FEATURE ARTICLE

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# Biologic Agents for Moderate-to-Severe Plaque Psoriasis

## *Mechanisms of Action and Treatment Considerations*

Wendy Cantrell, Rhonda Kaler

**ABSTRACT:** Psoriasis is a chronic, inflammatory, immune-mediated skin disease that affects roughly 2% of adults in the United States. The immunopathogenic pathways associated with psoriasis are complex, and to effectively target the underlying cytokine networks involved in disease progression, drugs are needed that act on specific components of the immune system. As understanding of the role of proinflammatory signaling molecules in the psoriatic disease process has evolved, several biologic agents have been engineered to block key cytokines associated with psoriasis. Recently, improvements in the understanding of the pathogenesis have led to the development of agents that may target the mechanism of disease more directly. This review describes the immunopathogenesis of psoriasis and how targeting disease-specific mechanisms with biologic agents may improve clinical outcomes and potentially result in better safety profiles than conventional agents. Results from pivotal clinical studies evaluating the efficacy and safety of approved tumor necrosis factor-α antagonists (etanercept, infliximab, and adalimumab) and the interleukin-12/23 inhibitor ustekinumab are summarized. In addition, we include clinical findings to date evaluating a new class of biologics that neutralize interleukin-17A (secukinumab, ixekizumab) or act as an interleukin-17 receptor antagonist (brodalumab). Finally, this review discusses efficacy and safety factors, as well as patient characteristics to consider, when selecting a biologic agent for psoriasis disease management.

**Key words:** Biologics, Efficacy, Pathogenesis, Psoriasis, Safety

Psoriasis is a chronic, inflammatory, immune-mediated skin disease affecting an estimated 7.5 million Americans (approximately 2.2% of the population), making it the most prevalent immune-mediated disease in the country (National Psoriasis Foundation, 2012). The most common (>80% of cases) manifestation of psoriasis is chronic plaque psoriasis, which is characterized by distinctive, raised, red skin lesions that have an adherent, silvery, or silvery-white scale (Ladizinski et al., 2013). These plaques, which typically appear on the scalp, elbows, knees, and trunk, can persist for months to years and cause symptoms of pain, itching, burning sensations, stinging, and bleeding in affected areas (Ladizinski et al., 2013; Villaseñor-Park, Wheeler, & Grandinetti, 2012). In addition to these physical symptoms, psoriasis can significantly impair patients' quality of life, in part because it is a visually apparent skin disease associated with social stigma. The psychological manifestations of psoriasis can cause feelings of shame, embarrassment, and stress; interfere with personal relationships; create occupational burdens (e.g., lost days of work, reduced productivity,

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workplace discrimination); and increase the likelihood of abusing alcohol and illicit substances (Feldman, Behnam, Behnam, & Koo, 2005; Hong, Koo, & Koo, 2008; Kimball, Jacobson, Weiss, Vreeland, & Wu, 2005; Young, 2005). Patients with psoriasis are also significantly more likely to receive a diagnosis of depression, anxiety, or suicidality compared with control patients without psoriasis (Kurd, Troxel, Crits-Christoph, & Gelfand, 2010).

Comorbidities are also common in patients with psoriasis. In a population-based, cross-sectional study, Yeung and colleagues found that, compared with age- and practice-matched controls ($n$ = 90,350), patients with psoriasis ($n$ = 9035) were significantly more likely to have one or more comorbidities, including diabetes, rheumatologic disease, renal disease, diabetes with systemic complications, atherosclerotic outcomes (defined as the aggregate of cerebrovascular disease, myocardial infarction, and peripheral vascular disease), mild liver disease, chronic pulmonary disease, peripheral vascular disease, myocardial infarction, or peptic ulcer disease (Yeung, Takeshita, et al., 2013). The authors also observed that the burdens of these comorbidities increased with increasing psoriasis severity (Yeung, Wan, et al., 2013). The link between psoriasis and these comorbidities supports the classification of psoriasis as a systemic inflammatory condition caused by the up-regulation of various cytokines, including tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), and IL-17 (Villaseñor-Park et al., 2012). In psoriasis, these cytokines are consequently associated with inflammation and plaque formation; disruption of insulin signaling and lipid metabolism; and increased atherosclerotic changes in coronary, cerebral, and peripheral arteries (Golden, McCormick, & Ward, 2013; Villaseñor-Park et al., 2012).

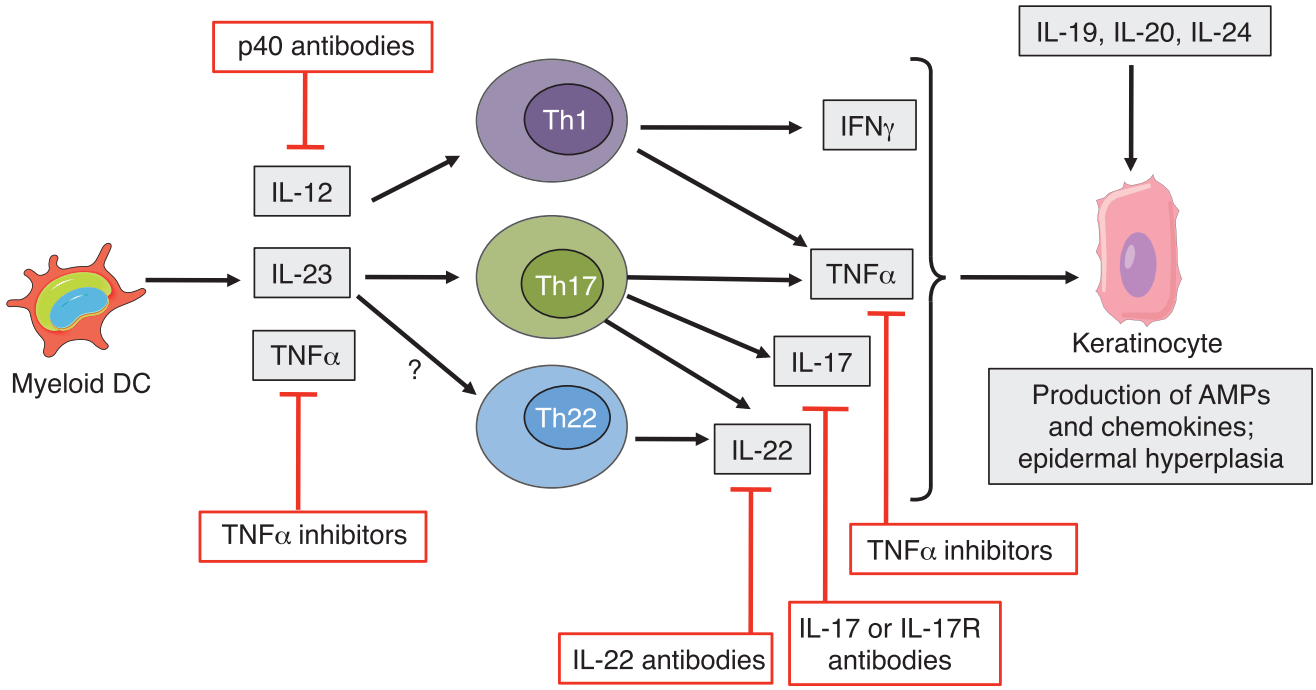
As understanding of the role of proinflammatory signaling molecules in the psoriatic disease process has evolved, several therapies have been developed that inhibit select cytokines and kinases associated with the disease (Schafer, 2012; Sivamani et al., 2013). More recently, improvements in the understanding of psoriasis pathogenesis have led to the development of agents that may target the mechanism of disease more directly. This review describes the immunopathogenesis of psoriasis and how targeting psoriasis-specific disease mechanisms in the moderate-to-severe category with biologic agents may improve clinical outcomes and potentially result in less treatment-related toxicity compared with conventional agents. In addition, this review will discuss efficacy and safety factors to consider when selecting biologic agents for disease management. Although other systemic therapies are available, treatment has evolved with the biologics.

