Highlights of Skin Disease Education Foundation’s 12th Annual Psoriasis Forum

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INTRODUCTION

Research into the pathophysiology and treatment of psoriasis has advanced substantially. Attendees at Skin Disease Education Foundation’s 12th Annual Psoriasis Forum were provided with current insights into the inflammatory underpinnings of psoriasis and the efforts to apply that knowledge to the development of new treatment. The faculty included some of the leading investigators in this field.

Within the last 10 years or so, research has elucidated the role of T helper 17 (Th17) cells in psoriasis inflammation. The first article in this supplement lays a foundation for the others by describing these findings and the role of the Th17 cytokine pathway in perpetuating this disease.

The next article focuses on two nonbiologic, oral therapies: the retinoid acitretin and the Janus kinase inhibitor tofacitinib. The first is an older agent that offers efficacy for certain patient types. The second is approved by the US Food and Drug Administration (FDA) for use in rheumatoid arthritis but not for psoriasis.

The introduction of the tumor necrosis factor (TNF)-α inhibitors for treatment of psoriasis revolutionized the care of this disease. The anti-TNF agents remain the cornerstone of therapy for psoriasis. More than a decade of experience using the TNF-α inhibitors in clinical practice has yielded a large body of data regarding their safety and efficacy. Our faculty reviews these findings.

Two subsequent articles focus on newly introduced and investigational medications. Secukinumab, an interleukin (IL)-17A antagonist, received FDA approval last year for psoriasis therapy, and ixekizumab, just this year. Another sharing this mechanism—brodalumab—is under review at the FDA. Ustekinumab, an agent approved for psoriasis, targets both IL-12 and IL-23. Applications for marketing approval of another IL-12/23 inhibitor, briakinumab, were withdrawn due to safety issues. Our faculty reviews the safety and efficacy data for both of the agents. Three medications selectively targeting IL-23 show promise in early phases of development—guselkumab, tildrakizumab, and BI 655066—and published findings on these medications are reviewed.

All new systemic therapies for psoriasis are not biologics. An oral, small-molecule phosphodiesterase 4 inhibitor, apremilast, was introduced in the United States for psoriasis therapy in 2014. Our faculty summarizes the studies on this agent.

Loss of response is a phenomenon observed with all biologic therapies for psoriasis. Our concluding article reviews its frequency of occurrence and apparent causes, along with suggestions for reducing the risk of this undesirable outcome.

The plethora of new therapies reflecting ever-developing insights into the mechanisms of psoriasis keep the field of dermatology especially challenging and compelling. We hope that you can apply the updates in this supplement to your clinical practice.

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As recently as 12 years ago, it was believed that psoriatic inflammation was driven by T helper 1 (Th1) cells.1 More recent evidence elucidates the role of IL-23 and Th17 effector cytokines (eg, IL-17) in disease pathogenesis.2,3 Many current and investigational therapies appear to act through these cytokines.

Th17 Pathway

The tumor necrosis factor (TNF)-α inhibitor etanercept, for example, acts at least in part through its effect on Th17 cytokines. Evidence suggests that TNF-α-producing dendritic cells increase levels of IL-23, which in turn leads to Th17 cell proliferation and IL-17 and IL-22 induction.2 Blocking TNF-α downregulates Th17 cytokines and the inflammatory products of dendritic cells, including IL-23.3 Clinical improvement has been correlated with early (ie, within 2 weeks of etanercept initiation) reduction in Th17 and dendritic cell products (eg, IL-23). Final disease resolution is associated with downregulation of Th1 cells.2

Normal human skin contains both Th1 and Th17 cells. The former produce gamma interferon but not IL-17. The latter produce gamma interferon but not IL-17. The former produce gamma interferon but not IL-17. The latter produce gamma interferon but not IL-17. IL-22 is associated with downregulation of Th1 cells.2

Normal human skin contains both Th1 and Th17 cells. The former produce gamma interferon but not IL-17. The latter produce gamma interferon but not IL-17. IL-22 appears to delay normal keratinocyte differentiation.4

IL-17 signaling targets both keratinocytes and dermal fibroblasts. IL-17 signaling to dermal fibroblasts promotes cellular infiltration, as well as increased accumulation of IL-17–producing cells in the skin. IL-17 signaling to keratinocytes contributes to hyperproliferation and attenuates differentiation.5 These findings suggest that IL-17 plays an important role in both activating and maintaining inflammation in psoriasis. At least six IL-17 cytokine isoforms (IL-17A through IL-17F) and five IL-17 receptors (IL-17RA through IL-17RE) have been identified.6 Levels of IL-17A, IL-17C, and IL-17F are increased in psoriatic skin, suggesting that these proteins may play roles in the pathogenesis of psoriasis.6 Secukinumab and ixekizumab, US Food and Drug Administration (FDA)-approved treatments for psoriasis, target IL-17A, and brodalumab, an investigational therapy, targets IL-17RA.7,8

IL-23

IL-23 appears to induce differentiation of Foxp3+ regulatory T cells—which typically inhibit autoimmune responses—into proinflammatory Th17 cells. Evidence suggests that regulatory T-cell differentiation into Th17 cells leads to increased IL-17A production in psoriasis. These changes may perpetuate chronic autoimmune conditions.3 Ustekinumab, an FDA-approved treatment for psoriasis, targets a protein subunit (p40) used by IL-23 and IL-12.9 Ustekinumab is administered once every 3 months. Yet its mean half-life is much shorter, ranging from roughly 2 weeks to 6.5 weeks (14.9 ± 4.6 days to 45.6 ± 80.2 days).9 It is possible that ustekinumab exerts its prolonged benefit effect by promoting normalization of regulatory T cells.

Summary

The identification of Th17 cells and their role in psoriasis inflammation has greatly increased our understanding of the disease and the mechanisms of therapies. It also illuminates additional possible targets for new therapies.

References


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Small Molecules for Psoriasis
Craig L. Leonardi, MD*

Abstract
Acitretin is an older, oral, non-immunosuppressive medication for the treatment of psoriasis. Tofacitinib is an oral Janus kinase inhibitor that has been studied for use in psoriasis. Each offers efficacy in certain settings and patient types but carries substantial safety risks.

Keywords
Acitretin; psoriasis; pustular psoriasis; tofacitinib; toxicity

A
n oral retinoid, acitretin is thought to promote cellular differentiation and maturation. Its onset of action is relatively slow (3-6 months). Acitretin is the active metabolite of etretinate and was introduced in 1997 to replace etretinate, largely because of its shorter half-life. The terminal elimination half-life of acitretin is 49 hours (range, 33-96 hours). The half-life of etretinate is roughly 120 days. Etretinate is highly lipophilic and can be detected in serum as long as 2 years after stopping treatment.1

The long half-life is an issue because both agents are teratogenic. Etretinate is no longer marketed and acitretin is US Food and Drug Administration (FDA) pregnancy category X. Exposure during the first 3 to 6 weeks of gestation—before most women are aware of pregnancy—is associated with neurotoxicity. Fetal abnormalities reported with acitretin include death, absent hand/wrist, clubfoot, limb abnormalities, gastrointestinal malformations, premature birth, and neonatal ichthyosis, apnea, and anemia.1,4

Consumption of undetermined amounts of alcohol can precipitate the conversion of acitretin to etretinate.1 Teratogenic levels of etretinate have been detected in the plasma of patients treated during the first 3 to 6 weeks of gestation—before most women are aware of pregnancy.6 Acitretin is associated with mucocutaneous side effects, including lip fissuring and cracking, thinning nail plates, a sticky sensation on the skin, and peeling of the palms and soles. Many patients lose hair at doses of 1 mg/kg daily. Muscle aches and pains are common.5 Many side effects are dose-dependent and may be alleviated by dose reduction.1

Assessing the efficacy of acitretin is difficult. The concept of psoriasis measurement has changed since many studies of this agent were performed. Additionally, some studies included a large number of dropouts. A review cited findings that 34% and 52% of patients with plaque psoriasis achieved Psoriasis Area and Severity Index (PASI) 75 after 12 weeks of acitretin monotherapy (initial doses of 50 mg daily and 40 mg daily, respectively, followed by individual dose adjustments).1 The most recent American Academy of Dermatology (AAD) guidelines for the use of traditional systemic agents in psoriasis characterize acitretin efficacy as dose-dependent and “somewhat less effective than other traditional systemic agents” when used as monotherapy.6

Combination Therapy
Adding acitretin to phototherapy enables the use of lower-dose acitretin, and lower doses and fewer treatments with ultraviolet B (UVB) or psoralen-ultraviolet A photochemotherapy (PUVA).7 In a double-blind, randomized study (n=65), adding acitretin to PUVA was superior to PUVA plus placebo after 6 weeks in terms of decreased lesion scores, number of PUVA exposures, and total UVA dose until remission.8 In another study, adding lower-dose (25 mg daily) acitretin to narrowband UVB therapy three times per week yielded more than 75% improvement in 72.5% (29/40) of patients. The majority of subjects had plaque psoriasis refractory to treatment with various monotherapies (broadband UVB, narrowband UVB, acitretin), or with acitretin combined with broadband UVB.9

Adding acitretin (25 mg daily) to UVB delivered through a commercial tanning bed (mean UVB output, 4.7%, 4-5 days per week for 12 weeks) led to 83% (19/23) of patients with moderate to severe plaque psoriasis achieving clearance or near clearance in a retrospective review.10 More than half of subjects (59%; 10/17) achieved PASI 75 with this therapy in a prospective study. Adverse events were mild to moderate in severity. Such facilities may offer an option for patients without access to

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physician-directed UVB therapy. The variability of light quality in a commercial facility suggests the need for caution. Little information is available about the combination of acitretin with biologic therapy. Combining acitretin with cyclosporine requires monitoring of lipids. Combination with methotrexate is contraindicated due to the risk of hepatotoxicity.

