New and Emerging Therapies in Psoriasis
Craig L. Leonardi, MD,* and Kenneth B. Gordon, MD†

Abstract
This article discusses the scientific rationale for the use of cytokine inhibitors, including ustekinumab, an inhibitor of the interleukin (IL)-12 and IL-23 pathways in psoriasis. Also addressed are the efficacy and safety data for this agent, as well as for several emerging therapies that target other cytokine pathways in psoriasis: the IL-17 inhibitors secukinumab, ixekizumab, and brodalumab; the IL-23 blocker tildrakizumab; and the small-molecule kinase inhibitors apremilast (a phosphodiesterase-4 blocker) and tofacitinib (a Janus kinase inhibitor).

Keywords
Apremilast; brodalumab; interleukin-12/23 inhibitors; interleukin-17 inhibitors; ixekizumab; JAK, Janus kinase inhibitors; phosphodiesterase-4 inhibitors; psoriasis treatment; secukinumab; tildrakizumab; tofacitinib; tumor necrosis factor inhibitors; ustekinumab

Developed and introduced within the last 5 years, agents that block inflammatory pathways other than tumor necrosis factor (TNF) represent new options for treating psoriasis (Table). Among them are ustekinumab, a monoclonal antibody that targets the p40 subunit that is shared by IL-12 and IL-23 (IL-12/23); three IL-17 inhibitors—secukinumab, ixekizumab, and brodalumab; the IL-23 blocker tildrakizumab; and two small molecules that target the kinase pathway—apremilast (a phosphodiesterase-4 [PDE-4] inhibitor) and tofacitinib (a Janus kinase [JAK] inhibitor).

As the Figure illustrates, blockade of IL-12 results in down-regulation of a type 1 response and a consequent decrease in production of interferon-γ and TNF-α. Blockade of IL-23 results in down-regulation of T-helper (Th17) and Th22 responses, reducing levels of a number of cytokines, including IL-17, all their isoforms including A and F, as well as TNF-α.

It is known that production of IL-17 cytokines is increased in psoriatic skin, induces neutrophilia, and enhances both inflammation and angiogenesis. IL-22 levels correspond to disease activity. In psoriasis, IL-22 levels are increased in both skin and plasma, and IL-22 is known to induce keratinocyte hyperproliferation.

Ustekinumab
The IL-12/23 inhibitor ustekinumab, a subcutaneously administered agent, was approved by the US Food and Drug Administration (FDA) in 2009 for the treatment of patients 18 years of age or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The Psoriasis Followed by Long-Term Extension (PHOENIX) studies, two phase III multicenter, randomized, double-blind, placebo-controlled trials, were the pivotal trials that led to the approval of the drug for psoriasis.* The PHOENIX 1 study is discussed below. The results of a recently completed phase III trial of ustekinumab (PSUMMIT 1) led to the approval of this agent for psoriatic arthritis.†

PHOENIX 1 Study
PHOENIX 1 was an efficacy study of long-term use of ustekinumab for up to 76 weeks. A randomized-withdrawal design was used (described below); the primary end point was the proportion of patients who achieved a 75% improvement in the Psoriasis Area Severity Index (PASI 75) from baseline. Chief among the secondary end points were the proportion of patients determined to be clear or minimal at week 12, as well as time to loss of the PASI 75 response in the group on maintenance therapy compared to the group withdrawn from treatment at week 40.

The 766 patients in the study were randomized into three groups (in a 1:1:1 ratio) to receive ustekinumab 45 mg, ustekinumab 90 mg, or placebo at weeks 0 and 4, and then every 12 weeks thereafter. At week 12, the patients who had been assigned to the placebo group at baseline were crossed over to receive ustekinumab 45 mg or ustekinumab 90 mg at weeks 12 and 16, and then every 12 weeks thereafter.

At week 28, patients who had not achieved a 50% improvement on the PASI (PASI 50) discontinued ustekinumab. Those who had achieved PASI 50 but had a response less than PASI 75 at either week 28 or 40 began a dosage schedule of every 8 weeks.

*Both ustekinumab and briakinumab are IL-12/23 inhibitors that were demonstrated to be effective in phase III clinical trials in patients with psoriasis. However, because of unresolved safety concerns (cardiovascular events, squamous cell carcinoma, and serious infections) that emerged in the studies of briakinumab, further development of this agent currently is on hold.

