Clinical Monograph for Drug Formulary Review: Systemic Agents for Psoriasis/Psoriatic Arthritis

VICKI S. FISHER, BS, PharmD

ABSTRACT

BACKGROUND: Significant advances in the pharmacologic treatment of psoriasis, most notably the introduction of the biologic agents efalizumab and alefacept, have occurred recently. In addition, another biologic agent, etanercept, was recently approved for the treatment of psoriasis and psoriatic arthritis, thus adding to the list of biologic agents approved for the treatment of these disease states. A review was conducted by the Drug Information Service of a pharmacy benefits manager (PBM) to determine the relative merits and place in therapy of commonly used systemic agents for the treatment of psoriasis and psoriatic arthritis.

OBJECTIVE: To provide readers with a comprehensive clinical monograph on psoriasis and psoriatic arthritis agents, written with a managed care perspective, as used in actual drug formulary decision making by a PBM.

METHODS: The drug formulary of this PBM is designed to provide health plans with an evidence-based review of drugs, therapeutic classes, and disease states with a managed care focus. For each therapeutic class or disease review, an extensive and thorough literature search of MEDLINE is conducted for efficacy, safety, effectiveness, and humanistic and economic data. Drug/disease-state databases (UpToDate online, MICROMEDEX), U.S. Food and Drug Administration clinical reviews, key Internet sites, medical/pharmacy-related news sites, clinical guidelines, and AMCP dossiers are also reviewed. Formulary drug monographs produced by the Drug Information Service of the PBM include a critical analysis and summary of disease-oriented and patient-oriented clinical outcomes, effectiveness, and humanistic data. Additional data considered and included in the formulary review process are clinical attributes, patent expirations/generic competition, off-label or pending indications, and pharmacoeconomic data.

RESULTS: The biologic agents do not appear to be as efficacious as traditional systemic therapies but are associated with fewer long-term toxicities that often limit treatment duration with traditional systemic agents. Although no head-to-head comparisons between alefacept and efalizumab exist, efalizumab appears to offer slightly higher efficacy rates, while alefacept has a longer duration of action. Etanercept at the higher approved dose appears more efficacious compared with efalizumab or alefacept for the treatment of psoriasis, and it is the only biologic currently approved for the treatment of psoriatic arthritis. Efalizumab and alefacept are generally well tolerated, but rebound flare of psoriasis is associated with efalizumab, thus requiring continuous treatment to avoid a flare in disease. Efalizumab and etanercept can be self-administered by the patient, while alefacept and infliximab require administration by a health care professional.

CONCLUSIONS: Systemic therapy is reserved for patients with moderate-to-severe psoriasis or patients with psoriatic arthritis. The biologic agents are not as efficacious as traditional therapies but, due to better tolerability, are gaining acceptance in the treatment of psoriasis and psoriatic arthritis. The biologic agents differ in efficacy rates and are generally well tolerated. Clinical attributes, overall efficacy, and economic costs associated with the biologic agents will be significant factors in selecting agents for the treatment of psoriasis and psoriatic arthritis.

KEYWORDS: Psoriasis, Psoriatic arthritis, Alefacept, Efalizumab, Etanercept, Infliximab, Methotrexate, Acitretin, Cyclosporine, Sulfasalazine, Drug monograph, Outcomes-based formulary, Evidence-based medicine

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Editor's Note: This article contains the information presented in nearly identical facsimile to the Pharmacy and Therapeutics (P&T) committee for the pharmacy benefit manager (PBM) and its health plan clients. Only the cost data have been updated, and the P&T committee sees actual cost and utilization data for the PBM during its deliberations. Part of the purpose of this article is to present for readers an example of the information that is actually reviewed in contemporary P&T processes in managed care today.

1. Introduction

Psoriasis

An immune-mediated chronic skin disease, psoriasis is characterized by red, thickened, scaly plaques that are the result of hyperproliferation and incomplete terminal differentiation of the epidermis, vascular changes, and migration of activated neutrophils and T lymphocytes into the dermis and the epidermis. There is a genetic association with psoriasis in that 40% of patients have a family history of psoriasis. Not all patients with the gene develop psoriasis, but it is thought that triggers such as emotional stress, skin injury, infection (human immunodeficiency virus [HIV] or streptococcal infection), or a reaction to a drug may cause a psoriasis outbreak. Notably, patients with HIV may have a higher incidence of psoriasis or it may be more severe in these patients.

Psoriasis is one of the most common chronic skin diseases, with prevalence in the general population of 1% to 3%. It affects approximately 4.5 million Americans (2.1%), and 1 million (0.5%) have psoriatic arthritis. Approximately 250,000 new cases are diagnosed each year. Of those patients diagnosed with psoriasis, 1.5 million, or one third, have moderate-to-severe psoriasis. Psoriasis is more common in individuals of European descent, with Asians and Africans at lowest risk. This condition is not specific to age or gender, but it is slightly more prevalent in women than in men. The average age of onset is 28 years (range of 15-35 years), but psoriasis can actually develop at any age. Approximately 20,000 children under the age of 10 years are diagnosed with psoriasis.

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Psoriasis may be typed as plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, pustular psoriasis, nail psoriasis, scalp psoriasis, and/or inverse psoriasis. These forms of psoriasis vary in severity and respond differently to treatment. Although a patient can have 2 types of psoriasis at one time, normally patients have only one type, but one type can convert to another type. The most common type of psoriasis is plaque psoriasis, accounting for approximately 80% of cases. The degree of skin involvement may range from just a few lesions to total skin involvement, and it is usually symmetrically distributed. Disease of the scalp is common and may be the only site affected. Plaque psoriasis can appear on any skin surface, but the most common areas are the knees, elbows, scalp, trunk, and nails. The majority of patients have mild disease, with approximately 30% of psoriasis patients progressing to moderate-to-severe disease.

Severity has typically been based on the amount of body surface area (BSA) affected; however, the current line of thinking is that severity of disease should also take into account quality-of-life (QOL) issues. For example, a patient with psoriasis involving primarily the hands or feet may be classified as severe even though BSA affected is low, due to the impact on the patient’s ability to function normally. A recent survey found that 75% of patients with moderate-to-severe psoriasis felt it had a moderate-to-large impact on their daily living. Studies have documented that psoriasis has a profound effect on health-related quality of life (HRQOL). Approximately 25% of patients stated that it caused them to alter or stop normal daily activities, 40% stated that it affected their clothing choices in that they chose clothes to cover arms and legs, and 36% stated that it affected sleeping or caused them to bathe more than normal. One study showed that psoriasis impacts HRQOL to the same degree as cancer, arthritis, hypertension, diabetes, and depression. Severe psoriasis has also been shown to be associated with a higher incidence of depression and suicidal ideation compared with the general population.7

### Psoriatic Arthritis
Psoriasis is associated with psoriatic arthritis, with 10% to 30% of patients having psoriasis developing psoriatic arthritis. Psoriatic arthritis occurs in approximately 1 million (0.5%) Americans, typically developing in patients between the ages of 30 to 50 years. Psoriasis usually appears approximately 10 years before psoriatic arthritis, but, rarely, some patients do present without psoriasis.

Psoriatic arthritis is similar to rheumatoid arthritis, but it is typically milder. It can be difficult to diagnose and can be confused with rheumatoid arthritis, osteoarthritis, gout, Reiter’s syndrome, and ankylosing spondylitis. It is generally diagnosed by a process of elimination using x-rays of the affected joints, medical history, physical examination, and blood tests. Because it is difficult to diagnose, approximately 50% of patients already have bone loss by the time they are diagnosed. Symptoms of the disease include stiffness, pain, swelling, and tenderness of joints and surrounding soft tissue; decreased range of motion; morning stiffness and tiredness; pain and redness of the eye; and nail changes (pitting or lifting of the nail) are common. The joints most commonly affected are the wrist, knees, ankles, lower back, and neck. Interestingly, a link between psoriasis and Crohn’s disease has also been suggested. There are 5 types of psoriatic arthritis, with the most common types being symmetric and asymmetric. Less commonly occurring forms are distal interphalangeal predominant (DIP),

### Table 1: Monograph Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer/Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>(Rheumatrex - Stada Pharma, various generics)</td>
</tr>
<tr>
<td>Acitretin</td>
<td>(Soriatane - Roche)</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>(Hydra, Droxia - BMS; various generics)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>(Neoral - Novartis; various generics-cyclosporine modified; Gengraf - Abbott)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>(Imuran - Prometheus; various generics)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>(Azulfidine - Pharmacia/Upjohn; various generics)</td>
</tr>
<tr>
<td>Auranofin</td>
<td>(Ridaura - Promethus)</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>(Depen - MedPointe Pharm; Cuprimine - Merck &amp; Co.)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>(Aralen - Sanofi Pharm; generic)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>(Plaquenil - Sanofi Pharm; various generics)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>(Enbrel - Amgen)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>(Remicade - Centocor)</td>
</tr>
<tr>
<td>Alefacept</td>
<td>(Amevive - Biogen)</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>(Raptiva - Genentech/XOMA)</td>
</tr>
</tbody>
</table>

### Table 2: Evidence-Based Medicine Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-oriented evidence</td>
<td>Refers to surrogate markers associated with a specific-disease state such as blood pressure reduction or glucose and cholesterol lowering</td>
</tr>
<tr>
<td>Patient-oriented evidence</td>
<td>Also referred to as patient-oriented evidence that matters (POEM) and refers to clinical events associated with a disease such as myocardial infarction, stroke, and death</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Evaluation of beneficial effects of a treatment when assessed under the usual conditions of clinical practice, also referred to as efficacy measured in a real-world setting</td>
</tr>
<tr>
<td>Humanistic</td>
<td>Measures of quality-of-life, functional status, patient satisfaction, and symptom scores</td>
</tr>
<tr>
<td>Economic</td>
<td>Measures of direct (hospitalization, physician visits, drug costs) and indirect costs (work loss, restricted activity days)</td>
</tr>
</tbody>
</table>
spondylitis, and arthritis mutilans. Symmetric arthritis occurs in about half of psoriatic arthritis patients and can be disabling in about 50% of patients. Asymmetric arthritis is typically milder and occurs in about 35% of patients with psoriatic arthritis. This monograph will give an overview of the systemic treatment options available for the most common type of psoriasis—plaque psoriasis—and for psoriatic arthritis, with a focus on the newest biological agents and their role in treating these conditions (Table 1). This review will include a critical analysis and summary of disease-oriented and patient-oriented clinical outcomes, effectiveness, and humanistic data (Table 2).

II. Pathophysiology

Psoriasis and psoriatic arthritis are similar in that both diseases are immune-mediated chronic diseases with a genetic link. Psoriasis is caused by a hyperproliferative state, characterized by increased numbers of epidermal stem cells and numbers of cells undergoing DNA synthesis, keratinocytes undergoing a shortened cell cycle compared with normal skin (36 hours versus 311 hours), and a decrease in the turnover time of the epidermal skin layer compared with normal skin (4 days versus 27 days). The presence of T lymphocytes and neutrophils in the epidermal and dermal layers, activation of growth factors (epidermal growth factor and transforming growth factor-alpha, and cytokines including interleukin-8 (IL-8), IL-6, IL-2, and interferon-gamma support immune regulation as a factor in psoriasis. Psoriasis is characterized by patches of red, scaly, flaky skin that can be associated with intense itching and burning.

Similar to psoriasis, psoriatic arthritis is linked to the presence of cytokines, including tumor necrosis factor (TNF)-alpha, IL-1beta, IL-2, IL-10, and interferon-gamma found to be present in the synovial tissue. These cytokines stimulate the inflammatory process in the skin and synovium, thus leading to migration of activated T cells through the vascular endothelium causing leukocyte infiltration into the synovium. Activated T cells can also cause release of matrix metalloproteinases that cause joint damage. Historically, it was thought that psoriatic arthritis was not as debilitating or destructive a disease as rheumatoid arthritis, thus treatment was not as aggressive. However, recent data indicate that, because these patients have both psoriasis and psoriatic arthritis, they tend to report greater functional impairment. Thus, careful monitoring of patients with psoriasis is necessary to determine which patients may be developing psoriatic arthritis and which patients may require more aggressive therapy to prevent significant functional impairment.