**Pustular Psoriasis**

A survey of 325 physicians from Japan who treated 385 cases showed that acitretin was considered effective in 84.1% of the cases. The lesions started to resolve within as little as 10 days. After clearance occurred, acitretin doses were reduced for maintenance therapy.

**Tofacitinib**

An oral Janus kinase (JAK) inhibitor, tofacitinib blocks JAK1, JAK3, and to a lesser extent JAK2. It inhibits multiple inflammatory cytokines. The FDA approved it for treating rheumatoid arthritis (RA; 5 mg twice daily) in 2012 but declined to approve the agent for the treatment of plaque psoriasis in 2015.

A phase III, 12-week-long study compared two doses of tofacitinib (5 or 10 mg twice daily) with etanercept 50 mg weekly and placebo in patients with plaque psoriasis (n=1101 treated). Higher-dose, but not lower-dose, tofacitinib was noninferior to etanercept in terms of both coprimary endpoints (PASI 75 and Physician’s Global Assessment [PGA]). PASI 75 responses after 12 weeks of therapy were 5.6%, 39.5%, 63.6%, and 58.8% (placebo, 5 mg tofacitinib, 10 mg tofacitinib, and etanercept, respectively). Proportions of patients achieving a PGA score of “clear” or “almost clear” were 15.0%, 47.1%, 68.2%, and 66.3% (placebo, 5 mg tofacitinib, 10 mg tofacitinib, and etanercept, respectively).

The risk of infection and malignancy is an issue with tofacitinib. Pooled data from 1-year-long phase II and III clinical trials, and a long-term extension trial, of patients who have received tofacitinib for psoriasis (n=3623) indicate that incidence rates for serious infections, herpes zoster, and non-melanoma skin cancers were numerically though not significantly higher with the higher dose (10 mg vs 5 mg twice daily). Incidence rates were calculated as the number of patients with events/100 patient-years for the 1-year-long randomized controlled trials and for total exposure. Incidence rates for serious infections were 1.37 and 2.42 events per 100 patient-years for 1-year clinical trials with the lower and higher dose, respectively, and 1.68 for all exposures (including long-term data). Incidence rates for herpes zoster were 1.00, 2.32, and 2.55 (lower and higher dose in 1-year trials and total exposure, respectively).

Data from the RA studies of tofacitinib suggest “significant immunosuppression,” according to the FDA briefing document submitted to the agency advisory committee that reviewed the drug for its RA indication. Nearly all fatal infections (14/15) and all (35) opportunistic infections recorded in the tofacitinib RA development program occurred among patients receiving the agent. The advisory committee briefing document also noted that tofacitinib is associated with a numerical though not statistically significant increased risk of malignancy over a 24-month period. As the document states, “This pattern is consistent with a scenario where increasing exposure to tofacitinib increases the risk of malignancy.” The sponsor plans to provide additional safety analyses of tofacitinib to support the psoriasis indication.

**Summary**

Acitretin is an older, oral, systemic retinoid for the treatment of psoriasis that offers a non-immunosuppressive mechanism of action. It may provide greater effectiveness when combined with phototherapy than when used alone. It appears to be beneficial for pustular psoriasis. As it is FDA pregnancy category X, associated with substantial teratogenicity, and can convert to a form with a prolonged half-life, its use should avoided in women of childbearing age whenever possible.

Tofacitinib is an oral JAK inhibitor that the FDA has approved for use in RA but not in psoriasis. It has demonstrated noninferiority to etanercept when used at the higher of two doses studied in a phase III trial. Evidence from the RA development program suggests “significant immunosuppression” and the possibility of increased risk of malignancy with increased exposure, according to the FDA. The sponsor plans to provide additional safety data supporting the psoriasis indication.

**References**

Update on TNF Inhibitors

Francisco A. Kerdel, BSc, MBBS*

Abstract

The introduction of tumor necrosis factor (TNF)-α inhibitors dramatically improved the management of psoriasis. Some newer or investigational biologics with different mechanisms of action have demonstrated noninferiority or superiority to etanercept, the first self-injectable anti-TNF-α agent to become available in the United States. Nonetheless, TNF-α inhibitors are likely to remain a mainstay of therapy for many years.

Efficacy; investigational agents; psoriasis; psoriatic arthritis; safety; tumor necrosis factor inhibitors

Five anti–tumor necrosis factor (TNF) agents are approved in the United States for the treatment of psoriasis, psoriatic arthritis (PsA), or both conditions (Table). This article reviews the evidence for the use of these agents in psoriasis.

Etanercept

The first self-injectable agent approved for psoriasis, etanercept, generated response (measured as a 75% improvement in the Psoriasis Area and Severity Index [PASI 75]) at 12 weeks in nearly half (49%) of those receiving the recommended starting dose for psoriasis (50 mg twice weekly).1,2 Proportions of responders rose with treatment duration in this phase III trial (n=652 treated), to 59% at 24 weeks of treatment. Rates of adverse events (AEs) were similar in the placebo group and both treatment groups through week 12.

A subsequent analysis evaluated whether patients maintained response if they stopped, then resumed therapy. Patients with at least a PASI 50 response at week 24 discontinued etanercept until relapse, then restarted therapy at their prior dose. Psoriasis returned gradually, on average within 3 months after treatment cessation. Twelve weeks of retreatment produced similar clinical responses to the initial 12 weeks of therapy.3

Interrupted therapy produced lower rates of clinical response than continuous therapy. Patients treated with uninterrupted etanercept at the recommended starting dose (50 mg twice weekly for 12 weeks) were randomized to receive either continuous (n=1272; mean of 33.4 doses) or interrupted (n=1274; mean of 28.0 doses) therapy at the recommended maintenance dose (50 mg once weekly) for the next 12 weeks. Proportions of responders (ie, attaining Physician’s Global Assessment [PGA] score ≤2 and improvement from baseline) were nearly identical after the first 12 weeks of therapy (71.3% and 72.0%, continuous and interrupted therapy, respectively) but lower thereafter with interrupted therapy (71.0% vs 59.5% at week 24; P<0.0001).4

Etanercept is the only biologic agent that has been studied in children with psoriasis (ages 4-17; n=211).5,6 It was dosed by body weight in this population (0.8 mg/kg, to a maximum of 50 mg/wk; n=211). A total of 57% of children randomized to etanercept attained PASI 75 at 12 weeks (vs 11% with placebo; P<0.001). The proportion of PASI 75 responders rose to 68% at 36 weeks, and was largely maintained at weeks 96 and 264 (60%-70%).5,6 Rates of “medically important” infections did not rise with etanercept exposure. Through week 264, eight serious adverse events (SAEs), including two infections (cellulitis, infectious mononucleosis) were reported in seven patients.6

Etanercept offers a noteworthy record of safety. A 49-trial review (n=13,977 patients) covering all approved indications found generally similar rates of serious infection with etanercept and controls. The standardized incidence ratio (SIR) for malignancy was 1.00 (95% CI, 0.83-1.19). The SIR for lymphoma was similar to that observed in the general population except in patients with rheumatoid arthritis (3.45; 1.83-5.89). The SIRs for cutaneous squamous cell carcinoma in patients with psoriasis relative to the general population with high or low sun exposure were 2.09 (1.27-3.22) and 4.96 (3.03-7.66), respectively. Incidence ratios for this cancer fell below 1.0 for all other indications regardless of sun exposure. Rates of melanoma and basal cell carcinoma did not differ significantly from those in the general population.7

Infliximab

More than three-quarters of patients with psoriasis attained a PASI 75 response after 10 weeks of infliximab therapy (5 mg/kg) in two randomized, placebo-controlled trials (n=378; 80%, and n=835; 75.5%).8,9 A high proportion of patients (61%) maintained PASI 75 responses at week 50.9 A lower dose (3 mg/kg) yielded a PASI 75 response rate of 70.3% at 10 weeks.8 Intermittent (as-needed) maintenance dosing (at 5 mg/kg or 3 mg/kg) and lower dosing (standard or as-needed maintenance regimen) did not maintain responses as well as the standard (ie, every 8 weeks) 5 mg/kg dosing.8

Infliximab has demonstrated superiority to methotrexate in a head-to-head, open-label trial (n=868; PASI 75 rates of 78% and 42% at week 16, infliximab and methotrexate, respectively; P<0.001). The rate of AEs was similar with both therapies,
though the rate of SAEs was higher with infliximab (6% and 2% at week 16, infliximab and methotrexate, respectively). Onset of effectiveness was faster with infliximab. Median time to achieving PASI 75 was 46 days (95% CI, 45-50) with infliximab and 127 days (95% CI, 113-154; P<0.0001) with methotrexate.10

Does its weight-based dosing enable infliximab to achieve efficacy in overweight or obese patients? Evidence indicates that the answer is yes. A review concluded that “Infliximab response appears to be independent of body mass index (BMI).”11

Infusion reactions occur with this agent; published rates vary widely. A Canadian observational registry reported infliximab infusion reactions in 12.3% of patients and 1.3% of infusions (n=1632; any indication, and 24,852 infusions).12 Most reactions were mild to moderate in severity.