## PATHOGENESIS OF PSORIASIS

Triggers for the initiation of psoriasis may include both chemical and physical insults, such as cutaneous injury, obesity, smoking, alcohol consumption, infection, stress, pregnancy, hypocalcemia, and certain medications (e.g., lithium, antimalarials, beta blockers, interferon; Villaseñor-Park et al., 2012). In patients with a genetic predisposition for psoriasis, these insults initiate a cascade that results in hyperproliferation of keratinocytes. This cascade starts when stressed keratinocytes release self-DNA that forms complexes with the antimicrobial protein LL-37, thereby activating dendritic cells (Nestle, Kaplan, & Barker, 2009). As shown in Figure 1 (Johnson-Huang, Lowes, & Krueger, 2012), the activated dendritic cells release various cytokines (e.g., IL-12, IL-23, TNFα), which induce T helper 1 (Th1) cells to produce interferon-γ and TNFα; Th17 cells to produce IL-17, TNFα, and IL-22; and Th22 cells to produce IL-22 (Johnson-Huang et al., 2012). The increased production of these cytokines promotes formation and exacerbation of psoriatic plaques through various mechanisms. Interferon-γ, TNFα, and IL-17 induce chemokine expression and production of antimicrobial peptides by keratinocytes, which enhance local immune-cell recruitment and inflammation, and IL-22 production results in aberrant keratinocyte proliferation and epidermal hyperplasia (Johnson-Huang et al., 2012).

An understanding of these cytokine pathways has contributed to the development and use of various biologic agents for the management of psoriasis. These biologics are complex molecules that have been engineered to block key overproduced proinflammatory cytokines or their receptors (Focosi, Maggi, Pistello, Boggi, & Scatena, 2011). The first biologic agents to be used to treat moderate-to-severe psoriasis were TNFα antagonists. The therapeutic potential of TNFα inhibition for the treatment of psoriasis was discovered serendipitously when the monoclonal antibody infliximab was found to improve the psoriatic plaques of a patient being treated for Crohn's disease (Oh, Das, & Gottlieb, 2000). Since this discovery, three biologics that target TNFα have been studied and approved for the treatment of moderate-to-severe (etanercept and adalimumab) or severe (infliximab) plaque psoriasis (AbbVie, 2013; Immunex Corporation, 2013; Janssen Biotech, 2013a). More recently, a fourth biologic agent with a novel mechanism of action, ustekinumab, has also been approved for treating moderate-to-severe plaque psoriasis (Janssen Biotech, 2013b). Ustekinumab is a first-in-class monoclonal antibody that binds and neutralizes the common p40 subunit of IL-12 and IL-23 (Benson et al., 2011), which, as described above and in Figure 1, are important cytokines in psoriasis pathogenesis.

On the basis of evidence showing that some cytokines of the IL-17 family are expressed at significantly higher levels in lesional compared with nonlesional psoriatic skin, numerous studies have been conducted to elucidate the roles of these cytokines in psoriasis (Cai et al., 2011; Chiricozzi et al., 2011; Krueger et al., 2012). IL-17A has been identified as a central driver in the pathogenesis of psoriasis; neutralization of this cytokine has been shown to rapidly inhibit downstream cytokine and chemokine networks in




AMP, antimicrobial peptides; DC, dendritic cell; IFN, interferon; IL, interleukin; Th, T helper; TNF, tumor necrosis factor.

**FIGURE 1.** Immunopathogenesis of psoriasis. Reprinted with permission from Johnson-Huang, L. M., Lowes, M. A., and Krueger, J. G. (2012).

the psoriatic cascade, resulting in near-complete reversal of the psoriatic phenotype (Hueber et al., 2010; Krueger et al., 2012). Two biologics targeting IL-17A (secukinumab and ixekizumab) and one targeting the IL-17 receptor (brodalumab) are currently under research clinical development.

The next sections of this review discuss key findings from randomized controlled trials (RCTs) of the approved TNFα antagonists and IL-12/IL-23 inhibitor as well as inhibitors of the IL-17 family of cytokines. Tables 1 and 2 provide a summary of each of the RCTs discussed. Several oral medications are also in development for the treatment of psoriasis, but this review focuses only on injectable biologic agents.

## TNFα ANTAGONISTS

TNFα antagonists are the current gold standard among biologic therapies for the treatment of psoriasis as well as being treatment options for psoriatic arthritis, rheumatoid arthritis, and Crohn's disease (Tak & Kalden, 2011). However, because TNFα acts broadly to stimulate immune responses and induce other inflammatory cytokines, inhibiting TNFα can potentially result in adverse events (AEs) such as infections, malignancies, neurologic complications, and autoimmune disorders (Silva, Ortigosa, & Benard, 2010; Tak & Kalden, 2011). Key efficacy findings from psoriasis RCTs of etanercept, infliximab, and adalimumab are presented here, followed by a discussion of safety and tolerability factors to consider when prescribing TNFα antagonists.

### *Etanercept*

The first biologic agent approved for the treatment of moderate-to-severe plaque psoriasis was etanercept, a recombinant human TNFα receptor protein that inhibits both soluble and membrane-bound TNFα (Levy, Solomon, & Emer, 2012). Etanercept received United States Food and Drug Administration (FDA) approval for this indication in 2004 (U.S. FDA, n.d.), with a recommended starting dose of 50 mg twice weekly for 3 months, followed by maintenance dosing of 50 mg once weekly (Immunex Corporation, 2013). Etanercept is administered via subcutaneous injection; with proper training, etanercept can be self-administered using prefilled syringes or autoinjectors (Immunex Corporation, 2013).

In a 24-week double-blind RCT in 652 patients with moderate-to-severe plaque psoriasis, Psoriasis Area and Severity Index (PASI) improvements of 75% or more (PASI 75) from baseline were achieved at Week 12 (primary end point) by 49% of patients treated with etanercept 50 mg twice weekly (high dose), 34% of patients treated with etanercept 25 mg twice weekly (medium dose), and 14% of patients treated with etanercept 25 mg once weekly (low dose), compared with 4% of patients receiving placebo (all *p*s < .001; Leonardi et al., 2003). At the same time point, PASI improvements of 90% or more (PASI 90) were achieved by 22%, 12%, and 3% of patients in the etanercept high-, medium-, and low-dose groups, respectively, compared with 1% in the placebo group ($p < .001$ for the high- and medium-dose groups vs. placebo). After

**TABLE 1.** Summary of Key Clinical Trials of Biologics Approved for the Treatment of Moderate-to-Severe Plaque Psoriasis

| Study | *n** | Study Design | Treatment Regimens | Efficacy Outcomes | Safety Outcomes |
|---|---|---|---|---|---|
| Etanercept | | | | | |
| Leonardi et al., 2003 | 652 | 24-week multicenter, randomized DB study | From baseline to Week 12, patients were randomized to receive:<br>• Etanercept, 50 mg twice/week<br>• Etanercept, 25 mg twice/week<br>• Etanercept, 25 mg once/week<br>• Placebo | Week-24 PASI 75 response:<br>• 59% with 50 mg twice/week<br>• 44% with 25 mg twice/week<br>• 25% with 25 mg once/week | AEs in ≥10% of patients in any treatment group at Week 24 included injection-site reactions, headache, and upper respiratory infection. |
| | | | At Week 12, patients in the placebo group were switched to etanercept 25 mg twice/week. | Week-24 PASI 90 response:<br>• 30% with 50 mg twice/week<br>• 20% with 25 mg twice/week<br>• 6% with 25 mg once/week | No cases of TB or opportunistic infections were reported. |
| Papp et al., 2005 | 583 | 24-week multicenter, randomized DB study | From baseline to Week 12, patients were randomized to receive:<br>• Etanercept, 50 mg twice/week<br>• Etanercept, 25 mg twice/week<br>• Placebo | Week-24 PASI 75 response:<br>• 54% of patients switched from 50 mg twice/week to 25 mg twice/week<br>• 45% with continuous etanercept 25 mg twice/week<br>• 28% of patients switched from placebo to etanercept 25 mg twice/week | AEs in ≥10% of patients in any treatment group from baseline to Week 12 or Weeks 13–24 included injection-site reactions, upper respiratory infection, headache, and injection-site ecchymosis. |
| | | | At Week 12, all patients were switched to etanercept 25 mg twice/week. | | Twelve patients experienced serious AEs, including one serious infectious event. |
| Infliximab | | | | | |
| EXPRESS (Reich et al., 2005) | 378 | 50-week multicenter, randomized DB study | From baseline to Week 24, patients were randomized to receive infusions at Weeks 0, 2, and 6 and then every 8 weeks of:<br>• Infliximab, 5 mg/kg<br>• Placebo | At Week 24:<br>• PASI 75 was achieved by 82% with infliximab versus 4% with placebo ($p < .0001$)<br>• PASI 90 was achieved by 58% with infliximab versus 1% with placebo ($p < .0001$) | AEs in ≥10% of patients in any treatment group from baseline to Week 24 included upper respiratory tract infection and headache. |
| | | | At Week 24, patients in the placebo group switched to infliximab infusions at Weeks 24, 26, and 30 and then every 8 weeks to Week 46. | At Week 50:<br>• PASI 75 was achieved by 61% with infliximab versus 77% with placebo/infliximab<br>• PASI 90 was achieved by 45% with infliximab versus 50% with placebo/infliximab | Serious AEs reported by 3% with placebo versus 6% with infliximab. |