It is not clearly defined which patients should be considered to have mild, moderate, or severe psoriasis, which is important in determining the optimal therapy for treatment. The National Psoriasis Foundation position paper provides some guidance in defining severity using QOL-based definitions in the absence of standardized criteria. (See Table 3.)

### TABLE 3 Quality-of-Life–Based Definitions of Severity of Psoriasis From the National Psoriasis Foundation

<table>
<thead>
<tr>
<th>Severity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No alteration in patient QOL; patient can manage impact of disease and may not need treatment; treatments selected are not associated with any serious risks; BSA &lt; 5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>Some alteration in patient QOL; patient requires therapy to improve QOL; treatments selected are associated with only minimal health risks in the short or long term; BSA 2% to 20%</td>
</tr>
<tr>
<td>Severe</td>
<td>Alteration in patient QOL; disease unresponsive to treatments associated with minimal risks; patient is willing to accept life-altering adverse effects to improve disease or clear disease; BSA &gt; 10%. Also takes into consideration location of disease such as hands, feet, face; symptoms (pain, tightness, bleeding, or severe itching); presence of arthralgias or arthritis</td>
</tr>
</tbody>
</table>

QOL = quality of life; BSA = body surface area.

### TABLE 4 Pharmacology of Biologic Response Modifiers

<table>
<thead>
<tr>
<th>Biologic Response Modifiers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectex</td>
<td>a dimeric fusion protein consisting of the extracellular CD2-binding portion of the LFA-3 that is linked to the Fc portion of IgG1. It works by inhibiting lymphocyte activation by binding to CD2 on T and NK cells. Decreases lymphocyte count (CD2 and memory cells). Studies have shown alectex to exert greater effects on CD4+ memory cells, than CD4+ naive cells.</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>a recombinant humanized IgG1 monoclonal antibody that binds to the CD11a (subunit of the LFA-1) and prevents adhesion to ICAM-1, thus inhibiting T-cell activation and migration.</td>
</tr>
<tr>
<td>Etanercept</td>
<td>a dimeric fusion protein consisting of the extracellular ligand-binding portion of the TNF receptor linked to the Fc portion of IgG1. It exerts its effect by binding TNF and prevents interaction with cell surface TNF receptors, thus inhibiting the inflammatory process.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>a humanized monoclonal antibody to TNF-alpha that neutralizes the activity of TNF-alpha, thus preventing induction of IL-1 and IL-6, inhibiting leukocyte migration, induction of acute phase reactants, and tissue-degrading enzymes.</td>
</tr>
</tbody>
</table>

Ig = immunoglobulin; IL = interleukin; LFA-1 = leukocyte function antigen-1; LFA-3 = leukocyte function antigen-3; ICAM-1 = intercellular adhesion molecule-1; NK = natural killer cells; TNF = tumor necrosis factor.
traditional agents are primarily administered orally.

In one study evaluating the pharmacokinetic/pharmacodynamic effects of alefacept, the Psoriasis Area Severity Assessment Index (PASI) and Physician Global Assessment (PGA) were correlated with increasing alefacept serum levels. Dose-dependent decreases in peripheral CD4+ memory cells occurred during treatment with alefacept, which was shown to correlate with improvements in psoriasis. It is this specificity for reducing CD4+ memory cells that has been attributed to the sustained efficacy observed with this agent.

The pharmacokinetics of etanercept in treating psoriasis are similar to what is observed in patients treated with etanercept for rheumatoid arthritis. The pharmacokinetics were similar whether patients were treated with 25 mg twice weekly or 50 mg once weekly, supporting that this dose would be efficacious in treating psoriasis patients. Long-term treatment was also shown to result in similar pharmacokinetics regardless of whether treatment was continuous or intermittent, thus suggesting the potential efficacy of etanercept when used in a sequential or rotational dosing scheme (Table 5).

**Methotrexate**

Methotrexate reduces the synthesis of tetrahydrofolate (by binding to dihydrofolate reductase) and subsequently inhibits pyrimidine synthesis. These actions result in a reduction in DNA synthesis, inhibition of mitosis, and a decrease in the proliferation of rapidly dividing cells. Methotrexate is known to decrease T and B cell function and suppress the secretion of cytokines (IL-1, interferon-gamma, TNF).

**Acitretin**

Acitretin is an oral retinoid with anti-inflammatory, antiproliferative, and keratolytic activity. Acitretin is the active metabolite of etretinate, previously known as Tegison. While etretinate takes years to be eliminated from the body, acitretin elimination takes several months. However, alcohol may precipitate conversion of acitretin back to etretinate, resulting in prolonged elimination. Because of the prolonged action of acitretin and teratogenic effects, women must avoid pregnancy during and for 3 years after discontinuing treatment.

**Cyclosporine**

Cyclosporine is an immunosuppressant that binds with the immunosuppressant-binding protein cyclophilin. The immunosuppressive effects of cyclosporine result from the inhibition of cytokine promoters, which eventually inhibits the transcription and processing of cytokines (IL-2, interferon-gamma) within the T cells and decreases T-cell growth and migration. Cyclosporine absorption is variable and incomplete, although a newer emulsion formulation of cyclosporine has better absorption, at 43%.

**Additional Agents**

Several additional agents have been used in the treatment of psoriasis/psoriatic arthritis but are not U.S. Food and Drug Administration (FDA)-approved for these indications. Hydroxyurea is an antineoplastic agent that inhibits DNA synthesis, which slows basal cell replication in the epidermis. Hydroxyurea also inhibits vascular proliferation in the dermis; lowers the neutrophil count, which decreases pustule and papule formation; and reverses abnormal keratin formation. Sulfasalazine is an anti-inflammatory agent that works by inhibiting prostaglandin synthesis and interfering with the arachidonic pathway. Azathioprine is an immunosuppressive agent that metabolizes to 6-mercaptopurine and inhibits DNA and RNA synthesis. The mechanism of action of auranofin in treating psoriatic arthritis is unclear, but it is thought to work by reducing T-cell activity and inhibiting neutrophil migration. Similarly, it is unclear how penicillamine exerts its effects in

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**TABLE 5** Pharmacokinetics of Systemic Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>Elimination Half-Life</th>
<th>Protein Binding (%)</th>
<th>Metabolism</th>
<th>Primary Route of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>60% (&lt;30 mg/m2) dose-dependent</td>
<td>3-10 hours</td>
<td>50</td>
<td>Liver</td>
<td>Renal</td>
</tr>
<tr>
<td>Acitretin</td>
<td>72%</td>
<td>49 hours</td>
<td>99.9</td>
<td>Liver</td>
<td>Feces (34%-54%) and urine (16%-53%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Variable (30% conventional formulation; 43% oral emulsion)</td>
<td>8.4-27 hours</td>
<td>90-98</td>
<td>Liver</td>
<td>Biliary (6% urine)</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td>8-9.5 days (IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>58% (SC)</td>
<td>102+ 30 hours (SC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efalizumab</td>
<td>50% (SC)</td>
<td>25 days (mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alefacept</td>
<td>63% (IM)</td>
<td>IV- 270 hours (11.25 days)</td>
<td>IM- 289+123 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV = intravenous; SC = subcutaneous; IM = intramuscular.
IV. Clinical Efficacy

Efficacy Measures

Various measures have been used to evaluate efficacy, including changes to BSA coverage, the Salford Psoriasis Index (SPI), PASI, self-administered PASI (SPASI), Psoriasis Disability Index (PDI), and various QOL scales.21 The PASI is the most frequently encountered scale in the trials that follow and describes overall psoriasis severity and coverage, based on the amount of skin and degree of itching and scaliness involved in 4 defined body sections. A PASI75 is defined as a 75% improvement from baseline in PASI score and PASI50 is a 50% improvement in PASI score. Achievement of PASI50 is considered a clinically significant improvement. The PASI is a measure primarily used in clinical trials to demonstrate efficacy for FDA approval, but because it is both time-consuming to administer and complex, it is not commonly used in the clinical setting. New tools for measuring response are being developed that will take into consideration the effect on QOL in determining severity of disease and response to treatment.21 Little information is available about recurrence or length of remission rates among various treatment approaches. The variable outcome measures should be considered when comparing outcomes from one trial to the next.

Treatment Strategies

A number of treatment options are available for treating psoriasis, both topical and systemic. Selection of treatment is dependent on the areas affected, type, severity level, and risk-to-benefit ratio of treatments. In general, first-line therapy for patients with mild disease consists of topical agents such as topical emollients, topical corticosteroids with or without coal tar, or calcipotriene. Second-line topical therapies include anthralin and tazarotene. For mild-to-moderate disease, low- to mid-potency corticosteroids are generally the first choice of therapy.23 Usually, more potent corticosteroids, other topical agents, or systemic therapies are used for more severe disease or on areas of thicker skin. For thinner skin areas and for maintenance, a low-potency corticosteroid can be used. Low-potency products or noncorticosteroid agents are generally preferred in infants and elderly patients.25,26 For patients with more severe disease that is unresponsive to topical therapies, systemic therapies are generally used.

Systemic Therapies for Psoriasis

For more severe disease unresponsive to topical agents or that involves large areas, phototherapy, with or without a topical agent or with methoxsalen, has been used. In addition, oral agents, such as acitretin, cyclosporine, and methotrexate, may be used as first-line therapy in patients with severe disease. Ultraviolet B (UVB) was considered a therapy of choice used alone or in combination with topical or oral agents; however, inconvenience and costs associated with this therapy have led to decreased use.27 Psoralen plus ultraviolet A (PUVA) light is an effective therapy that has been shown to induce remission in patients; additional maintenance therapy adds to the high efficacy rates of 80% with this therapy.28 However, long-term use can result in an increased risk of nonmelanoma and potentially melanoma skin cancer that may persist even after therapy is discontinued, which is a potential concern.29,30

In addition, PUVA treatment can be inconvenient for the patient either because of a lack of availability of PUVA equipment in close proximity to the patient or because of a requirement for frequent treatments in the physician’s office. This may limit patient acceptance of this very effective therapy. PUVA is often combined with acitretin, an oral retinoid, to increase efficacy and decrease the amount of UVA energy required.31 Combination therapy has been shown to be superior to PUVA alone, with clearance rates of 80% for PUVA compared with 96% with combination therapy, and was associated with a 42% reduction in the mean cumulative dose of UVA.32 This combination is thought to potentially decrease toxicity and costs associated with use of either agent alone.33

Spuls et al. conducted a systematic review of 5 systemic treatments for psoriasis.33 A total of 665 studies involving systemic therapies—methotrexate, retinoids, cyclosporine, UVB, or PUVA—were identified. Patient series, focusing on treatment outcome, were used as the unit of analysis. After application of exclusion criteria, a total of 129 patient series (13,677 patients) were included in the analysis. The largest number of patient series evaluated PUVA; however, no studies on methotrexate remained in the analysis following exclusion. Two outcomes were evaluated—clearance and treatment response—defined as good (75% - 100% improvement), moderate (50% - 75% improvement), poor (< 50% improvement), and clearance (100% improvement). Good response was seen in 83% of patients treated with PUVA, 68% with UVB, 64% with cyclosporine, 56% with etretinate, and 56% with acitretin. The percentage of patients achieving clearing in each group was 70%, 44%, 13%, 22%, and 9%, respectively. The incidence of adverse events was also lowest with PUVA (0.6%). The authors suggested that phototherapy may be the first choice of systemic therapy for patients with severe psoriasis. A potential limitation of this review is that the exclusion rate was high due to concomitant use of other psoriasis agents, outdated dosages, or inadequate documentation in these studies. Of 821 patient series identified, 692 were excluded, for an inclusion rate of only 19%. This is primarily attributed to the fact that these agents have been used for many years, with many studies published as far back as 1958 for methotrexate, the 1970s for PUVA, and early 1980s to 1990s for many of the other agents;
thus study design was not as stringent for the older agents.