Infusion reactions appear to be related to anti-infliximab antibodies. Among patients with Crohn's disease, infusion reactions were more common among those with anti-infliximab antibodies (38% vs 24%, antibody-positive and -negative patients, respectively).13 What triggers antibody formation? Compared with the recommended regimen, episodic maintenance based on loss of response was associated with a higher rate of anti-infliximab antibody formation at 72 weeks in patients with Crohn's disease (30% vs 8%; odds ratio [OR], 0.21; 95% CI, 0.13-0.36; P<0.0001).14 Concomitant administration of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate) reduced anti-infliximab antibody formation (10% vs 18%; P=0.02) and infusion reactions (3% vs 6%; P<0.001).14 Analysis of data from a series of psoriasis patients (n=59 patients, 858 infusions) confirmed the value of an immunomodulator (rate of infliximab-associated infusion reactions with and without methotrexate, 4% vs 27%, respectively; P=0.05).15

**Adalimumab**

Nearly three-quarters of patients with psoriasis randomized to adalimumab (71%) reached PASI 75 at week 16 in a phase III trial. Response to adalimumab was rapid, with 19% of patients attaining PASI 75 at week 4 and 54% reaching this level at week 8.16 Efficacy was largely maintained over time.16,17 At 3-year follow-up, 76% of those who had achieved PASI 75 at week 33 maintained a PASI 75 response.17

Adalimumab demonstrated significantly higher rates of efficacy in psoriasis patients compared with methotrexate in a randomized trial (n=271). At week 16, a higher proportion of patients receiving adalimumab had attained PASI 75 (79.6%, 35.5%, and 18.9% for adalimumab, methotrexate, and placebo, respectively; P<0.001 for adalimumab vs methotrexate and placebo). Adalimumab also was associated with rapid response, ie, a 57% improvement in mean PASI at week 4.18

BMI affected response to adalimumab and methotrexate in this trial, according to an analysis of a subset of participants. Proportions of normal weight (BMI <25 kg/m²), overweight (BMI 25-<30 kg/m²), and obese (BMI ≥30 kg/m²) patients achieving PASI 75 with adalimumab were 85.0%, 85.7%, and 61.3%, respectively; comparable PASI 75 rates with methotrexate were 43.3%, 29.3%, and 26.1%, respectively.19 A post hoc analysis of another clinical trial concluded that body weight influenced mean percentage change in PASI score with adalimumab at week 16.20

**Certolizumab Pegol**

A pegylated anti-TNF agent approved for PsA, certolizumab pegol is in phase III trials for psoriasis (clinicaltrials.gov). A phase II study in psoriasis patients (n=176) yielded PASI 75 response rates of 75% and 83% at 12 weeks with certolizumab 200 mg or 400 mg given every other week, respectively, following an initial loading dose of 400 mg.21

More than half of patients with PsA demonstrated joint symptom response (ie, American College of Rheumatology 20% improvement criteria [ACR20]) to certolizumab pegol in a phase III clinical trial (n=409). Specifically, 51.9% and 58.0% of patients receiving certolizumab pegol 200 mg every 2 weeks and 400 mg every 4 weeks, respectively, met ACR20 criteria at week 12. ACR20 response rates rose to 56.3% and 63.8%, respectively, at 24 weeks.22 Among study participants with psoriasis affecting at least 3% of the body surface, 46.7% and 47.4% achieved PASI 75 at 24 weeks.22

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**TABLE**

**FDA-Approved Anti-TNF Agents for Plaque Psoriasis and/or Psoriatic Arthritis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PsO</th>
<th>PsA</th>
<th>PASI 75 Response in Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>80 mg initial dose, followed by 40 mg every other week, starting 1 week after initial dose</td>
<td>40 mg every other week&lt;sup&gt;14&lt;/sup&gt;</td>
<td>71% (578/814) at 16 weeks&lt;sup&gt;14&lt;/sup&gt;**</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>NA</td>
<td>400 mg initially and at weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered</td>
<td>75% (44/59) and 83% (48/58) at 12 weeks; 200 mg or 400 mg given every other week, respectively, following 400-mg loading dose&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg twice weekly for 3 months, followed by 50 mg once weekly&lt;sup&gt;2&lt;/sup&gt;</td>
<td>50 mg once weekly with or without MTX&lt;sup&gt;2&lt;/sup&gt;</td>
<td>49% (81/164) at 12 weeks&lt;sup&gt;1&lt;/sup&gt;**</td>
</tr>
<tr>
<td>Golimumab</td>
<td>NA</td>
<td>50 mg once a month&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks&lt;sup&gt;37&lt;/sup&gt;</td>
<td>5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks&lt;sup&gt;37&lt;/sup&gt;</td>
<td>80% (242/301) at 10 weeks&lt;sup&gt;9&lt;/sup&gt;**</td>
</tr>
</tbody>
</table>

<sup>*Phase III trials; †Phase II trial; ‡No phase II-III trials in psoriasis to report.<br>MTX=methotrexate; NA=not approved for this indication; PASI=Psoriasis Area and Severity Index; PsA=psoriatic arthritis; PsO=plaque psoriasis.</sup>
Golimumab
This agent is FDA approved for PsA; it is not under study for a psoriasis indication, although it has shown significant benefit in reducing skin and nail psoriasis associated with PsA.23 Roughly half (51%; 74/146) of patients with PsA receiving the recommended dose of golimumab (50 mg/month) in a phase III clinical trial met ACR20 criteria at week 14. This response rate was maintained 10 weeks later (52%).23 In this same study, golimumab also showed significant benefit in reducing skin and nail psoriasis.

Skin also improved. Among the study participants with psoriasis affecting at least 3% of body area at baseline, PASI 75 response rates for golimumab were 40%, 56%, and 62.4% at 14 weeks, 24 weeks, and 1 week, respectively.23 This response was maintained at 1 year (62.4%).24 SAEs were reported in 6% of placebo patients and 2% of those receiving golimumab.24

Reducing CVD Risk
Inflammation is central to the pathophysiology of both psoriasis and cardiovascular disease (CVD). Psoriasis has been associated with an increased risk of myocardial infarction (MI), coronary artery disease, peripheral arterial disease, and stroke.25 As TNF-α inhibitors target systemic inflammation, authors have evaluated their impact on the rate of CVD. A retrospective analysis of health plan data (n=8845 patients with psoriasis or PsA; median duration of follow-up, 4.3 years) found that, compared with those receiving no systemic or phototherapy and after adjusting for MI risk factors, anti-TNF treatment was associated with a significantly lower risk of MI (adjusted hazard ratio, 0.50; 95% CI, 0.32-0.79; Figure). The incidence of MI was similar for patients treated with anti-TNF agents and either phototherapy or systemic therapy other than TNF-α inhibitors.26

Anti-TNFs vs Other Biologics
Some newer biologic therapies more recently approved or under study for the treatment of psoriasis have demonstrated superiority to a TNF-α inhibitor. Ustekinumab is an IL-12 and IL-23 antagonist. Compared with etanercept, significantly higher proportions of patients randomized to either dose of ustekinumab (45 or 90 mg at weeks 0 and 4, depending on body weight) attained PASI 75 at 12 weeks (67.5%, 73.8%, and 56.8% for ustekinumab 45 mg and 90 mg, and etanercept, respectively; P=0.01 and P<0.001 vs etanercept, respectively). Rates of SAEs, participants developing at least one AE, and discontinuations due to AEs were similar across treatment groups in this phase III trial (n=903).27

