



Addressing Cardiovascular Comorbidities in

Activity Overview

Guidelines on the management of patients with psoriasis and psoriatic arthritis are primarily based on data from clinical trials. However, clinical trial study populations do not necessarily reflect the patients seen in everyday practice. Clinicians require practical strategies for achieving and maintaining control of psoriatic disease in a wide range of patients. This *Biologic Bulletin* presents three clinical scenarios and examines the selection and rationale for the best management options for each patient.

Target Audience

This activity has been designed to meet the educational needs of dermatologists, dermatology residents and fellows, dermatology nurses, nurse practitioners, physician assistants, and other health care professionals involved in the care of patients with moderate to severe psoriasis.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Formulate a practical plan for the integration of agents with new mechanisms of action into clinical practice
- Develop strategies for managing a diverse set of patients with psoriasis that include consideration of comorbid disease and concomitant conditions
- Explain the pathology of interleukin (IL)-12 immunodeficiency and implement appropriate screening, monitoring, and vaccinations in patients receiving IL-12/23 inhibitors
- Compare safety issues relating to the various systemic therapies used to treat moderate to severe psoriasis

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Method of Participation

There are no fees for participating in this CME/CE activity. To receive credit during the period January 2011 to January 31, 2012, participants must (1) read the learning objectives and disclosure statements, (2) study the educational activity, and (3) complete the postsurvey and activity evaluation, including the certificate information section.

The postsurvey can be accessed at the end of the activity. Please e-mail any questions to cmeinfo@curatiocme.com.

Medium

The Internet was selected as the instructional format to accommodate the learning preferences of a significant portion of the target audience.

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Speaker: Abbott, Amgen, Centocor Ortho Biotech, Galderma

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- Version 5.0 or higher for Microsoft Internet Explorer or Netscape 6 or higher
- If you are using a Mac computer system and are experiencing problems with your browser, we suggest downloading the latest version of Firefox for Mac
- Adobe Flash Player plugin v.8.0+

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Generic Name	Trade Name	Approved Use (if any)	Unapproved Use
Adalimumab	Humira	Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Use in combination with methotrexate or 40 mg/week dose
Briakinumab	N/A	N/A	Investigational agent for the treatment of psoriasis
Etanercept	Enbrel	Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Use in combination with methotrexate, cyclosporine, narrowband UVB or as a twice-weekly 50-mg maintenance dose
Infliximab	Remicade	Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Use in combination with methotrexate
Ustekinumab	Stelara	Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Use in combination with methotrexate; treatment of psoriatic arthritis



Ongoing Developments in Psoriasis

Cases and Commentaries in Psoriasis



Kyle B: Patient With Long-Term Response on Biologic Agent (Anti-TNF)

Initial History, Presentation, and Treatment

Kyle B is a 27-year-old male with a 5-year history of psoriasis. He presented with a psoriasis flare that began 6 months prior, correlating with a motor vehicle accident and subsequent loss of his job as a sales representative for a publishing company. At the time of presentation, Kyle was single and had no past medical history of psoriatic arthritis, cancer, or lymphoma. He denied a history of hepatitis, congestive heart failure, recurrent infections or hospitalizations, or tuberculosis. Furthermore, he reported no family history of lymphoma, leukemia, or demyelinating diseases. The decision was made to treat Kyle with narrowband UVB (NB-UVB) therapy. In total he received 36 NB-UVB treatments, which resulted in greater than 95% clearing, but his remission was short-lasting (ie, only a few months).

Phototherapy for the Treatment of Psoriasis

Stress has long been recognized as playing a role in the pathogenesis of psoriasis. In the present case, the patient experienced considerable stress prior to his psoriasis flare (a motor vehicle accident and subsequent loss of employment). This is consistent with the findings of a recent case-control study in which recent emotionally stressful events, particularly family and job problems, were significantly more often associated with onset, recurrence, and extension of lesions among patients with psoriasis than among age- and gender-matched controls with other skin disorders.¹⁰

Traditionally, phototherapy is reserved for patients with psoriasis that affects more than 10% of their body surface area (BSA).⁶ Phototherapy is believed to exert its effect through local immunosuppression, inhibition of keratinocyte proliferation and angiogenesis, and the induction of apoptosis of T cells.⁶

Table 1. Dosing guidelines for narrowband UVB therapy.⁶

Reprinted from *J Am Acad Dermatol* 62(1). Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy, 114-135. Copyright 2010, with permission from by the American Academy of Dermatology, Inc.