In a systematic review by Griffiths et al., sufficient evidence from randomized controlled trials (RCTs) was identified to support the efficacy of cyclosporine, systemic retinoids in combination with PUVA, photochemotherapy, phototherapy, combinations of topical vitamin D3 analogues, and topical steroids in combination with photochemotherapy or phototherapy and fumarates. In contrast, there was a lack of RCTs to support the use of methotrexate, hydroxyurea, azathioprine, and sulfasalazine. Because methotrexate was approved prior to requirement of RCTs for approval, limited RCTs are available.

Lebwohl et al. reviewed the use of cyclosporine in the treatment of psoriasis, concluding that it is best reserved for patients with severe psoriasis that have failed first-line therapies. Several small studies have shown hydroxyurea in doses of 0.5 grams to 1.5 grams per day to be efficacious in improving psoriasis in patients refractory to or failing conventional therapies. Recently it was shown to be efficacious and safe in treating psoriasis in a patient with psoriatic arthritis when used in combination with infliximab.

**Systemic Therapies for Psoriatic Arthritis**

In a Cochrane Database Systematic Review of treatments for psoriatic arthritis, parenteral high-dose methotrexate and sulfasalazine were the two agents found to have the most data published demonstrating efficacy in treating psoriatic arthritis. Of the 20 RCTs identified, 6 studies of sulfasalazine, 2 each of auranofin and etretinate, and 1 each of azathioprine, colchicine, fumaric acid, and low, pulse-dose methotrexate were included. A parenteral high-dose methotrexate study was also included. All agents were shown to be better than placebo, but only parenteral high-dose methotrexate, sulfasalazine, azathioprine, and etretinate reached statistical significance. It was also noted that patients receiving placebo improved over baseline, thus suggesting that noncontrolled trials are limited in their findings when evaluating treatments for psoriatic arthritis. The overall poor quality of studies limited the inclusion of studies and, thus, these findings.

Low-dose methotrexate (maximum 15 mg/week) was compared with cyclosporine (3 - 5 mg/kg/day) in treating 35 patients with psoriatic arthritis. Both agents significantly improved measures of disease activity—physician and patient assessments of disease activity at 6 and 12 months. More patients withdrew on cyclosporine therapy, while increases in liver enzymes were significantly more common with methotrexate, thus indicating the potential tolerability issues with each agent. In a study comparing cyclosporine (3 mg/kg/day) with sulfasalazine (2,000 mg/day) plus standard therapies or standard therapies alone (nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone 5 mg/day, analgesics), cyclosporine was more efficacious overall compared with sulfasalazine or standard therapies, with only mild reversible kidney dysfunction reported more commonly with cyclosporine therapy. Overall, sulfasalazine was superior to standard therapy alone in improving PASI, spondylitis functional index, and improved erythrocyte sedimentation rate but not in pain measures. Response to cyclosporine occurred at 8 weeks versus 34 weeks with sulfasalazine. In 3 studies evaluating the efficacy of sulfasalazine in treating psoriatic arthritis, although superior to placebo, efficacy was minimal, with high response rates reported in placebo patients.

Several small studies have evaluated the efficacy of auranofin (oral gold) and gold sodium thiomalate (injectable gold). In general, the studies were small and not controlled, but results indicate that, while injectable gold is more potent in efficacy compared with oral gold, tolerability is better with oral gold. Data were not consistent across all studies, but, overall, they suggested superiority of gold compounds over placebo/control in improving symptoms of psoriatic arthritis. However, results of one study indicate gold compounds do not prevent progression of joint damage.

Data are limited regarding the safety and efficacy of antimalarial agents (chloroquine/hydroxychloroquine) or penicil-
laminate in treating psoriatic arthritis. Several small studies evaluated the efficacy of chloroquine and hydroxychloroquine in treating psoriasis, indicating potential efficacy; however, conflicting data indicating the potential to exacerbate psoriasis limit the use of these agents. Although penicillamine is approved for use in the treatment of rheumatoid arthritis, limited data are available to support efficacy and safety in treating psoriatic arthritis.60

However, the availability of biologic agents for the treatment of psoriasis and psoriatic arthritis may change how these chronic diseases have been managed in the past. Tables 6 through 8 summarize the studies evaluating the efficacy of biologic agents in the treatment of psoriasis and psoriatic arthritis.

### V. Humanistic Outcomes

The impact of psoriasis on patient QOL is well documented. Several QOL measures have been used in assessing humanistic outcomes in psoriasis patients, including the Dermatology Life Quality Index (DLQI), PDI, and the Short-Form 36 Health Survey (SF-36). The DLQI is commonly used, but it is a general measure for dermatologic QOL. Thus, a new QOL instrument is being developed and validated that is specific to psoriasis, the Psoriasis Quality of Life Questionnaire, which should help differentiate between levels of disease severity and clinically important improvements with topical and systemic therapies.

Several studies have evaluated improvements in QOL associated with biologic agents for psoriasis.51

#### TABLE 6 Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriatic Arthritis With or Without Psoriasis

<table>
<thead>
<tr>
<th>ETANERCEPT</th>
<th>Mease et al., 200074</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design:</td>
<td>R, DB, PC trial in pts. with active psoriatic arthritis (&gt;3 swollen joints and &gt;3 tender/painful joints and failed NSAIDs) and psoriasis (n=60). Additional Txs allowed: (MTX&lt;25 mg/wk if stable for 4 wks, corticosteroids &lt; prednisone 10 mg, stable NSAIDs therapy)</td>
</tr>
<tr>
<td>Treatment(s):</td>
<td>ETA 25 mg SC twice weekly or placebo for 12 weeks.</td>
</tr>
<tr>
<td>OUTCOMES:</td>
<td>Improvements in psoriatic arthritis: Primary efficacy measure for psoriatic arthritis was % pts. meeting psoriatic arthritis response criteria at week 12: ETA 87% vs. placebo 23% (P&lt;.0001; NNT=2). ACR response at week 12: ACR20—ETA 73% vs. placebo 13% (P&lt;.0001; NNT=2); ACR50—ETA 50% vs. placebo 3% (P=.0001; NNT=2); ACR70—ETA 13% vs. placebo 0% (P=.04; NNT=8). Improvements in psoriasis: % pts. achieving PASI75 at week 12: ETA 26% vs. placebo 0% (P&lt;.01; NNT=2). ETA pts. had significant improvement in physical component score vs. placebo (43% vs. 9%; P=.003; NNT = 5). Improvements in HAQ: ETA 83% vs. placebo 3% (P&lt;.0001; NNT = 1). Tolerability: ETA was well tolerated with similar AEs vs. placebo. Mild/moderate injection site reactions and upper respiratory infections were the most common AEs.</td>
</tr>
<tr>
<td>Comments:</td>
<td>Limitation: small study size. 63% of pts. (n=38) had &gt;3% BSA affected by psoriasis.</td>
</tr>
</tbody>
</table>

| Study design: | R, DB, PC, MC trial in pts. with active psoriatic arthritis (>3 swollen or >3 tender joints; failure to conventional therapy) (n=205). Additional Txs allowed: (MTX<25 mg/wk if stable for 4 weeks, corticosteroids < prednisone 10 mg, stable NSAIDs therapy). |
| Treatment(s): | ETA 25 mg SC twice weekly or placebo for 24 weeks. |
| OUTCOMES: Improvements in PsA: Primary efficacy measure for psoriatic arthritis was % pts. achieving ACR20 at week 12: ETA 58% vs. placebo 13% (P<.0001; NNT=2) at week 24: ETA 50% vs. placebo 13% (P<.0001; NNT=3). ACR50 at week 12: ETA 38% vs. placebo 4% (P<.0001; NNT=3) at week 24: ETA 37% vs. placebo 4% (P<.0001; NNT=3). ACR70 at week 12: ETA 11% vs. placebo 0% (P<.0001; NNT=9) at week 24: ETA 9% vs. placebo 1% (P<.01; NNT=13) |
| Humanistic Outcomes: | HAQ were significantly lower with ETA beginning at week 4 - 12. % pts. with clinically significant improvements in HAQ at week 24: ETA 54% vs. placebo 6% (P<.0001; NNT=2). ETA pts. had significant improvement in physical component score on the SF-36 vs. placebo (43% vs. 9%; P<.0001; NNT=3). No significant improvement between groups on the mental component score of the SF-36. |
| Comments: | Full study not published. |
Chills occurred more commonly with ALE, PPs. achieving PASI75 during or after TX, without phototherapy or systemic therapy, maintained PASI 50 or greater for 7 months (21687% of pts. (482/553) completed course 1 TX; 89% of pts. (401/449) completed course 2 TX. Full effects not observed during TX. Maximal No cases of rebound or flare of psoriasis were observed after ALE TX ended. Improvements in PASI and PGA were correlated with increasing ALE = .02; NNT = 4-9); PASI50: ALE 36% - 60% = .02; NNT = 5-13); PASI50: ALE 42% - 63% vs. 32% placebo PASI75 or greater 33% with ALE 15 mg and 28% with ALE 10 mg vs. 8% with placebo (P<001; NNT=6). PGA (clear/almost clear) response rate, 37% with ALE vs. 19% with placebo (P<001; NNT=6). PASI50 or greater overall response rate, 64% with ALE vs. 49% with placebo (P<05; NNT=7). PGA (clear/almost clear) overall response rate, 30% with ALE vs. 18% with placebo (P<05; NNT=8). ALE was well tolerated. Accidental injury, dizziness, nausea, chills and cough were slightly more common with ALE vs. placebo, but all AEs were mild. The incidence of infection was similar between TX groups. Clinical Monograph for Drug Formulary Review: Systemic Agents for Psoriasis/Psoriatic Arthritis

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**TABLE 7** Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Study design (n): R, DB, PC, MC trial in pts. with moderate-to-severe chronic plaque psoriasis (&gt;1 year and BSA &gt;10%), age &gt;18 years, who were candidates for phototherapy or systemic therapy (n=507).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment(s)</strong>: ALE 10 mg, ALE 15 mg, or placebo IM once weekly for 12 weeks, then followed up for 12 weeks.</td>
</tr>
<tr>
<td><strong>OUTCOMES</strong>: Primary end point: % pts. with PASI75 or greater at 2 weeks post-TX was 21% with ALE 15 mg vs. 5% with placebo (P&lt;001; NNT=6). Overall response rate after TX course 1: PASI75 or greater with ALE 15 mg and 28% with placebo (P&lt;001; NNT=5-7); PASI50 or greater with ALE 15 mg and 33% with placebo (P=001 and P=002), respectively, NNT=5-6); PGA clear/almost clear 24% with ALE 15 mg and 22% with ALE 10 mg vs. 8% with placebo (P&lt;001; NNT=6-7). Tolerability: Overall, ALE was well tolerated, with headache (typically single event) and mild injection site reactions (pain, pruritis, and inflammation—mild, transient that did not cause withdrawal from study) reported most commonly. No significant infections, reductions in CD4+ counts, serious drug-related AEs, or increases in malignancy were noted. AST elevations up to 3 times the ULN were noted in 8%-13% of ALE pts. vs. 9% in placebo pts., primarily in pts. with a history of hepatic illness or taking hepatotoxic drugs. No other alterations in liver function were noted. Antialefacept antibodies detected in 4% (14 pts.), but were low titers, did not increase, and were not neutralizing.</td>
</tr>
<tr>
<td><strong>Comments</strong>: Similar baseline characteristics, median duration of disease was 19 years (range 2-77 years), median BSA 21%. Pts. with more severe disease and pts. with no prior history of systemic therapy had higher response rates.</td>
</tr>
</tbody>
</table>