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Address reprint requests to: Craig L. Leonardi, MD, Central Dermatology, 1034 S. Brentwood Boulevard, St. Louis, MO 63117; craig.leonardi@centralderm.com.

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At week 40, patients who had been randomized to ustekinumab at baseline and who had achieved a PASI 75 response at week 28 or 40 were randomized again to one of two groups: half received ustekinumab every 12 weeks (maintenance therapy) and the other half received placebo. In those randomized to the placebo group at week 40 who subsequently lost at least 50% of the PASI improvement achieved at week 40, treatment with ustekinumab was reinstituted on their previous regimen (interrupted therapy).

**Efficacy.** At week 12, significantly more patients in both the 45-mg and the 90-mg treatment groups had achieved the primary end point—PASI 75—than did those in the placebo group ($P<0.0001$). Specifically, PASI 75 was achieved at week 12 by 67% of patients in the 45-mg treatment arm ($n=255$), 66% of those in the 90-mg group ($n=256$), and 3% of those who received placebo ($n=255$). Patients who had been randomized to the placebo group initially achieved similar results in the crossover phase of the trial.3

Rapid onset of efficacy was an important finding in this study, as was long duration of improvement. At week 40, the long-term responders were randomized to either withdrawal or maintenance groups. Through year 1, persistence of PASI 75 (that is, time to loss of the PASI 75 response) was significantly better in the patients on maintenance therapy than in those in whom treatment was withdrawn ($P<0.0001$). In addition, those on maintenance therapy maintained PASI 50, PASI 75, PASI 90, and Physician Global Assessment responses up to at least week 76.3

Decline following cessation of therapy in the withdrawal groups began gradually after 4 weeks (ie, by week 44); the rate of decline accelerated after week 52. The withdrawal groups had 96% improvement at week 40, and, by week 64, this rate had dropped to about 40%. The median time to loss of PASI 75 response was approximately 15 weeks. No cases of rebound (rapid recurrence of symptoms) occurred in this trial.3

**IL-12/23 Safety Data**

Several important, potentially drug-related serious adverse events were seen in the phase III trials of ustekinumab in psoriasis—both PHOENIX 13 and PHOENIX 24—including infection, cancer, cardiovascular issues, and death. Among patients who received 45 mg of ustekinumab, one case each of angina and stroke occurred. Among those who received 90 mg of ustekinumab, the infections were two cases of cellulitis and one case of disseminated herpes zoster. At that same dosage level, one patient underwent coronary artery bypass surgery and one patient died. The single fatality was an unwitnessed death that was determined to result from congestive cardiomyopathy in a patient who had had symptoms several months prior to the start of the study.

Recently, Papp and colleagues5 presented 5-year postmarketing surveillance data on 3,117 patients with a total of 8,998 patient years of experience: 3,766 patient years of experience with the 45-mg dose of ustekinumab and 5,232 patient years of experience with the 90-mg dose.

The events of interest in the 5-year cumulative data (through 2011) included serious infections (1.10/100 patient years [95% CI, 0.89-1.14]), nonmelanoma skin cancer (0.52/100 patient years [95% CI, 0.39-0.70]), malignancy other than nonmelanoma skin cancer (0.60/100 patient years [95% CI, 0.45-0.78]), and major adverse cardiovascular events (MACE) (0.44/100 patient years [95% CI, 0.32-0.61]).5

### TABLE Biologic Agents and Small Molecules in Psoriasis

<table>
<thead>
<tr>
<th>Class/Target Pathway</th>
<th>Generic Drug Name</th>
<th>Current Status*</th>
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<tr>
<td><strong>Biologic agents</strong></td>
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<tr>
<td>TNF-α inhibition</td>
<td>Adalimumab</td>
<td>Approved for psoriasis, 2008</td>
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<td></td>
<td>Etanercept</td>
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<td>Infliximab</td>
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<td>IL-12 and IL-23 inhibition</td>
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<td>Direct inhibition of IL-17</td>
<td>Brodalumab</td>
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<tr>
<td></td>
<td>Ilekizumab</td>
<td>Phase III trials under way</td>
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<td>Phase III trials complete</td>
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<td>IL-23 blocker</td>
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<td><strong>Small molecules</strong></td>
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<td>PDE-4 inhibitor</td>
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<tr>
<td>JAK inhibitor</td>
<td>Tofacitinib</td>
<td>Phase III trials complete</td>
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IL=interleukin; JAK=Janus kinase; PDE-4=phosphodiesterase-4; TNF=tumor necrosis factor.