(continued)

**TABLE 1.** Summary of Key Clinical Trials of Biologics Approved for the Treatment of Moderate-to-Severe Plaque Psoriasis, Continued

| Study | *n** | Study Design | Treatment Regimens | Efficacy Outcomes | Safety Outcomes |
|---|---|---|---|---|---|
| EXPRESS II (Menter et al., 2007) | 835 | 50-week multicenter, randomized DB study | At baseline, patients were randomized to receive infliximab 3 or 5 mg/kg or placebo.<br>At Week 14, patients in the infliximab groups were rerandomized to continuous (every 8 weeks) or intermittent (as-needed) therapy.<br>Patients in the placebo group switched to infliximab 5 mg/kg at Weeks 16, 18, and 22 and then every 8 weeks. | Week-26 PASI 75 and PASI 90:<br>• 65% and 33% with 3 mg/kg every 8 weeks<br>• 42% and 20% with 3 mg/kg as needed<br>• 78% and 56% with 5 mg/kg every 8 weeks<br>• 58% and 24% with 5 mg/kg as needed<br>Week-50 PASI 75 and PASI 90:<br>• 44% and 25% with 3 mg/kg every 8 weeks<br>• 25% and 10% with 3 mg/kg as needed<br>• 54% and 34% with 5 mg/kg every 8 weeks<br>• 38% and 10% with 5 mg/kg as needed | AEs in ≥10% of patients in any treatment group from baseline to Week 14 included upper respiratory tract infection, headache, and infusion reaction.<br>From Weeks 0 to 50, two cases of TB and 12 malignancies were reported. |
| Adalimumab | | | | | |
| Gordon et al., 2006 | 147 | 12-week multicenter, randomized DB study with 48-week extension | From baseline to Week 12, patients were randomized to receive:<br>• 80-mg adalimumab at Weeks 0 and 1 and then 40 mg/week starting at Week 2<br>• 80-mg adalimumab at Week 0 and then 40 mg eow starting at Week 1<br>• Placebo weekly<br>Patients who completed 12 weeks could enter a 48-week extension:<br>• Patients in adalimumab groups continued their assigned doses<br>• Patients on placebo switched to adalimumab 80 mg at Week 12 and then 40 mg eow | Week-24 PASI 75 and PASI 100:<br>• 72% and 24% with 40 mg/week<br>• 64% and 13% with 40 mg eow<br>• 55% and 11% with placebo/40 mg eow<br>Week-36 PASI 75 and PASI 100:<br>• 68% and 36% with 40 mg/week<br>• 62% and 22% with 40 mg eow<br>• 57% and 19% with placebo/40 mg eow<br>Week-60 PASI 75 and PASI 100:<br>• 64% and 26% with 40 mg/week<br>• 56% and 16% with 40 mg eow<br>• 45% and 19% with placebo/40 mg eow | AEs in ≥10% of patients in any treatment group from Weeks 12 to 60 included nasopharyngitis, upper respiratory tract infection, skin papilloma, and headache.<br>Fourteen patients receiving adalimumab experienced serious AEs, including two malignant melanomas, one squamous cell carcinoma, one breast carcinoma, and one gastric adenocarcinoma.<br>In the adalimumab groups, one patient was diagnosed with coccidioidomycosis, and one patient was diagnosed with TB. |

(continued)

**TABLE 1.** Summary of Key Clinical Trials of Biologics Approved for the Treatment of Moderate-to-Severe Plaque Psoriasis, Continued

| Study | *n** | Study Design | Treatment Regimens | Efficacy Outcomes | Safety Outcomes |
|---|---|---|---|---|---|
| REVEAL (Menter et al., 2008) | 1,212 | 52-week multicenter, randomized DB study | From baseline to Week 15, patients were randomized (2:1) to:<br>• Adalimumab 80 mg at Week 0 and then 40 mg eow<br>• Placebo-matching adalimumab<br>From Weeks 17 to 31, all patients received OL adalimumab 40 mg eow.<br>At Week 33, patients originally randomized to active treatment who achieved PASI 75 were rerandomized to adalimumab 40 mg eow or placebo through Week 52. | At Week 24, PASI 75 and PASI 90 were achieved by 70% and 49% of patients in the pooled adalimumab group.<br>From Weeks 33 to 52, PASI response fell below 50% for 28% of patients rerandomized to placebo versus 5% rerandomized to continue adalimumab ($p < .001$). | AEs in ≥5% of patients in any treatment group from baseline to Week 16 included upper respiratory tract infection, nasopharyngitis, and headache.<br>Through Week 16, serious infections occurred in four patients (1%) with placebo and five patients (0.6%) with adalimumab (including one case of TB); malignancies excluding NMSC occurred in 0.3% and 0.2%, respectively; and NMSC occurred in 0.3% and 0.5%, respectively. |
| Ustekinumab | | | | | |
| PHOENIX 1 (Leonardi et al., 2008) | 766 | 76-week multicenter, randomized DB study | From baseline to Week 12, patients were randomized to receive:<br>• Ustekinumab 45 mg at Weeks 0 and 4 and then every 12 weeks<br>• Ustekinumab 90 mg at Weeks 0 and 4 and then every 12 weeks<br>• Placebo at Weeks 0 and 4<br>At Week 12, placebo group switched to ustekinumab 45 or 90 mg at Weeks 12 and 16 then every 12 weeks.<br>At Week 40, PASI 75 responders in the ustekinumab groups were rerandomized to placebo or continuous therapy. | Week-28 PASI 75 and PASI 90:<br>• 71% and 49% with ustekinumab 45 mg<br>• 79% and 56% with ustekinumab 90 mg<br>• 66% and 45% with placebo to ustekinumab 45 mg<br>• 85% and 62% with placebo to ustekinumab 90 mg<br>Among patients rerandomized at Week 40, maintenance of PASI 75 was better with maintenance therapy versus withdrawal from therapy through at least 1 year ($p < .0001$). Median PASI % improvement was stable to at least Week 76 in the continuous-therapy groups. | AEs in ≥5% of patients in any treatment group (reported from Weeks 0–12, 12–40, and 40–76) included upper respiratory tract infection, nasopharyngitis, arthralgia, and headache.<br>Seven serious infections, four cutaneous cancers, three noncutaneous cancers, and four cardiovascular events were reported across treatment groups and treatment phases for incidences of ≤1.3%, ≤1.2%, ≤0.8%, and ≤0.8%, respectively. |

(continued)

**TABLE 1.** Summary of Key Clinical Trials of Biologics Approved for the Treatment of Moderate-to-Severe Plaque Psoriasis, Continued

