Biologics in the management of psoriasis

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Abstract: Psoriasis is a chronic inflammatory systemic disease for which there exist topical, ultraviolet, systemic, and biologic treatments. Biologic agents selectively interfere with the immune mechanisms responsible for psoriasis. Etanercept, infliximab, and adalimumab target tumor necrosis factor-alpha and have demonstrated efficacy in the treatment of psoriasis and psoriatic arthritis. Alefacept and efalizumab target T lymphocytes, are effective in the treatment of psoriasis, but are not approved for psoriatic arthritis. Finally, ustekinumab and ABT-874 target interleukin-12 and interleukin-23, and they have demonstrated efficacy in the treatment of psoriasis. The objective of this review is to present efficacy and safety data from randomized controlled trials of the biologic agents in the treatment of psoriasis.

Keywords: biologics, psoriasis, tumor necrosis factor, interleukin-12/23

Introduction
Psoriasis is a chronic inflammatory systemic disease which affects approximately 1% to 3% of the world’s population,¹ and it is the most prevalent immune-mediated skin disease in adults.² Psoriasis can have significant physical, psychological, and economic impacts on patients, leading to reduced quality of life,³–⁹ especially for patients with severe disease.¹⁰ Approximately 25% of patients have moderate to severe psoriasis.¹¹ Additionally, individuals with psoriasis have increased incidence of other chronic disorders including metabolic syndrome, coronary artery disease, diabetes mellitus, hypertension, fatigue, and depression.¹²–¹⁵

Depending on the study, between 5% and 42% of psoriasis patients develop psoriatic arthritis (PsA).¹⁶ PsA, once considered a benign arthropathy, is in fact a severe disease. A growing body of literature suggests that PsA is often progressive and is associated with accelerated mortality, substantial morbidity, and impaired quality of life.¹⁷,¹⁸

Conventional systemic treatments for moderate to severe psoriasis, including phototherapy with ultraviolet B (UVB), photochemotherapy with psoralens and ultraviolet A (PUVA), methotrexate, cyclosporine, and acitretin are limited by well-known and characteristic side effects, incomplete effectiveness in some patients, and demanding treatment schedules which result in decreased patient compliance.¹⁹ Likewise, treatment of moderate to severe PsA with conventional disease modifying anti-rheumatic drugs (DMARDs) has not uniformly been shown to have efficacy, especially in treating cutaneous symptoms.²⁰–²³ A meta-analysis of published randomized controlled trials (RCTs) on DMARDs found that only parenteral high-dose methotrexate
and sulfasalazine had efficacy in PsA,24 while another trial showed moderate efficacy of leflunomide in PsA.25

The biologic agents have greatly increased the treatment choices for patients with moderate to severe psoriasis as well as those with moderate to severe PsA. The biologics used in treating psoriasis and PsA may be categorized as those inhibiting tumor necrosis factor-alpha (TNF-α) (ie, etanercept, infliximab, adalimumab), those inhibiting T cells (ie, efalizumab, alefacept), and those that block interleukin-12 and interleukin-23 (IL-12/23) (ie, ustekinumab, ABT-874).

Biologic agents should be used with caution, as robust, long-term data in psoriasis are not yet available. Physicians must continue to monitor for long-term adverse events such as chronic immunosuppression, which may lead to increased risks of infection and malignancy.2 It is also important to consider the high cost of biologic agents and the patient selection criteria used thus far in clinical trials and other studies.26 Before initiating therapy with a biologic agent, patients must be screened (Table 1) to ensure that they are appropriate candidates and to minimize adverse events.

### Role of TNF-α in psoriasis

TNF-α is a pro-inflammatory cytokine that is a member of a growing family of cytokines known as the TNF superfamily.27 Binding of TNF-α to its receptors induces downstream signaling that ultimately augments the expression of pro-inflammatory genes.27,28 TNF-α has numerous effects important in the pathogenesis of psoriasis and PsA. TNF-α production and activity are elevated in lesional psoriatic skin compared with non-lesional psoriatic skin and non-psoriatic skin.29–32 TNF-α production and activity have also been shown to be higher in non-lesional psoriatic skin than non-psoriatic skin.30 Furthermore, serum TNF-α levels are higher in individuals with psoriasis than those without it.33,34 and synovial fluid TNF-α levels are higher in individuals with PsA.35–37 Lesional and serum TNF-α levels correlate with psoriasis disease severity as measured by the psoriasis area and severity index (PASI)35 score. With effective therapy and clinical improvement, psoriasis patients exhibit decreased levels of lesional skin and serum TNF-α.33–39

### Etanercept

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding domain of the human TNF-α receptor fused to the constant fragment (Fc domain) of human immunoglobulin G1 (IgG1).27 It is currently approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe psoriasis, moderate to severe PsA, adult rheumatoid arthritis, juvenile rheumatoid arthritis in patients as young as 4 years old, and ankylosing spondylitis. Etanercept is administered via subcutaneous injection (SC), and the FDA-approved regimen for psoriasis is 50 mg twice weekly (BIW) for 12 weeks followed by 50 mg weekly (QW) thereafter. Although numerous clinical trials have been conducted with etanercept 25 mg BIW,40–42 recent studies have shown etanercept 50 mg QW to have comparable efficacy, safety, and pharmacokinetic profiles, with improved convenience.43,44 In a study in which subjects were treated with etanercept 50 mg BIW for 12 weeks followed by 12 weeks of etanercept 25 mg BIW, 77% of subjects maintained response despite dose reduction.45 For PsA, the dosing regimen is 25 mg BIW or 50 mg QW, and etanercept is often used in combination with methotrexate.

Improvement in PsA may be noticeable as soon as 2 weeks after starting treatment, while skin improvement is usually slower.46 In one trial, improvements in psoriasis were observed for up to 96 weeks with continuous etanercept therapy, with a peak in response after 48 weeks of treatment.47 Nevertheless, etanercept loses efficacy over time in some patients, possibly due to the development of antibodies. In one open-label trial, clinical response was maintained in a higher proportion of psoriasis patients treated with continuous rather than as-needed etanercept therapy;48 however, the trial only examined one round of re-treatment, and patients in the continuous group received more total medication. Patients do not typically experience rebound psoriasis after etanercept is discontinued.45,48,49

In contrast to infliximab and adalimumab, etanercept is able to bind to both TNF-α and lymphotoxin-α

### Table 1 Recommended actions before initiating biologic therapy for psoriasis and psoriatic arthritis

| Age appropriate history |
| Physical examination |
| Current medication list |
| Baseline laboratory tests |
| Liver function tests |
| Complete blood cell count, including platelet count |
| Hepatitis panel |
| Tuberculosis skin test (PPD) |
| Urine pregnancy test |
| Ensure up-to-date status in standard vaccinations, including pneumococcal, hepatitis A and B, influenza, tetanus-diphtheria |

**Abbreviation:** PPD, purified protein derivative.
(TNF-β), although the clinical significance of its binding to lymphotoxin-α is unknown. Since etanercept has two binding sites for TNF-α, it binds TNF-α with greater affinity than do natural monomeric receptors. Consequently, etanercept competitively inhibits membrane-associated and soluble TNF-α from binding its natural receptors and inducing downstream signal transduction, resulting in a decrease in inflammatory activity.