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**Krueger et al., 2002**

<table>
<thead>
<tr>
<th>Study design (n): R, DB, PC, MC trial in pts. with chronic plaque psoriasis (&gt;1 year and BSA &gt;10%), age &gt;16 years, who were candidates for phototherapy or systemic therapy (n=553).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment(s)</strong>: ALE 7.5 mg IV once weekly for 12 weeks then placebo for 12 weeks, ALE 7.5 mg IV once weekly for two 12 week courses, or placebo for 12 weeks, then ALE 7.5 mg IV once weekly for 12 weeks. There was a 12-week TX-free follow-up period after each TX course. Additional TXs allowed: low-potency corticosteroids allowed, but not for 12 hours before efficacy evaluation; moderate-potency corticosteroids; vitamin D analogs; topical retinoids; keratolytics; and coal tar allowed on groin, scalp, palms, and soles only.</td>
</tr>
<tr>
<td><strong>OUTCOMES</strong>: Primary end point: % pts. achieving PASI75 or greater at 2 weeks after course 1. TX course 1: 14% of ALE pts. achieved PASI75 or greater vs. 4% placebo pts. (P&lt;001; NNT=10) at 2 weeks, overall response rate 28% of ALE pts. vs. 8% of placebo pts. (P&lt;001; NNT=5). PASI 50 or greater overall response rate, 56% of ALE pts. vs. 24% with placebo (P&lt;001; NNT=3). PGA (clear/almost clear) overall response rate, 23% with ALE vs. 11% placebo (P&lt;001; NNT=8). TX course 2: PASI75 or greater overall response rate, 37% with ALE vs. 19% with placebo (P&lt;001; NNT=6). PASI50 or greater overall response rate, 57% with ALE vs. 52% with placebo (P&lt;05; NNT=7). PGA (clear/almost clear) overall response rate, 30% with ALE vs. 18% with placebo (P&lt;05; NNT=8). Duration of response: Pts. achieving PASI75 during or after TX, without phototherapy or systemic therapy, maintained PASI 50 or greater for 7 months (216 days) following 1 course of TX and beyond 48 weeks (379 days) for pts. following 2 courses of TX. Tolerability: Chills occurred more commonly with ALE, which occurs within 24 hours of dose and decreased with a subsequent course of therapy. Increased ALT &lt; 3 times normal occurred more commonly with ALE vs. placebo (17% vs. 8%) with second course of TX, but mild with no other alterations in liver function. Dose reduction required in 10% of ALE pts. due to increased CD4+ lymphocyte counts. Antialefacept antibodies detected in &lt; 1% (n = 5) of pts.</td>
</tr>
<tr>
<td><strong>Comments</strong>: 87% of pts. (482/553) completed course 1 TX; 89% of pts. (401/449) completed course 2 TX. Full effects not observed during TX. Maximal improvement occurred at 8 weeks post-TX. Overall response rate included pts. achieving end point at any time during 12-week TX or 12-week follow-up period. No rebound disease detected with discontinuation.</td>
</tr>
</tbody>
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**Ellis et al., 2001**

<table>
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<tr>
<th>Study design: R, DB, PC, MC trial in pts. with chronic plaque psoriasis (&gt;1 year and BSA &gt;10%), age &gt;18 years, who were candidates for phototherapy or systemic therapy (n=229).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment(s)</strong>: ALE 0.025, 0.075, 0.150 mg/kg IV (30 second injection) or placebo once weekly for 12 weeks with follow-up for 12 weeks after TX. Additional TXs allowed: emollients, but not for 12 hours before efficacy evaluation; moderate-potency corticosteroids, vitamin D analogs, topical retinoids, keratolytics, and coal tar allowed on groin, scalp, palms, and soles only.</td>
</tr>
<tr>
<td><strong>OUTCOMES</strong>: End point: % pts. achieving PASI75 or 50. At 2 weeks post-TX: PASI75: ALE 21%-33% vs. 10% (P = 0.2; NNT = 4-9); PASI50: ALE 36%-60% vs. 27% placebo (P = 0.01; NNT = 3-11). At 12 weeks post-TX: PASI75 : ALE 19%-33% vs. 11% (P = 0.2 ; NNT = 5-13); PASI50 : ALE 42%-63% vs. 32% placebo (P = 0.2; NNT = 3-10). Tolerability: ALE was well tolerated. Accidental injury, dizziness, nausea, chills and cough were slightly more common with ALE vs. placebo, but all AEs were mild. The incidence of infection was similar between TX groups.</td>
</tr>
<tr>
<td><strong>Comments</strong>: No cases of rebound or flare of psoriasis were observed after ALE TX ended. Improvements in PASI and PGA were correlated with increasing ALE serum levels. Dose-dependent decreases in CD4+ memory cells were noted. Dose-dependent decreases in CD4+ memory and naive cells were correlated with improvements in psoriasis.</td>
</tr>
</tbody>
</table>

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*AEs = adverse events; ALE = alefacept; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; ETA = etanercept; IM = intramuscular; INF = infusion; IV = intravenous; MC = multicenter; NNT = numbers needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; PC = placebo-controlled; PGA = Physician Global Assessment; Pts. = patients; QOL = quality of life; R = randomized; SC = subcutaneous; TX = treatment; ULN = upper limit of normal; VAS = Visual Analog Scale.*
TABLE 7  Placebo-Controlled Trials of Biologic Agents for the Treatment of Psoriasis

Krueger GG, Ellis CN, 2002a (follow-up to Ellis et al., 2001 study)

Subgroup analysis: R, DB, PC, MC trial in pts. with chronic plaque psoriasis (> 1 year and BSA >10%), age >18 years, who were candidates for phototherapy or systemic therapy (n=229).

Treatment(s): ALE 0.025, 0.075, 0.150 mg/kg IV (30-second injection) or placebo once weekly for 12 weeks with follow-up for 12 weeks after TX.

OUTCOMES: Follow-up evaluation of Ellis et al., 2001 study. Primary objective was to evaluate the remission period following TX with ALE. Of the 148 pts. completing TX with ALE, 118 (80%) required no additional TX for up to 3 months after stopping therapy. Of the 118 pts., 16 pts. were clear or almost clear for 3 months post-TX. Twenty-six of the ALE pts. subsequently were treated with a second course of ALE. Pts. did not require re-TX for several months, with a mean time between TXs of 10 months (range 6-18 mos).

Comments: This study suggests a long duration of efficacy with ALE TX.

Lowe et al., 2003b

Interim report of ongoing trial: OL, MC, re-TX study in pts. previously treated in Phase II trials with ALE or placebo, requiring additional systemic TX.

Treatment(s): ALE 7.5 mg IV bolus once weekly for 12 weeks. Re-TX course 1 (n=170), Re-TX course 2 (n=50). Additional TXs allowed after wash-out period: low-potency corticosteroids allowed, but not for 12 hours before efficacy evaluation; moderate-potency corticosteroids, vitamin D analogs, topical retinoids, keratolytics, and coal tar allowed on groin, scalp, palms, and soles only.

OUTCOMES: Re-TX course 1: % of pts. achieving overall response—PGA of clear or almost clear 29%, PASI75 or greater 39%, PASI 50 or greater 66%

Re-TX course 2: response rates for PASI75 were higher compared with course 1, pts. baseline measures were lower than before course 1, indicating some reduction of BSE.

Tolerability: AEs were similar to those seen in previous TX courses, with pharyngitis and rhinitis the most common reported AEs. No complicated infections were reported. TX discontinuation occurred in 3 pts. due to low CD4+ t-cell counts. Five pts. with a positive family or medical history of risks for cancer were diagnosed with cancer (1 colon, 1 lung, 3 skin cancer). 1.7% (3/174) of pts. tested positive for antialefacept antibodies, but titers were low and not associated with AEs.

Comments: Pharmacodynamic data showed selectivity for CD4+ memory cells over CD4+ naïve cells. Additional data are being collected in pts. receiving a third re-TX course.

ETANERCEPT

Leonardi et al., 2003b

Study design: DB, R, PC, MC trial in pts. with moderate-to-severe stable plaque psoriasis (PASI of 10, BSA>10%; candidate for systemic therapy) (n=652).

Additional TXs allowed: stable doses of low or moderate potency corticosteroids applied to scalp, axillae, or groin.

Treatment(s): ETA (Low dose) 25 mg SC once weekly, ETA (medium dose) 25 mg SC twice weekly, ETA (high dose) 50 mg SC twice weekly, or placebo for 24 weeks. After 12 weeks, patients in the placebo group received ETA 25 mg SC twice weekly in a double-blind fashion.

OUTCOMES: Primary measure: % pts. achieving PASI75 or greater at week 12: ETA low dose 14%, ETA medium dose 34%, ETA high dose 49% vs. 4% placebo (P<0.001 vs. placebo for all ETA groups; NNT=2-10). % pts. achieving PASI75 or greater at week 24: ETA low dose 25%, ETA medium dose 44%, ETA high dose 59%. No placebo group at week 24, as these pts. had begun ETA medium dose at week 12, and 33% of these pts. had achieved PASI75 or greater at week 24: % pts. achieving PASI50 or greater at week 12: ETA low dose 41%, ETA medium dose 58%, ETA high dose 74% vs. placebo 14% (P<0.001 vs. placebo; NNT=2-4).

At week 24: ETA low dose 58%, ETA medium dose 70%, ETA high dose 77%. % pts. clear/almost clear at week 12: ETA low dose 23%, ETA medium dose 34%, ETA high dose 49% vs. placebo 5% (P<0.001 vs. placebo; NNT=2-3). At week 24: ETA low dose 26%, ETA medium dose 39%, ETA high dose 55%. Pt-oriented improvements: % mean improvement in DLQI at week 12: ETA low dose 47%, ETA medium dose 51%, ETA high dose 61% vs. placebo 11% (P<0.001 vs. placebo; NNT=2-3).

Outcomes in PGA were significantly better in all ETA groups vs. placebo at week 12. Tolerability: ETA was well tolerated with similar incidence of AEs and infections across all groups. Eight ETA pts. had non-neutralizing ETA antibodies, but there were no differences in efficacy or safety noted.

Comments: Statistically significant improvements noted at 4 weeks in the ETA high dose and at 8 weeks in the ETA medium dose groups. Mean percentage improvements in QOL from baseline, as measured by PGA and DLQI, were statistically significant beginning at week 2. No significant increase in AEs noted with increasing doses of ETA. Data on follow-up period to evaluate duration of response not provided in this publication.

Gottlieb AB, Gordon KB et al., 2004a [poster]; Krueger GC, Lebwohl MG et al., 2004a [poster]; Leonardi CL, Elewski BE et al. 2004a [poster]

Study design: Follow-up extension of above study (of 652 pts.; 409 pts. were responders and entered withdrawal period).

Treatment(s): Active-treatment pts. were withdrawn from study drug after 24 weeks and followed for relapse.

OUTCOMES: Median time to relapse (loss of 50% of PASI improvement): ETA 25 mg once weekly 70 days, 25 mg twice weekly 85 days, 50 mg twice weekly 91 days. No reports of flare or rebound, with duration of response of approximately 3 months. Additional analysis (Krueger et al, 2004) showed for pts. not responding at 24 weeks, additional pts. (27%, 6/22 pts.) responded at 60 weeks with the 25 mg twice weekly and 6% (3/18 pts.) with the 50 mg twice weekly doses. Further analysis of re-TX pts. showed that pts. treated with etanercept after relapse had similar response to TX as observed with original TX (Leonardi, 2004). Pts. who were responders at week 24, showed similar response (PASI75 scores) upon re-TX with etanercept across all doses.

Comments: Poster presentations; full studies not published.

AES = adverse events; ALE = alefacept; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; ETA = etanercept; IV = intravenous; MC = multicenter; NNT = numbers needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; PC = placebo-controlled; PGA = Physician Global Assessment; Pts. = patients; QOL = quality of life; R = randomized; SC = subcutaneous; TX = treatment; ULN = upper limit of normal; VAS = Visual Analog Scale.

(Continued on next page)
Eucerin cream, tar or salicylic acid agents for scalp, limited application of low-potency corticosteroids, and oral antipruritic agents.

EFA 4 mg/kg/wk 13% vs. 2% (Step-down dosing showed similar efficacy to that observed in 50 mg twice weekly dosing in study by Leonardi et al., 2003. Additional one third of pts. achieving PASI75 at 12 weeks: ETA 30% vs. placebo 2% (P<0.01; NNT=2).% pts. that were nonresponders at week 4 that went on to become responders with continued treatment: Of pts. who were not responders at week 4: 33% of 25 mg twice-weekly and 53% of 50 mg twice weekly pts. achieved PASI50 by week 8. Of pts. who were not responders at 4 weeks: those that became responders at 12 weeks were 51% for 25 mg twice weekly and 67% for 50 mg twice weekly.

Comments: Improvements have been reported beginning at 2 weeks, however, these data indicate response can increase in nonresponders following 3 months of therapy. Limitation: Poster presentation, statistical significance not stated, full study not published.