| Study | *n** | Study Design | Treatment Regimens | Efficacy Outcomes | Safety Outcomes |
|---|---|---|---|---|---|
| PHOENIX 2 (Papp et al., 2008) | 1,230 | 52-week multicenter, randomized DB study | From baseline to Week 12, patients were randomized to receive:<br>• Ustekinumab 45 mg at Weeks 0 and 4 and then every 12 weeks<br>• Ustekinumab 90 mg at Weeks 0 and 4 and then every 12 weeks<br>• Placebo at Weeks 0 and 4<br>At Week 12, the placebo group switched to ustekinumab 45 or 90 mg at Weeks 12 and 16 and then every 12 weeks.<br>At Week 28, partial responders (PASI 50 to <75) to ustekinumab rerandomized to treatment every 8 or 12 weeks. | Week-28 PASI 75 and PASI 90:<br>• 70% and 45% with ustekinumab 45 mg<br>• 79% and 54% with ustekinumab 90 mg<br>• 70% and 42% with placebo to ustekinumab 45 mg<br>• 79% and 52% with placebo to ustekinumab 90 mg<br>Dosing intensification for partial responders at Week 28 did not improve response in the 45-mg group. In contrast, intensification in the 90-mg group improved outcomes: PASI 75 was achieved by 69% of patients dosed every 8 weeks versus 33% dosed every 12 weeks ($p$ = .004). | AEs in ≥5% of patients in any treatment group (reported from Weeks 0–12, 12–28, and 28–52) included upper respiratory tract infection, nasopharyngitis, arthralgia, headache, injection-site erythema, and cough.<br>Seven serious infections, eight cutaneous cancers, two noncutaneous cancers, and one cardiovascular event were reported across treatment groups and treatment phases for incidences of ≤1.2%, ≤1.3%, ≤1.3%, and ≤0.2%, respectively. |
| ACCEPT (Griffiths et al., 2010) | 903 | 64-week multicenter, randomized study | From baseline to Week 12, patients were randomized to receive:<br>• Ustekinumab 45 mg at Weeks 0 and 4<br>• Ustekinumab 90 mg at Weeks 0 and 4<br>• Etanercept 50 mg twice/week through Week 12<br>Treatment was interrupted at Week 12 for responders.<br>Patients in ustekinumab groups were retreated if moderate, marked, or severe disease recurred. Etanercept nonresponders switched to ustekinumab 90 mg at Weeks 16 and 20. | After being switched to ustekinumab 90 mg for 12 weeks, PASI 75 was achieved by 49% and PASI 90 was achieved by 23% of patients who did not respond to etanercept by Week 12. | AEs in >10% of patients in any treatment group (reported from Weeks 0–12 and 0–64) included nasopharyngitis, upper respiratory tract infection, headache, back pain, and injection-site reaction.<br>Rates of malignancies other than nonmelanoma skin cancer were ≤1.0%; rates of NMSC were ≤1.7%. |

Abbreviations: AE = adverse event; DB = double-blind; eow = every other week; NMSC = nonmelanoma skin cancer; OL = open-label; PASI = Psoriasis Area and Severity Index; TB = tuberculosis.
*Number randomized and treated.

**TABLE 2.** Summary of Preliminary Results or Study Designs for Phase 3 Clinical Trials of Biologics in Development for the Treatment of Moderate-to-Severe Plaque Psoriasis

| Study | *n* | Study Design | Treatment Regimens | Efficacy End Points/Outcomes | Safety End Points/Outcomes |
|---|---|---|---|---|---|
| Secukinumab | | | | | |
| FIXTURE (NCT01358578; Langley et al., 2013) | 1,306 | 52-week multicenter, randomized DB study with 8-week follow-up | Patients were randomized to receive:<br>• Secukinumab 150 mg once a week for 5 weeks and then 150 mg once monthly<br>• Secukinumab 300 mg once a week for 5 weeks and then 300 mg once monthly<br>• Etanercept 50 mg twice/week for 12 weeks and then once/week<br>• Placebo | Week-12 PASI 75 and IGA mod 2011 0/1 response:<br>• 77% and 63% with secukinumab 300 mg<br>• 44% and 27% with etanercept (both *p*s = .0250 vs. secukinumab)<br>Week-16 PASI 90 and 100 response:<br>• 72% and 37% with secukinumab 300 mg<br>• ~30% and <10% with etanercept<br>Responses to secukinumab were sustained through Week 52. | Nasopharyngitis and headache were the most common AEs.<br>Serious AEs experienced by 5.8%, 5.1%, and 6.2% of patients in the 300-mg-secukinumab, 150-mg-secukinumab, and etanercept groups, respectively. |
| SCULPTURE (NCT01406938; Mrowietz et al., 2013) | 966 | 52-week multicenter, randomized DB study with 8-week follow-up | Patients were randomized to receive:<br>• Secukinumab 150 mg once a week for 5 weeks<br>• Secukinumab 300 mg once a week for 5 weeks<br>At Week 12, patients with PASI 75 response were rerandomized to the same dose of secukinumab as continuous therapy (once/month) or as needed for relapse. | Week-12 PASI 75, PASI 90, and PASI 100 response:<br>• 90%, 64%, and 26% with secukinumab 300 mg<br>• 84%, 49%, and 16% with secukinumab 150 mg<br>Patients who achieved PASI 75 at Week 12 were more likely to maintain their response if they received secukinumab at fixed monthly intervals compared with as-needed treatment at the start of relapse. | Nasopharyngitis, upper respiratory tract infection, and headache were the most common AEs.<br>Serious AEs experienced by 6.5%–8.3% and 5.9%–6.4% of patients in the 300-mg-secukinumab and 150-mg-secukinumab groups, respectively. |
| ERASURE (NCT01365455; Elewski et al., 2013) | 738 | 52-week multicenter, randomized DB study with 8-week follow-up | Patients were randomized to receive:<br>• Secukinumab 150 mg once a week for 5 weeks and then 150 mg once monthly<br>• Secukinumab 300 mg once a week for 5 weeks and then 300 mg once monthly<br>• Placebo | Secukinumab 300 mg was more effective than 150 mg for improving PASI 75 ($p < .01$) or IGA mod 2011 0/1 ($p < .002$) response at Week 12. | Nasopharyngitis, upper respiratory tract infection, and headache were the most common AEs.<br>Serious AEs experienced by 5.4%, 5.4%, and 2.0% of patients in the 300-mg-secukinumab, 150-mg-secukinumab, and placebo groups, respectively. |

(continued)

**TABLE 2.** Summary of Preliminary Results or Study Designs for Phase 3 Clinical Trials of Biologics in Development for the Treatment of Moderate-to-Severe Plaque Psoriasis, Continued

| Study | *n* | Study Design | Treatment Regimens | Efficacy End Points/Outcomes | Safety End Points/Outcomes |
|---|---|---|---|---|---|
| Ixekizumab | | | | | |
| UNCOVER-3 (NCT01646177) | 1,225* | 12-week multicenter, randomized DB study with a multiyear extension<br>Estimated completion date: April 2019 (primary end point: July 2014) | Patients were randomized to receive:<br>• Ixekizumab 2 × 80 mg at Week 0 and then 1 × 80 mg per dosing regimen 1 to Week 12 and then switched to dosing regimen 2<br>• Ixekizumab 2 × 80 mg at Week 0 and then 1 × 80 mg per dosing regimen 2 to Week 264<br>• Etanercept 50 mg twice a week from Weeks 0 to 12 and then switched to dosing regimen 2<br>• Placebo from Weeks 0 to 12 and then switched to dosing regimen 2 | Primary outcomes are PASI and sPGA at Week 12. Secondary outcomes include PASI, sPGA, and QoL assessments at Week 12. | Safety outcomes were not specified. |
| UNCOVER-2 (NCT01597245) | 1,225* | 60-week multicenter, randomized, DB study<br>Estimated completion date: December 2018 (primary end point: September 2014) | Patients randomized to receive:<br>• Ixekizumab 2 × 80 mg at Week 0 and then 1 × 80 mg per dosing regimen 1 to Week 12<br>• Ixekizumab 2 × 80 mg at Week 0 and then 1 × 80 mg per dosing regimen 2 to Week 12<br>• Etanercept 50 mg twice a week from Weeks 0 to 12<br>• Placebo | Primary outcomes are PASI and sPGA at Week 12.<br>Secondary outcomes include PASI, sPGA, and QoL assessments at Week 60. | Safety outcomes were not specified. |
| UNCOVER-A (NCT01777191) | 180* | 12-week RCT with optional 40-week safety extension<br>Estimated completion date: January 2015 | Patients randomized to receive:<br>• Ixekizumab 80 mg administered subcutaneously with an autoinjector<br>• Ixekizumab 80 mg administered subcutaneously with a prefilled syringe | Primary outcomes are PK properties: $C_{max}$ from Days 2 to 14 and AUC from time 0 to Day 14.<br>Secondary outcomes include PASI, sPGA, number of device failures at Week 12, and QoL assessments at Week 8. | Safety outcomes were not specified. |

(continued)