Although excessive TNF-α contributes to the pathogenesis of psoriasis and PsA, a physiological level of TNF-α is important in protecting the body against opportunistic infection and malignancy. Hence, TNF-α antagonists should be administered in doses within the therapeutic window, reducing systemic and local TNF-α levels to within physiologically normal ranges but not so low as to lead to adverse events. Unlike infliximab and similar to adalimumab, the combination of slow absorption rate following SC administration, slow elimination rate, and appropriate dosing frequency give etanercept a smooth and uniform concentration-time profile, minimizing the occurrence of overexposure and resultant adverse events, as well as underexposure and consequent symptom recurrence.

Obesity, defined as body mass index (BMI) greater than or equal to 30 kg/m², is on the rise. Recent studies have demonstrated higher prevalence of obesity and overweight in individuals with psoriasis than those without psoriasis. Obese patients also tend to have more severe psoriasis than those with psoriasis who are not obese. Additionally, some conditions associated with obesity, such as nonalcoholic fatty liver disease, are relative contraindications to systemic treatments for psoriasis.

Etanercept is administered via a fixed-dose regimen that is not dependent on the patient’s weight. Gordon et al performed subgroup analyses of data pooled from three large clinical trials. Among all subjects receiving etanercept, a 75% or greater reduction in the psoriasis area and severity index score (PASI 75 response) was achieved by 47% of subjects weighing less than and 33% of those weighing greater than the median weight (89.36 kg). Strober et al conducted a subgroup analysis of a phase III trial where 618 patients were randomized to receive etanercept 50 mg SC BIW or placebo. “Superior response” was defined as PASI 90 response at 3 or more visits, and “sub-optimal response” was defined as failure to attain at least PASI 50 response at 3 or more visits. Superior response was achieved by 41% of normal-weight subjects and 15% of extremely obese (BMI ≥ 40) subjects. Sub-optimal response was reported in only 9% of normal-weight patients, compared to 27% of extremely obese patients. These results suggest that normal-weight patients have a greater response to etanercept than heavier patients and support the idea of using etanercept less frequently in the most overweight patients. Interestingly, recent reports suggest that treatment with the TNF-α inhibitors, but not with efalizumab or methotrexate, may lead to weight gain.

There have been a number of clinical trials assessing the efficacy and safety of etanercept in treating psoriasis and PsA (Table 2) as well as demonstrating improvement in dermatology-related quality of life. Furthermore, etanercept is the only biologic agent that has data in pediatric and adolescent psoriasis patients, and it has demonstrated efficacy and safety in this patient population.

The most common adverse events (AEs) with etanercept use are injection site reaction and infection. Other common AEs include fever, headache, mild allergic reaction, and pruritus. There exist rare reports of anaphylaxis, angioedema, exacerbation of or new-onset congestive heart failure (CHF), cytopenia, increased liver function tests (LFTs), leukocytoclastic vasculitis, lupus erythematosus syndrome, malignancy (eg, Hodgkin’s lymphoma, cutaneous T-cell lymphoma (CTCL), nonmelanoma skin cancer [NMSC]), multiple sclerosis (MS) or other demyelinating disease, sepsis, severe infection (eg tuberculosis [TB]), and urticaria. The incidence of AEs, serious adverse events (SAEs), and infection occurring in clinical trials of etanercept is summarized in Table 2.

Contraindications for etanercept use include chronic, active, serious, and recurrent infection, active TB, latent TB in the absence of chemoprophylaxis, hepatitis B, MS and other demyelinating disease, a first-degree relative with MS, New York Heart Association (NYHA) class III or IV CHF, pregnancy or lactation, and hypersensitivity to etanercept or its ingredients. During treatment with etanercept, patients should avoid live and live-attenuated vaccines. Table 3 lists monitoring recommendations for all TNF-α inhibitors. Note that most safety information about TNF-α inhibitors is derived from studies of their use in rheumatoid arthritis and inflammatory bowel disease.

**Infliximab**

Infliximab is a chimeric TNF-α monoclonal antibody consisting of the human constant and mouse variable regions of the IgG antibody. It is currently FDA-approved for treating severe psoriasis, moderate to severe PsA, adult rheumatoid arthritis, ankylosing spondylitis, adult and pediatric Crohn’s disease, and ulcerative colitis. Infliximab is administered via intravenous infusions (IV) which span
Table 2 Clinical trials of biologic agents for chronic plaque psoriasis

<table>
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<tr>
<th>Lead author, journal</th>
<th>Design</th>
<th>N</th>
<th>Dose, route, frequency</th>
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<td><strong>Etanercept</strong></td>
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<tr>
<td>Gottlieb, Arch 4-6</td>
<td>R, DB, PC, MC</td>
<td>112</td>
<td>Weeks 0–24: 25 mg vs placebo SC BIW</td>
<td>Week 12 PASI 75: etanercept 25 mg BIW: 30% placebo: 2%</td>
<td>SAE: Similar incidence between groups. No SAE considered related to drug. AE: Similar incidence between groups. Infection: URI more common in etanercept (35%) than placebo (20%).</td>
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<tr>
<td>Leonardi, NEJM 42</td>
<td>R, DB, PC, MC</td>
<td>652</td>
<td>Weeks 0–24: 30 mg SC BIW vs 25 mg SC BIW vs 25 mg SC QW vs Weeks 0–12: placebo + Weeks 13–24: 25 mg SC BIW</td>
<td>Week 12 PASI 75: etanercept 50 mg BIW: 49% etanercept 25 mg BIW: 34% etanercept 25 mg QW: 14% placebo: 4%</td>
<td>SAE: Not reported. AE: Similar incidence between groups. Most were mild-moderate. Infection: Similar incidence between groups.</td>
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<tr>
<td>Papp, Br J Derm 45</td>
<td>R, DB, PC, MC</td>
<td>583</td>
<td>Weeks 0–12: 25 vs 50 mg vs placebo SC BIW Weeks 13+: OL extension 25 mg SC BIW</td>
<td>Week 12 PASI 75: etanercept 50 mg BIW: 49% etanercept 25 mg BIW: 34% placebo: 3%</td>
<td>SAE: Incidence by treatment group not reported. Total N = 12 in first 12 weeks. AE: Similar incidence between groups. Most were mild-moderate. Infection: Similar incidence between groups.</td>
</tr>
<tr>
<td>Tyring, Lancet 61</td>
<td>R, DB, PC, MC</td>
<td>618</td>
<td>Weeks 0–12: 50 mg vs placebo SC BIW Weeks 13+: OL extension (50 mg SC BIW)</td>
<td>Week 12 PASI 75: etanercept 50 mg BIW: 47% placebo: 5%</td>
<td>SAE: Similar incidence between groups. AE: More patients on etanercept (11%) than placebo (1%) had ≥1 injection site reaction. All other AE similar incidence between groups. Infection: More patients on etanercept (28%) than placebo (23%) had ≥1 infection.</td>
</tr>
<tr>
<td>Paller, NEJM 65</td>
<td>R, DB, PC, MC</td>
<td>211</td>
<td>In subjects 4–17 years old Weeks 0–12: 0.8 mg/kg (max 50 mg) vs placebo SC QW Weeks 13–35: OL extension Weeks 36–48 withdrawal re-treatment period</td>
<td>Week 12 PASI 75: etanercept 0.8 mg/kg QW: 57% placebo: 11%</td>
<td>SAE: No SAE in placebo-controlled phase. AE: Similar rate of AE between groups. Most were mild-moderate. Infection: Similar rate of infection between groups.</td>
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### Infliximab