Gottlieb et al., 2002** [poster]

Study design: R, DB, MC trial in pts. with stable plaque psoriasis (BSA >10%, trial of at least one systemic therapy) (n=112).

Treatment(s): EFA 25 mg SC twice weekly or placebo.

OUTCOMES: Primary efficacy measure: % pts. achieving PASI75 at week 12: EFA 30% vs. placebo 2% (P<0.001; NNT=4) and at 24 weeks: EFA 56% vs. placebo 5% (P<0.001; NNT=2). % PGA at week 12 (clear/almost clear): ETA ~45% vs. placebo ~3% (P<0.001; NNT=2). Tolerance: AEs were similar, except injection site reactions were higher with ETA. Rates of AEs overall were similar, except the rate per pt. year of any infection was significantly higher with ETA.

Comments: Statistically significant improvements in PASI began at week 8, PGA at week 4, and Patient Global Score at week 2.

Elewski et al., 2004* [poster]

Study design: R, DB, MC trial in pts. with stable plaque psoriasis (BSA >10%, trial of at least one systemic therapy or a candidate for systemic therapy) (n=583).

Treatment(s): EFA 50 mg twice weekly for 12 weeks then 25 mg twice weekly (step-down) for 12 weeks, ETA 50 mg twice weekly for 12 weeks, or placebo for 12 weeks followed by EFA 25 mg twice weekly for 12 weeks.

OUTCOMES: Primary efficacy measure: % pts. achieving PASI75 at week 12: EFA 49% vs. placebo 34%, placebo 3% (P<0.001 both vs. placebo; P=0.002 for 25 mg twice weekly vs. 50 mg twice weekly). % pts. achieving PASI75 at week 24: ETA 50 mg twice weekly/EFA 25 mg twice weekly (step-down) 54%, ETA 25 mg twice weekly 45%, placebo/25 mg twice weekly 28%.

Comments: Step-down dosing showed similar efficacy to that observed in 50 mg twice weekly dosing in study by Leonardi et al., 2003. Additional one third of pts. not responding on 50 mg twice weekly did go on to respond even following step-down dosing to 25 mg twice weekly. P-values were not provided to determine statistical significance.

EFALIZUMAB

Lebwohl and Tyring et al., 2003*

Study design: R, DB, MC trial in pts. with moderate-to-severe plaque psoriasis (PASI of >12, BSA>10%, candidate for systemic therapy) (n=597).

Additional TXs allowed: Ciclosporin, etretinate, dapsone, dexamethasone, and other systemic agents. See Gottlieb et al., 2002.

Treatment(s): Phase 1 (n=597): EFA 1 mg/kg/wk SC, EFA 2 mg/kg/wk SC, or placebo for 12 weeks. Phase 2 (n=434): Pts. achieving >PASI50 were rerandomized to ETA 25 mg twice weekly or placebo. Pts. achieving <PASI50 were rerandomized to EFA 4 mg/kg/wk or placebo. Pts. were then followed for an additional 12 weeks.

OUTCOMES: Week 12 results—% pts. achieving PASI75 or greater: EFA 2 mg/kg 28%, EFA 1 mg/kg 22% vs. placebo 5% (P<0.01; NNT=6). % pts. achieving PASI50 or greater: EFA 2 mg/kg 57%, EFA 1 mg/kg 52% vs. placebo 16% (P<0.01; NNT=2-3). PASI scores were significantly lower in patients treated with EFA vs. placebo (9 vs. 17, P<0.001). Week 24 results following 12 additional weeks of TX: Pts. with PASI75 or greater at week 12, % pts. achieving PASI75 or greater: EFA 2 mg/kg/wk 78%, ETA 2 mg/kg every other week 77% vs. placebo 20% (P<0.01; NNT=2-3). Pts. with PASI50 or greater at week 12, % pts. achieving PASI75 or greater: ETA 2 mg/kg, 53%, ETA 2 mg/kg/every other week 29% vs. placebo 4% (P<0.01 and P=0.002, respectively; NNT=2-4). Pts. with <PASI50 at week 12, % pts. achieving PASI 75 or greater: ETA 4 mg/kg/wk 13% vs. 2% (P<0.02; NNT=9). Tolerance: AEs was well tolerated. Acute AEs (headache, chills, fever, nausea, myalgia) were most common following the first dose, were transient, and mild. AEs during the second phase were similar with fewer acute AEs noted. Antiefalizumab antibodies were found in 5% of pts., with no difference in AEs.

Duration of response: At week 36, 30% of pts. maintained PASI50. Time to loss of PASI50 after 24 weeks of TX was 84 days.

Comments: Mean PASI at baseline was 20, mean duration of psoriasis was 19 years, 67% of pts. had received previous TX with systemic therapy. Significant difference in efficacy was noted at week 4 of TX with ETA vs. placebo. This study did not evaluate PGA of improvement. The 2 mg/kg/wk and 4 mg/kg/wk doses are higher than the FDA-recommended dose of 1 mg/kg/wk. There were no statistically significant differences in efficacy between the 1 mg/kg/wk and the 2 mg/kg/wk doses. Of pts. who achieved PASI75 with ETA during the initial 12 weeks and were then switched to placebo, only 20% maintained that improvement at week 24 vs. 77% of pts. who continued with ETA. At week 24, relapse (50% or more loss in improvement) occurred in 8% of pts. who continued on ETA and in 67% of pts. who discontinued ETA therapy after 12 wks.

AEs=adverse events, ALE=alefacept, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BSA=body surface area, DB=double-blind, DLQI=Dermatology Life Quality Index; EFA=efalizumab, ETA=etanercept, IM=intramuscular, INF=infusion, IV=intravenous, MC=multicenter, NNT=numbers needed to treat, OL=open label, PASI=Psoriasis Area Severity Index; PC=placebo-controlled, PGA=Physician Global Assessment; Pts.=patients; QOL=quality of life; R=randomized; SC=subcutaneous; TX=treatment, ULN=upper limit of normal, VAS=Visual Analog Scale.

(Continued on next page)
observed in patients who experienced a 50% or 75% improvement in PASI at 12 weeks compared with patients treated with placebo (P <.05). The general QOL survey (SF-36) was found to be less specific in determining QOL in these patients. Similar results were noted in 509 patients with moderate-to-severe chronic plaque psoriasis who were treated with alefacept 15 mg administered intramuscularly. At 12 weeks, patients treated with alefacept experienced statistically significant improvements in DLQI, DQOLS, and SF-36 compared with patients treated with placebo.

**Efalizumab**

Efalizumab was shown to improve DLQI scores in a pooled

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analysis of 2 phase III studies. QOL was assessed in 1,095 patients with moderate-to-severe psoriasis treated with efalizumab or placebo. DLQI scores decreased from 12 to 6 with efalizumab 1-2 mg/kg/wk compared with an improvement from 12 to 10 with placebo. Similar results were shown in a phase III trial in 556 patients with moderate-to-severe psoriasis. Significantly greater improvements were reported with efalizumab-treatment compared with placebo treatment at 12 weeks (47% versus 14%; P<.001). Significant improvements were noted in the efalizumab-treated patients beginning at week 4 and were consistent across all DLQI components, with the greatest improvements in the symptoms and feelings sections. Additional analyses showed the greatest improvements in DLQI were observed in patients achieving a PASI50.

**Etanercept**

In a follow-up to the study by Mease et al., which evaluated the efficacy of etanercept in treating 205 patients with active psoriatic arthritis, etanercept was shown to result in significant improvements in HRQOL compared with treatment with placebo at 24 weeks. Patients receiving etanercept experienced significantly greater improvements in Health Assessment

## TABLE 8

### Combination Therapy Trials of Biologic Agents for the Treatment of Psoriatic Arthritis With or Without Psoriasis

<table>
<thead>
<tr>
<th><strong>ETANERCEPT</strong></th>
<th>Study design: Case control series in pts. with severe recalcitrant psoriasis (n=3) failing systemic therapies (n=10).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment(s): ETA 25 mg SC twice weekly. Additional TXs: oral MTX (2 pts.), oral cyclosporine (1 pt.), acitretin/hydroxyurea on alternate days (1 pt.), acitretin/UVB on alternate days (1 pt.), or topical calcipotriene (1 pt.).</td>
<td></td>
</tr>
<tr>
<td>OUTCOMES: PASI scores improved by approximately 50% in all pts. Pts. with psoriatic arthritis experienced a moderate-to-major improvement in arthritis. Combination therapy was well tolerated with no significant AEs reported.</td>
<td></td>
</tr>
<tr>
<td>Limitations: Uncontrolled case-series study. Time frame for response not stated in all pts., 2 pts. showed improvements within 5-8 weeks.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>INFILIXIMAB</strong></th>
<th>Study design: Case series of pts. with severe psoriatic arthritis (n=10).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment(s): INF 5 mg/kg on week 0, 2, 6. Additional TXs included NSAIDs, MTX, steroids.</td>
<td></td>
</tr>
<tr>
<td>OUTCOMES: 1 pt. with ACR70 at week 10 stopped therapy and was in remission for 5 months. Four pts. with ACR70 and 1 pt. with ACR 50 at week 10 received INF 3-4 mg/kg Q 8 weeks. For 3 cases, pts. stopped therapy after 5-8 months due to remission. At 1 year, all 5 pts. maintained ACR70. Remaining 4 pts. TX with INF 3-4 mg/kg every 8 weeks. 3 had ACR50 at 1 year. One pt. had a flare that responded to increased dose and frequency of INF.</td>
<td></td>
</tr>
<tr>
<td>Comments: Case series provides low evidence, due to small size and lack of controls.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Dechant et al., 2000</strong> [abstract]</th>
<th>Study design: Case series of pts. with severe psoriatic arthritis (n=6).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment(s): INF 5 mg/kg on week 0, 2, 6. Additional TXs: MTX, sulfasalazine.</td>
<td></td>
</tr>
<tr>
<td>OUTCOMES: 100% pts. achieved ACR50 at week 10, 83% of patients achieved ACR70 at week 10. HAQ improved by 78%, PASI decreased from 5.3 to 2.6 by week 10.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Dechant et al., 2000</strong> [abstract]</th>
<th>Study design: Case series of pts. with severe psoriatic arthritis (n=6).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment(s): INF 5 mg/kg on week 0, 2, 6. Additional TXs: MTX, sulfasalazine.</td>
<td></td>
</tr>
<tr>
<td>OUTCOMES: PASI scores were dramatically improved in all pts. at week 10.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ogilvie et al., 2001</strong> [abstract]</th>
<th>Study design: Case series of pts. with severe psoriatic arthritis resistant to DMARD therapy (n=3).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment(s): INF 3 mg/kg on weeks 0, 2, 6, and every 8 weeks. Additional TXs: MTX and azathioprine.</td>
<td></td>
</tr>
<tr>
<td>OUTCOMES: All pts. experienced reduced symptoms of psoriatic arthritis. One pt. experienced recurrent flares in arthritis, thus requiring INF every 4 weeks, with successful response.</td>
<td></td>
</tr>
</tbody>
</table>

**ACR = American College of Rheumatology score; AEs = adverse events; DMARDs = disease-modifying anti-rheumatic drugs; ETA = etanercept; HAQ = Health Assessment Questionnaire; INF = infusion; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs; PASI = Psoriasis Area Severity Index; Pts. = patients; SC = subcutaneous; TX = treatment; UVB = ultraviolet B.**
Questionnaire scores, with an improvement of 0.6 units compared with a 0.1 unit improvement with placebo (54% versus 7%; P < .001). An improvement of 0.22 units is considered clinically significant. Similarly, a significant improvement in the Medical Outcomes Study SF-36 scores was observed with etanercept compared with placebo (mean change of 9.3 versus 0.7 with placebo; P < .001). This was primarily attributed to improvements in the Physical Component Summary with a trend toward improvement in the Mental Component Summary, which did not reach statistical significance. A significant improvement in the EuroQOL Feeling Component Summary, which did not reach statistical significance, was reported with etanercept compared with placebo (mean improvement of 14.3 units versus 2.1 units; P < .001).