The IL-17A antagonist secukinumab also evidenced superiority to etanercept in a phase III trial for treatment of psoriasis (n=1297). Higher proportions of patients randomized to secukinumab attained PASI 75 at 12 weeks (77.1%, 67.0%, 44.0%, and 4.9% for secukinumab 300 mg and 150 mg, etanercept, and placebo, respectively; P<0.001 vs etanercept and placebo for each secukinumab dose).28 The higher dose of secukinumab reflects the FDA-approved regimen for psoriasis (ie, 300 mg at weeks 0, 1, 2, 3, 4, then every 4 weeks).29 Onset of action (defined as 50% reduction in mean PASI score from baseline) was faster with secukinumab (median of 3.0 weeks with a 300-mg dose, vs 7.0 weeks with etanercept). Rates of AEs and of infection were similar with both agents.28

Another anti–IL-17A agent, ixekizumab, has demonstrated superiority to etanercept at 12 weeks in two phase III studies. Rates of participants attaining PASI 75 at 12 weeks were 89.7%, 77.5%, 41.6%, and 2.4% in one phase III study (n=1224; ixekizumab 80 mg every 2 or 4 weeks after a 160-mg starting dose, or etanercept 50 mg twice weekly, respectively), and 87.3%, 84.2%, 53.4%, and 7.3%, respectively, in the other phase III study (n=1346). PASI 75 response rates for both ixekizumab doses in both studies were significantly higher than those of etanercept.30

The Janus kinase inhibitor tofacitinib (10 mg twice daily) displayed noninferiority to etanercept (50 mg twice weekly for 12 weeks) in a phase III trial of patients with psoriasis (n=1101 treated). A lower dose of tofacitinib (5 mg twice daily) did not reach the threshold for noninferiority. Proportions of patients achieving PASI 75 at 12 weeks were 39.5%, 63.6%, 58.8%, and 5.6% for tofacitinib 5 and 10 mg, etanercept, and placebo, respectively. Rates of AEs associated with immunomodulation were similar across active therapy groups. Rates and types of other AEs were generally similar across all treatment groups. Rates of serious AEs were the same in all 4 treatment groups.31

A phase II study compared various doses of the investigational anti–IL-23 monoclonal antibody guselkumab to adalimumab (at the FDA-approved dose for psoriasis) and placebo in patients with moderate to severe plaque psoriasis (n=293).32 Compared with placebo, significantly higher proportions of patients receiving any active therapy attained PASI 75 at week 16. Compared with adalimumab, numerically but not statistically higher proportions of those receiving all but the lowest dose of guselkumab achieved PASI 75 at week 16 (5%, 44%, 47%, 81%, 79%, 81%, and 70%; placebo: guselkumab 5 mg, 15 mg, 50 mg, 100 mg, 200 mg; adalimumab, respectively). The overall rate of AEs through week 16 was similar across treatment groups.32

Safety
The Psoriasis Longitudinal Assessment and Registry (PSOLAR) offers a large body of real-world data about the rate of serious infections associated with psoriasis therapy. A multicenter registry, it opened in 2007 and follows adults with psoriasis who received or were eligible to receive conventional systemic or biologic agents.33 A recent analysis (n=11,466) reported serious infection
rates (per 100 patient-years) of 0.83, 1.47, 1.97, and 2.49 among patients who received ustekinumab, etanercept, adalimumab, and infliximab, respectively. Rates among those given methotrexate but not biologic therapy, and those treated with neither methotrexate nor biologic therapy, were 1.28 and 1.05 per 100 patient-years, respectively. Nearly 80% of patients (9154/11,466) had received a biologic agent. Risk factors for serious infection were older age, diabetes, smoking, history of significant infection, and exposure to infliximab or adalimumab. Pneumonia and cellulitis were the most commonly reported serious infections.33

**Summary**

Infliximab and adalimumab, two of the three anti-TNF agents approved for the treatment of psoriasis, produced response rates (PASI 75) of 70% to 80% in short-term (10- or 16-week) phase III clinical trials.8,16 Responses were generally maintained at long-term follow-up (50 weeks or 3 years).9,17

Etanercept, the third drug in this class approved for psoriasis therapy, has demonstrated response rates (PASI 75) of nearly 50% and 60% at 12 and 24 weeks of therapy, respectively.1 It is the only anti-TNF medication studied in children with psoriasis.5,6 As the first self-injectable TNF inhibitor on the US market, it offers a long record of safety.7

Infliximab is associated with infusion reactions and anti-infliximab antibodies, which raise the risk of infusion reactions.12,13 Concurrent administration of immunomodulators reduces the rate of infusion reactions.14,15 Infliximab appears to achieve effectiveness regardless of body mass,11 unlike adalimumab.19

Newer approved biologics (ustekinumab, secukinumab, and ixekizumab) have demonstrated significantly higher PASI 75 response rates compared with etanercept at 12 weeks in phase III trials.27,28,30 These findings suggest that the next generation of therapy may supplant TNF-α inhibitors. However, in part due to their long-term safety record, anti-TNF agents remain a cornerstone of psoriasis therapy.

**References**

The newer therapies for psoriasis involve novel mechanisms of action. Secukinumab, a human IgG1 monoclonal antibody, binds to the cytokine interleukin (IL)-17A, thereby inhibiting its interaction with the IL-17 receptor. It has demonstrated superiority to the anti–tumor necrosis factor (TNF) agent etanercept in a phase III clinical trial. Proportions of patients meeting the coprimary endpoints (ie, ≥75% reduction from baseline in the Psoriasis Area and Severity Index score [PASI 75] and ≤1 on a 5-point modified Investigator’s Global Assessment [IGA] at week 12) were significantly higher with secukinumab than with etanercept (Table 1). The rate of PASI 75 response at 12 weeks was slightly greater than that observed with the TNF-α inhibitor adalimumab at 16 weeks (77.1% and 71% for secukinumab and adalimumab, respectively). More than half (54.2%) of patients randomized to the recommended dose of secukinumab (300 mg once a month) achieved PASI 90 at 12 weeks. Responses generally were maintained at 1 year (Table 1).

The overall safety profile for secukinumab in this study is similar to that of etanercept. The rate of any adverse event (AE) was similar with both therapies. However, secukinumab is associated with a higher rate of Candida infection compared with etanercept (4.7% vs 1.2%, respectively). All such infections associated with secukinumab were mild to moderate in severity.

Secukinumab also has been linked to rare cases of inflammatory bowel disease exacerbation (0.11 cases/100 patient-years of Crohn’s disease exacerbation and 0.08 cases/100 patient-years of ulcerative colitis exacerbation), as well as new cases of ulcerative colitis (0.08 cases/100 patient-years) in the psoriasis clinical development program. No such cases occurred among patients randomized to receive placebo. A study of secukinumab in patients with active Crohn’s disease was stopped early due to lack of efficacy; a higher rate of serious AEs occurred with secukinumab than with placebo, often involving worsening of the Crohn’s colitis. As in the psoriasis trial cited earlier, some local fungal infections were observed with secukinumab (4, vs none with placebo).

Apremilast
An oral, twice-daily, small-molecule phosphodiesterase 4 (PDE4) inhibitor that is FDA approved for the treatment of psoriasis, apremilast has inhibited TNF-α, IL-12, and IL-23 in an in vitro model of psoriasis. Like secukinumab, it also is indicated for PsA. One-third (33%) of patients randomized to apremilast achieved PASI 75 at week 16 in a phase III study of psoriasis (Table 2). Proportions achieving this milestone were somewhat lower in a similarly designed phase III study, though still superior to rates achieved with placebo (Table 2). Response to apremilast did not differ by body mass index, according to a subgroup analysis of pooled data through week 16 of both trials. Nonsignificant trends pointed to higher PASI 75 response rates in patients who had not previously received systemic therapies.

The rates of serious and severe AEs were similar among patients receiving apremilast and placebo in both phase III trials (Table 2). Although the primary endpoint of each phase III study was efficacy at week 16, patients were monitored through week 52. Rates of patients experiencing at least one AE were numerically higher with apremilast than with placebo. Rates of AEs did not appear to rise with duration of apremilast exposure. No clinically meaningful effects on laboratory measurements were reported. No tuberculosis reactivation was reported in either trial. Rates of major cardiac events, malignancies, and serious opportunistic infections were very low and similar between apremilast and placebo.

Keywords
Apremilast; efficacy; psoriasis; safety; secukinumab

Abstract
Among the newer medications for treating psoriasis are the interleukin-17A inhibitor secukinumab and the phosphodiesterase 4 inhibitor apremilast. Secukinumab offers a level of efficacy greater than that of the tumor necrosis factor-α inhibitor adalimumab. Apremilast is associated with lower levels of efficacy than the biologic therapies for psoriasis. Apremilast may cause diarrhea and nausea and is associated with weight loss and rare instances of depression.
Tolerability may be an issue for some patients (Table 2). Roughly one-sixth of patients developed diarrhea and a similar proportion reported nausea during apremilast therapy. Tension headache and headache also occurred more commonly with apremilast than placebo. These events were mild or moderate in severity and rarely led to discontinuation. Diarrhea and nausea occurred most commonly with apremilast in the first 2 weeks of treatment. A titration regimen for apremilast initiation is intended to reduce the risk of gastrointestinal side effects.