**Gottlieb, JAAD**

R, DB, PC, MC  

249  

Weeks 0, 2, 6:  

3 vs 5 mg/kg vs placebo IV  

Week 10 PASI 75:  

- infliximab 5 mg/kg: 88%  
- infliximab 3 mg/kg: 72%  
- placebo: 6%  

**SAE:** All in infliximab (6%) of which 33% considered “reasonably related” to drug. 

**AE:** More patients on infliximab (78%) than placebo (63%) reported ≥1 AE. 

**Infection:** One serious infection in infliximab group; none in placebo.

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**Reich, Lancet**

R, DB, PC, MC  

378  

Weeks 0, 2, 6, then Q8W:  

5 mg/kg IV vs Weeks 0–22: placebo  

+ Weeks 24, 26, 30, then Q8W:  

- infliximab 5 mg/kg IV  

Week 10 PASI 75:  

- infliximab 5 mg/kg: 80%  
- placebo: 3%  

**Week 24 PASI 75:**  

- infliximab 5 mg/kg: 82%  
- placebo: 4%  

**SAE:** Higher incidence in infliximab (6%) than placebo (3%). 

**AE:** More patients on infliximab (82%) than placebo (71%) reported ≥1 AE. 

**Infection:** Similar incidence between groups.

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**Menter, JAAD**

R, DB, PC, MC  

835  

Weeks 0, 2, 6: 3 mg/kg vs 5 mg/kg vs placebo IV  

Week 14 re-randomize: continuous infliximab 3 vs 5 mg/kg Q8W or infliximab only when <PASI 75 vs placebo crossover to 5 mg/kg  

Week 10 PASI 75:  

- infliximab 5 mg/kg: 76%  
- infliximab 3 mg/kg: 70%  
- placebo: 2%  

Week 26 PASI 75:  

- infliximab 3 mg/kg Q8W: 65%  
- infliximab 3 mg/kg as needed: 42%  
- infliximab 5 mg/kg Q8W: 78%  
- infliximab 5 mg/kg as needed: 58%  

**SAE:** Similar incidence between groups. 

**AE:** More patients on infliximab 3 mg/kg (63%) and 5 mg/kg (69%) than placebo (56%) reported ≥1 AE. 

**Infection:** Similar incidence between groups. Two cases tuberculosis in infliximab-treated patients.

### Adalimumab

**Gordon, JAAD**

R, DB, PC, MC  

147  

Weeks 0–1: 80 mg SC QW + Weeks 2–60: 40 mg SC QW vs Week 0: 80 mg SC + Weeks 1–60: 40 mg SC EOW vs Weeks 0–1: placebo + Week 12: 80 mg SC + Weeks 13–60: 40 mg SC EOW  

Week 12 PASI 75:  

- adalimumab QW: 80%  
- adalimumab EOW: 53%  
- placebo: 4%  

**SAE:** Higher incidence in adalimumab 40 mg QW (8%) vs 40 mg EOW (2%) vs placebo (0%). 

**AE:** Similar incidence between groups. Most were mild–moderate, unrelated. 

**Infection:** Similar incidence between groups.

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**Menter, JAAD**

R, DB, PC, MC  

1212  

Weeks 0–15 (RCT): placebo vs 80 mg SC × 1 then 40 mg SC EOW + Weeks 16–33 (OL): 40 mg SC EOW (if PASI 75) + Weeks 34–50 (RCT): 40 mg SC EOW vs placebo (if PASI 75)  

Week 16 PASI 75:  

- adalimumab: 71%  
- placebo: 7%  

**Week 33–52 loss of response:**  

- placebo: 28%  
- continuous adalimumab: 5%  

**SAE:** Similar incidence between groups. 

**AE:** Higher in adalimumab (62%) than placebo (56%). Most were mild–moderate. 

**Infection:** Higher in adalimumab (29%) than placebo (22%).

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**Saurat, Br J Derm**

R, DB, PC, MC  

271  

Weeks 0–16: 80 mg SC × 1 then 40 mg EOW vs methotrexate 7.5–25 mg po QW vs placebo  

Week 16 PASI 75:  

- adalimumab: 80%  
- methotrexate: 36%  
- placebo: 1%  

**SAE:** Similar incidence between groups. 

**AE:** Similar incidence between groups. 

**Infection:** Similar incidence between groups.

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Table 2 (Continued)