According to skin type:			
Skin type	Initial UVB dose, mJ/cm ²	UVB increase after each treatment, mJ/cm ²	Maximum dose, mJ/cm ²
I	130	15	2,000
II	220	25	2,000
III	260	40	3,000
IV	330	45	3,000
V	350	60	5,000
VI	400	65	5,000
According to MED:			
Initial UVB		50% of MED	
Treatments 1–20		Increase by 10% of initial MED	
Treatments ≥21		Increase as ordered by physician	
If subsequent treatments are missed for:			
4–7 d		Keep dose same	
1–2 wk		Decrease dose by 25%	
2–3 wk		Decrease dose by 50% or start over	
3–4 wk		Start over	
Maintenance therapy for NB-UVB after >95% clearance:			
1×/wk	NB-UVB for 4 wk	Keep dose same	
1×/2 wk	NB-UVB for 4 wk	Decrease dose by 25%	
1×/4 wk	NB-UVB	50% of highest dose	

MED, minimal erythema dose; NB, narrowband; UV, ultraviolet; mJ, millijoule
Administered 3–5×/wk.

Because there is broad range of MED for NB-UVB by skin type, MED testing is generally recommended.

It is critically important to meter UVB machine once weekly. UVB lamps steadily lose power. If UV output is not periodically measured and actual output calibrated into the machine, the clinician may have the false impression that the patient can be treated with higher doses when the machine is actually delivering a much lower dose than the number entered.

Minimum frequency of phototherapy sessions required per week for successful maintenance, as well as length of maintenance period, varies dramatically between individuals. Above table represents most ideal situation where the patient can taper off phototherapy. In reality, many patients require 1×/wk NB-UVB phototherapy indefinitely for successful long-term maintenance.

Phototherapy is a well-established, reasonably efficacious, and low-risk treatment that avoids the systemic immunosuppression associated with many other options. It is, however, rather time-consuming, requiring two to three office visits per week. Additionally, insurance copayments for in-office phototherapy sessions are typically 3-fold higher than the copayments for biologic treatments.¹¹

NB-UVB therapy utilizes light within the wavelengths of 311 to 313 nm, whereas broadband UVB (BB-UVB) spans a larger wavelength spectrum. In comparison to BB-UVB, NB-UVB is associated with superior short- and long-term efficacy.^{6,12} Guidelines regarding the use of light-based therapies for the management of psoriasis were recently released by the AAD.⁶ Prior to the initiation of any phototherapy, patients should undergo a complete history and physical examination, as phototherapy is contraindicated in patients with a history of systemic lupus erythematosus, xeroderma pigmentosum, diseases that produce photosensitivity, melanoma, multiple nonmelanoma skin cancers, or organ transplantation.⁶

As per AAD guidelines, NB-UVB treatments are typically administered 3 to 5 times per week.⁶ The initial UVB dose can be calculated based on either the patient's Fitzpatrick skin type or his or her minimal erythema dose (MED). Doses are typically increased over the course of treatment, and clearance is often obtained in fewer than 20 treatments.⁶ Once at least 95% clearance is achieved, the use of maintenance therapy appears to prolong remission.¹³ Some patients may require maintenance therapy indefinitely (1 treatment/week) to maintain a clinical response.⁶

The most common acute adverse events associated with UVB therapy are erythema, pruritus, burning, and stinging.⁶ To prevent cataract formation and genital tumor development, goggles and genital shielding (for men) should be utilized during treatments. Although there is a theoretical association between NB-UVB and skin cancer, to date no such correlation has been observed in follow-up studies.^{6,14} Nevertheless, it is prudent to periodically examine patients undergoing UVB therapy for cutaneous malignancies as well as signs of photoaging and pigmentary changes.⁶