*The status listed for each agent is current as of March 1, 2014.
A comparison of the year-by-year data over this same time period (2007 through 2011) shows that the number of serious adverse events decreases with time.5

With regard to MACE, specifically—that is, heart attack, stroke, or cardiovascular death due to heart attack or stroke—the data on ustekinumab are fairly constant over the years. However, during the first year of experience with ustekinumab (the period covering the phase III trials), a small increase was seen in MACE, particularly in the first 12 weeks. This increase was then followed by a reduction in MACE events, suggesting that by reducing systemic inflammation, improvement in cardiovascular status occurred.5

An analysis of the cumulative data from the controlled trials of ustekinumab, briakinumab, and three TNF inhibitors (infliximab, etanercept, and adalimumab) showed that a total of 10 events occurred during active treatment with the IL-12/23 inhibitors vs none in the placebo groups.6 Statistically, using the Mantel-Haenszel method, the difference in MACE between the active-treatment and placebo populations was not significant (P=0.11). In the TNF-inhibitor trials, one event was seen in the active-treatment and one occurred in the placebo group (P=0.94).

It is important to note that the clinical trials were not powered to detect rare events and that statistical analyses performed on the same data sets have yielded conflicting results with respect to MACE risk.7 Thus, clinicians are advised to consider all options in selecting biologic treatment. As Kerdel and Strober8 discussed in their article on page 31S of this supplement, the TNF inhibitors have a cardioprotective effect, and patients with psoriasis have an increased incidence of cardiovascular risk factors. Additional experience with these agents over time will help clarify the significance of some of the safety signals that have been seen in the clinical studies to date.

**IL-12/23 Inhibitor vs Anti-TNF Biologic**

In the first head-to-head trial of biologic agents in psoriasis, Griffiths and colleagues9 compared the anti-TNF agent etanercept to ustekinumab in 903 patients with moderate to severe psoriasis in the Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial (ACCEPT). Patients were randomly assigned to receive subcutaneous injections of high-dose etanercept (50 mg twice weekly for 12 weeks) or ustekinumab, either 45 mg or 90 mg, at weeks 0 and 4. The primary end point was the proportion of patients who achieved PASI 75 or greater at week 12.

At week 12, 56.8% (n=347) of patients who received etanercept had PASI 75 improvements or greater. In the ustekinumab groups, 67.5% (n=209) of those who received 45 mg had a PASI 75 score (superiority vs etanercept, P=0.012), and 73.8% (n=347) of patients in the 90-mg dosage group achieved PASI 75 (superiority vs etanercept, P<0.001).5
IL-17 Inhibitors

As discussed above, IL-17 production is an important cytokine in psoriasis pathogenesis, and IL-12/23 blockade (as with ustekinumab) results in downregulation of Th17 and Th22 responses. Another approach is to target IL-17 directly, either with antibodies against specific subtypes of IL-17, IL-17A, or IL-17F or by blocking the entire family of IL-17 through blockade of a common receptor subunit. Both of those strategies are being incorporated in new agents. Two of these (secukinumab and ixekizumab) bind and eliminate IL-17A. Brodalumab blocks the entire IL-17 population by blocking the IL-17A receptor.

Secukinumab

Secukinumab is the first of the IL-17 antibody biologics to complete phase III studies; the results of three of these trials—Efficacy and Safety of Subcutaneous Secukinumab for Moderate to Severe Chronic Plaque-Type Psoriasis for Up to 1 Year (ERASURE), Full Year Investigative Examination of Secukinumab vs Etanercept Using 2 Dosing Regimens to Determine Efficacy in Psoriasis (FIXTURE), and Study Comparing Secukinumab Use in Long-Term Psoriasis Maintenance Therapy: Fixed Regimens vs Re-treatment Upon Start of Relapse (SCULPTURE)—were presented at the 22nd Annual Congress of the European Academy of Dermatology and Venereology in Istanbul, Turkey. Secukinumab (previously called AIN457) targets IL-17A.

In the ERASURE study, the objective was to establish efficacy, safety, and tolerability of two doses of secukinumab (150 and 300 mg) compared to placebo at 12 weeks and up to 52 weeks. PASI 75 was achieved at week 12 in 81.6% of the patients who received 300 mg of secukinumab, 71.6% of those who received 150 mg of the drug, and 4.5% of those in the placebo group (P < 0.0001 for both active treatment groups vs the placebo group).