<table>
<thead>
<tr>
<th>Lead author, journal</th>
<th>Design ¹</th>
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<th>Efficacy ⁴</th>
<th>Safety ⁵</th>
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<td><strong>Alefacept</strong></td>
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<td>Ellis, NEJM ⁶</td>
<td>R, DB, PC, MC</td>
<td>229</td>
<td>Weeks 0–12: 0.025 mg/kg vs 0.075 mg/kg vs 0.150 mg/kg vs placebo QW</td>
<td>Week 14 PASI 75: alefacept 0.150 mg/kg: 31% alefacept 0.075 mg/kg: 33% alefacept 0.025 mg/kg: 21% placebo: 10%</td>
<td>SAE: None related to alefacept. AE: Acute injury, dizziness, nausea, chills, cough each ≥5% more common in alefacept than placebo. Infection: Similar incidence between groups.</td>
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<tr>
<td>Krueger, JAAD ⁷</td>
<td>R, DB, PC, MC</td>
<td>533</td>
<td>7.5 mg vs placebo 12-week courses</td>
<td>1st course PASI 75: alefacept 7.5 mg IV QW: 28% placebo: 8% 2nd course PASI 75: alefacept 7.5 mg IV QW: 37% placebo: 19%</td>
<td>SAE: None related to alefacept. AE: Chills more common with alefacept (10% vs 1%), most within 24 hours of dose, limited to 1st and 2nd dose. Infection: Similar incidence between groups.</td>
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<tr>
<td>Lebwohl, Arch ⁸</td>
<td>R, DB, PC, MC</td>
<td>507</td>
<td>Weeks 0–12: 15 mg vs 10 mg vs placebo IM QW</td>
<td>PASI 75: alefacept 15 mg: 33% alefacept 10 mg: 28% placebo: 13%</td>
<td>SAE: Similar incidence between groups. AE: Similar incidence between groups. Infection: Higher in alefacept (15%) than placebo (11%); not significant.</td>
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<tr>
<td>Krueger, JDT ⁹</td>
<td>MC, OL A-49 B-340 C-203</td>
<td>Up to three 12-week courses of 15 mg IM QW + other therapy: ~33% none ~33% topical ~33% systemic or UVB</td>
<td>PGA “mild” or better (MOB): 1st course: 30% 2nd course: 38% 3rd course: 40% PGA MOB across all courses: alefacept 15 mg IM QW: 31–48% alefacept + topical: 33–45% alefacept + UVB: 29–50%</td>
<td>SAE: Similar incidence between groups. AE: Similar incidence between groups. Infection: No increased risk of infection over multiple courses of treatment.</td>
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<td><strong>Efalizumab</strong></td>
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<tr>
<td>Lebwohl, NEJM ¹¹</td>
<td>R, DB, PC, MC</td>
<td>597</td>
<td>Weeks 0–12: 1 vs 2 mg/kg vs placebo SC QW Weeks 13–24: PASI 50: 2 mg/kg SC QW vs EOW vs placebo</td>
<td>Week 12 PASI 75: efalizumab 2 mg/kg QW: 28% efalizumab 1 mg/kg QW: 22% placebo: 5% Week 24 PASI 75: PASI 50 at week 12: efalizumab 2 mg/kg QW: 64%</td>
<td>SAE: Similar incidence between groups. AE: Acute AE (HA, pain, F/C) more common in efalizumab 1st and 2nd dose. Most mild–moderate. Infection: Similar incidence between groups.</td>
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<td>Reference</td>
<td>Authors</td>
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<td>Year</td>
<td>Study Design</td>
<td>Treatment</td>
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<td>Gordon, JAMA 56</td>
<td>R, DB, PC, MC</td>
<td>556</td>
<td>2006</td>
<td>Weeks 0–12: placebo vs efalizumab 0.7 mg/kg SC x 1 then 1 mg/kg SC QW</td>
<td>efalizumab 4 mg/kg QW: 13% placebo: 2%</td>
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<tr>
<td>Menter, Arch 157</td>
<td>MC, OL</td>
<td>516</td>
<td>2007</td>
<td>Efalizumab 2 mg/kg EOW: 52% placebo: 12%</td>
<td>efalizumab 4 mg/kg QW: 13% placebo: 2%</td>
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<tr>
<td>Leonardi, JAAD 105</td>
<td>R, DB, PC, MC</td>
<td>498</td>
<td>2007</td>
<td>PASI 50: 4 mg/kg vs placebo SC QW</td>
<td>PASI 50 at week 12: efalizumab 4 mg/kg QW: 13% placebo: 2%</td>
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<tr>
<td>Papp, Int J Derm 144</td>
<td>R, DB, PC, MC</td>
<td>686</td>
<td>2009</td>
<td>Re-randomize efalizumab-treated subjects with PASI 75</td>
<td>PASI 75 (patients with week 12 &lt;PASI 75): efalizumab 2 mg/kg: 20% efalizumab 1 mg/kg: 21% placebo: 7%</td>
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<tr>
<td>Dubertret, Br J Derm 145</td>
<td>R, DB, PC, MC</td>
<td>793</td>
<td>2009</td>
<td>Weekly: 0–12: placebo vs 0.7 mg/kg SC x 1 then 1 mg/kg SC QW</td>
<td>Week 12 PASI 75: efalizumab 2 mg/kg: 27% placebo: 2%</td>
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<td>Ustekinumab</td>
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<td>Krueger, NEJM 134</td>
<td>R, DB, PC, MC</td>
<td>320</td>
<td>2009</td>
<td>Ustekinumab 45 vs 90 mg SC x 1 (week 0) vs 45 vs 90 mg SC QW (weeks 0–4) vs placebo</td>
<td>Week 12 PASI 75: ustekinumab 90 mg QW x 4: 81% ustekinumab 45 mg QW x 4: 67% ustekinumab 90 mg x 1: 59% ustekinumab 45 mg x 1: 52% placebo: 2%</td>
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<tr>
<td>Leonardi, Lancet 137</td>
<td>R, DB, PC, MC</td>
<td>766</td>
<td>2009</td>
<td>Ustekinumab 90 mg: 66% ustekinumab 45 mg: 67% placebo: 3%</td>
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Table 2 (Continued)

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<tr>
<th>Lead author, journal</th>
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<td>Papp, Lancet(^{24})</td>
<td>R, DB, PC, MC</td>
<td>1230</td>
<td>45 vs 90 mg SC vs placebo at weeks 0, 4 then Q12W. Placebo crossover at week 12</td>
<td>Week 28 PASI 75: ustekinumab 90 mg: 79%; ustekinumab 45 mg: 71%; crossover to 90 mg: 85%; crossover to 45 mg: 66%</td>
<td>SAE Similar incidence between groups. AE Similar incidence between groups. Infection: Similar incidence between groups.</td>
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<td>ABT-874</td>
<td>R, DB, PC, MC</td>
<td>180</td>
<td>200 mg SC QW vs 200 mg SC EOW vs 200 mg SC QW × 4 vs 100 mg SC EOW vs 200 mg SC × 1</td>
<td>Week 12 PASI 75: ABT-874 200 mg QW: 90%; ABT-874 200 mg EOW: 93%; ABT-874 200 mg × 4: 90%; ABT-874 100 mg EOW: 93%; ABT-874 200 mg × 1: 63% placebo: 3%</td>
<td>SAE Similar incidence between groups. AE Significantly more AE at least &quot;possibly related to study drug&quot; in all ABT-874 groups than placebo; most were injection site reactions. Infection: Similar incidence between groups.</td>
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Notes:
- R, randomized; DB, double-blind; PC, placebo-controlled; MC, multi-center; OL, open-label.
- SC, subcutaneous; IV, intravenously; IM, intramuscular; QW, once weekly; BIW, twice weekly; TIW, three times weekly; QXW, every X weeks.
- PASI, psoriasis area and severity index; PASI X, X % or greater decrease in PASI score; PGA, physician's global assessment; re-tx, retreatment.
- SAE, serious adverse event; URI, upper respiratory tract infection; HA, headache; FC, fever/chills.
Clinical responses are better and patients are less likely to develop antibodies against infliximab if they are treated concurrently with methotrexate to help maintain infliximab’s efficacy over time; this may be due to a reduction in the formation of antibodies.69 Another meta-analysis found infliximab to have superior efficacy for treating moderate to severe psoriasis than adalimumab, etanercept, efalizumab, alefacept, methotrexate, cyclosporine, acitretin, and fumaric acid ester.74