**TABLE 2.** Summary of Preliminary Results or Study Designs for Phase 3 Clinical Trials of Biologics in Development for the Treatment of Moderate-to-Severe Plaque Psoriasis, Continued

| Study | *n* | Study Design | Treatment Regimens | Efficacy End Points/Outcomes | Safety End Points/Outcomes |
|---|---|---|---|---|---|
| Brodalumab | | | | | |
| AMAGINE-1 (NCT01708590) | 600* | 5-year multicenter, randomized DB study<br>Estimated completion date: September 2018 (primary end point: March 2014) | From baseline to Week 12, patients were randomized to receive:<br>• sc brodalumab 210 mg<br>• sc brodalumab 140 mg<br>• Placebo<br>At Week 12, patients in the brodalumab groups rerandomized to placebo or continued treatment. | Primary outcomes are PASI and sPGA at Week 12.<br>Secondary outcomes are PASI, sPGA, and patient symptom scores at Weeks 12 and 52. | Safety to be assessed at 12 weeks and 5 years, including AEs, AEs of interest, and presence of antibrodalumab antibodies. |
| AMAGINE-2 (NCT01708603) | 1,800* | 5-year multicenter, randomized DB study<br>Estimated completion date, September 2018 (primary end point August 2014) | From baseline to Week 12, patients were randomized to receive:<br>• sc brodalumab 210 mg<br>• sc brodalumab 140 mg<br>• sc ustekinumab according to label<br>• Placebo<br>At Week 12, patients in the brodalumab groups were rerandomized to one of four dosing schedules. | Primary outcomes are PASI and sPGA at Week 12.<br>Secondary outcomes are PASI, sPGA, and patient symptom scores at Weeks 12 and 52. | Safety to be assessed at 12 weeks and 5 years, including AEs, AEs of interest, and presence of antibrodalumab antibodies. |
| AMAGINE-3 (NCT01708629) | 1,881* | 5-year multicenter, randomized DB study<br>Estimated completion date: October 2018 (primary end point: September 2014) | From baseline to Week 12, patients were randomized to receive:<br>• sc brodalumab 210 mg<br>• sc brodalumab 140 mg<br>• sc ustekinumab according to label<br>• Placebo<br>At Week 12, patients in the brodalumab groups were rerandomized to one of four dosing schedules. | Primary outcomes are PASI and sPGA at Week 12.<br>Secondary outcomes are PASI, sPGA, and patient symptom scores at Weeks 12 and 52. | Safety to be assessed at 12 weeks and 5 years, including AEs, AEs of interest, and presence of antibrodalumab antibodies. |

Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; $C_{max}$ = maximum plasma concentration; DB = double-blind; IGA mod 2011 = Investigator's Global Assessment modified 2011; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; QoL = quality of life; sc = subcutaneous; sPGA = static Physician's Global Assessment.
*Estimated enrollment.

12 weeks, patients in the placebo group were switched to double-blind etanercept 25 mg twice weekly. From Weeks 12 to 24, PASI responses were generally maintained in a dose-dependent manner (Table 1; Leonardi et al., 2003).

Subsequently, Papp and colleagues conducted a 24-week RCT to further assess the efficacy and safety of etanercept in patients with clinically stable moderate-to-severe plaque psoriasis (Papp et al., 2005). In this study, 583 patients were randomized (1:1:1) to receive double-blind etanercept 25 or 50 mg twice weekly or placebo for 12 weeks; thereafter, all patients received open-label etanercept 25 mg twice weekly through Week 24. At the Week-12 primary end point, PASI 75 was achieved by 49% of patients in the higher dose group, 34% in the lower dose group, and 3% in the placebo group (both *p*s < .0001 vs. placebo), and PASI 90 was achieved by 21%, 11%, and 1%, respectively (both *p*s < .0001 vs. placebo). PASI responses were generally maintained through Week 24, with no apparent decrease observed in patients who underwent a dose reduction at Week 12 (Table 1; Papp et al., 2005).

### Infliximab

Infliximab, a chimeric immunoglobulin (Ig)G1 antibody that neutralizes TNFα by binding to both its soluble and transmembrane forms (Levy et al., 2012), received FDA approval in 2006 for the treatment of severe plaque psoriasis (U.S. FDA, n.d.). Infliximab is administered by intravenous infusion, with a recommended starting dose of 5 mg/kg at 0, 2, and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter (Janssen Biotech, 2013a).

In the 50-week double-blind European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study (EXPRESS), 378 patients with moderate-to-severe plaque psoriasis were randomized (4:1) to receive infusions of infliximab 5 mg/kg or placebo at Weeks 0, 2, and 6 and then every 8 weeks to Week 46. At Week 24, patients in the placebo group were switched to infliximab (Reich et al., 2005). At the Week-10 primary end point, PASI 75 was achieved by 80% of patients in the infliximab group and 3% of patients in the placebo group ($p < .0001$), and PASI 90 was achieved by 57% and 1%, respectively ($p < .0001$). PASI improvements were maintained through Week 24, and more than half of all patients achieved PASI 75 at Week 50 (Table 1; Reich et al., 2005).

The subsequent double-blind Evaluation of Infliximab for Psoriasis in a Remicade Efficacy and Safety Study was conducted to compare the efficacy and safety of infliximab 3 or 5 mg/kg administered to 835 patients at Weeks 0, 2, and 6, followed by either continuous (every 8 weeks) or intermittent (as needed) maintenance infusions through Week 50 (Menter et al., 2007). At the Week-10 primary end point, PASI 75 was achieved by 70% of patients in the lower dose group, 76% of the higher dose group, and 2% of the placebo group (both *p*s < .001 vs. placebo), and PASI 90 was achieved by 37%, 45%, and 0.5%, respectively (both *p*s < .001 vs. placebo). At Week 50, PASI scores were better maintained with continuous versus intermittent therapy within each group and with the higher versus lower dose (Table 1; Menter et al., 2007).

### Adalimumab

Adalimumab was the first fully human IgG1 monoclonal antibody to TNFα approved for the treatment of moderate-to-severe plaque psoriasis (Levy et al., 2012). Adalimumab received FDA approval for this indication in 2008 (U.S. FDA, n.d.), with recommended subcutaneous administration at an initial dose of 80 mg, followed by 40 mg every other week (eow) starting 1 week after the initial dose (AbbVie, 2013). With proper training, adalimumab can be self-administered with single-use pens or prefilled syringes (AbbVie, 2013).

In a 60-week double-blind RCT in 147 patients with moderate-to-severe plaque psoriasis, patients were randomized (1:1:1) to receive adalimumab 80 mg at Weeks 0 and 1, then adalimumab 40 mg every week; adalimumab 80 mg at Week 0, and then adalimumab 40 mg eow; or placebo for 12 weeks. At Week 12, patients taking adalimumab could continue taking their assigned dose for a 48-week extension, and patients in the placebo group were switched to adalimumab 80 mg at Week 12 and then adalimumab 40 mg eow (Gordon et al., 2006). For the primary end point, PASI 75 was achieved at Week 12 by 80% of patients taking adalimumab once weekly, 53% of those taking adalimumab eow, and 4% of the placebo group (both *p*s < .001 vs. placebo); PASI 90 was achieved by 48% and 24% of patients in the active groups, respectively (PASI 90 data not provided for placebo group), and PASI 100 was achieved by 26%, 11%, and 0%, respectively (both *p*s < .001 vs. placebo). PASI responses were sustained through 60 weeks of treatment for most patients (Table 1; Gordon et al., 2006).

In the randomized controlled evaluation of adalimumab every other week in moderate-to-severe psoriasis, Menter and colleagues evaluated the short- and long-term efficacy and safety of adalimumab as a continuous or interrupted therapy (Menter et al., 2008). Patients ($n = 1{,}212$) were randomized (2:1) to receive an initial dose of adalimumab 80 mg at Week 0 followed by adalimumab 40 mg eow or placebo for 15 weeks in a double-blind fashion. From Weeks 17 to 31, all patients received open-label adalimumab of 40 mg eow. Patients who were originally randomized to active treatment and who achieved PASI 75 at Week 33 were rerandomized to adalimumab of 40 mg eow or placebo through Week 52. At the Week-16 primary end point, PASI 75 was achieved by 71% of the adalimumab group and 7% of the placebo group ($p < .001$), and PASI 90 was achieved by 45% and 2%, respectively ($p < .001$). Between Weeks 33 and 52, PASI improvements were lost in 28% of patients rerandomized to placebo compared with 5% of patients who received continuous adalimumab ($p < .001$; Table 1; Menter et al., 2008).

### *Safety and Tolerability of TNFα Antagonists*

Overall, the RCTs summarized in Table 1 showed that etanercept, infliximab, and adalimumab are generally safe and well tolerated, with similar AE profiles. However, a number of rare but serious safety issues have been observed in large patient registries and in longer-term safety evaluations, including demyelination, infections, tuberculosis, reactivation of hepatitis B, malignancies, lymphoma, and major adverse cardiovascular events (MACE; Papp, Dekoven, et al., 2012; Rustin, 2012). Black-box warnings related to these safety concerns as well as other warnings and precautions, contraindications, required monitoring, and known drug–drug interactions are summarized in Table 3.