Kyle: Second Visit

Kyle returned to the dermatologist 8 months after his initial visit with psoriasis affecting 18% of his BSA. After discussing various treatment options, it was decided that therapy with an anti-tumor necrosis factor (TNF) agent would be initiated. Pretherapy

testing demonstrated that both a complete blood count (CBC), liver function tests, and comprehensive metabolic panel were within normal limits. A hepatitis B and C profile was negative, and a tuberculosis skin test (purified protein derivative [PPD]) exhibited 0 mm induration at 72 hours. At the time, the patient's weight was 180 lbs. Following review of the above test results, Kyle was prescribed etanercept 50 mg twice/week as a subcutaneous injection for 12 weeks.

Initiation of Therapy With TNF Inhibitors

Given the patient's extensive psoriasis and the relatively short duration of remission achieved with NB-UVB, initiation of therapy with a systemic agent was advised. Current guidelines do not generally recommend the use of one biologic over another for the treatment of psoriasis. Etanercept, a fusion protein comprising the ligand-binding portion of the TNF receptor and the Fc portion of human IgG1, inhibits the binding of both TNF- α and TNF- β to their cognate receptor.¹⁵ Although etanercept, and other approved TNF inhibitors, are generally safe and effective, proper baseline monitoring is warranted to avoid potential toxicity. A proper history and physical examination should be used to identify patients with infections, liver disease, neurologic disorders, and malignancy.^{1,16} In addition, patients with NY Heart Association stage III or IV congestive heart failure should be identified, because these conditions may be worsened by anti-TNF agents.^{1,16}

Laboratory testing should be used to further identify patients in whom anti-TNF therapy is contraindicated or should be used with caution. In its guidelines, the AAD recommends baseline PPD, CBC, and liver function testing for all patients beginning treatment with an anti-TNF agent.¹ A baseline CBC ensures that there are no pretherapy hematologic abnormalities and can act as a comparator for follow-up testing.^{1,16} The National Psoriasis Foundation (NPF) reports that the practice of testing for hepatitis varies by physician, although the AAD recommends this for patients who will begin therapy with adalimumab and infliximab.^{1,16} Lastly, because TNF- α is involved in the physiologic response to tuberculosis exposure, baseline tuberculosis testing is necessary.^{1,16}

Prior to beginning etanercept therapy (or any biologic), it is important to review the immunization status of patients. The immunosuppressive nature of biologic agents requires that patients avoid live and live-attenuated vaccines.^{1,16,17} Therefore, patients should receive any necessary vaccinations prior to the initiation of therapy.^{1,16,17} Annual inactivated influenza vaccination



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is recommended for patients on anti-TNF agents, and general recommendations should follow those by the CDC for patients on immunosuppressive therapy.^{16,18}

Kyle: Third Visit

Following 12 weeks of etanercept therapy, Kyle demonstrated considerable clinical improvement; with a reduction of BSA involvement to 3%. Twice weekly treatments with excimer laser to persistent plaques were begun, and the frequency of etanercept was decreased to once weekly. After 6 weeks of excimer laser therapy, Kyle exhibited complete resolution of his psoriasis. He remained lesion-free for 6 months, at which point he developed psoriatic plaques on approximately 3% of his BSA. These lesions were adequately treated with topical corticosteroids.

Adjunctive Therapy

The patient's response to etanercept is consistent with pivotal trial data. An integrated analysis of that data showed an improvement from baseline of at least Psoriasis Area Severity Index (PASI) 50, 75, or 90 in 76%, 49%, and 21% of patients, respectively.¹⁹

Excimer lasers utilize monochromatic light of 308 nm wavelength (from a xenon-chloride gas combination) to target individual psoriatic plaques (this treatment is not recommended for plaques covering a large proportion of BSA).⁶ Excimer laser therapy may be capable of clearing plaques with fewer treatments and lower cumulative UV doses than NB-UVB.^{20,21} Potential advantages of excimer laser over NB-UVB include tolerance of higher doses of UV than normal skin, deeper penetration into the dermis, higher rate of delivery of UV energy, and induction of T-cell apoptosis.