Loss of efficacy may occur over time with infliximab treatment, especially in patients who do not achieve stable infliximab serum concentrations.75 This loss of efficacy may be due to the development of anti-chimeric antibodies. Clinical responses are better and patients are less likely to develop antibodies against infliximab if they are treated continuously rather than as-needed.72 Low-dose methotrexate or other immunosuppressive agents are sometimes prescribed concurrently with infliximab to help maintain infliximab’s efficacy over time; this may be due to a reduction in the formation of antibodies.76

Infliximab binds to and neutralizes soluble and membrane-bound TNF-α with high specificity, affinity, and avidity, thereby decreasing inflammation.77 It is even able to inactivate TNF-α bound to TNF receptors.11 The infliximab/TNF-α complex is much more stable than the etanercept/TNF-α complex.78

The IV administration of infliximab, along with its long elimination half-life, significant loading doses (630 to 2100 mg administered within 6 weeks for a 70-kg patient), and relatively high maintenance doses (210 to 700 mg for a 70-kg patient) create concentration-time profiles with very high peaks and low troughs.52,73 Although this pharmaco-kinetic profile is not the most desirable one, the high efficacy rates of infliximab may balance these effects.

Unlike etanercept and adalimumab, infliximab dosing is weight-based. In a subgroup analysis of 1462 subjects in three RCTs of infliximab for moderate to severe psoriasis, Reich et al demonstrated infliximab’s comparable efficacy in subjects of varying weights.79 Similar proportions of overweight (78%), obese (74%), and normal-weight (78%) subjects achieved PASI 75 response.

A number of clinical trials have demonstrated the efficacy and safety of infliximab in treating psoriasis and PsA (Table 2). According to one meta-analysis, patients treated with infliximab had a higher rate of adverse events compared to those treated with placebo (RR = 1.18, \( P < 0.001 \)).69 Infusion reactions are among the most common AEs, and they are more frequent in patients who have developed anti-chimeric antibodies, those using infliximab in an as-needed fashion, and those not being treated concurrently with methotrexate or cyclosporine.66,73 Infusion reactions present typically as fever, chills, headache, flushing, nausea, dyspnea, dysgeusia, pruritus, and urticaria; they present less frequently as chest pain, hypertension, hypotension, or anaphylaxis. These reactions can usually be managed by slowing the infusion rate or stopping treatment.66 Other common AEs include infection, increased LFTs, pruritus, and serum sickness. There exist rare reports of anaphylaxis, exacerbation of or new-onset CHF, cytopenia, hepatitis, interstitial pneumonitis or fibrosis, leukocytoclastic vasculitis, lupus erythematosus syndrome, malignancy (eg, Hodgkin’s lymphoma, CTCL, NMSC, hepatosplenic T-cell lymphoma), MS or other demyelinating disease, optic neuritis, pancreatitis, seizure, sepsis, and severe infections.66,68,72,73,75

Contraindications for infliximab use include chronic, active, serious, and recurrent infection, active TB, latent TB in the absence of chemoprophylaxis, hepatitis B, MS and other demyelinating disease, optic neuritis, pancreatitis, seizure, sepsis, and severe infections.66,68,72,73,75

Table 3 lists monitoring recommendations for all TNF-α inhibitors.

### Adalimumab

Adalimumab is a fully human TNF-α monoclonal IgG1 antibody which blocks soluble and membrane-bound TNF-α from binding their natural receptors.80 It is currently
FDA-approved for treating moderate to severe psoriasis, moderate to severe PsA, adult rheumatoid arthritis, juvenile rheumatoid arthritis in patients as young as 4 years old, ankylosing spondylitis, and Crohn’s disease.27,40,50,66 For psoriasis, adalimumab is administered SC at a dose of 80 mg the first week, followed by 40 mg the next week and every other week (EOW) thereafter. For PsA, adalimumab is administered SC at 40 mg EOW.

Clinical response to adalimumab is substantial and rapid, with statistically significant improvement in PASI occurring as early as 1 week after initiation of treatment.80,81 One meta-analysis reported that adalimumab has superior efficacy in treating moderate to severe psoriasis when compared to etanercept, efalizumab, alefacept, methotrexate, cyclosporine, acitretin, and fumaric acid esters.74 Rebound is uncommon upon discontinuation of adalimumab, but clinical response is better maintained with continuous than as-needed therapy.82 Sustained clinical response has been noted for as long as 60 weeks with continuous adalimumab treatment.80 A relatively small proportion of patients experience loss of adalimumab efficacy with continued use.80,82 In one phase III active comparator trial, adalimumab demonstrated significantly higher efficacy and was better tolerated than methotrexate.81

Similar to etanercept, the slow absorption rate following SC administration, slow elimination rate, and appropriate dosing frequency give adalimumab a smooth and uniform concentration-time profile, minimizing the occurrences of overexposure and resultant adverse events, as well as underexposure and consequent symptom recurrence.52,53

Like etanercept, adalimumab is administered via a fixed-dose regimen and does not take the patient’s weight into account. In a recent study of 144 patients with psoriasis and PsA treated with adalimumab, PASI 50 response was achieved by significantly more patients with BMI less than 30 (79%) than obese patients with BMI 30 or higher (58%).83 This supports the notion that adalimumab may be less efficacious in treating heavier patients than normal-weight individuals.

Several clinical trials have reported the efficacy and safety of adalimumab in treating psoriasis and PsA (Table 2). There are, however, less data available for adalimumab than for etanercept and infliximab, since adalimumab is the newest of the three TNF-α inhibitors.