Case reports of worsening or new-onset congestive heart failure (CHF) have been reported with TNFα antagonists; thus, it is recommended that these agents be used with caution in patients with a history of CHF, and infliximab >5 mg/kg is contraindicated in patients with moderate-to-severe CHF (Papp, Dekoven, et al., 2012). However, it should be noted that a meta-analysis of 22 RCTs involving more than 10,000 patients treated with biologics for plaque psoriasis failed to show an association between use of biologic agents and MACE rates (Ryan et al., 2011). In addition to the broad warnings about the risk for malignancies listed in Table 3, periodic skin examinations should be considered for all patients, especially those with other risk factors for skin cancer, such as prior treatment with psoralen plus ultraviolet A light or cyclosporine (Kamangar, Neuhaus, & Koo, 2012). Patients taking infliximab or adalimumab should also be monitored for the development of antidrug antibodies, as these can lower drug-serum concentrations and reduce clinical efficacy (Hsu, Snodgrass, & Armstrong, 2014). Antidrug antibodies have also been observed in clinical studies of etanercept, but these antibodies are nonneutralizing and are not associated with any apparent changes in clinical response (Hsu et al., 2014).

## IL-12/IL-23 INHIBITOR

Ustekinumab is a fully humanized IgG1 monoclonal antibody specific for the common p40 subunit of IL-12 and IL-23, which prevents interaction between these cytokines and their receptor and inhibits T-cell differentiation (Levy et al., 2012). Ustekinumab was approved by the FDA in 2009 for the treatment of moderate-to-severe plaque psoriasis (U.S. FDA, n.d.), with recommended subcutaneous injections at Weeks 0 and 4 and then every 12 weeks (Janssen Biotech, 2013b). The recommended ustekinumab dose is 45 mg for patients weighing ≤100 kg (220 lbs) and 90 mg for patients weighing >100 kg (220 lbs; Janssen Biotech, 2013b). With proper training, ustekinumab can be self-administered with single-use prefilled syringes (Janssen Biotech, 2013b).

The double-blind Psoriasis followed by long-term extension-1 (PHOENIX 1, $n$ = 766; Leonardi et al., 2008) and Extension-2 (PHOENIX 2, $n$ = 1,230; Papp et al., 2008) RCTs evaluated the efficacy and safety of ustekinumab (45 or 90 mg) administered at Weeks 0 and 4 and then every 12 weeks, compared with placebo given at Weeks 0 and 4 with crossover to ustekinumab at Week 12. At the Week-12 primary end point in PHOENIX 1 (Leonardi et al., 2008), PASI 75 was achieved by 67% of the 45-mg group, 66% of the 90-mg group, and 3% of the placebo group (both $p$s < .0001 vs. placebo), and PASI 90 was achieved by 42%, 37%, and 2% of patients, respectively (both $p$s < .0001 vs. placebo). Then, PASI 75 responders receiving ustekinumab were rerandomized at Week 40 to their current treatment or placebo. Over the course of this 76-week study, patients who received continuous ustekinumab therapy maintained their PASI improvements better than those who were withdrawn from treatment at Week 40 (Table 1; Leonardi et al., 2008).

Similarly, in PHOENIX 2, at the Week-12 primary end point, PASI 75 was achieved by 67% of the 45-mg group, 76% of the 90-mg group, and 4% of the placebo group (both $p$s < .0001 vs. placebo), and PASI 90 was achieved by 42%, 51%, and 1%, respectively (both $p$s < .0001 vs. placebo; Papp et al., 2008). At Week 28, ustekinumab partial responders (PASI 50 to <75) were rerandomized to continue receiving the same dose every 12 weeks or to receive intensified therapy with the same dose every 8 weeks through Week 52. Results indicated that dose intensification to 90 mg every 8 weeks may elicit a full response in patients who only partially respond to initial therapy (Table 1; Papp et al., 2008).

The first head-to-head trial of biologic agents for the treatment of moderate-to-severe psoriasis was the 64-week Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial, which compared ustekinumab 45 or 90 mg at Weeks 0 and 4 versus etanercept 50 mg twice weekly for 12 weeks in 903 patients (Griffiths et al., 2010). At Week 12, PASI 75 was achieved by 67% of patients treated with ustekinumab 45 mg and 74% of patients treated with ustekinumab 90 mg, compared with 57% of those who received etanercept 50 mg ($p$ = .01 and $p$ < .001, respectively); PASI 90 was achieved by 36%, 45%, and 23% of patients, respectively (both $p$s < .001 vs. etanercept). At Week 12, patients in the etanercept group who did not have a response (i.e., still had moderate, marked, or severe psoriasis) received ustekinumab at Weeks 16 and 20. Switching from etanercept to ustekinumab resulted in achievement of PASI 75 by 49% of patients (Table 1; Griffiths et al., 2010).

### *Safety and Tolerability of the IL-12/IL-23 Inhibitor*

The PHOENIX 1 and 2 trials, as well as long-term safety studies, have shown that ustekinumab is generally safe and well tolerated (Table 1); the most common AEs with ustekinumab are similar to those observed with TNFα antagonists (e.g., nasopharyngitis, upper respiratory infection, headache, injection-site reactions, arthralgias; Leonardi et al., 2008; Papp et al., 2008; Papp, Griffiths, et al., 2013;

**TABLE 3.** Safety Warnings and Considerations Associated With Approved Biologic Agents (AbbVie, 2013; Immunex Corporation, 2013; Janssen Biotech, 2013a, 2013b)

| Safety Issue | Etanercept | Infliximab | Adalimumab | Ustekinumab |
|---|---|---|---|---|
| Black-box warnings | • Serious infections (i.e., TB, bacterial sepsis, invasive fungal infections, other opportunistic pathogens)<br>• Lymphoma and other malignancies | • Serious infections (i.e., TB, bacterial sepsis, invasive fungal infections, other opportunistic pathogens)<br>• Lymphoma and other malignancies<br>• Hepatosplenic T-cell lymphoma in patients receiving azathioprine or 6-mercaptopurine | • Serious infections (i.e., TB, bacterial sepsis, invasive fungal infections, other opportunistic pathogens)<br>• Lymphoma and other malignancies<br>• Hepatosplenic T-cell lymphoma in patients receiving azathioprine or 6-mercaptopurine | • None |
| Other warnings | • Demyelinating disease exacerbation or new onset<br>• CHF worsening or new onset<br>• Pancytopenia or aplastic anemia<br>• Anaphylaxis or serious allergic reaction<br>• Autoantibodies rarely associated with development of lupus-like syndrome or autoimmune hepatitis | • Demyelinating disease exacerbation or new onset<br>• CHF worsening or new onset<br>• Cytopenias<br>• Hypersensitivity, serious infusion reactions, anaphylaxis, serum sickness<br>• Autoantibodies rarely associated with development of lupus-like syndrome<br>• Hepatotoxicity | • Demyelinating disease exacerbation or new onset<br>• CHF worsening or new onset<br>• Cytopenias, pancytopenia<br>• Anaphylaxis or serious allergic reaction<br>• Autoantibodies rarely associated with development of lupus-like syndrome | • Serious infections (e.g., mycobacteria, salmonella, BCG vaccination, TB)<br>• Malignancies<br>• Anaphylaxis or serious allergic reaction<br>• Reversible posterior leukoencephalopathy syndrome |
| Contraindications | • Sepsis | • Doses > 5 mg/kg in patients with moderate-to-severe HF | • None | • None |
| Precautions | • Pregnancy category B<br>• Avoid in patients with Wegener's granulomatosis<br>• Use with caution in patients with moderate-to-severe alcoholic hepatitis | • Pregnancy category B | • Pregnancy category B | • Pregnancy category B |
| Recommended monitoring | • TB (even if initial latent test is negative)<br>• Infections<br>• Reactivation of hepatitis B | • TB (even if initial latent test is negative)<br>• Infections<br>• Reactivation of hepatitis B<br>• Jaundice or elevated liver enzymes | • TB (even if initial latent test is negative)<br>• Infections<br>• Reactivation of hepatitis B<br>• Elevated liver enzymes | • Evaluate for TB before initiating therapy<br>• Infections |

(continued)

**TABLE 3.** Safety Warnings and Considerations Associated With Approved Biologic Agents (AbbVie, 2013; Immunex Corporation, 2013; Janssen Biotech, 2013a, 2013b), Continued

| Safety Issue | Etanercept | Infliximab | Adalimumab | Ustekinumab |
|---|---|---|---|---|
| Drug interactions | • Live vaccines<br>• Anakinra<br>• Abatacept<br>• Cyclophosphamide | • Live vaccines<br>• Anakinra<br>• Abatacept<br>• Tocilizumab | • Live vaccines<br>• Anakinra<br>• Abatacept | • Live vaccines |
| Antidrug antibodies | • ~6% of patients develop no neutralizing antibodies to etanercept | • Development of anti-infliximab antibodies reported in up to 51% of patients with psoriasis | • ~8% of patients develop antibodies to adalimumab | • ~6% of patients develop antibodies to ustekinumab |

Abbreviations: BCG = bacillus Calmette–Guérin; CHF = congestive heart failure; TB = tuberculosis.