The precise dose of excimer laser treatments is dictated by the patient's skin type, the thickness of the plaque being treated, and response to treatment.⁶ Treatments must be spaced at least 48 hours apart and are typically administered two to three times weekly.⁶ Adverse reactions to excimer laser treatments are limited to the area treated and include burning, stinging, hyperpigmentation, erythema, and blisters at the treated sites.⁶

Although the use of excimer laser therapy in combination with systemic therapies for psoriasis has not been systematically evaluated, it is one of several reasonable adjunctive options including UVB, acitretin, methotrexate, or topical agents as noted by the roundtable participants.^{6,21}

Topical corticosteroids are the mainstay of therapy for many patients with psoriasis.⁵ For some patients, they can be used as monotherapy, but in Kyle's case, they are being combined with a systemic agent (etanercept) and used intermittently for the control of flares. Although this combination therapy has not been extensively studied, it is commonly used in clinical practice. The combination of clobetasol propionate and other systemic biologic and nonbiologic agents or other treatment modalities was the subject of a 4-week open-label community-based study.^{22,23} Clinicians can choose from a wide variety of topical corticosteroids ranging from superpotent class I agents (eg, halobetasol propionate 0.05 ointment) to least potent class VII topicals (eg, hydrocortisone 1% cream). Generally, high-potency topical corticosteroids should be reserved for thick plaques located on nonfacial skin, and they should be used for relatively short periods of time (eg, less than 4 weeks).⁵ The vehicle in which topical steroids are formulated (and prescribed) can affect not only potency of the agent (ie, because of increased penetration of the skin), but also the ease of application and cosmetic appearance when applied.⁵ (which may in turn influence adherence). Topical corticosteroids are generally well tolerated but can be associated with local cutaneous effects such as atrophy, striae, and exacerbation of some dermatoses (eg, rosacea).⁵ Systemic side effects, while rare, occur most often with more potent steroids and prolonged use.

Kyle: Case Conclusion

Kyle continued to exhibit a positive response to etanercept therapy following a dose reduction to 25 mg BIW, as per the approved dosing regimen. He was evaluated by his dermatologist every 3 months to assess the status of his psoriatic disease and to evaluate tolerability. At follow-up visits, he was questioned about potential adverse events that can be associated with anti-TNF therapy, including fevers, chills, night sweats, weight loss, fatigue, headaches, blurry vision, facial droopiness, paresthesia, and infections. Kyle did not report any of these symptoms. The patient was reminded that if any of these occur he should hold etanercept administration and notify his primary care physician and the dermatologist to determine an appropriate management strategy.

At 6-month intervals, the patient was scheduled for repeat CBC and comprehensive metabolic panels; all were within normal limits. Annually, Kyle was screened for tuberculosis exposure via PPD and hepatitis B and C via a hepatitis profile. The patient

was reminded that nonlive vaccinations such as the killed influenza vaccine are appropriate while on etanercept, but that if live vaccines were necessary, he should discontinue etanercept 3 weeks prior to vaccination and should not restart it until 3 weeks afterwards. Kyle was also reminded to keep his primary care physician informed about his treatments for psoriasis and to coordinate with his primary care clinician regarding any vaccinations, infections, or surgical procedures.

Monitoring Patients on Biologic Agents and Insurance Coverage

In addition to providing an opportunity to monitor patients for continued response to anti-TNF therapy, follow-up visits offer an opportunity to assess for potential side effects and to continue educating patients about psoriasis and their prescribed treatment regimen. In its guidelines the NPF recommends follow-up testing of CBCs and liver function tests every 2 to 6 months for patients receiving etanercept and all TNF inhibitors.¹⁶ As noted, annual testing for tuberculosis should also be conducted. Patients should be kept up-to-date on new data regarding the safety of their medications. Recent regulatory changes, such as the addition of a black box about the risk of opportunistic infections (such as tuberculosis, invasive fungal infections, and bacterial sepsis) and about lymphoma and other malignancies in patients receiving anti-TNF agents,^{15,24,25} should be reviewed with patients. As such updates are often reported by the press, patients may have concerns or misconceptions about the issues, which clinicians should aim to clarify.