The most common AEs associated with adalimumab use are infection, injection site reaction, increased LFTs, and pruritus. There exist rare reports of anaphylaxis, angioedema, exacerbation of or new-onset CHF, cytopenia, fever, flushing, interstitial pneumonitis or fibrosis, leukocytoclastic vasculitis, lupus erythematosus syndrome, malignancy (eg, Hodgkin’s lymphoma, CTCL, NMSC), menorrhagia, MS and other demyelinating disease, sepsis, and severe infection.50,56,68,69,80–82

Contraindications for adalimumab use include chronic, active, serious, and recurrent infection, active TB, latent TB in the absence of chemoprophylaxis, hepatitis B, MS and other demyelinating disease, first-degree relative with MS, NYHA class III or IV CHF, pregnancy or lactation, and hypersensitivity to adalimumab or its ingredients. During treatment with adalimumab, patients should avoid live and live-attenuated vaccines. Table 3 lists monitoring recommendations for all TNF-α inhibitors.

**Alefcept**

In January 2003, alefacept became the first biologic agent approved by the FDA for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic or ultraviolet therapy. Alefacept is a fully human fusion protein which acts to prevent the interaction between lymphocyte function-associated antigen-3 (LFA-3) and CD2. This blocks the activation of T cells, thus modifying the inflammatory process. Additionally, alefacept’s immunoglobulin G1 domain interacts with natural killer cells to induce apoptosis of T cells. Both actions preferentially target memory/effector T cells, which have a high level of CD2 expression.84

The marketed dosing regimen of alefacept for psoriasis is a 12-week course of 15 mg intramuscularly (IM) given once weekly.97 An additional 12-week course may be given after 12 or more weeks off of treatment if the CD4+ lymphocyte count is within the normal range. Phase I studies showed alefacept to be well-tolerated when administered via 30-second IV bolus or 30-minute IV infusion as well as IM;55,56 however, pharmacokinetic studies favor IV bolus and IM administration. Phase III data (Table 2) confirm the efficacy of IV and IM alefacept for plaque-type psoriasis.87–90 In an attempt to achieve more rapid or complete response than the approved regimen (15 mg IM QW), Cafardi et al91 performed a small-scale comparison study of high-dose alefacept (30 mg IM QW for 12 weeks) versus loading dose followed by maintenance therapy (30 mg IM QW for 6 weeks + 15 mg IM QW for 6 weeks). There was no difference in efficacy between the groups, but there was a higher rate of adverse events in the group receiving higher doses of alefacept. Thus the dosing regimen remains 15 mg IM QW for a 12-week course.

Efficacy data from clinical trials of alefacept via both IV and IM routes as treatment for chronic plaque psoriasis
are summarized in Table 2. In general, up to one-third of patients achieve PASI 75 response during or after treatment with alefacept. Patients who achieve a physician’s global assessment (PGA) score of “clear” or “almost clear” do not, in general, require further anti-psoriasis treatment for 10 months following a course of alefacept.85

Alefacept has been studied in but is not FDA-approved for PsA. In a phase II study, 185 patients received 12 weeks of methotrexate (MTX) plus either alefacept or placebo followed by 12 weeks of treatment with methotrexate alone.89 At week 24, 54% of patients in the alefacept + MTX group and 23% in the placebo + MTX group achieved at least a 20% decrease in the American College of Rheumatology response criteria (ACR-20). Further studies are needed to confirm the efficacy of alefacept in the treatment of psoriatic arthritis.

Per data from phase II and III randomized controlled trials, patients receiving alefacept have significantly greater improvements in dermatology-related quality of life (QOL) measures than patients receiving placebo.91,94 This improvement is sustained up to twelve weeks after completion of the treatment course, and a second 12-week course provides additional QOL benefit.99 PASI 50 or greater response is associated with significantly greater improvement in QOL scores, and alefacept therapy does not negatively impact QOL.

AEs reported in patients treated with alefacept are generally mild. Adverse events reported with at least 5% higher incidence with alefacept than placebo are chills, headache, pruritus, infection, rhinitis, injection site pain, injection site inflammation, and accidental injury (Table 2). The majority of infectious AEs reported with alefacept are due to the common cold.

Consistent with its mechanism of action, alefacept is known to cause a dose-dependent reduction in the total number of circulating lymphocytes as well as CD4+ and CD8+ memory T lymphocyte subsets.85 The reduction in CD4+ T lymphocyte (CD4) count correlates with disease activity.96 The vast majority of patients experience a return in CD4 count to within normal limits by 12 weeks following cessation of therapy.96 Current recommendations are to monitor CD4 count weekly throughout the treatment course, to withhold one dose for CD4 count less than 250 cells per microliter, and to discontinue therapy if CD4 count remains under 250 cells per microliter for 1 month.97 There have been no reports of opportunistic infection related or unrelated to CD4 count, increased risk of TB or viral reactivation, or increased incidence of malignancy, even with repeated courses of alefacept.98

The addition of localized use of topical corticosteroids provides no increased efficacy over alefacept alone and in fact is associated with further decrease in circulating memory T-cells over alefacept with vehicle.99 In another report, systemic anti-psoriasis therapy was added to alefacept in a small group of patients.100 Concomitant therapies used were methotrexate (n = 4), acitretin (n = 2), and cyclosporine (n = 1). Combination alefacept + systemic anti-psoriasis therapy led to slight increase in efficacy with no impact on CD4 count. Krueger et al99 report on an open-label study of 449 patients with plaque psoriasis treated with up to three 12-week courses of alefacept. Approximately one-third of patients were treated with alefacept alone or in combination with low-potency topical therapy, one-third were treated with alefacept plus medium- to high-potency topical therapy, and one-third were treated with alefacept plus a systemic or ultraviolet B (UVB) therapy. Because patients were permitted to receive different concomitant therapies between courses, the study was not powered to compare efficacy between therapies. Combination therapy did improve efficacy, however, particularly alefacept plus UVB. The improved efficacy of treatment with alefacept plus UVB over alefacept alone has been demonstrated in two other open-label clinical trials.98,101

**Efalizumab**

Efalizumab is a monoclonal humanized form of a murine antibody directed against CD11a, the α subunit of lymphocyte function-associated antigen-1 (LFA-1). By binding to CD11a, efalizumab inhibits cutaneous T cell trafficking,102 T cell activation, and T cell adhesion to keratinocytes.103 In 2003 it was approved by the FDA for continuous treatment of moderate to severe plaque psoriasis for adults who are eligible for systemic therapy, and in 2004 it was approved by the European Medicines Agency for adults who have failed to respond to or are intolerant of other systemic therapies. The marketed regimen of efalizumab use was one initial dose of 0.7 mg/kg SC followed by weekly injections of 1 mg/kg SC to a maximum 200 mg. In April 2009, efalizumab was withdrawn from the market based on several reports of progressive multifocal leukoencephalopathy (PML) in patients being treated with efalizumab.

