosing may escalate with infliximab over time. Charts of patients under the care of 125 geographically distributed rheumatologists were reviewed. Results of the review indicated that 37% of patients were receiving infliximab maintenance doses above the starting dose of 3 mg every 8 weeks, while 100% of patients who were receiving etanercept maintained the starting dose of 25 mg twice a week (Table 2). The possibility of dose escalation with infliximab must be taken into account in comparative cost models.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of Patients</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>Etanercept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg biw</td>
<td>352</td>
<td>100</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg/kg q 6 weeks</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3 mg/kg q 8 weeks</td>
<td>195</td>
<td>66</td>
</tr>
<tr>
<td>4 mg/kg q 6 weeks</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>5 mg/kg q 6 weeks</td>
<td>3</td>
<td>1</td>
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<tr>
<td>5 mg/kg q 8 weeks</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>6 mg/kg q 8 weeks</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>8 mg/kg q 8 weeks</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2** The Maintenance Dose of Etanercept and Infliximab Necessary to Maintain Clinical Response in Patients With Rheumatoid Arthritis

### Inconvenience, irritation, limited costs associated with topicals

Currently, it is estimated that more than 31 million Americans are diagnosed with asthma at some point in their lives. Approximately 32% to 40% of patients with asthma report that asthma interferes with daily work, school, or social activities; 4% require a physician office visit each year; 0.6% are seen in the emergency department; and 0.17% are hospitalized. Despite this, the majority of patients with asthma who are prescribed controller drug therapy do not use one regularly. Fewer than 50% of patients with asthma do not use the controller therapy recommended by the national guidelines—inhaled corticosteroids.

Omalizumab, a humanized monoclonal anti-immunoglobulin E (IgE) antibody, was approved in 2003 as maintenance therapy of moderate to severe perennial allergic asthma. The inclusion criteria for the pivotal trials were strict. Patients were required to have a documented allergy to perennial allergens, a history of regular inhaled or oral corticosteroid use for a minimum of 3 months, and elevated IgE levels as well as be assessed by their physician as having uncontrolled disease. The trials required forced steroid dose reduction. The primary end point was the number of asthma exacerbations, which was defined as a doubling of the inhaled corticosteroid dose or a burst of oral steroids. Secondary end points included changes in pulmonary function tests, total beta-agonist use, and asthma symptom scores. Physician office visits, emergency department use, and hospitalizations were not primary or secondary end points and were not reported in the clinical trials. Differences in these end points were subsequently published in a separate analysis.

Benefits from omalizumab therapy were observed during both the forced steroid reduction phases and the maintenance phases of the studies. Asthma exacerbations were reduced by approximately one half of an exacerbation per patient over 24 to 28 weeks, peak flow increased by approximately 30 L/min (6%) versus 10 L/min (2%) for placebo, and forced expiratory volume in 1 second improved 4% with active drug versus 1% with placebo. Symptom scores improved by almost 1 point (on a scale of 0 to 4), and albuterol inhalations were reduced by 1 puff per day. In the separate analysis, unscheduled office visits were reduced by 14 per 100 patient years, emergency department visits were reduced by 2 per 100 patient years, and hospitalizations were reduced by 3 per 100 patient years.

### Summary

Dosing, the route of administration, and the need for cotherapy all influence the cost of therapy with biologic agents for the treatment of RA. Health Net’s decision to prefer etanercept allowed for greater control of dosing and distribution. A retrospective analysis of Health Net of Arizona pharmacy and medical claims demonstrated that per-patient drug costs were slightly less with etanercept than with infliximab in the treatment of RA, without factorizing uncontrolled disease. The trials required forced steroid dose reduction. The primary end point was the number of asthma exacerbations, which was defined as a doubling of the inhaled corticosteroid dose or a burst of oral steroids. Secondary end points included changes in pulmonary function tests, total beta-agonist use, and asthma symptom scores. Physician office visits, emergency department use, and hospitalizations were not primary or secondary end points and were not reported in the clinical trials. Differences in these end points were subsequently published in a separate analysis.

### Case Study 2. Agents Offering Only Marginal Incremental Benefit: Asthma

This case study reviews data on a new biologic therapy for asthma to emphasize the need to establish tight controls on the use of drugs that provide only marginal incremental clinical benefits over existing options, but at a substantially increased cost. Asthma affects a much larger number of patients than RA, with the current prevalence estimated at 8% of the U.S. population. Currently, it is estimated that more than 31 million Americans are diagnosed with asthma at some point in their lives. Approximately 32% to 40% of patients with asthma report that asthma interferes with daily work, school, or social activities; 4% require a physician office visit each year; 0.6% are seen in the emergency department; and 0.17% are hospitalized. Despite this, the majority of patients with asthma who are prescribed controller drug therapy do not use one regularly. Fewer than 50% of patients with asthma do not use the controller therapy recommended by the national guidelines—inhaled corticosteroids.