Patients on biologic therapy require careful follow-up. Even if they are “doing well,” visits should be scheduled to allow for monitoring of adverse events and to address any concerns patients may have.

The cost of therapy can be a barrier to care. Biologic therapy with an anti-TNF agent can cost approximately \$20,000 to \$25,000 annually.^{26,27} This can be compared to an annual cost of less than \$10,000 for cyclosporine and less than \$1,500 for methotrexate.²⁶ Of course, the cost of therapy should be weighed against the economic cost of inadequate treatment of moderate to severe psoriasis—loss of productivity, disability, hospitalizations. It is worth noting that in light of the fact that phototherapy was attempted prior to the initiation of anti-TNF

therapy, Kyle’s insurance company did not provide any barriers to etanercept approval. A prerequisite that patients receive a trial of phototherapy has been adopted by some payors.²⁸ It is important to document BSA, quality-of-life issues, history of psoriasis, and previous response to therapies to facilitate insurance approval for biologic agents. To provide access to the policies of most insurance companies regarding coverage of treatments, the NPF developed the Health Insurance Action Center.²⁹ The site also provides information on various pharmaceutical company–sponsored financial assistance programs. These tools may be valuable to both patients and their clinicians.

Getting medications, particularly biologic agents, approved by insurance companies can often be difficult and frustrating to clinicians and patients. A number of resources to help us navigate the challenges of managed care companies are available.

Lucas: New Onset Joint Disease in Addition to Moderate To Severe Psoriasis

Initial History, Presentation, and Treatment

Lucas F, a 42-year-old male with a 20-year history of psoriasis, presented to his dermatologist concerned that his current regimen of adalimumab “stopped working.” He had been successfully managed with adalimumab (40 mg every other week) for the prior 18 months. His monitoring laboratory values had always been within normal limits. At the time of presentation, the patient was married with two teenage daughters and worked as an attorney. On physical examination, the patient weighed 240 lbs. and had psoriatic plaques affecting 15% BSA. An attempt was made to increase the adalimumab dose to 40 mg weekly, but Lucas’s insurance company would not authorize this off-label dose. After a discussion regarding other treatment options and consideration of Lucas’s weight, it was decided that Lucas would be switched to ustekinumab. Treatment with ustekinumab commenced 4 weeks after discontinuation of adalimumab to avoid possible immunosuppression. Given his weight, he was prescribed ustekinumab 90 mg, administered subcutaneously at weeks 0 and 4, followed by 90 mg every 12 weeks thereafter. Following the first two injections of ustekinumab, Lucas exhibited an 80% improvement in his psoriasis. Following the third injection, he exhibited complete resolution of psoriasis.



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Secondary Failure of Monotherapy With an Anti-TNF Agent

The short-term efficacy of available biologic therapies for psoriasis is well characterized. Considerably less data exist regarding the long-term response to these agents, as most studies have not extended beyond 2 years.³⁰ In a 60-week trial of adalimumab, PASI 75 response was generally sustained over time for the treatment group receiving 40 mg every other week. Approximately 6% fewer patients achieved PASI 75 at week 60 as compared to week 36 (56% vs 62%). Data suggest that response rates also decrease over time for the other TNF inhibitors, as well as for etanercept and infliximab.³⁰ It is important to distinguish loss of response from a flare that may occur in a patient who missed some medication doses, had a recent illness or stressor, or that developed close to the next scheduled dose (ie, 1 to 2 weeks prior to the next injection of ustekinumab). If the patient's condition has continually worsened and he or she has been adherent, loss of response is likely the cause.