Wu et al., 2012). Analyses of safety data from more than 3,000 patients treated with ustekinumab for up to 5 years showed no dose-related or accumulated toxicities and low rates of antidrug antibody formation (Papp, Griffiths, et al., 2013; Wu et al., 2012). In the Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial study, the safety profile of ustekinumab was similar to that of etanercept; the most notable disparity was the reported rates of injection-site reaction AEs (4% with ustekinumab vs. 25% with etanercept; Griffiths et al., 2010). As with the TNFα antagonists, serious infections and malignancies have been observed as rare but potentially serious side effects of ustekinumab; however, unlike the TNFα antagonists, ustekinumab has no black-box warnings (Table 3; Janssen Biotech, 2013b). Although studies to date support that ustekinumab is generally safe and well tolerated, the most current (2009) guidelines from the British Association of Dermatology recommend ustekinumab as a second-line biologic therapy because the long-term safety profiles of the TNFα antagonists are better established (Smith et al., 2009). Furthermore, increased MACE rates were observed in early-stage trials of ustekinumab and briakinumab (an IL-12/IL-23 inhibitor that was in development but was withdrawn in 2011) compared with placebo, which prompted concern about the cardiovascular safety of targeting these cytokines (Ryan et al., 2011). However, recent studies have failed to show an increased risk for MACE with ustekinumab relative to placebo or TNFα antagonists (Papp, Griffiths, et al., 2013; Ryan et al., 2011).

## IL-17 INHIBITORS

As discussed in the previous sections, several recent studies have identified IL-17A as a central driver of the direct activation of keratinocytes in psoriasis, and three biologic agents (secukinumab, ixekizumab, and brodalumab) that target members of the IL-17 family or their receptors are currently in research clinical development for the management of moderate-to-severe plaque psoriasis (Chiricozzi et al., 2011; Chiricozzi & Krueger, 2013; Krueger et al., 2012). Unlike the other cytokines implicated in the pathogenic psoriasis pathway, it is hypothesized that IL-17A is a downstream cytokine, meaning that altering its levels may have fewer adverse effects on other biologic processes than alterations in TNFα or IL-12/IL-23 levels (Girolomoni, Mrowietz, & Paul, 2012).

### *Secukinumab*

Secukinumab (AIN457) is a fully human IgG1κ monoclonal antibody that selectively binds to and neutralizes IL-17A (Rich et al., 2013). Several phase 3 studies are evaluating the efficacy and safety of subcutaneous secukinumab for the treatment of plaque psoriasis (Table 2). The pivotal Full year Investigative eXamination of secukinumab versus eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis (FIXTURE) study consisted of four periods:

screening, induction (of 12 weeks), maintenance (of 40 weeks), and follow-up (of 8 weeks; Langley et al., 2013). Patients ($n$ = 1,306) were randomized to receive secukinumab 150 or 300 mg once weekly for 5 weeks followed by once-monthly dosing thereafter, etanercept 50 mg twice weekly for 12 weeks followed by 50 mg once weekly thereafter, or placebo. Overall, it was observed that patients' skin cleared faster, and improvements were maintained longer with secukinumab compared with etanercept. At Week 12, assessment of the coprimary end points of PASI 75 and Investigator's Global Assessment showed that the efficacy of secukinumab was superior to placebo ($p < .0001$) and to etanercept ($p = .0250$; Langley et al., 2013). In the Study Comparing secukinumab Use in Long-term Psoriasis maintenance therapy: fixed regimens vs reTreatment Upon start of RElapse (SCULPTURE), 966 patients received secukinumab 150 or 300 mg once weekly for 5 weeks (Mrowietz et al., 2013). Those who achieved PASI 75 were rerandomized at Week 8 to the same doses at either once-monthly intervals or as needed in response to psoriasis relapse. Patients who achieved PASI 75 at Week 12 were more likely to maintain their response if they received secukinumab at fixed monthly intervals compared with as-needed treatment at the start of relapse (Mrowietz et al., 2013). Results from SCULPTURE (Mrowietz et al., 2013) and the Efficacy of Response and Safety of 2 Fixed Secukinumab Regimens in Psoriasis study showed that secukinumab of 300 mg was more effective than secukinumab 150 mg (Table 2; Elewski et al., 2013). The most common AEs across these phase 3 studies were nasopharyngitis (exposure-adjusted incidence rates: 18.1%–31.1%, secukinumab 150 mg; 18.5%–35.2%, secukinumab 300 mg; 35.7% of etanercept; and 30.8%–32.8% of placebo), upper respiratory tract infection (5.8%–12.7%, 6.6%–11.1%, 6.4%, and 3.0%–3.5%, respectively), and headache (7.5%–12.4%, 5.0%–15.7%, 15.2%, and 15.1%–29.6%, respectively; Elewski et al., 2013; Langley et al., 2013; Mrowietz et al., 2013). Serious AE rates were 5.1%–6.4% with secukinumab 150 mg, 5.4%–8.3% with secukinumab 300 mg, 6.2% with etanercept, and 2.0%–2.1% with placebo.

In a regimen-finding, phase 2 study, patients ($n$ = 404) were randomized to receive either a single injection of secukinumab 150 mg at Week 0; "early" secukinumab 150 mg at Weeks 0, 1, 2, and 4; once-monthly secukinumab 150 mg at Weeks 0, 4, and 8; or placebo (Rich et al., 2013). At Week 12, PASI 75 was achieved by 11% with a single injection, 54.5% with early treatment, and 42% with once-monthly treatment, compared with 1.5% with placebo ($p < .001$ for early and once-monthly regimens vs. placebo); PASI 90 was achieved by 3%, 32%, 17%, and 1.5% of patients, respectively ($p < .001$ for early and once-monthly regimens vs. placebo; Rich et al., 2013). In a second regimen-finding, phase 2 study ($n$ = 125), PASI 75 was achieved at Week 12 by 82% of patients who received secukinumab 150 mg three times and 57% of patients who received secukinumab 75 mg three times (at Weeks 0, 4, and 8), compared with 9% with placebo ($p < .001$ and $p = .002$, respectively; Papp, Langley, et al., 2013). The types and frequencies of AEs, as well as rates of serious AEs, in the phase 2 studies (Papp, Langley, et al., 2013; Rich et al., 2013) were similar to those reported in the abovementioned phase 3 studies.

### Ixekizumab

Ixekizumab (LY2439821) is a humanized IgG4 monoclonal antibody that binds and neutralizes IL-17A. In a phase 2 RCT, 142 patients with moderate-to-severe plaque psoriasis were randomized to receive subcutaneous ixekizumab (10, 25, 75, or 150 mg) or placebo at Weeks 0, 2, 4, 8, 12, and 16, with follow-up through 20 weeks (Leonardi et al., 2012). At the Week-12 primary end point, PASI 75 was achieved by 82%, 83%, 77%, and 29% of patients treated with ixekizumab 150, 75, 25, and 10 mg, respectively, compared with 8% with placebo ($p < .001$ for all doses except 10 mg); PASI 90 was achieved at the same time point by 71%, 59%, 50%, and 18% with the four ixekizumab doses, respectively, compared with no patient with placebo ($p < .001$ for all doses except 10 mg). The most common AEs included nasopharyngitis (ixekizumab, 10%–14%; placebo, 19%), upper respiratory infection (3%–10% and 4%), injection-site reaction (0%–10% and 0%), and headache (3%–14% and 4%). The AEs did not appear to be dose related, and no serious AEs were reported (Leonardi et al., 2012).