VI. Pharmacoeconomics

In an economic study published by Feldman et al., methotrexate was the least costly treatment at $1,600 annually, followed by phototherapy $3,600, PUVA $4,600, acitretin $5,200, cyclosporine $6,500 to $10,000 (3 - 5 mg/kg/day), alefacept $16,000 to $20,000 (1.5 courses/year—assumes intravenous [IV] administration, labs tests and office visits), and etanercept $16,900 to $33,000 (25 mg twice weekly - 50 mg twice weekly). Assumptions included costs of laboratory tests, office visits, and drug acquisition costs (average wholesale price) but did not include costs associated with rare adverse events. The analysis also included assessment of the cost per treatment success based on efficacy from published studies but not from head-to-head comparisons. Methotrexate remained the least costly therapy at $5,400; both UVB and PUVA had similar costs per treatment at $5,100 to $5,700, while costs per treatment were somewhat higher for cyclosporine (5 mg/kg/day) at $14,200 and acitretin monotherapy at $17,300. However, costs per treatment with the biologic agents were higher than the traditional therapies at $35,900-$40,600 annually for etanercept (25 mg twice weekly - 50 mg twice weekly). Infliximab costs per treatment were lower at $22,500 for 5 mg/kg (6 infusions) but were based on a high efficacy rate of 80% noted in a single trial.

In a decision-analytic model by Chiou et al., the cost-efficacy of biologics was compared in treating psoriasis. Data were based on package insert information and published clinical trial data that were then reviewed by an expert panel of dermatologists. The analysis was conducted from a managed care perspective and was evaluated over a 6-month period, based on efficacy at 12 to 14 weeks that was assumed to be maintained at 6 months. Costs included drug costs, laboratory monitoring, and costs of treating moderate-to-severe adverse events. Costs of therapy over 6 months were $13,342 for alefacept (dosed for 12 weeks); $11,295 for efalizumab; $9,781 for etanercept (25 mg twice weekly); $14,273 for etanercept step-down dosing (50 mg twice weekly for 12 weeks, then 25 mg twice weekly for 12 weeks); and $18,600 for etanercept 50 mg twice weekly. However, additional analyses of incremental cost-efficacy showed etanercept to be the most cost-effective agent because of higher efficacy rates. Limitations included lack of head-to-head data and use of expert opinion to classify adverse events. It should be noted that the study was supported by a grant from Immunex/Amgen, the manufacturer of Enbrel (etanercept).

Additional useful measures of the costs associated with use of biologic agents would be to calculate cost per day of response to therapy or the cost of treatment failure compared with conventional therapies or other biologic agents. See Table 9 for sample annual costs for 1 year of treatment for psoriasis or psoriatic arthritis.

VII. Adverse Effects

Many of the systemic agents used in treating psoriasis and psoriatic arthritis work by affecting the immune system, thus causing concern over their long-term use and the potential for an increased risk of infection. The commonly reported adverse effects associated with conventional systemic therapies for psoriasis are provided in Table 10. These data highlight the safety and toxicity issues associated with these therapies that have led to development and increased utilization of biologic agents.

Alefacept

The most common adverse effects reported with alefacept were chills, dizziness, nausea, increased cough, and injection site pain. Serious adverse effects were uncommon but included lymphopenia (dose-dependent reductions in CD4+ and CD8+ counts), which accounted for 4% of patients receiving intra-
TABLE 10 Adverse Effects of Conventional Systemic Therapies for Psoriasis/Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Hepatotoxicity, gastrointestinal malaise, headache, reactivation of phototoxic reactions, ulcerative stomatitis, myelosuppression, anemia, pulmonary fibrosis, induction of lymphomas</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Black box warning regarding teratogenicity and hepatotoxicity, hyperlipidemia, mucocutaneous skin reactions, alopecia, gastrointestinal effects, arthralgias and myalgias, pseudotumor cerebri, hyperostosis; may worsen psoriasis initially</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Renal toxicity, hypertension, gastrointestinal effects, flu-like symptoms, hypertrichosis, gingival hypertrophy, skin malignancies with PUVA</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Myelosuppression, gastrointestinal effects, hyperpigmentation, renal dysfunction, oral and leg ulcers, dermato(myelitis)-like skin changes</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Block box warning regarding increased risk of neoplasia with chronic use, gastrointestinal hypersensitivity, hematologic toxicities</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Gastrointestinal effects, headache, rash, fever, dizziness, stomatitis, pruritis, abnormal liver function tests, leukopenia, thrombocytopenia, rare immunoglobulin suppression (serum-like sickness), hypersensitivity reactions</td>
</tr>
<tr>
<td>Auranofin</td>
<td>Gastrointestinal effects, rash, pruritis, stomatitis, conjunctivitis, abnormal liver function tests, proteinuria</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Allergic reactions, generalized puritities/rashes/drug eruptions, gastrointestinal effects, leukopenia, thrombocytopenia, renal dysfunction, abnormal liver function tests</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Long-term, high-dose therapy can result in ocular dysfunction, seizures, auditory dysfunction, gastrointestinal effects, skin eruptions/rash/pruritis, headache, rarely hypotension</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Headache, dizziness, gastrointestinal effects</td>
</tr>
</tbody>
</table>

PUVA = psoralen plus ultraviolet A light

is not known, but because it is an immunosuppressive therapy, patients should be monitored for malignancy or the drug discontinued in patients diagnosed with a malignancy. Severe thrombocytopenia occurred in patients during clinical trials, with 0.3% of efalizumab-patients experiencing thrombocytopenia (platelet counts below 50,000 cell/μl) compared with no cases reported with placebo. In 3 of the 8 patients experiencing severe thrombocytopenia, all cases were consistent with an immune-mediated reaction. Worsening of psoriasis occurred in 0.7% (19 patients) of efalizumab-treated patients, with most cases occurring after discontinuation of therapy. Some cases were severe and required hospitalization (17 of 19 patients) or alternative psoriasis therapy, with conversion to psoriatic erythroderma and pustular psoriasis reported in some patients. The rate of psoriasis adverse events, including both nonserious and serious cases, observed during placebo-controlled trials was 3.2% (52 of 1,620) with efalizumab compared with 1.4% (10 of 715) with placebo.12

Recent analysis of safety data from 13 clinical trials in 2,762 patients showed 13.8% of efalizumab-treated patients experienced psoriasis that returned to worse than baseline with discontinuation of therapy compared with 11.1% of patients.87 First-dose reactions of headache, fever, nausea, and vomiting occur with efalizumab, which are dose-related; thus, an initial lower conditioning dose is recommended. Hypersensitivity reactions were uncommon but occurred more commonly with efalizumab compared with placebo (1% versus 0.4%). Inflammatory/immune-mediated reactions occurred in 0.5% of patients treated with efalizumab, including 2 cases of interstitial pneumonitis. Elevations in alkaline phosphatase occurred more frequently with efalizumab compared with placebo (4% versus 0.6%), and the percentage of patients with above-normal liver function tests was also higher with efalizumab compared with placebo (3.1% versus 1.5%). Long-term immunogenicity of efalizumab is not known; however, 6.3% of patients developed antibodies to efalizumab.

Etanercept

The most frequent adverse event is injection site reactions (37%).11 Injection site reactions tend to decrease in severity over time. Recently published data analyzing safety from 1 phase II and 2 phase III trials showed the incidence of injection site reactions was lower than observed in rheumatoid arthritis trials.88 The incidence of infections overall was low, at less than 1% with no reports of conversion of psoriasis to other types. Etanercept has been associated with rare postmarketing reports of pancytopenia, including aplastic anemia, although a causal relationship has not been established.11 Caution is advised for use in patients with a history of significant hematologic abnormalities. Treatment with etanercept and other agents with similar mechanisms of action have been associated with rare reports of new onset of demyelinating disease such as multiple muscular injections to temporarily discontinue therapy. Subsequent courses resulted in a higher portion of patients experiencing below-normal counts.86 Data also showed a higher incidence of serious infections requiring hospitalization compared with placebo (0.9% versus 0.2%), which increased with subsequent courses (1%). Maximum effects on lymphocyte counts were observed at 6 to 8 weeks after initiation of therapy. The incidence of malignancy was also slightly higher with alefacept, with 1.3% of patients diagnosed compared with 0.5% of patients in the placebo group. The majority of cases were basal or squamous cell cancers, but 3 cases of lymphoma were reported. There were rare reports of increased transaminase levels 5 to 10 times the upper limit of normal (9 patients) during clinical trials.10

Efalizumab

Serious infections occurred in 0.4% of efalizumab-treated patients and 0.1% of placebo-treated patients during the initial 12 weeks of therapy.12 The risk of malignancy with efalizumab

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sclerosis, and exacerbations of preexisting disease. Caution is advised when prescribing etanercept in patients with preexisting disease. Adverse events with etanercept treatment in pediatric patients are similar in frequency and type as those seen in adult patients. Non-neutralizing antibodies to etanercept have been reported in clinical studies, but no correlation to clinical response or adverse events was noted. Analysis of clinical trials in psoriasis patients showed a 6% incidence of antietanercept antibodies, although titers were low and antibodies were non-neutralizing with no apparent effects on safety or efficacy. 

### Infliximab

Safety of infliximab is based on data from clinical trials in rheumatoid arthritis. Safety data for treatment of psoriasis have not been fully elucidated in large well-controlled trials. Similar to etanercept, demyelinating syndromes have been associated with infliximab. Use should be avoided in patients with preexisting multiple sclerosis. Efficacy with infliximab is more durably sustained when combined with methotrexate in treating rheumatoid arthritis. Data are not available to clarify if infliximab should be administered only in combination with methotrexate for psoriasis and psoriatic arthritis, but in preliminary studies, it was often used in combination with other agents, including methotrexate.

### Congestive Heart Failure With Infliximab or Etanercept

During clinical trials evaluating the efficacy of etanercept and infliximab in patients with congestive heart failure (CHF), it was determined that these agents may not improve CHF and could decrease survival. Two phase II studies with etanercept (RENAISSANCE and RECOVER) were stopped early due to lack of efficacy and an increased incidence of worse outcomes in patients in one study. During the postmarketing period, cases of worsening heart failure have been reported in patients treated with etanercept in both patients with and without precipitating factors. In the ATTACH trial, infliximab was shown to increase the risk of mortality or worsen CHF; thus, this agent is contraindicated in patients with CHF. For CHF patients already on infliximab therapy, infliximab should be discontinued in patients whose CHF is worsening, and discontinuation should be considered in patients with stable concomitant CHF. Current labeling contraindicates use of infliximab in patients with moderate-to-severe CHF and cautions use of etanercept in patients with CHF. The FDA and manufacturers of these products are conducting ongoing surveillance of the risk of CHF with these agents.

### VIII. Drug/Food Interaction

Formal drug/food interaction studies have not been conducted with the biologic response modifiers. However, drug interactions are minimal compared with conventional therapies.

---

**TABLE 11 Drug/Food Interactions**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Food Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alefacept</td>
<td>No formal studies—caution concomitant use with other immunosuppressive agents or phototherapy</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>No formal studies—caution concomitant use with other immunosuppressive agents or phototherapy; do not administer with acellular, live, or live-attenuated vaccines</td>
</tr>
<tr>
<td>Etanercept</td>
<td>No formal studies—caution use with anakinra; do not administer with live vaccines</td>
</tr>
<tr>
<td>Infliximab</td>
<td>No formal studies—do not administer with live vaccines</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Aminoglycosides, chloramphenicol, folic acid, NSAIDs, penicillins, salicylates, sulfonamides, tetracyclines, trimethoprim, digoxin, phenytoin, theophylline, thiopurines, food delays absorption</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Drugs that affect cytochrome P450, nephrotoxic drugs</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Ethanol, glibenclamide, progestin-only contraceptives, methotrexate, phenytoin, tetracyclines, vitamin A, or oral retinoids</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>No formal studies conducted</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>ACE inhibitors, allopurinol, methotrexate, anticoagulants, cyclosporine, nondepolarizing neuromuscular blockers</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Digoxin, folic acid, sulfonlyureas</td>
</tr>
<tr>
<td>Auranofin</td>
<td>Phenyltoin</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Gold therapy, antimalarial, cytotoxic drugs, iron salts, antacids, digoxin</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Hepatotoxic drugs</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Digoxin</td>
</tr>
</tbody>
</table>

NSAIDs = nonsteroidal anti-inflammatory drugs.