When evaluating a patient with a loss of response to therapy, clinicians should rule out nonadherence to the prescribed regimen prior to implementing changes in pharmacotherapy.

Given Lucas's loss of response to maintenance therapy, it is clear that a change in pharmacotherapy should be made. There is a relative dearth of trial-based evidence available to guide this decision. Led by Strober, a group of dermatologists published consensus-based guidelines on the handling of such treatment decisions.⁹ When faced with secondary failure of an anti-TNF agent, the group's top-ranking therapeutic options were (1) switch to another agent in the same class, (2) add methotrexate to the regimen, and (3) switch to therapy with an antibody targeting interleukin (IL)-12 and IL-23.⁹ In practice, some clinicians increase the dose of a TNF inhibitor (eg, using 50 mg etanercept BIW or 40 mg adalimumab weekly), though this is off-label and sometimes not approved by insurance.

There is growing evidence that patients who do not respond to one TNF inhibitor can successfully be treated with another. There are no head-to-head trials comparing adalimumab to other TNF inhibitors. Data on switching from one anti-TNF agent to another is also lacking. In fact, the majority of studies

examine the response of patients switching to adalimumab from another TNF inhibitor rather than vice versa. For instance, in a cohort of 82 patients exhibiting suboptimal response to etanercept, approximately 49% responded to therapy with adalimumab.³¹ In a recent registry study of 14 patients who exhibited secondary failure to etanercept, 11 (79%) exhibited primary response to adalimumab at week 12.³²

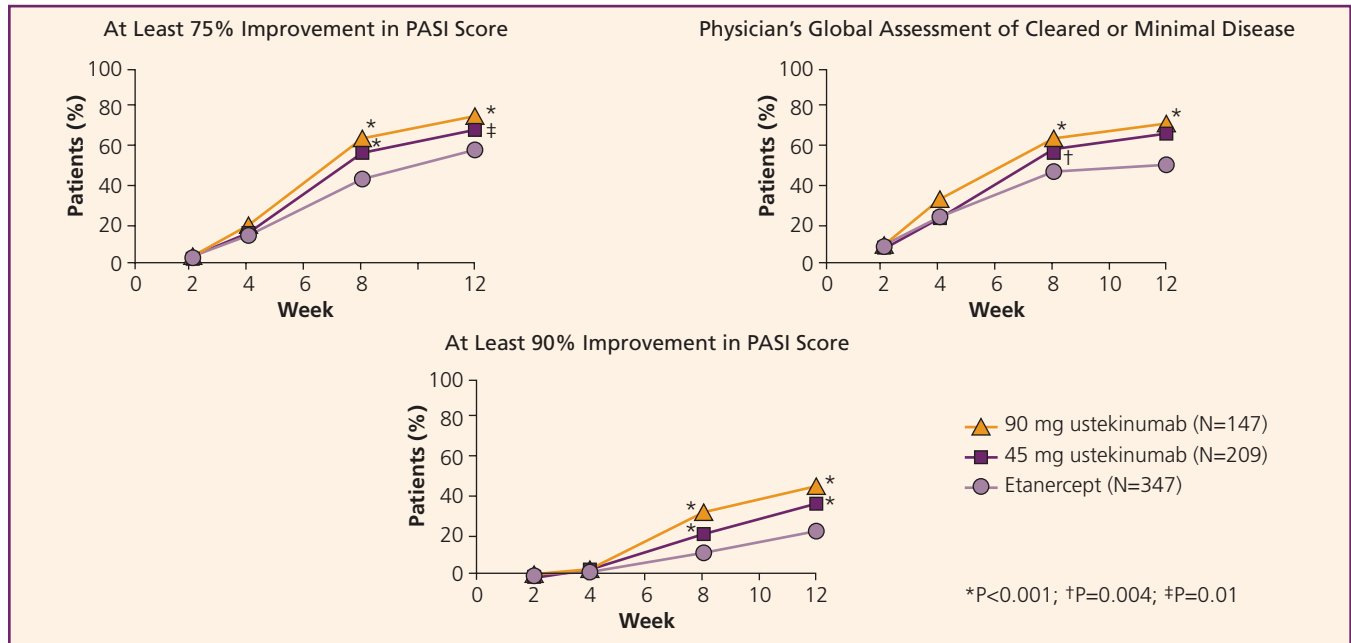
Although there is sparse data systematically evaluating the addition of methotrexate to biologic therapy for the treatment of psoriasis, methotrexate has been used in combination with each of the available biologics.³ This combination is often associated with greater efficacy than either agent alone.³³ Although data in the area of psoriasis is limited, combining methotrexate with biologics for the treatment of rheumatoid arthritis has been well studied.³⁴