Apremilast is associated with weight loss. Nearly one-fifth (19.2%) of patients receiving apremilast lost more than 5% of their body weight through week 52 in two phase III trials. This effect was reported as an AE in 1.4% of participants. Analysis identified no clear association between weight loss and diarrhea and nausea or vomiting.

Apremilast labeling carries a warning about the risk of depression, which was reported during the first 16 weeks of therapy in 1.2% of patients receiving the drug, compared with 0.5% randomized to placebo, in the two phase III clinical trials. Risk of depression did not appear to rise with duration of apremilast exposure. The rate of serious depression was 0.1% (1/1184). One patient receiving apremilast attempted suicide; one patient in the placebo group committed suicide. Patients should be monitored for mood changes. The author has noted that some patients have reported feeling sad or anxious after starting the medication. Therefore, it is important to inform patients about the issue and instruct them to call the office and report any mood changes after starting apremilast, especially changes that are unusual for the individual.

Summary

Secukinumab, an IL-17A inhibitor, has demonstrated PASI 75 response rates greater than those observed with adalimumab in two different trials and safety generally comparable to that of etanercept in a head-to-head trial. It is associated with mild candidiasis infections and rare exacerbation of inflammatory bowel disease, the presence of which should be considered a relative contraindication.

Apremilast offers a lower PASI 75 rate than the biologic medications. Diarrhea, nausea, and to a lesser extent, headache may pose tolerability issues for some patients. The agent also is associated with weight loss and, rarely, depression. Both secukinumab and apremilast are indicated for PsA as well as for psoriasis.

### TABLE 1  FDA-Approved Anti-TNF Agents for Plaque Psoriasis and/or Psoriatic Arthritis

<table>
<thead>
<tr>
<th></th>
<th>Secukinumab 300 mg†</th>
<th>Secukinumab 150 mg†</th>
<th>Etanercept</th>
<th>Placebo</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75* rates (12 weeks)</td>
<td>77.1% (249/323)</td>
<td>67.0% (219/327)</td>
<td>44.0% (142/323)</td>
<td>4.9% (16/324)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>IGA ≤1* (12 weeks)</td>
<td>62.5% (202/323)</td>
<td>51.1% (167/327)</td>
<td>27.2% (88/323)</td>
<td>2.8% (9/324)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>PASI 75 maintained from week 12-52</td>
<td>84.3% (210/249)</td>
<td>82.2% (180/219)</td>
<td>72.5% (103/142)</td>
<td>NE</td>
<td>&lt;0.001 (300 mg); 0.009 (150 mg)§</td>
</tr>
</tbody>
</table>

*Coprimary endpoints.
† Once weekly for 5 weeks, then every 4 weeks. The recommended dose is 300 mg, though the 150-mg dose may be acceptable for some patients. Each secukinumab dose vs each comparator.
§ Each secukinumab dose as noted vs etanercept.

IGA=Investigator’s Global Assessment; NE=not evaluated; PASI=Psoriasis Area and Severity Index, TNF=tumor necrosis factor.

### TABLE 2  Apremilast in Psoriasis: Safety and Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Apremilast</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75 at 16 weeks</td>
<td>33.1% (186/562)†; 28.8% (79/274)†</td>
<td>5.3% (15/282)†; 5.8% (8/137)†</td>
</tr>
<tr>
<td>Safety, weeks 0-16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 AE</td>
<td>68.9% (573/832)</td>
<td>57.2% (239/418)</td>
</tr>
<tr>
<td>≥1 Serious AE</td>
<td>2.0% (17/832)</td>
<td>2.6% (11/418)</td>
</tr>
<tr>
<td>≥1 Severe AE</td>
<td>3.8% (32/832)</td>
<td>3.6% (15/418)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.8% (148/832)</td>
<td>6.7% (28/418)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16.6% (138/832)</td>
<td>6.7% (28/418)</td>
</tr>
<tr>
<td>Tension headache</td>
<td>7.3% (61/832)</td>
<td>3.3% (14/418)</td>
</tr>
<tr>
<td>Headache</td>
<td>5.8% (48/832)</td>
<td>3.3% (14/418)</td>
</tr>
</tbody>
</table>

*P<0.0001 vs placebo; †P<0.001 vs placebo.
AE=adverse event; PASI=Psoriasis Area and Severity Index.
References

Antibodies in the Treatment of Psoriasis: IL-12/23 p40 and IL-17α

Craig L. Leonardi, MD*

Abstract
The anti–tumor necrosis factor (TNF-α) agents represent the second generation of psoriasis therapy. Research has produced a third generation of biologic treatments, some of which offer greater efficacy than the TNF-α inhibitors. This article reviews the data documenting the efficacy and safety of three types of biologics. Semin Cutan Med Surg 35(supp4):S74-S77 © 2016 published by Frontline Medical Communications

Keywords
IL-12/23 inhibitors; IL-17/IL-17A inhibitors; IL-23 inhibitors

Received years have witnessed the development of new treatments for psoriasis directed to a variety of cytokines implicated in disease pathophysiology (Figure). Evidence suggests that the T helper 17 (Th17) cytokines (eg, interleukin [IL]-17A, IL-22) contribute to psoriasis pathogenesis. IL-17A induces neutrophil recruitment and activation, and enhances inflammation and angiogenesis. IL-22 stimulates keratinocyte hyperproliferation. IL-23 stimulates the survival and proliferation of Th17 cells. This article will review marketed and investigational psoriasis therapies directed at these cytokines (Tables 1 and 2).

IL-12/23 Inhibitors
IL-23 and IL-12 share the p40 subunit. Compared with nonpsoriatic skin, human psoriasis lesions contain higher levels of the p40 subunit. Ustekinumab and briakinumab, two human monoclonal antibodies, target the p40 subunit. Ustekinumab is approved in the United States for psoriasis and psoriatic arthritis (PsA). Briakinumab has demonstrated efficacy in psoriasis but is associated with major adverse cardiovascular events (MACE).

Applications for its marketing approval were withdrawn in 2011.

Ustekinumab
Roughly two-thirds and three-quarters of patients randomized to the recommended dose of ustekinumab (90 mg) in two phase III clinical studies achieved ≥75% improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12 (primary endpoint). Given more time, PASI 75 rates with this dose rose to 79% at 28 weeks in each trial. Proportions of patients achieving PASI 75 were somewhat lower with the lower dose of ustekinumab (45 mg; Table 1).

Ustekinumab therapy is initiated with subcutaneous injections at weeks 0 and 4, followed by an injection every 12 weeks. Some patients experience a diminution of response within less than 12 weeks, and might benefit from dosing once every 8 weeks. Canadian labeling allows for consideration of dosing every 8 weeks in patients with inadequate response to dosing every 12 weeks; US labeling does not incorporate this flexibility.

The rates of overall adverse events (AEs), common AEs, serious AEs (SAEs), and investigator-reported infections with ustekinumab were comparable to those reported with placebo during the placebo-controlled periods of phase II and III trials (average, 12.6 and 13.4 weeks, placebo and ustekinumab, respectively). Ustekinumab demonstrated long-term safety in an analysis of data from four phase II and III trials (n=3117 patients, 8998 patient-years of follow-up; 1482 patients treated for ≥4 years). No trends suggesting dose-response or cumulative effects of exposure on safety were observed. Rates of infection were comparable between ustekinumab doses and decreased over time. Serious infections were rare (0.98 and 1.19/100 patient-years, respectively). The rate of MACE in patients treated with ustekinumab was 0.44/100 patient-years—comparable to that reported with anti–tumor necrosis factor (TNF) agents in psoriasis.

Ustekinumab also has demonstrated efficacy in PsA. More than 40% of patients attained the American College of Rheumatology 20% improvement criteria (ACR20) at 24 weeks with ustekinumab in two phase III clinical trials (49.5% [101/204] and 43.8% [46/105] with 90 mg, 42.4% [87/205] and 43.7% [45/103] with 45 mg). These proportions are numerically lower than those reaching ACR20 with the TNF-α inhibitors (59% at 12 weeks with etanercept [primary endpoint], 57% at 24 weeks with adalimumab, and 54% at 24 weeks with infliximab).

Briakinumab
More than 80% of patients with psoriasis achieved PASI 75 with this agent at 12 weeks in a phase III study (Table 1). Multiple safety signals surfaced, however, with excesses of serious AEs, MACE, nonmelanoma skin cancers (NMSCs), and serious infections compared with placebo observed over the 52-week-long study.