---

A summary of food/drug interactions with systemic therapies is presented in Table 11.

No formal drug interaction studies have been performed with alefacept, and the optimal time period between initiating other therapies following use of alefacept is not known. The safety and efficacy of administering live or live-attenuated vaccines with alefacept have not been fully evaluated. However, the effects of alefacept on the immune response were specifically evaluated in a randomized, controlled, open-label trial in 46 patients with chronic plaque psoriasis. Patients were randomized to treatment with alefacept 7.5 mg IV once weekly for 12 weeks or to a control group. Patients were then exposed to an antigen as well as to a recall antigen (tetanus toxic) to determine if there was a significant difference in the immune response between patients treated with alefacept or who were in the control group. Results showed similar mean antibody titers to both the antigen and tetanus toxic, thus suggesting that alefacept selectively inhibits T cells, allowing patients to retain a significant immune response to fight infection or to be able to respond appropriately to vaccinations. Conversely, although
IX. Indications/Monitoring/Precautions

A summary of indications, monitoring recommendations, and precautions with systemic therapies is presented in Table 12. FDA-approved dosing recommendations and a summary of patent information are presented in Table 13.

X. Conclusions

Psoriasis is a chronic skin condition that varies in extent and severity. The majority of patients have mild-to-moderate disease with approximately 30% of patients progressing to moderate-to-severe psoriasis. In general, the disease is not life-threatening, but for patients with more severe disease, it can greatly impact QOL. The goal in treating plaque psoriasis is to obtain rapid control and maintain such, which includes drug therapy with minimal adverse effects as well as a planned approach to address psychosocial implications of the disease. The approach to treatment is variable and dependent on the type of psoriasis, the extent of the disease, and the areas of involvement. The mainstay of therapy for localized disease is topical corticosteroids, calcipotriene, coal tar, tazarotene, and anthralin, while systemic therapy is usually reserved for generalized and more severe disease. For patients with progressive disease despite the aforementioned topical therapies, phototherapy (PUVA) can be used with or without a topical agent. Adjunctive therapy with emollients free of lactic acid or alpha-hydroxy acids can hasten lesion resolution with any of the treatments and should be encouraged. Systemic therapy—acitretin, methotrexate, cyclosporine, infliximab, efalizumab, alefacept, etanercept—should be reserved for patients with moderate-to-severe generalized disease. Furthermore, because of the potentially serious adverse effects associated with some of these agents, rotational therapy may be needed.

The American Academy of Dermatology is in the process of updating the evidence-based guidelines on the treatment of psoriasis published in 1991 and recently published a consensus statement on treatment to provide guidance in the interim. The statement suggests that selection of therapy include the following considerations: type of psoriasis; location of lesions; severity of the lesions, specifically thickness, redness, scaling; extent of the disease based on BSA or PASI score; age of the patient; symptoms, including pain and pruritus; response to previous therapies; accessibility to a dermatologist or ultraviolet light facility; physician preferences; economic factors; cost/benefit ratios; quality of life, specifically the ability to perform daily activities; employability; and interpersonal relationships. Additional considerations are comorbid diseases that may limit or affect treatment options, such as liver disease, hepatitis C, HIV infection, hypertension, and alcohol intake. Consideration must also be given to child-bearing potential, pregnancy, desire to become pregnant, and desire to impregnate.

Mild disease includes patients with limited BSA involvement and, with selection based on severity and location of lesions, is generally responsive to topical therapies such as topical corticosteroids, tazarotene, calcipotriene, anthralin, tar preparations, salicylic acid, lactic acid, urea, lubrication products, or combinations of these agents.

Moderate-to-severe disease generally includes patients with BSA > 10%, but patients with lower BSA involvement may be classified as moderate-to-severe if the palms, soles, head and neck, or genitalia are involved. These patients usually have more generalized or severe disease that is unresponsive to topical agents alone, thus prompting use of systemic therapies.

Phototherapy (UVB with or without topicals) or phototherapy (PUVA) with or without oral retinoids may be a first option for systemic therapy, depending on the availability of light facilities. Methotrexate and cyclosporine have similar efficacy and are alternative choices; often these agents are used in a rotational or sequential method to avoid toxicities observed with long-term use. For more chronic use, methotrexate may be preferred over cyclosporine since chronic use of this agent is typically limited to 1 year in duration. Acitretin, an oral retinoid, can be used alone, but it is also used in combination with phototherapy or photochemotherapy to reduce the doses required and decrease toxicity of light therapy.

The newer biologic agents, efalizumab and alefacept, are potential options, as is infliximab, which has shown some efficacy in psoriasis, although published data are currently limited. Etanercept was recently approved for psoriasis and has published data to support efficacy and safety. Notably, dosing is higher with etanercept for treating psoriasis than for the other approved indications. Thus, cost will be higher with the initially higher dose, but will be comparable with other biologics when the dose is reduced to the typical dose after the first 3 months of therapy. One economic analysis showed that step-down dosing with etanercept, which is the approved dose, was higher than efalizumab and alefacept at 6 months. However, based on a higher efficacy rate, it was deemed the most cost-effective agent, although this was not based on head-to-head trials.

In addition to this guidance, additional considerations are that long-term data are not available with the biologic response modifiers. Exceptions are that long-term data are available with etanercept and infliximab in treating other conditions. Biologic agents do appear less efficacious compared with methotrexate and cyclosporine, but they may be less toxic in the long-term. Other differences in systemic therapies that must be compared include onset of action and ease of administration. Alefacept has...
| TABLE 12 | Indications for Agents for Psoriasis/Psoriatic Arthritis |

ALEFACEPT: FDA-approved indications: TX of moderate-to-severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Investigational uses: Psoriatic arthritis. Routine monitoring: CD4+ T-cell lymphocyte counts weekly during 12-week regimen, hold dose if count < 250 cells/mL and stop therapy if below 250 cells/mL for 1 month. Monitor for signs or symptoms of infection and stop therapy if infection develops. Monitor for hypersensitivity reactions. Special considerations: Do not initiate in pts. with below-normal CD4+ counts. Contraindicated in patients with history of systemic malignancy. Caution use if at high risk for malignancy. Discontinue use if malignancy develops. Caution use in pts. at risk of or with a history of chronic infection. Pregnancy category B, not recommended while breastfeeding. Caution use in pts. over age 65; no significant differences were noted during studies, but limited data are available in this population who may be at a higher risk for infection.

EFALIZUMAB: FDA-approved indications: Treatment of moderate-to-severe chronic plaque psoriasis in adults (age 18 years and older) who are candidates for systemic therapy or phototherapy. Investigational uses: Psoriatic arthritis. Routine monitoring: Monthly platelet counts upon initiation, then every 3 months with continued therapy. Discontinue therapy if thrombocytopenia develops. Special considerations: Caution use if at high risk for malignancy. Discontinue use if malignancy develops. Caution use in pts. at risk of or with a history of chronic infection. Pregnancy category C, not recommended while breast-feeding.

ETANERCEPT: FDA-approved indications: Treatment of adult pts. (age 18 years and older) with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Reduction in the signs and symptoms and inhibiting the progression of structural damage of active arthritis in pts. with psoriatic arthritis. Reducing signs and symptoms and improving physical function in moderate-to-severe active RA. In combination treatment with MTX for pts. who do not respond to MTX alone. Moderate-to-severe active polyarticular-course juvenile RA in pts. with inadequate response to > 1 DMARD. Reduce signs and symptoms and inhibit progression of structural damage of psoriatic arthritis. Ankylosing spondylitis. Investigational uses: Sjögren's syndrome, mouthwash to treat stomatitis and oral pain in chemotherapy patients. Wegener's granulomatosis, pain/swelling after third molar extraction. Routine monitoring: Monitor for injection site reactions. Monitor for signs or symptoms of new or worsening heart failure. Ascertain TB risk before starting TX; monitor for signs of infection (PPD test). Special considerations: May be given in combination with MTX, salicylates, glucocorticoids, NSAIDs, or analgesics. Bold warning regarding risk of serious infection, sepsis, or TB. Pregnancy category B, not recommended while breastfeeding.


METHOTREXATE: FDA-approved indications: Symptomatic control of severe recalcitrant, disabling psoriasis refractory to other therapies. If used in combination with topical therapy, the dose of MTX may be reduced. RA as monotherapy or in combination with other DMARDs. Various cancers. Investigational uses: Psoriatic arthritis, various cancers, Crohn's disease, eczema, cutaneous lupus, hepatitis, multiple sclerosis, organ transplant rejection, vasculitis. Routine monitoring: CBC with platelets, hepatic enzymes, renal function, and chest x-ray initial, then CBC with platelets, renal/hepatic function monthly. Cholesterol and lipoprotein levels, serum electrolytes, signs/symptoms of infection. Special considerations: Pregnancy category X. Risk of hepatotoxicity is higher in pts. with alcoholism, obesity, diabetes, and advanced age.

ACITRETIN: FDA-approved indications: TX of severe psoriasis. Investigational uses: Palmoplantar pustulosis, lichen planus, Sjögren-Larsson syndrome, cutaneous T-cell lymphoma. Routine monitoring: Blood lipids and LFTs every 2 weeks for 4-8 weeks. Special considerations: Contraindicated if severe liver or kidney dysfunction, or chronic abnormally elevated blood lipids. No blood donation or pregnancy for 3 years after therapy. Pregnancy category X.

CYCLOSPORINE: FDA-approved indications: TX of adult, nonimmunocompromised pts. with severe recalcitrant, plaque psoriasis who have failed at least one other systemic therapy or are contraindicated for other systemic therapies. Alone or in combination with MTX for severe active RA if patients fail MTX alone. Prophylaxis for organ rejection. Investigational uses: Acne rosacea, AIDS, alopecia, AML, aplastic anemia, asthma, atopic dermatitis, Crohn's disease, diabetes mellitus, hepatitis, leukemia, inflammatory bowel disease, multiple sclerosis, nephritic syndrome, myelodysplastic syndrome. Routine monitoring: Renal function tests and blood pressure every 2 weeks for 6 weeks, then monthly. Cholesterol and lipoprotein levels, serum electrolytes, signs/symptoms of infection. Special considerations: Rebound is rare but does occur with cyclosporine 6-16 weeks after discontinuation of therapy. Pregnancy category C. Continued use beyond 1 year not recommended. Should rotate use with other agents.

AZATHIOPRINE: FDA-approved indications: For management of severe RA, unresponsive to NSAIDs or DMARDs. For prevention of rejection in renal transplant patients. Investigational uses: Psoriasis, rejection in organ transplantation patients, ankylosing spondylitis, atopic dermatitis, hepatitis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, vasculitis. Routine monitoring: Monitor CBCs and platelets weekly for first month, then twice monthly for 2 months, then monthly. Special considerations: Pregnancy category D; temporary infertility in men.

HYDROXYUREA: FDA-approved indications: Treatment of tumors (melanoma, CML, ovarian, squamous cell carcinoma), sickle cell anemia. Investigational uses: Psoriasis, various malignancies, HIV. Routine monitoring: CBC with platelet count, renal function tests, LFTs. Special consideration: Pregnancy category D.

SULFASALAZINE: FDA-approved indications: Ulcerative colitis. For management of RA or juvenile RA unresponsive to NSAIDs. Investigational uses: Psoriatic arthritis and psoriasis, ankylosing spondylitis, multiple sclerosis, Crohn's disease, irritable bowel disease, scleroderma. Routine monitoring: CBC, LFTs every 2 weeks for 3 months, then periodic, renal function tests. Special consideration: Pregnancy category B.

AURANOFIN: FDA-approved indications: Treatment of RA unresponsive to NSAIDs. Investigational uses: Psoriatic arthritis, asthma. Routine monitoring: CBC with platelet count and urinalysis monthly. Special consideration: Pregnancy category C.

PENICILLAMINE: FDA-approved indications: Severe active RA, unresponsive to conventional therapies. TX of Wilson's Disease, cystinuria. Investigational uses: Psoriatic arthritis, acetaminophen poisoning, AML, ankylosing spondylitis, lead/mercury poisoning, schizophrenia.