In the present case, the decision was made to initiate therapy with ustekinumab. Approved in 2009 for the treatment of adults with moderate to severe plaque psoriasis, ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit of IL-12 and IL-23.³⁵ US Food and Drug Administration (FDA) approval of ustekinumab was based on data from two large, phase 3, double-blind, placebo-controlled studies (PHOENIX 1 and 2).^{36,37} In both trials, patients were randomized to receive either ustekinumab 45 mg or 90 mg at weeks 0 and 4 and every 12 weeks thereafter, or placebo.^{36,37} During the placebo-controlled portion of each trial (weeks 0–12), serious adverse events were rare, occurring at comparable rates in the active treatment and placebo groups.^{36,37} Although the assignment of subjects in the PHOENIX trials to treatment groups was random, a subanalysis examined the effect of weight on response. Patients weighing less than 100 kg in both ustekinumab dose groups exhibited similar PASI 75 response rates (80.8% [90-mg group] vs 76.9 [45-mg group]), whereas patients weighing more than 100 kg were significantly more likely to achieve PASI 75 if they were randomized to the 90-mg dose group compared with the 45-mg dose group (74.2% vs 54.6; $P < 0.0001$).³⁸ The safety and tolerability of ustekinumab did not appear to vary by weight.³⁸ These findings were incorporated into the approved dosing recommendations for ustekinumab.³⁵ Data from an extension study of PHOENIX 1 indicate that the response to weight-based dosing of ustekinumab is largely sustained for up to 3 years.³⁹

The safety and efficacy of ustekinumab was also compared to those of an active comparator, the TNF inhibitor etanercept.⁴⁰ In

Figure 1. Clinical response to etanercept or ustekinumab through week 12.⁴⁰

Griffiths CEM, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362:118-128. Copyright © 2010 Massachusetts Medical Society. All rights reserved.



Ustekinumab groups received either 45 or 90 mg at weeks 0 and 4. Etanercept group received etanercept 50 mg twice weekly for 12 weeks.

a randomized, prospective trial, patients were randomized to one of three treatment groups: ustekinumab at a dose of 45 or 90 mg at weeks 0 and 4 or etanercept at a dose of 50 mg twice weekly for 12 weeks.⁴⁰ By week 12, clinical responses as assessed by PASI 75 and PASI 90 and Physician's Global Assessment (PGA) scores were significantly greater in each of the ustekinumab groups (vs etanercept) (Figure 1).⁴⁰

Though not yet approved by the FDA, briakinumab (formerly ABT-874), also a monoclonal antibody directed against IL-12/23, is in late-stage development for treatment of psoriasis. Data from three phase 3 trials of briakinumab were recently presented at the Third International Congress on Psoriasis in July 2010. In a pair of similarly designed trials, treatment with briakinumab (200 mg at weeks 0 and 4 followed by 100 mg at week 8) resulted in a significantly greater proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at week 12 than did treatment with placebo or etanercept (50 mg twice weekly).^{41,42} Efficacy was also demonstrated using the PGA scale, a global measure of disease severity.^{41,42} No deaths or major adverse cardiac events were reported in either trial. Among subjects receiving briakinumab, common adverse events included upper respiratory tract infection and nasopharyngitis.^{41,42}