Several phase 3 studies of ixekizumab are ongoing. The study designs for these trials are summarized in Table 2.

### Brodalumab

Brodalumab (AMG 827) is a human IgG2 monoclonal antibody that binds to and blocks IL-17RA, the receptor subunit shared by IL-17A, IL-17F, and IL-17A/F heterodimer ligands. In a phase 2 RCT, 198 patients with moderate-to-severe plaque psoriasis were randomized to receive subcutaneous brodalumab (70, 140, 210, or 280 mg) or placebo on Day 1 and at Weeks 1, 2, 4, 6, 8, and 10 (280 mg was only given on Day 1 and at Weeks 4 and 8), with a follow-up assessment at 12 weeks (Papp, Leonardi, et al., 2012). At the Week-12 primary end point, mean PASI improvement from baseline was 45%, 86%, 86%, and 76% among patients treated with brodalumab 70, 140, 210, and 280 mg, respectively, compared with 16% in the placebo group (all $p$s < .001). At the same time point, PASI 75 was achieved by 33%, 77%, 82%, and 67% of patients in the brodalumab groups, respectively, compared with no patients who received placebo (all $p$s < 0.001); PASI 90 was achieved by 18%, 72%, 75%, and 57% of patients in the four brodalumab groups, respectively, and by zero patients in the placebo group (all $p$s < .01). The most common AEs included nasopharyngitis (brodalumab, 8%; placebo, 8%), upper respiratory infection (8% and 5%),

injection-site erythema (6% and 3%), arthralgia (4% and 3%), pain in extremity (5% and 0%), and nausea (4% and 3%). With the exception of nasopharyngitis and nausea, these events were most common in the high-dose group. Across the brodalumab groups, serious AEs were reported by two patients (renal colic and grade 3 neutropenia; Papp, Leonardi, et al., 2012).

Several phase 3 studies of brodalumab are ongoing. The study designs for these trials are summarized in Table 2.

## TREATMENT CONSIDERATIONS

In terms of efficacy, available biologic therapies can be expected to provide good PASI responses in patients with moderate-to-severe plaque psoriasis; however, efficacy differences exist between the various agents. Although head-to-head data are limited, data suggest that ustekinumab and infliximab may provide better efficacy than etanercept and adalimumab (Bansback et al., 2009; Griffiths et al., 2010; Lin, Ringold, & Devine, 2012; Reich, Burden, Eaton, & Hawkins, 2012) and that secukinumab may be superior to etanercept (Langley et al., 2013). Results from ongoing head-to-head studies (e.g., ixekizumab vs. etanercept [NCT01597245] and brodalumab vs. ustekinumab [NCT01708603 and NCT01708629]) may further identify differences among the biologic therapies and help define a treatment hierarchy for managing patients with plaque psoriasis.

Available evidence suggests that the IL-17 inhibitors may provide an alternative approach to achieving targeted efficacy. As described herein, in clinical studies to date, a substantial proportion of patients have reported near-complete psoriasis clearance with IL-17A inhibitors, with maintenance of these improvements for up to 1 year (e.g., one study showed up to approximately two thirds of patients achieving PASI 90 at 1 year; Langley et al., 2013). This is a very relevant observation, as lack of efficacy and loss of efficacy over time are the most commonly cited reasons patients have given for discontinuing treatment with TNFα antagonists; for example, in a survey of over 1,000 patients who discontinued their psoriasis treatment regimen, lack of efficacy was the main reason patients discontinued TNFα therapy (reported by up to 34% of patients), followed by loss of efficacy over time (reported by up to 32% of patients; Yeung, Wan, et al., 2013).

For patients who do not achieve an adequate response with conventional systemic therapy or a previous biologic therapy, switching to a different biologic agent is a valid treatment strategy (Gottlieb et al., 2012; Strober et al., 2011). For example, in one study, roughly two thirds of patients who had an inadequate response to etanercept achieved cleared or minimal disease 10 weeks after switching to infliximab (Gottlieb et al., 2012). Similarly, a study by Strober and colleagues showed that more than half of patients who switched to adalimumab achieved cleared or minimal disease after having an inadequate response to etanercept, methotrexate, or narrow-band ultraviolet B therapy.

Safety and tolerability are also important factors when choosing psoriasis treatments. In a survey of expert European dermatologists, long-term safety was identified as the most important attribute these physicians consider when selecting a biologic agent to treat psoriasis (Guibal, Iversen, Puig, Strohal, & Williams, 2009). Because available biologics are all generally well tolerated, with similar long-term safety profiles and low reported rates of serious AEs, the choice of therapy is usually based on each patient's underlying risk factors for serious infection and malignancy. For instance, TNFα antagonists should be used with caution in patients with CHF or risk factors for developing this condition (AbbVie, 2013; Immunex Corporation, 2013; Janssen Biotech, 2013a). Weight gain is also a potentially undesirable side effect that has been observed in patients taking TNFα inhibitors but not the IL-12/IL23 inhibitor ustekinumab (Gisondi et al., 2013), so it may be advisable to avoid these agents when obesity or weight gain are significant concerns. Early cardiovascular safety concerns with IL-12/IL-23 inhibitors (Ryan et al., 2011) may warrant caution when using ustekinumab until larger-scale, longer-term data are available on these risks. Although the long-term safety profiles of IL-17 inhibitors have yet to be confirmed, it has been hypothesized that, by providing more downstream-targeted therapy than existing biologics, these agents may have a more favorable AE profile, offering a new variant in the options for patients with psoriasis (Girolomoni et al., 2012).

Dosing frequency and route of administration may affect patient and physician preferences for one biologic agent over another, with less-frequent dosing often the preferred option for both providers and patients (Richter, Anton, Koch, & Dennett, 2003). Of the approved agents, ustekinumab has the most convenient dosing schedule, with administration required every 12 weeks after the initial dosing period (Sivamani et al., 2013). Many patients may also prefer self-administration over intravenous infusion, which may make infliximab a less desirable choice than the other available biologics that can all be self-administered by subcutaneous injection (Scarpato et al., 2010). Some biologic agents currently in development may be available as oral formulations (e.g., apremilast, tofacitinib), which may be more appealing than injectables to many patients (Schafer, 2012).

Patient-reported outcomes (e.g., improving quality of life and reducing feelings of frustration, self-consciousness, and depression) are an area of growing interest and should also be considered when deciding on the best treatment approach (Heller et al., 2012). Speaking with patients about their treatment goals, life circumstances, and preferred approach to disease management may help healthcare professionals decide which options are most suitable for different individuals (Uhlenhake & Mehregan, 2012). Noncompliance with therapy may be a sign that a patient's therapy choice is not right for him or her, and understanding the causes of noncompliance may assist in providing

better guidance for an alternative choice (Uhlenhake & Mehregan, 2012).

Special consideration is also required when deciding whether to use biologic agents to treat children with psoriasis. No biologic agents are currently approved in the United States to treat pediatric psoriasis, and data are limited in this population. However, etanercept and adalimumab are approved in the United States to treat juvenile idiopathic arthritis, and infliximab is approved to treat pediatric Crohn's disease and ulcerative colitis (AbbVie, 2013; Immunex Corporation, 2013; Janssen Biotech, 2013a). The TNFα inhibitors are also approved to treat pediatric psoriasis in the European Union and Brazil (Luu & Cordoro, 2013). One RCT of etanercept (Paller et al., 2008) and numerous case studies of TNFα antagonists support their efficacy in the treatment of pediatric patients with moderate-to-severe psoriasis (Luu & Cordoro, 2013). Data are extremely limited on the use of ustekinumab in pediatric patients, but a phase 3 study with this agent is ongoing in adolescents with moderate-to-severe plaque psoriasis (NCT01090427). By far, the greatest concern with using biologics in pediatric patients is the lack of long-term safety data in this population; given this limitation, biologic agents should be used with caution in children.

## CONCLUSIONS

Biologic agents used for the management of moderate-to-severe plaque psoriasis are generally well-tolerated and effective treatment options that may result in clinical improvements. Not all agents work in all patients; therefore, it is critical to be aware of the multiple treatment options, many with different mechanisms of action. New agents in development may provide alternative options to existing biologic therapies for the achievement of rapid and sustained clearance of psoriatic lesions. ■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