(Continued on next page)
TABLE 12  Indications/Monitoring/Precautions for Agents for Psoriasis/Psoriatic Arthritis

ROUTINE MONITORING: CBC with platelet counts, urinalysis, and body temperature every 2 weeks for 6 months. LFT every 6 months. Special consideration: Pregnancy category D.

CHLOROQUINE: FDA-approved indications: Amebiasis, extraintestinal amebiasis, malaria-suppression and TX. Investigational uses: Psoriatic arthritis, cholera, lupus erythematosus, pneumonia, rheumatoid arthritis, sarcoidosis, ulcerative colitis. Routine monitoring: Eye function tests initially and then periodically thereafter. Special consideration: Pregnancy category C.


TABLE 13  Adult Dosing/Patent Issues

Alefacept: Administered under the supervision of a physician—15 mg IM or 7.5 mg IV bolus administered once weekly for 12 weeks. Following 12 weeks off treatment, another course can be administered if CD+ counts are within normal range. Data on courses beyond 2 are limited. Note: Based on study data, it is estimated that most patients may require 1.5 treatments per year depending on the patient's duration of response.

Efalizumab: Initial conditioning dose of 0.7 mg/kg SC followed by 1 mg/kg/week (maximum 200 mg/dose). Note: typically given continuously to prevent rebound/flare.

Etanercept: For psoriasis—50 mg twice weekly (administered 3 to 4 days apart) for 3 months, then the dose can be reduced to 50 mg once weekly. The 25 mg and 50 mg once-weekly doses were also found to be efficacious, but response rates were related to dose. For psoriatic arthritis—50 mg/wk SC.

Infliximab: Not FDA-approved for psoriasis or psoriatic arthritis.

Methotrexate: For psoriasis—10 mg to 25 mg once weekly, can be titrated by 2.5 mg/week up to 30 mg/week.

Acitretin: For psoriasis—25 mg to 50 mg/day as single dose with a main meal. Maintenance doses of 25 mg to 50 mg/day can be used based on response to initial therapy. Decrease dose of phototherapy if used in combination with acitretin.

Cyclosporine (modified): 2.5 mg/kg/day (as 2 divided doses 1.25 mg/kg) for 4 weeks, can be titrated to response (and as tolerated) as increase of 0.5 mg/kg/day every 2 weeks to maximum of 4 mg/kg/day.

Azathioprine: Not FDA-approved for psoriatic arthritis. Doses used in studies for psoriatic arthritis: 3 mg/kg/day.

Sulfasalazine: Not FDA-approved for psoriatic arthritis. Doses used in studies for psoriatic arthritis: initiated at 500 mg/day then titrated up to 2 grams/day.

PATENT ISSUES: Because of the complexity of producing biologic proteins, the potential for immunogenicity, safety concerns, and the ability to produce therapeutically equivalent generic products, it is unclear when or if generic biologic agents will become available. The FDA is currently reviewing and monitoring: therapeutically equivalent generic products, it is unclear when or if generic biological agents may be approved for the treatment of psoriatic arthritis.

An additional consideration is the high cost of the biologic agents in comparison with conventional therapies used to treat psoriasis. The overall value of these agents in treating this chronic relapsing and remitting condition must be considered when selecting appropriate therapy. The biologic agents would best be used in patients with moderate-to-severe psoriasis who have failed or are not candidates for other systemic therapies. (See Table 14).

First-line treatment of psoriatic arthritis focuses on the use of NSAIDs, particularly for patients with mild disease activity. It should be noted that the use of NSAIDs may exacerbate psoriasis. Patients with more severe disease who are unresponsive to NSAID therapy should be treated with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and cyclosporine. Intra-articular injections of corticosteroids may be used concomitantly when patients with limited disease in only one or two joints, but systemic use of corticosteroids is not recommended. For patients unable to tolerate DMARDs, biologic agents, such as etanercept and infliximab, are efficacious and safe. For patients with psoriatic arthritis with spinal involvement such as spondyloarthritis, biologic agents may be used more as a first-line therapy compared with other forms such as DIP, symmetric disease, or asymmetric disease, which primarily affects joints in the hands and feet.
However, safety and efficacy of the biologic agents in the long-term treatment of psoriatic arthritis are not available.

**Author's Note:** As part of the formulary review process, we provide P&T committee members with a summary of available data on the agents under review (see Table 15, page 52) in addition to the full clinical monograph. This table is designed to highlight key points pertinent to the decision criteria the committee uses to decide product formulary status, including effectiveness and efficacy outcomes, safety, and clinical attributes. Cost is considered only if all other decision criteria are similar and it provides a differentiation point in determining the value of the products under review.

**ACKNOWLEDGMENTS**

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**DISCLOSURES**

No outside funding supported this study. The author discloses no potential bias or conflict of interest relating to this article.

**REFERENCES**


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### TABLE 15 Summary of Available Data

<table>
<thead>
<tr>
<th>Decision Criteria</th>
<th>Alefacept (Amevive)</th>
<th>Efalizumab (Raptiva)</th>
<th>Etanercept (Enbrel)</th>
<th>Other Systemic Therapies: Methotrexate, Soriatane (Acitretin), Cyclosporine</th>
</tr>
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<tr>
<td><strong>Effectiveness outcomes</strong></td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Yes—Methotrexate (MTX)—psoriasis: (PASI90 by 40% of pts., PASI75 by 60% of pts.), similar to cyclosporine, better than biologics; psoriatic arthritis: significant improvements in disease activity, and patient and physician assessments of disease. Cyclosporine—psoriasis: (PASI90 by 33% of pts., PASI75 by 71% of pts.) similar to MTX, better than biologics, slow onset of effects (discontinue if satisfactory response not observed by 6 weeks at dose of 4 mg/kg/day); psoriatic arthritis: significant improvements in disease activity, and patient and physician assessments of disease, better than sulfasalazine. Soriatane—increases efficacy of PUVA in combination with 96% clearance rates, 56% as monotherapy, FDA-approved for psoriasis; not FDA-approved for psoriasis/psoriatic arthritis. Sulfasalazine and azathioprine—psoriatic arthritis: some data from small trials show positive results, but systematic reviews show efficacy of both agents compared with placebo; slow onset of effects; psoriasis: azathioprine has not been extensively studied in psoriasis and sulfasalazine is not used for this indication. No—Penicillamine (psoriatic arthritis—very limited data), chloroquine/hydroxychloroquine (limited to small studies in psoriatic arthritis [&lt;30 pts.]), hydroxyurea (psoriasis—small studies), auranofin (limited data with some data from small studies showing efficacy for psoriatic arthritis), infliximab (psoriasis/psoriatic arthritis, limited studies published to fully evaluate).</td>
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<tr>
<td><strong>Efficacy outcomes</strong></td>
<td>Delayed onset of effects with full effects not seen until 8 weeks after treatment period; slightly lower efficacy than Raptiva</td>
<td>Long duration of response (7 months, higher with second treatment) DOE—21% pts. achieved PASI75 at 14 weeks (NNT = 6) POE—significant improvements in DLQI and DQOLS noted starting at 12 weeks</td>
<td>Rapid onset of effects compared with Amevive; slightly higher efficacy than Amevive Duration of response is shorter than Amevive (9-10 weeks vs. 7 months); requires continuous dosing to maintain effects DOE—27% pts. achieved PASI75 at 12 weeks (NNT = 4) POE—significant improvements in DLQI starting at 4 weeks</td>
<td>Psoriatic arthritis—Efficacy as monotherapy DOE—(ACR20, ACR50 NNT = 2) improves QOL POE—decreases signs and symptoms of disease as measured by ACR response rates and improvement in QOL measures Psoriasis—At 50 mg, twice-weekly or step-down dosing, appears more efficacious than Amevive or Raptiva At 25 mg, twice-weekly dosing, efficacy similar to Raptiva DOE—PASI75, PASI50; (NNT = 4-5) POE—significant improvements in QOL at 24 weeks</td>
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<tr>
<td><strong>Safety</strong></td>
<td>No long-term safety data Must monitor CD4 counts weekly during therapy Pregnancy category B No rebound/flare reported with discontinuation, similar efficacy achieved after readministration</td>
<td>Safety data up to 5 years No rebound or flare noted after discontinuation (ARI=2.7% vs. placebo; NNH=37); must give continuously to maintain efficacy Monitor for thrombocytopenia monthly Pregnancy category C</td>
<td>Safety data up to 5 years No rebound or flare noted after discontinuation, in preliminary studies Primarily injection site reactions; bold warning on serious infection and TB risk Demyelinating effects possible; increased risk of lymphoma may exist with all TNF inhibitors May worsen CHF; caution; patients must dilute multidose vial, which contains 2 doses and is stable for 14 days Safety at 50 mg twice weekly, used in psoriasis; not fully studied Pregnancy category B</td>
<td>Many years of use, thus most toxicities and monitoring requirements are known for these agents. Long-term toxicities are associated with these agents, thus they are usually used in a rotational/sequential or intermittent method to avoid long-term toxicities. MTX—hepatotoxicity (liver biopsy every 1.5 to 3 years with continued long-term use), requires monitoring, often used in rotation/sequential pattern (low-dose intermittent therapy) alternating with other agents to avoid cumulative toxicities. Highly teratogenic. Cyclosporine—duration of response is about 6 weeks, rebound/flare has rarely been observed. Continued use beyond 1 year not recommended. Hypertension, renal toxicity: Rotation with other agents used to decrease cumulative toxicity. Acitretin—may worsen psoriasis initially, mucocutaneous reactions, hepatotoxic, increases lipids. Monitor lipids and liver function tests every 2 weeks for 6-8 weeks. Azathioprine—black box warning regarding increased risk of neoplasia with long-term use. Monitor CBC and platelets weekly for first month, then twice monthly for 2 months, then monthly. Most agents can cause hematologic and hepatotoxic abnormalities and require regular monitoring. Sulfasalazine is pregnancy category B, all others are C-X</td>
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### TABLE 15  Summary of Available Data

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<tr>
<th>Decision Criteria</th>
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<tbody>
<tr>
<td><strong>Clinical attributes</strong></td>
<td>Psoriasis—long remission rates of approximately 7 months noted, higher following 2 courses of therapy, Administered IM, but not patient-administered, Administered once weekly for 12 weeks, then off for 12 weeks</td>
<td>Psoriasis—rapid onset of effects, Administered SC by patient; distributed through specialty pharmacies only</td>
<td>Psoriasis—Administered SC by patient; distributed through specialty pharmacies only</td>
<td>MTX, cyclosporine, and acitretin are FDA-approved for the treatment of severe psoriasis. MTX can be used alone or in combination with topicals (decreased dose needed). All are administered orally and can be administered in sequential or rotational pattern for maintenance and to decrease toxicities. All agents, except acitretin, are approved and primarily used for other indications/disease states.</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>More than traditional agents, similar to Raptiva</td>
<td>More than traditional agents, similar to Amevive</td>
<td>More than NSAIDs and DMARDs for psoriatic arthritis, less than Amevive and Raptiva at traditional doses (50 mg once weekly), but higher, if administered at higher doses (50 mg BIW or step-down dose); the step-down dose is the approved dose for psoriasis</td>
<td>Less than biologics, generics least expensive</td>
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</table>

CBC = complete blood count; CHF = congestive heart failure; DLQI = Dermatology Life Quality Index; DMARDs = disease-modifying antirheumatic drugs; DOE = disease-oriented evidence; DQOL = dermatology quality of life; FDA = U.S. Food and Drug Administration; IM = intramuscular; MTX = methotrexate; NNH = number needed to harm; NNT = number needed to treat; NSAIDs = nonsteroidal anti-inflammatory drugs; PASI = Psoriasis Area Severity Index; POE = patient-oriented evidence; Pts. = patients; PUVA = psoralen plus ultraviolet A light; QOL = quality of life; RA = rheumatoid arthritis; SC = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor.


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56. Gladman DD. Treatment of psoriatic arthritis. Up-To-Date online database 11.3; 2003 (expired February 2004).


73. Finlay AY, Salek MS, Haney J, for the Alefacept Clinical Study Group.