These findings prompted an analysis of MACE in randomized controlled studies of both IL-12/23 inhibitors (ustekinumab and briakinumab) and the TNF-α inhibitors (22 psoriasis trials included). During the placebo-controlled phases of these studies, MACE occurred in 10/3179 patients receiving ustekinumab or briakinumab and 0/1474 receiving placebo.
(P=0.12 for difference in risk; not significant). In psoriasis studies of TNF-α inhibitors, the rate of MACE was 1/3858 patients receiving active therapy and 1/1812 receiving placebo (P=0.94 for difference in risk; not significant).\(^{16}\)

A group of authors evaluating the same data using a different statistical method concluded that significantly more MACE events occurred with IL-12/23 inhibitors than with placebo (P=0.94 for difference in risk; not significant).\(^{17}\) Debates have arisen about the correct statistical method to use in analyzing this issue and whether any increase in MACE is a class effect of IL-12/23 inhibitors.\(^{18-21}\) Some authors advise identifying and optimizing cardiovascular risk factors in patients prior to treatment with ustekinumab, and monitoring for cardiovascular events during therapy.\(^{5,19}\)

**Investigational IL-23 Inhibitors**

Targeting the p40 subunit inhibits both IL-23 and IL-12. IL-12 promotes the development of Th1 cells. Some evidence suggests that the efficacy of agents directed against the p40 subunit stems from their effect on IL-23 rather than IL-12. It was postulated that inhibiting IL-23 while allowing IL-12 to function normally might produce efficacious psoriasis therapy.\(^1\)

Unlike p40, the p19 subunit appears in IL-23 but not in IL-12.\(^1\) At least three investigational monoclonal antibodies block IL-23 by targeting this subunit.

**Guselkumab**

This fully human IgG1 lambda monoclonal antibody has demonstrated greater efficacy than adalimumab in psoriasis during a phase II, dose-ranging study (Table 1).\(^{22}\) Significantly higher proportions of patients achieved the primary endpoint (Physician’s Global Assessment [PGA] score ≤1 at week 16) with the three highest doses of guselkumab studied than with adalimumab (34%, 61%, 79%, 86%, and 83% with guselkumab 5-mg, 15-mg, 50-mg, 100-mg, and 200-mg, respectively; and 58% with adalimumab). The difference in patients meeting this milestone (PGA score ≤1) at week 40 also was significant in favor of guselkumab compared with adalimumab for the same three doses of guselkumab. Proportions attaining PASI 75 at week 16 were not compared statistically but were numerically higher with four of the five guselkumab doses studied than with adalimumab (Table 1).\(^{22}\)

The overall rate of at least one AE was similar across treatment groups for the 16-week placebo-controlled period. The rate of AEs was somewhat higher with adalimumab than with guselkumab thereafter (Table 2). There was no evidence of a dose-response relationship between guselkumab and the rate of AEs, during the 16-week or the 52-week periods. Infections occurred in 20%, 12%, and 14% with guselkumab, adalimumab, and placebo, respectively, during the first 16 weeks, and 30% and 37% through weeks 16 through 52 (guselkumab and adalimumab, respectively). Among patients receiving guselkumab, one developed malignancy, two had serious infections, and three had a
Tildrakizumab
A high-affinity, humanized, IgG1/κ, anti-IL-23 p19 monoclonal antibody, tildrakizumab has demonstrated efficacy in a phase IIb, dose-ranging study of psoriasis.23 Nearly two-thirds of those randomized to tildrakizumab 25 or 100 mg and three-quarters of those randomized to 200 mg tildrakizumab attained PASI 75 at week 16 (Table 1). Nearly 40% (39%) and slightly more than half (52%) of patients receiving 100 and 200 mg, respectively, attained PASI 90 at week 16. PASI 75 response generally persisted from week 16 through 52 (77% [10/13], 79% [49/62], 97% [30/31], 97% [32/33], for those maintained on 5, 25, 100, and 200 mg, respectively). Median time to PASI 75 was 57 and 84 days for the 100- and 200-mg doses, respectively.23

After week 52, treatment was discontinued and patients were followed through week 72. Virtually all (214/222) of those who attained PASI 75 response at week 52 and continued to week 72 maintained during the 20-week treatment-free follow-up period. The dosing schedule during this trial was similar to that of ustekinumab: a subcutaneous injection at weeks 0, 4, then every 12 weeks.23 A lower dosage, ixekizumab 80 mg every 2 weeks, yielded 12-week PASI 75 responses in more than three-quarters of trial participants.25,26 In two of three phase III studies, patients received an initiation dose of ixekizumab 160 mg followed by a subcutaneous injection of 80 mg every 2 or 4 weeks.26 Two phase III studies compared ixekizumab with etanercept as an active control, with response rates of nearly 90% in two out of three phase III studies in psoriasis (Table 1). A lower dosage, ixekizumab 80 mg every 4 weeks, yielded 12-week PASI 75 responses in more than three-quarters of trial participants.25,26 In two of three phase III studies, patients received an initiation dose of ixekizumab 160 mg followed by a subcutaneous injection of 80 mg every 2 or 4 weeks.26

**TABLE 2** Third-Generation Treatments for Psoriasis: Safety

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab</td>
<td>Two phase III trials; two doses studied (90 mg, 45 mg)7,8</td>
<td>Comparable rates of overall AEs, SAEs, infections vs placebo7,8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No dose-response or cumulative exposure trends for AEs in long-term safety analysis10</td>
</tr>
<tr>
<td>Briakinumab</td>
<td>Phase III trial5</td>
<td>Numerically higher rates of SAEs, MACE, NMSC, serious infections vs placebo (52 wk)</td>
</tr>
<tr>
<td>Guselkumab</td>
<td>Phase II trial vs adalimumab and placebo22</td>
<td>Overall AE rate similar vs placebo and adalimumab through wk 16; higher with adalimumab vs guselkumab thereafter (61% vs 49%, wk 16-52); no dose-response relationship for AEs</td>
</tr>
<tr>
<td>Tildrakizumab</td>
<td>Phase IIb trial23</td>
<td>Overall AE rate similar to that of placebo (through wk 16); numerically higher rates of HTN vs placebo (9/308 vs 0/45)</td>
</tr>
<tr>
<td>Bl 655066</td>
<td>Phase I, single, weight-based dose, one of six IV or two SC doses24</td>
<td>Overall AE rate similar to that of placebo. No treatment-related SAEs</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Three phase III trials; two vs etanercept and placebo25,26</td>
<td>Any TEAE: 44%, 54%, 58%, 58%; placebo, etanercept, lower-dose (80 mg q4w) and higher-dose (80 mg q2w) in iexikizumab, respectively. Comparable rates of SAEs and AE-related treatment discontinuations across treatment groups26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Numerically higher rate of infections with iexikizumab (26%, either dose) vs etanercept (22%) or placebo (21%); numerically higher rates of candidiasis with higher-dose iexikizumab vs lower-dose iexikizumab, etanercept, or placebo (12, 4, 5, 2, respectively)26</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>Two phase III trials vs ustekinumab and placebo27</td>
<td>2 suicides in patients receiving brodalumab; higher rate of mild to moderate Candida infections vs placebo</td>
</tr>
</tbody>
</table>
well as placebo. Both doses of ixekizumab displayed significantly higher PASI 75 and PASI 90 rates at 12 weeks than etanercept. PASI 90 rates of more than two-thirds (70.7% and 68.1%) with higher-dose ixekizumab and nearly two-thirds (65.3% and 59.7%) with lower-dose ixekizumab were superior to those of one-quarter to nearly one-fifth (25.7%, 18.7%) with etanercept. Compared with etanercept, higher proportions of patients receiving ixekizumab achieved a static Physician Global Assessment (sPGA) score ≤1 at 12 weeks (coprimary endpoint with PASI 75). Ixekizumab also displayed faster onset of action than etanercept.26

Speed of action was noteworthy. At week 4, roughly half of the patients receiving ixekizumab (either dose, both studies) had achieved PASI 75 compared with 8% and 12% of those treated with etanercept (both studies). The proportion of etanercept patients who achieved PASI 75 at 12 weeks (42%, 53%; both phase III studies) was roughly similar to the proportion of ixekizumab patients attaining PASI 75 at 4 weeks (49%, 50%, 52%, 54%; both doses, both studies). Prior biologic therapy did not appear to affect PASI 75 rates.26

Rates of SAEs and AE-related treatment discontinuation were comparable across treatment groups in both studies. Infections occurred more frequently in patients given ixekizumab than patients given either etanercept or placebo. Most infections were mild or moderate. Candida or likely Candida infections occurred most often in patients receiving the higher dose of ixekizumab (Table 2). No serious or invasive fungal infections were reported.26