A phase III dose-finding trial demonstrated significantly superior efficacy of each of 3 doses of efalizumab (1, 2, and 4 mg/kg/week) to placebo and provided evidence supporting weekly dosing over EOW dosing.104 This and other studies showed that increasing the weekly SC dose from 1 mg/kg to 2 mg/kg did not achieve a higher rate of response.105
Data from several phase III studies support continuous use of efalizumab dosed at 1 mg/kg SC QW in patients with good initial clinical response.\textsuperscript{105–108} Efalizumab also demonstrated efficacy in treating palmpoplantar psoriasis in several case reports and small open-label pilot studies.\textsuperscript{109–115} Treatment with efalizumab is also associated with significant improvement in dermatology-related quality of life and psoriasis symptoms severity measures.\textsuperscript{116} Efalizumab has been shown to be ineffective in the treatment of psoriatic arthritis.\textsuperscript{117}

The incidence of AEs reported in clinical trials of efalizumab are reported in Table 2. The most frequent AEs are flu-like symptoms: headache, chills, nausea, and myalgias are reported more frequently in patients receiving efalizumab than those receiving placebo. These are typically mild and acute, and their incidence decreases with ongoing treatment.\textsuperscript{118} In large RCTs, the frequency of SAEs was not significantly different in patients treated with efalizumab compared with placebo (Table 2). There have been reports of both immune-mediated thrombocytopenia\textsuperscript{119} and autoimmune hemolytic anaemia\textsuperscript{120} within the first 6 months of treatment with efalizumab for psoriasis. These events are rare but serious, and guidelines suggest monitoring complete blood counts in patients on efalizumab.\textsuperscript{121}

Both worsening of psoriasis and new-onset arthritis have been reported during therapy with efalizumab. Pooled data from four placebo-controlled trials indicate that the incidence of psoriasis adverse events, including worsening disease and onset of new psoriasis morphologies was 3% in patients treated with efalizumab and 1% in those treated with placebo. In a small retrospective analysis, ten patients with psoriasis-related AEs during long-term efalizumab treatment were treated with intercurrent cyclosporine.\textsuperscript{121} This combination therapy was generally well-tolerated and effectively controlled the relapse. No patient experienced a serious adverse event or psoriasis rebound or flare.

The FDA has received reports of three confirmed cases and one possible unconfirmed case of progressive multifocal leukoencephalopathy (PML), a life-threatening central nervous system infection in patients being treated with efalizumab for psoriasis.\textsuperscript{122} This initially led to a black box warning for PML and efalizumab, followed in April 2009 by efalizumab being withdrawn from the consumer market. All patients treated with efalizumab are expected to discontinue therapy by July 2009.

Psoriasis rebound or flare following abrupt withdrawal of efalizumab is well documented and must be considered when discontinuing efalizumab. This flare may be seen as soon as after missing a single dose of efalizumab.\textsuperscript{123} The post-efalizumab discontinuation flare may manifest as generalized erythrodermic or pustular psoriasis,\textsuperscript{124} guttate psoriasis,\textsuperscript{125} or recurrent plaque psoriasis. One study revealed efalizumab-responsive patients to be less likely to experience rebound than non-responders.\textsuperscript{126} Management of the post-efalizumab flare should be approached on a case-by-case basis. One must consider comorbidities, prior and planned future treatment, and contraindications to other psoriasis therapies. Cyclosporine and methotrexate have been proven efficacious in many but not all\textsuperscript{127} reports. In an open-label study comparing post-efalizumab treatments, cyclosporine and methotrexate were superior to systemic corticosteroids, retinoids, or combined corticosteroids and methotrexate in preventing rebound.\textsuperscript{128} In one study of 130 patients, no patient who was placed on cyclosporine or methotrexate immediately on discontinuation of efalizumab experienced rebound.\textsuperscript{126} These findings suggest that when transitioning a patient from efalizumab to another biologic agent, one may consider bridging therapy with cyclosporine or methotrexate in an attempt to decrease the likelihood and/or severity of psoriasis rebound until the new agent has taken effect.

**Ustekinumab**

In recent years, biologic agents targeting IL-12/23 have shown great promise.\textsuperscript{129} Both agents target the p40 subunit shared by IL-12 and IL-23, which are over-expressed in psoriasis plaques.\textsuperscript{130} The so-called “anti-IL-12” drugs include ustekinumab (CNTO 1275) and ABT-874. Ustekinumab is currently in the final approval stages at the FDA, while ABT-874 is currently in early phase III studies.

Ustekinumab (formerly CNTO-1275) is a human monoclonal antibody that binds with high affinity and specificity to p40, thereby preventing interaction with cell-surface IL12Rβ1 receptors. It has been proven efficacious in the treatment of Crohn’s disease\textsuperscript{131} in addition to psoriasis and psoriatic arthritis. It has been unsuccessful in the treatment of MS.\textsuperscript{132} A phase I first-in-human study demonstrated concentration-dependent improvement of psoriasis lesions following a single IV dose of ustekinumab.\textsuperscript{133} Twelve of 18 subjects (67%) achieved at least PASI 75 improvement between 8 and 16 weeks following administration. Dose-finding studies have determined that ustekinumab is efficacious in the treatment of psoriasis at 45 to 90 mg SC every 8 to 12 weeks. The marketed dosing regimen is expected to be 45 mg SC every 12 weeks.

Efficacy data from clinical trials of ustekinumab for moderate to severe chronic plaque psoriasis\textsuperscript{134} are summarized in Table 2. In the first comparator trial of two
Biologics agents, ustekinumab showed superiority compared with etanercept in the treatment of moderate to severe plaque psoriasis. In the study, ustekinumab 45 mg or 90 mg SC at weeks 0 and 4 was compared with etanercept 50 mg SC twice weekly from weeks 0 to 12. In the ustekinumab groups, 68% and 74% of participants (45 mg and 90 mg, respectively) achieved PASI 75 at week 12, compared with 57% of patients on etanercept.