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Case Study 3. Clinical Efficacy and Cost of Therapy: Psoriasis

This case study demonstrates the relationship between clinical efficacy and the cost of therapy with biologic agents in the treatment of moderate to severe psoriasis. Psoriasis is an inflammatory disease of the skin, with an estimated prevalence of nearly 3% of the U.S. population. According to the National Psoriasis Foundation (NPF), approximately 4.5 million Americans suffer from psoriasis, with up to 260,000 new cases diagnosed each year. The average age of onset is 28 years. Each year, psoriasis leads to nearly 400 patients annually are deemed permanently disabled because of psoriasis.

Approximately 30% of patients are considered to have moderate to severe disease, defined as having 10% or greater of their body surface area involved or localized involvement of areas such as the face, genitals, palms, or soles, that significantly interferes with their work or daily activities. Up to 30% of patients may also have joint involvement or psoriatic arthritis, a condition more prevalent in patients with severe skin involvement. The clinical course of psoriasis is highly variable, with periods of remission and relapse occurring over a lifetime and patients often requiring decades of therapy.

The American Academy of Dermatology (AAD) recently published a consensus statement on psoriasis therapies that called for more aggressive treatment. Topical corticosteroids remain a mainstay of therapy in patients with mild disease over limited body surface area. Topical steroids can also be used in moderate to severe psoriasis as initial therapy when the disease is limited to small areas. The AAD consensus statement recommends that systemic therapies be considered as first-line for patients with moderate to severe psoriasis. Systemic therapies include but are not limited to ultraviolet B light therapy, PUVA (a combination of the photosensitizing drug psoralen [P] with ultraviolet A [UVA] radiation), methotrexate, cyclosporine, and soritane. The choice of systemic therapy should be based on the type of psoriasis, availability of treatment sites, patient characteristics such as child bearing age, potential adverse effects, and cost to the patient.

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Addition of biologics to the “tool box” of first-line treatment options in candidates for systemic therapy has been recommend in the AAD consensus statement. The NPF has created a treatment algorithm to guide practitioners in the use of photo-
Injectable Biologic Case Studies

**TABLE 5** Summary of PASI End Points From Placebo-Controlled Trials in Patients With Moderate to Severe Psoriasis

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>PASI 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alefacept 15 mg q week x 12 weeks*</td>
<td>0.21</td>
</tr>
<tr>
<td>Efalizumab 1 mg/kg q week x 12 weeks*</td>
<td>0.22</td>
</tr>
<tr>
<td>Etanercept 25 mg twice a week x 12 weeks†</td>
<td>0.34*</td>
</tr>
<tr>
<td>Etanercept 50 mg twice a week x 12 weeks†</td>
<td>0.49*</td>
</tr>
<tr>
<td>Etanercept 50 mg twice a week x 12 weeks followed by 25 mg twice a week x 12 weeks† (response at 12 weeks)</td>
<td>0.49*</td>
</tr>
</tbody>
</table>

PASI 75 = 75% improvement in the Psoriasis Area and Severity Index.

* Etanercept is currently under FDA review for approval for use in moderate to severe psoriasis.
† 50 mg biweekly for first 12 weeks titrated to 25 mg biweekly for 12 weeks.

Data derived from:

Table adapted from:

**FIGURE 2** Annual Cost per Unit of Clinical Benefit (as Measured by the PASI Score) for Alefacept, Efalizumab, and Etanercept in the Treatment of Moderate to Severe Psoriasis

- * Represents annual cost per unit of clinical benefit and not drug acquisition cost.


Evaluating comparable efficacy of the 3 current biologic therapies that have sufficient clinical data for the treatment of psoriasis (i.e., etanercept, efalizumab, and alefacept) is difficult because of the lack of head-to-head studies and the limited duration of the clinical trials. However, a review of the currently available data from placebo-controlled clinical trials indicates that etanercept produces higher PASI 75 (75% improvement in the Psoriasis Area and Severity Index) response rates than either alefacept or efalizumab (Table 5).22

A separate review examined the impact of clinical efficacy on cost of therapy per unit of clinical benefit over 6 months in patients with psoriasis.22 In this report, PASI 75 scores achieved with the recommended doses of alefacept, efalizumab, and etanercept were compared with the estimated annual cost of therapy (acquisition costs only using AWP pricing). This analysis revealed that the average annual cost of etanercept, even when 50 mg was administered twice a week, was $13,383 less than efalizumab therapy and $25,576 less than alefacept (Figure 2).22 Greater cost differences were noted when etanercept was dosed at 25 mg biweekly.