Brodalumab

A fully human monoclonal antibody to human IL-17 receptor A (RA), brodalumab is under review at the FDA and the EMA.27 Two doses were studied in two phase II trials, compared with ustekinumab as well as placebo. More than 80% of participants receiving the higher dose (210 mg q2w) and more than two-thirds of those randomized to the lower dose (140 mg q2w) attained PASI 75 at 12 weeks (Table 1). PASI 75 rates with the lower dose of brodalumab were comparable to those of ustekinumab. PASI 100 rates at 12 weeks with higher-dose brodalumab were roughly double those of ustekinumab (44% vs 22% and 37% vs 19%). Brodalumab also produced rapid results: median time to PASI 75 with the higher dose was 4 weeks, roughly half that of ustekinumab.28

Safety signals have prompted concerns, however. Two patients receiving brodalumab during phase III trials committed suicide, compared with none in the ustekinumab group.27 “Events of suicidal ideation and behavior” led Amgen to end its role in the collaboration with Amgen partner AstraZeneca, filed for regulatory approval of brodalumab.28

Summary

The next generation of biological therapies for psoriasis targets IL-17 and IL-23 rather than TNF-α. Some investigational and approved agents have demonstrated PASI 75 rates of more than 80%, approaching 90%.22,26 Ixekizumab has generated PASI 90 in roughly two-thirds of patients in phase III trials.26 As these newer agents become available for clinical use, clearance may become a realistic possibility for increasing proportions of patients.26

References

3. Gandhi M, Alwawi E, Gordon KB. Anti-p40 antibodies ustekinumab and biak

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References

3. Gandhi M, Alwawi E, Gordon KB. Anti-p40 antibodies ustekinumab and broda...
Why Biologic Therapies Sometimes Lose Efficacy
Bruce E. Strober, MD, PhD*

Abstract
Biologic therapies for psoriasis are associated with loss of response over time. Immunogenicity, suboptimal dosing, low serum drug levels, and intermittent or episodic therapy have been documented as explanations for this phenomenon. Use of an immunomodulatory agent can reduce the risk of immunogenicity and improve clinical response. Semin Cutan Med Surg 35(supp4):S78–S80 © 2016 published by Frontline Medical Communications

Keywords
Anti-drug antibodies; biologics; immunogenicity; loss of response; psoriasis; serum drug levels

All biologic therapies approved in the United States for use in psoriasis therapy are associated with some loss of response over time. Immunogenicity, suboptimal dosing, or imperfect adherence all can reduce response to a previously effective therapy. Another theoretical explanation is that the disease evolves within the patient so that its pathophysiology is less dependent on the target of the therapy. If, for example, the role of tumor necrosis factor (TNF)-α in perpetuating psoriasis wanes, then anti–TNF-α therapy may become less effective.1

Documenting Loss of Response: Clinical Trials
A reduction in efficacy of biologics has been observed in clinical studies. The proportion of responders (≥75% reduction in the Psoriasis Area and Severity Index [PASI 75]) drops by about 11% from weeks 24 to 108 with adalimumab,2 12% from week 48 the Psoriasis Area and Severity Index [PASI 75]) drops by about 11% from weeks 24 to 108 with adalimumab,2 12% from week 48 with etanercept,3 and about 23% from week 10 to 50 with infliximab.4 Some patients require intensified maintenance therapy with ustekinumab to generate a response. Following the initial 2 doses, ustekinumab is given every 12 weeks as maintenance.5 In one phase III trial, about 16% of patients receiving the recommended dose (90 mg) and 23% of those randomized to receive 45 mg were partial responders (ie, ≥50% but <75% PASI improvement vs baseline at week 28).6 This study randomized partial responders at week 28 to intensified (once every 8 weeks, same dose) or continued, standard maintenance therapy (once every 12 weeks, same dose) for another 28 weeks.6

Intensified dosing significantly increased PASI 75 for the 90-mg partial responders (68.8% [22] vs 33.3% [11] at week 52; intensified vs standard maintenance therapy; P=0.004), though not for those receiving intensified therapy with the 45-mg dose. It also led to increased drug concentrations; mean trough serum drug concentrations were four to five times higher with intensified than standard therapy (both doses).5 US labeling does not allow for maintenance dosing every 8 weeks.2

Long-term (5-year) follow-up of this study permitted dose intensification at patient or investigator initiation and change of dose (eg, 45 to 90 mg) as well as frequency after week 52. Roughly 20% of patients received a dose adjustment before week 52, and another 30% received a dose adjustment after week 52. Approximately half of the latter group (so-called “late adjusters”) changed dosage after attaining PASI 75; the others were partial or nonresponders. Dose adjustment improved response in many patients; PASI 75 was achieved at week 144 by 88.6% of partial responders and 57.1% of nonresponders dose adjusted from 45 mg, and 44.4% and 77.8% of those dose adjusted from 90 mg, respectively.7 Clinically, it has been observed that some patients remain clear between the first few injections but later develop breakthrough symptoms between maintenance injections. Like infliximab, ustekinumab features higher dosing at initiation of therapy, with injections at 0 and 4 weeks, then every 12 weeks.5

Immunogenicity
All foreign proteins are immunogenic by definition, including those given for therapeutic reasons.8 Human and humanized proteins also have generated immunogenic responses, for multiple possible reasons. The manufacturing process may introduce protein modifications that promote immunogenicity. Degradation products may form during scale-up or storage. Patient factors (eg, human leukocyte antigen type, presence of infection, immunosuppression) also contribute to whether a therapeutic protein generates an immunogenic response.9

Biologics manufacturers acknowledge the problem of immunogenicity and discuss it in product labeling. Caution must be exercised in comparing rates of anti-drug antibody (ADA) development across medications. Rates are derived from drug-specific assays that vary in sensitivity and specificity.5,9,11 In infliximab therapy, ADAs were associated with lower drug levels, higher clearance rates, and a two- to three-fold increased risk of infusion reactions.8 ADAs also were associated with reduced efficacy in some studies of infliximab and adalimumab.9,10 ADA positivity

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was associated with lower rates of meeting the American College of Rheumatology 20% improvement criteria among patients receiving recommended adalimumab dosing (once every 2 weeks) as monotherapy.  

More frequent dosing and immunomodulator therapy may reduce the risk of ADAs. In adalimumab monotherapy for rheumatoid arthritis (RA), “patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing.” Concomitant administration of an immunomodulator (eg, methotrexate, azathioprine) was associated with reduced risk of immunogenicity to infliximab and adalimumab. Compared with adalimumab monotherapy, adding methotrexate reduced ADA development (1% and 12% with concomitant methotrexate and monotherapy, respectively). Rates of ADA to infliximab were lower among patients with RA or Crohn’s disease receiving an immunomodulatory agent. Adding an immunomodulator also “appeared” to reduce the risk of infusion reactions with infliximab.

Confirming the inherent risk of immunogenicity for adalimumab, a phase III study of an adalimumab biosimilar (ABP 501) in RA demonstrated similar incidence of binding and neutralizing antibodies to that of the reference adalimumab (Humira) (38.3% and 38.2%, binding antibodies, ABP 501 and adalimumab, respectively; 9.1% and 11.1%, neutralizing antibodies, ABP 501 and adalimumab, respectively). Patients (n=264, ABP 501; n=262, adalimumab) were treated for 22 weeks, then followed for another 4 weeks.

Duration of exposure was associated with risk of ADA development in etanercept studies of psoriasis patients. However, ADA development in etanercept studies was not correlated with either lowered clinical response or adverse events.

**Anti-drug Antibodies: Reduced Drug Levels, Reduced Response**

Adalimumab antibodies have been associated with treatment nonresponse, less improvement in disease activity, and significantly lower serum adalimumab levels in a prospective observational cohort study of patients with RA (n=121). Study participants were followed for 28 weeks. ADAs were detected in 17% of patients. Adalimumab nonresponders were significantly more likely to develop ADAs than good responders (P=0.006; European League Against Rheumatism response criteria used). Further, the presence of ADAs was associated with lower serum adalimumab concentrations (median, 1.2 mg/L; range, 0.0-5.6 vs median, 11.0 mg/L; range, 2.0-33.0, respectively; P<0.001). Nonresponders also had significantly lower serum adalimumab concentrations than good responders (P=0.001). Concomitant methotrexate use was less frequent among patients who developed ADAs (52% and 84%, methotrexate use in those with and without ADAs; P=0.003).

A smaller prospective observational cohort study of adalimumab use in psoriasis patients (n=29) corroborated these findings. Nearly half (45%; 13/29) of the participants developed adalimumab ADAs during 24 weeks of therapy. Treatment response and median serum adalimumab trough concentrations were inversely correlated with titers of ADAs. The median trough adalimumab concentration differed significantly among good, moderate, and nonresponders to adalimumab. Those with high ADA titers had undetectable median serum trough levels of adalimumab (0.0; range, 0.0-0.0). Three patients in this cohort used concomitant methotrexate; none developed ADAs to adalimumab.