In large phase III randomized controlled trials, participants treated with ustekinumab experienced greater decreases in dermatology life quality index (DLQI) scores than did placebo-treated participants. At week 12 in a trial of 1230 patients, significantly more subjects treated with ustekinumab 45 mg (55%) and 90 mg (56%) reached DLQI score of 0 or 1 than did those receiving placebo (3%). Results were similar in another phase III study of 766 patients: DLQI of 0 or 1 was achieved by 53% of those treated with ustekinumab 45 mg, 52% treated with ustekinumab 90 mg, and 6% receiving placebo. The efficacy results of these two large phase III trials demonstrated that 67% of patients in both studies treated with 45 mg of ustekinumab reached PASI 75 at week 12 and that 66% and 76% of patients treated with 90 mg of ustekinumab reached PASI 75 at 12 weeks.

In a phase II double-blind, randomized, placebo-controlled crossover study of 146 adults, ustekinumab significantly reduced signs and symptoms of active psoriatic arthritis compared with placebo. Active psoriatic arthritis was defined as 3 or more swollen joints and 3 or more tender joints plus either C-reactive protein (CRP) of at least 15 mg/L or morning stiffness for at least 45 minutes. Patients were required to have been diagnosed with PsA at least 6 months prior to enrollment in the study. At week 12, 42% of patients treated with ustekinumab (either 90 mg or 63 mg SC weekly at weeks 0–3) and 14% of patients receiving placebo achieved ACR-20 response. Patients were also required to have active plaque psoriasis with a target lesion of at least 2 cm diameter, and ustekinumab also improved cutaneous lesions compared to placebo. Of the 124 (85%) of patients with at least 3% or greater body surface area (BSA) involvement with psoriasis, 52% of ustekinumab-treated patients (33 of 63) and 5% of placebo-treated patients (3 of 55) achieved PASI 75 response at week 12.

The incidence of adverse events in clinical trials of ustekinumab is summarized in Table 2. The most common AEs are upper respiratory tract infection, headache, nasopharyngitis, injection site erythema, and arthralgias. In trials conducted to date, there does not appear to be a significant difference in the incidence of serious adverse events, infectious adverse events, malignancy, cardiovascular events, or adverse events leading to treatment discontinuation. There has also been no dose-response in adverse event incidence or severity.

**ABT-874**

ABT-874 is a fully human antibody with high affinity for the shared p40 subunit of IL-12 and IL-23. This antibody displays very potent in vitro neutralization of IL-12, was very effective in animal models, and has demonstrated clinical efficacy in the treatment of psoriasis in human studies. ABT-874 is also being investigated for use in the treatment of Crohn’s disease.

Phase II data reveal substantial and statistically significantly superior efficacy of ABT-874 at each of five different dosing regimens compared with placebo. This includes a single dose of ABT-874, after which 63% of patients demonstrated PASI 75 response 3 months later. These data are seen in Table 2. This effect is often sustained weeks to months following cessation of therapy.

Safety data thus far indicate that subjects treated with ABT-874 are not statistically significantly more likely than those treated with placebo to experience serious infectious, or malignant adverse events. Further safety and efficacy data are currently being obtained via numerous phase III studies.

**Summary**

When selecting a biologic agent for use in a patient with psoriasis, one must consider a number of characteristics both of the patient and of the medication. Patient-specific factors to consider include psoriasis morphology and severity, state of health, comorbidities, body mass index, concomitant therapy, and adherence. Medication-specific considerations include efficacy, adverse events and contraindications, method of administration, and physician experience with the agent. Unfortunately there is no simple way to determine which patient to treat with which agent. The choice of which agent to utilize is best made after obtaining a careful history and physical examination along with a detailed discussion with the patient about the advantages and disadvantages of all of the five currently available biologic therapies. Prior to initiating therapy with any biologic agent, appropriate screening studies include TB testing, complete blood count (CBC), hepatic function panel, hepatitis profile, and pregnancy testing as appropriate. Acceptable methods of TB screening include the purified protein derivative skin test and QuantiFERON Gold test (where available).
Chest x-ray may also be utilized based on results of screening tests and in special circumstances as indicated by Centers of Disease Control and Prevention (CDC) guidelines.\textsuperscript{66,140} Re-testing for TB should be performed in all patients who are exposed to or demonstrate symptoms of TB, and annually in all patients being treated with biologic agents. Alefacept, adalimumab, etanercept, and infliximab are pregnancy category B medications, and efalizumab is a pregnancy category C medication.

Patients initiating treatment with alefacept must have a CD4 count done prior to initiating treatment and then biweekly during treatment. Alefacept dose should be held for CD4 count less than 250 cells per microliter. Alefacept is contraindicated in HIV-infected patients, and because new CDC guidelines recommend HIV testing in all patients who present for medical care,\textsuperscript{141} one may consider HIV testing in all patients being screened for any biologic agent.

Anti-TNF-\(\alpha\) agents are contraindicated in the presence of serious infections such as TB, opportunistic infections, and hepatitis B. They should also not be used with live vaccines. Biologically inactive or recombinant vaccine use is acceptable in patients being treated with TNF-\(\alpha\) antagonists, but the immune response of the vaccine may be compromised. Because of the association between TNF-\(\alpha\) inhibitors and demyelinating disease, they should not be used in patients with these diseases. First-degree relatives of patients with MS have an increased risk of developing MS themselves; one should therefore avoid treatment with TNF-\(\alpha\) inhibitors in first-degree relatives of patients with MS. Use of TNF-\(\alpha\) inhibitors may lead to new-onset or exacerbation of CHF. Caution should therefore be exercised in patients with CHF, particularly those with left ventricular ejection fraction less than 50%. Use of TNF-\(\alpha\) antagonists should be avoided in patients with NYHA Functional Class 3 or 4 CHF, and in patients with left ventricular ejection fraction less than 50%. Use of TNF-\(\alpha\) antagonists should be avoided in patients with NYHA Functional Class 3 or 4 CHF, and infliximab use at doses greater than 5 mg/kg is contraindicated in these patients. Etanercept is contraindicated in sepsis. Patients who are treated with TNF-\(\alpha\) inhibitors should be alerted of common adverse events (such as the painful injection site reaction seen in some patients treated with adalimumab) as well as rare but serious adverse events such as drug-induced lupus, serum sickness, and malignancy (including hepatosplenic T-cell lymphoma in children treated with infliximab).

The biologic agents have greatly increased the treatment choices for patients with moderate to severe psoriasis as well as those with moderate to severe PsA. These newer agents not only offer new choices, but based upon the short- and intermediate-term data that are currently available, the biologic agents also appear to offer safer, more effective, and convenient therapies.

**Disclosures**

Dr. Korman has been a consultant for Abbott, Astellas, Centocor, and Genentech and been a speaker for Abbott, Amgen, Astellas, Centocor, and Genentech. Dr. Korman also receives residency/fellowship funding from Centocor. Dr. Bahner has been a sub-investigator in clinical trials conducted by Abbott, Amgen, Astellas, Centocor, and Genentech.

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