In the FIXTURE trial, patients were randomized to receive either 150 or 300 mg of secukinumab, 50 mg of etanercept, or placebo. The primary end points were percentage of patients achieving PASI 75 or greater at week 12 and improvement on the Investigator’s Global Assessment. PASI 75 was achieved at week 12 by 77.1% of patients who received secukinumab 300 mg and 67% of those who received 150 mg of the drug; in the etanercept group, 44% of patients achieved PASI 75, and 4.9% of patients in the placebo group had a PASI 75 response.

The SCULPTURE trial was designed to determine whether as-needed dosing of secukinumab would be effective in patients who had responded to a course of induction therapy with the drug. Patients who achieved a response of PASI 75 or greater on either 150 or 300 mg of secukinumab were rerandomized at week 8 to receive either maintenance therapy (monthly injections of the same dose they had been on since baseline) or re-treatment as needed when relapse occurred (ie, loss of PASI 75 response and a decrease of 20% or more from the maximum PASI improvement achieved over baseline). At week 52, 78.2% of the patients who received monthly injections of secukinumab 300 mg had maintained at least PASI 75, and 67.7% of those in the group who received 300 mg of secukinumab on an as-needed basis had PASI 75 at week 52. In the patients who received 150 mg of secukinumab, 62.1% maintained PASI 75 at week 52 with monthly dosing, as did 52% of those in the as-needed dosing group.

A significantly better outcome was seen with the fixed monthly 300-mg dosage than with the other three dosage regimens.

Although these efficacy data are impressive, the full analyses of safety data from the phase III studies are not yet available. No specific safety concerns have been identified to date, but attention will be on the rate of infections seen, especially infections that are known to be IL-17 dependent (in particular, localized infections with Staphylococcus aureus and Candida species). In addition, it is known that the class of anti-IL-17 drugs causes a decrease in neutrophil counts, although this is reversible on discontinuation of the medication.

Ixekizumab

In the ixekizumab phase II clinical trial of patients with moderate to severe plaque psoriasis, Leonardi et al found that after 12 weeks of injections (at 0, 2, 4, 8, and 12 weeks) of various doses of ixekizumab (10, 25, 75, or 150 mg), the percentage of patients who achieved PASI 75 was significantly greater than that in the placebo group for all dosages except the lowest. PASI 75 scores were achieved by 82.1% of patients in the 150-mg ixekizumab group, by 82.8% of those who received 75 mg of the drug, and by 76.7% of patients in the group who received the 25-mg dose; in contrast, 7.7% of patients in the placebo group achieved PASI 75 (P < 0.001 for each treatment group comparison).

In addition, the percentages of patients who achieved PASI 90 or greater or PASI 100 were as follows: 71.4% and 39.3%, respectively, in the 150-mg treatment group, and 58.6% and 37.9%, respectively, in the 75-mg treatment group. Half of the patients (50.0%) who received 25 mg of ixekizumab achieved PASI 90 after 12 weeks. No patients in the placebo group achieved PASI 90 or greater, a statistically significant difference compared to the results in the treatment arms (P < 0.001 for these comparisons). These differences were seen as early as week 1 (for the two highest doses) and persisted through week 20. Phase III studies currently are under way.

Brodalumab

The second anti-IL-17 drug now in phase III clinical trials is brodalumab (previously called AMG 827), which blocks the receptor as well as IL-17A, IL-17F, and IL-17C. In a 12-week phase II clinical trial in patients with moderate to severe plaque psoriasis, 198 patients were randomly assigned to receive placebo, one of three doses of brodalumab (70, 140, or 280 mg monthly) on day 1 and at weeks 1, 2, 4, 6, 8, and 10, or 280 mg monthly. The primary end point was percentage of improvement in PASI over baseline at week 12. In this study, achievement of PASI 75 or greater was a secondary end point. Significant improvements in PASI were seen in all treatment groups compared to placebo (P < 0.001). Improvements of PASI 75 or greater were seen in 77% of patients who received 140 mg of brodalumab and in 82% of those who received 210 mg; no patients in the placebo group achieved PASI 75, a significant difference for both doses (P < 0.001). In addition, 72% of those who received 140 mg of the drug achieved PASI 90 or greater, as did 75% of those who received 210 mg of brodalumab.