Serum drug levels and clinical response were correlated in a study of etanercept therapy for RA (n=292). Etanercept levels at 6 months were significantly higher among good responders compared with moderate and nonresponders (P<0.05). Patients were divided into quartiles by etanercept levels; 40% of nonresponders fell into the lowest quartile (<2.1 mg/L), whereas 35% of good responders were in the highest quartile (>4.7 mg/L). No anti-etanercept antibodies were detected. Although patients might lose response while receiving etanercept, there is some consensus that immunogenicity may not explain this phenomenon.

**Immunomodulator Therapy and Response**

In a study of infliximab in Crohn’s disease, adding an immunomodulatory agent (6-MP, azathioprine, or methotrexate) significantly lowered the risk of infliximab antibodies (10% and 18%, respectively; P=0.02) and of infusion reactions. The rate of infusion reactions was 3% (38/1174) among those receiving immunomodulator therapy and 6% (171/2666) in those not receiving such therapy (P<0.001). Continuous maintenance therapy also yielded superior efficacy and lower rates of ADA compared with episodic retreatment.

Etanercept therapy has not been associated with neutralizing ADAs. However, concomitant methotrexate therapy has been associated with improved clinical response compared with etanercept alone.

Patients with psoriasis (n=59) who had failed methotrexate monotherapy were randomized to continued methotrexate therapy plus etanercept, or etanercept with methotrexate tapered and discontinued over a 4-week period. Significantly more patients met the primary efficacy endpoint (Physician’s Global Assessment ≤1 at week 24) in the group that continued methotrexate therapy (66.7% and 37.0%, respectively; P=0.025). Mean improvement in PASI score at 18 weeks was significantly higher with combination therapy than with those tapered off of methotrexate (79.9% vs 62.8%, respectively; P=0.023).

In a larger study (n=478), patients with psoriasis who had not previously failed methotrexate or anti-TNF therapy were randomized to receive methotrexate or placebo therapy. All participants in both treatment arms also received etanercept as recommended for psoriasis (50 mg twice weekly for 12 weeks, then 50 mg once weekly for 12 weeks). Patients were followed for 24 weeks. Combination therapy was associated with higher efficacy. PASI 75 response rates were 77.3% and 60.3% for etanercept/methotrexate combination and methotrexate monotherapy, respectively; P<0.0001.

**Preventing Immunogenicity**

Concomitant therapy with methotrexate or another immunomodulator appears to reduce development of ADAs and improve clinical response to biologic therapy for psoriasis. Continuous maintenance therapy rather than episodic re-treatment based on symptoms also can reduce immunogenicity and improve clinical response. Starting an immunomodulator first, then adding a biologic therapy, may be more likely to prevent immunogenicity than initiating the biologic therapy first, as antibodies to the biologic therapy may develop early and become irreversible before the immunomodulator is started.

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to etanercept obtain lower etanercept concentrations compared with responding 

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methotrexate increases the effectiveness of treatment in active psoriasis despite 
1. Which of the following best describes the role of interleukin (IL)-23 in psoriatic inflammation?
   A. It is a T helper 17 (Th17) cytokine
   B. It is inhibited directly by secukinumab
   C. It appears to induce differentiation of regulatory T cells into proinflammatory Th17 cells
   D. It is not viewed as an important driver of psoriatic inflammation

2. Tofacitinib has been associated with:
   A. An excess of serious infections and cardiovascular events in the psoriasis development program
   B. An excess of fatal infections, opportunistic infections, and malignancy in the rheumatoid arthritis development program
   C. Noninferior efficacy compared with that of adalimumab in a head-to-head trial with psoriasis patients
   D. Has received FDA approval for rheumatoid arthritis

3. Which of the following treatments for psoriasis has demonstrated superior efficacy to that of etanercept in a head-to-head trial?
   A. Secukinumab
   B. Ustekinumab
   C. Brodalumab
   D. A and B

4. Which of the following most accurately describes acitretin?
   A. Its use should be avoided in pregnant women whenever possible as it is FDA pregnancy category X, associated with substantial teratogenicity, and can convert to a form with a prolonged half-life
   B. A highly effective monotherapy for plaque psoriasis
   C. Offers an immunosuppressive mechanism of action
   D. Well tolerated in most patients

5. Which of the following is true of apremilast?
   A. It is associated with Psoriasis Area and Severity Index 75 rates of 65% and 75% in phase III trials for psoriasis
   B. It is well tolerated
   C. It is associated with weight loss and, rarely, depression
   D. It has received FDA approval for psoriatic arthritis but not psoriasis

6. Which of the following agents has demonstrated superior efficacy compared with that of adalimumab in a head-to-head trial in psoriasis?
   A. Guselkumab
   B. Brodalumab
   C. Golimumab
   D. Tildrakizumab

7. Which of the following statements most accurately describes safety issues with approved or investigational psoriasis therapies?
   A. Anti–tumor necrosis factor agents are associated with elevated rates of candidiasis infection
   B. Brodalumab has been associated with reports of suicide in clinical trials
   C. A dose-response relationship was observed for infection rates in the clinical trials of ustekinumab
   D. Ixekizumab has been associated with an excess of major adverse cardiovascular events compared with placebo in clinical trials

8. Stopping treatment in patients with psoriasis who responded to etanercept, then resuming etanercept therapy after relapse, led to which of the following outcomes upon treatment resumption?
   A. Nonresponse in the majority of patients
   B. Increased incidence of treatment-associated adverse events, compared with therapy prior to the interruption
   C. Similar clinical response to the first round of therapy, after 12 weeks of retreatment
   D. Weaker response than those displayed in the prior round of treatment

9. A segment of patients with psoriasis displays a partial response to ustekinumab. Which of the following measures has been shown to improve response in this group of patients?
   A. Adding an immunomodulator
   B. Administering a dose higher than the 90-mg recommended dose at each treatment
   C. Administering treatment more frequently (once every 8 weeks rather than once every 12 weeks)
   D. Adding a second biologic therapy

10. Which measures have been shown to reduce the frequency of loss of response to infliximab?
    A. Continuous (ie, as recommended) maintenance therapy rather than episodic retreatment based on symptoms
    B. Concomitant use of an immunomodulator
    C. Adding an antihistamine to prevent infusion reactions
    D. A and B
TO THE READER

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: http://tinyurl.com/12thPsoriasisSupp.

Please indicate your profession/background: (check one)

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student
☐ Other; specify ______________________________________________________________

LEARNING OBJECTIVES: Having completed this activity, you are better able to:

<table>
<thead>
<tr>
<th>LEARNING OBJECTIVES</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe current findings about the role of T helper 17 (Th17) cytokines and interleukin (IL)-23 in the pathophysiology of psoriasis, and list the approved treatments for psoriasis targeted to these cytokines.</td>
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<td>Demonstrate familiarity with the efficacy and safety issues associated with the nonbiologic systemic agents acitretin, apremilast, and tofacitinib.</td>
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<td>Compare and contrast the efficacy and safety data for the tumor necrosis factor (TNF)-α inhibitors available in the United States with each other and with other therapies.</td>
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<td>Differentiate TNF-α and non–TNF-α biologic agents based on their mechanism of action, efficacy, safety, and clinical use.</td>
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<td>Apply understanding of the loss of response observed with biologics for psoriasis to the implementation of measures intended to reduce its frequency.</td>
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</tbody>
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If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)
☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Do nothing differently. Content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc)?

OVERALL EVALUATION

<table>
<thead>
<tr>
<th>OVERALL EVALUATION</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<td>This education increased my understanding of the subject.</td>
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<td>This education will influence how I do my job.</td>
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<tr>
<td>This education will help me improve my job performance.</td>
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<tr>
<td>This education will help me collaborate with other healthcare professionals.</td>
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<tr>
<td>This education addressed issues in cultural competency.</td>
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<td>This education was educationally sound and scientifically balanced.</td>
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<td>This education was free of commercial bias or influence.</td>
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<td>This education met my expectations.</td>
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Kenneth B. Gordon, MD
Author demonstrated current knowledge of the topic. 5 | 4 | 3 | 2 | 1
Author was organized in the written materials. 5 | 4 | 3 | 2 | 1

Francisco A. Kerdel, BSc, MBBS
Author demonstrated current knowledge of the topic. 5 | 4 | 3 | 2 | 1
Author was organized in the written materials. 5 | 4 | 3 | 2 | 1

Craig L. Leonard, MD
Author demonstrated current knowledge of the topic. 5 | 4 | 3 | 2 | 1
Author was organized in the written materials. 5 | 4 | 3 | 2 | 1

Bruce E. Strober, MD, PhD
Author demonstrated current knowledge of the topic. 5 | 4 | 3 | 2 | 1
Author was organized in the written materials. 5 | 4 | 3 | 2 | 1

What issues are you experiencing in your practice regarding your professional responsibilities that could be addressed in future programming?

Please provide additional comments pertaining to this activity and any suggestions for improvement.

Rutgers, The State University of New Jersey and Skin Disease Education Foundation thank you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.

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