The same review estimated the relative 6-month costs of adverse reactions associated with alefacept, efalizumab, and etanercept. The review used the types and frequencies of adverse reactions from published placebo-controlled clinical trials and referenced direct medical cost estimates for treating the adverse reactions6 (Table 6).22

**Summary**

The overall cost of therapy for treating moderate to severe psoriasis is dependent on the acquisition costs, clinical effectiveness, safety, and patient tolerability of the product. Based on the currently available data, etanercept appears to offer a balance of efficacy with affordability for the treatment of moderate to severe psoriasis. Continued analysis of the relative merits of the biologics for the treatment of psoriasis should be performed as more established efficacy, safety, and utilization data becomes available. It should be noted that, at the time this article was written, etanercept had not been approved by the U.S. Food and Drug Administration for the treatment of psoriasis.

**Case Study 4. Absence of a Clear Therapeutic Difference: Multiple Sclerosis**

There are 4 biologic drugs indicated for the treatment of relapsing-remitting multiple sclerosis (MS)—interferon beta-1a, interferon beta-1b, glatiramer, and mitoxantrone—yet none has been shown to be clearly superior to any other. In this case, the PA criteria developed for these biologics did not restrict coverage to a single
drug as initial therapy because clear therapeutic differences have not been demonstrated among the available agents. MS is the most common acquired neurologic disease in young adults, affecting 400,000 Americans. Twice as many women as men are diagnosed with MS. The initial symptoms occur between 20 and 40 years of age. MS has a significant impact on health, quality of life, productivity, and employment. Only 20% of patients with MS have no discernable disability, 30% have intermittent symptoms, 40% have a slow progression of the disease, and 50% have cognitive impairment. Annual direct and indirect costs associated with the disease are estimated to be $2.5 billion.

Currently, no well-controlled comparative clinical trials have been conducted between the available biologic drugs. However, there may be some differentiation among the products based on indications. For example, mitoxantrone is reserved for patients failing other therapies for relapsing-remitting disease, and low-dose interferon beta-1a is approved for attenuation of progression of MS following an initial event. Additionally, each drug possesses slightly different adverse reaction profiles, the potential for the development of transient neutralizing antibodies, dosing frequency, packaging, and cost.

In open-label trials, data has been generated that suggests interferon beta-1b and glatiramer are superior to low-dose interferon-beta-1a in reducing the frequency of relapses. In the only direct comparative trial in relapsing-remitting MS, high-dose interferon beta-1a was superior to low-dose interferon beta-1a over a period of 1 year, and this difference was maintained through the second year of the trial.

At the time of Health Net’s review, there was very little difference in the net cost of the 3 interferon products or glatiramer. The absence of clinical evidence to support the choice of a preferred agent in this class led Health Net of Arizona to create PA criteria that allowed physicians to choose low-dose interferon beta-1a, interferon beta-1b, or glatiramer as the initial agent for relapsing-remitting MS. Mitoxantrone was reserved for patients with relapsing-remitting MS that progressed during therapy with one of the other agents.

Summary

In the absence of data supporting clear clinical, safety, or cost differences, PA criteria can be created that allow for a number of initial therapies. This provides physicians and members the ability to choose a drug based on secondary considerations such as dosing route and frequency. Covering multiple drugs when possible should result in increased patient and physician satisfaction.

Conclusion

Because of the rapid increase in the number of biologic agents and the lack of head-to-head trials, determining the clinical superiority of one agent for a specific condition may be challenging. This challenge is compounded by the need to ensure patient access to these innovative products while simultaneously managing costs. In order to assist pharmacy and medical decision makers in overcoming these obstacles, case studies were presented to illustrate how one commercial health plan evaluated and prioritized the available biologic agents for the treatment of RA, asthma, psoriasis, and MS. The cases use the available evidence to demonstrate that differences in drug efficacy, safety, tolerability, administration, distribution, and need for cotherapy affect the overall cost of therapy. As biologic agents become more commonly available, pharmacy decision makers must continually evaluate the evidence to determine therapies that provide the greatest clinical and economic value.

DISCLOSURES

Author Robert J. Lipsy received an honorarium from Amgen Inc. and Wyeth Pharmaceuticals, Inc., for participation in the symposium upon which this article is based. He is a consultant to Amgen Inc.

REFERENCES


TABLE 6

<table>
<thead>
<tr>
<th></th>
<th>Alefacept 15 mg/wk</th>
<th>Efalizumab 1 mg/kg/wk</th>
<th>Etanercept 25 mg biw</th>
<th>Etanercept 50 mg biw</th>
<th>Etanercept Step-Down Dosing*</th>
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<tr>
<td>Severe</td>
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<tr>
<td>Total</td>
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<td>$2168.03</td>
<td>$884.58</td>
<td>$884.58</td>
<td>$884.58</td>
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* Step-down dosing: 50 mg biw for first 12 weeks titrated to 25 mg biw for 12 weeks. biw = biweekly.