Although a high level of efficacy has been demonstrated so far in ixekizumab and brodalumab clinical trials, it is important to remember that these results are from phase II studies; conclusions about efficacy and safety await results from the phase III studies, now under way.
Tildrakizumab (previously named MK3222) is a humanized monoclonal antibody that blocks the p19 subunit of IL-23. In a randomized, double-blind, placebo-controlled, parallel-group phase IIb trial in 355 adults with moderate to severe psoriasis, four doses of subcutaneous tildrakizumab (5, 25, 100, and 200 mg) were compared with placebo. In part 1 of the study (16 weeks), injections were administered at weeks 0 and 4. The primary end point, mean change in PASI from baseline to week 16, was significantly greater in all dose groups than in the placebo group (P<0.001 for all comparisons). Improvements of PASI 75 were seen in 76.2% of patients who received 200 mg, in 47.1% of patients who received 100 mg, in 64.5% of those who received 25 mg, and in 35.0% of patients who received 5 mg. In contrast, 4.9% of patients in the placebo group achieved PASI 75.

In part 2 of the study, patients who achieved at least a PASI 75 response continued to receive injections every 12 weeks to week 52. Patients who received 5-mg and 25-mg doses of tildrakizumab continued with no dose change. Patients who had received the higher doses of tildrakizumab (100 and 200 mg) were rerandomized, in a 1:1 ratio, to either maintain or reduce their previous dose. At week 52, the week 16 PASI 75 responders who continued on their previous doses of tildrakizumab showed no loss of efficacy from week 16 to week 52. The group whose dose was reduced from 200 mg to 100 mg showed a small decrease in response from peak; the group whose dosage was reduced from 100 mg every 12 weeks to 25 mg every 12 weeks showed the greatest loss of PASI response from peak levels.

Two phase III studies currently are under way.

**Small Molecules**

A number of agents classified as small molecules are in the early stages of development. Recently, two of these drugs—apremilast, a PDE-4 inhibitor, and tofacitinib—have completed phase III trials.

**Apremilast**

The Evaluate Safety and Effectiveness of Oral Apremilast (ESTEEM) 1 trial of apremilast, an oral medication, involved 844 patients who were randomized to receive apremilast, 30 mg twice daily or placebo. The investigators reported that 33.1% of those treated with apremilast achieved at least PASI 75 at week 16 of the trial, and 58.7% achieved at least PASI 50 (P<0.0001 for both groups vs placebo). Clearly, this medication yields lower response rates than those seen with biologics, but rates are comparable to those with other anti-inflammatory medications such as methotrexate. Nonetheless, apremilast may be a good choice for patients with psoriasis who also have psoriatic arthritis (against which this drug has demonstrated efficacy) and for those in whom an oral medication is preferred. Apremilast was approved by the FDA in March 2014 for the treatment of psoriatic arthritis and is the first oral medication approved for this indication. Additionally, no clear need for monitoring of this medication has been identified to date.

**Tofacitinib**

The other agent in the small-molecule class to reach late-stage clinical evaluation, tofacitinib, is a signal transduction molecule that blocks the JAK pathway. In a phase II trial, tofacitinib, an oral medication, was administered at three different dosages (2, 5, or 15 mg twice daily), which were compared to placebo. At week 12, significantly higher rates of PASI 75 improvements were seen in all three active-treatment groups than in the placebo group: 66.7% of the 15-mg twice-daily group (P<0.0001), 40.8% of the 5-mg group (P<0.0001), and 25.0% of the 2-mg group (P<0.001) compared with placebo.

The phase II data show that in patients with psoriasis, tofacitinib was generally safe and well tolerated, but certain adverse events are of interest—primarily, decreases in hemoglobin levels, changes in lymphocyte counts, and increased rates of infections seen especially at the higher (and more effective) treatment dosages. Until the results and analyses of the phase III clinical trials are available, conclusions about the risk-benefit profile of tofacitinib in psoriasis are pending.

**Conclusion**

Currently, many patients with moderate to severe psoriasis are benefiting from biologic therapy with several TNF inhibitors and the IL-12/23 agent ustekinumab. Other biologic agents (the IL-17 inhibitors secukinumab, ixekizumab, and brodalumab and the IL-23 inhibitor tildrakizumab) also may soon be available. Two small-molecule kinase inhibitors, apremilast and tofacitinib, have completed phase III trials. Tofacitinib is being considered for approval by the FDA, and apremilast was approved by the FDA in March 2014 for the treatment of psoriatic arthritis. These advances resulted largely from the newer understanding of pathophysiology that has developed within the past decade.

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