The efficacy and safety of briakinumab was also assessed in a 1-year, double-blind, placebo-controlled trial.⁴³ Patients were randomized at week 0 to receive placebo or briakinumab (200 mg at weeks 0 and 4 and 100 mg at week 8).⁴³ Patients exhibiting a response at week 12 (as assessed by PGA scores) were then randomized to one of three maintenance regimens: briakinumab 100 mg every 4 weeks, briakinumab 100 mg every 12 weeks, or placebo. Achievement of clinical response (PGA of 0 or 1) at week 12 was significantly more common in the active-treatment group (76.0% vs 4.3%; $P<0.0010$).⁴³ Briakinumab maintenance regimens were significantly more efficacious than placebo; the more-frequent dosing regimen (every 4 weeks) was associated with significantly greater rates of sustained clinical response than the less-frequent regimen (every 12 weeks).⁴³ During the induction phase of therapy, infection and malignancy were observed in 22.3% and 0.6% of briakinumab-treated subjects, respectively (vs 19.8% and 0% in the placebo group, respectively).⁴³ Unlike in the previously described shorter trials, seven major adverse cardiac events occurred in the briakinumab groups compared to none in patients receiving placebo throughout this study.⁴³



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Potential Safety Concerns With IL-12/23 Inhibitors

Because both ustekinumab and briakinumab block IL-12 and IL-23, there are some concerns regarding inhibition of cell-mediated immunity. Patients treated with these agents may be susceptible to infections from mycobacteria, *Salmonella*, and Bacillus Calmette-Guerin (BCG) vaccination.³⁵ Additionally, patients who receive IL-12/23 inhibitors may also be vulnerable to viral infections spread from persons vaccinated with live or live-attenuated viruses.³⁵ Although these adverse events were not observed in clinical trials, persons with genetic deficiency of IL-12 are predisposed to the infectious agents noted above. Thus, pre-initiation screening for tuberculosis, regular monitoring for infections, and avoidance of live, live-attenuated, and BCG vaccinations is recommended.

Lucas: Follow-Up

At the time of his fourth scheduled injection of ustekinumab (ie, 28 weeks after starting therapy), Lucas reported morning stiffness in his fingers upon waking that lasted approximately 15 minutes. He also described heel pain consistent with plantar fasciitis. The decision was made to add methotrexate to his current regimen. Following a test dose of 5 mg, methotrexate was administered as a weekly dosage of 7.5 mg for 2 weeks, followed by 10 mg weekly for 2 weeks, then 15 mg/week thereafter. At this dose, the patient experienced amelioration of arthritic symptoms, and the methotrexate dose was tapered back to 10 mg while maintaining good control of symptoms.

Joint Involvement

Though very rare among the general population, psoriatic arthritis affects a significant proportion of patients with psoriasis, with prevalence estimates as high as 40%.^{4,44} Dermatologists should suspect psoriatic arthritis in patients with psoriasis who

present with pain, swelling, tenderness, and/or stiffness of the joints and surrounding tissue.⁴ The diagnosis of psoriatic arthritis can be made clinically using one of several diagnostic definitions, including the CASPAR (CIAssification criteria for Psoriatic ARthritis) criteria proposed by Taylor and colleagues (Table 2).⁴⁵ In Lucas's case, the presence of enthesitis, as evidenced by inflammation at the point of insertion of the plantar fascia, strongly supported the diagnosis of psoriatic arthritis.⁴

Appropriate treatment of psoriatic arthritis is greatly dependent on the severity of disease. Mild disease can often be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections.⁴ Several biologic agents are indicated for the treatment of psoriatic arthritis, including the anti-TNF agents etanercept, infliximab, adalimumab, and golimumab.^{15,24,25,46} Although ustekinumab is not currently approved for the treatment of psoriatic arthritis, its safety and efficacy for the treatment of the disorder was evaluated in a phase 2, double-blind, placebo-controlled, crossover study.⁴⁷ Enrolled subjects (n=146) were initially randomized to receive ustekinumab 90 mg every week for 4 weeks and placebo at weeks 12 and 16 (Group 1) or placebo for 4 weeks followed by ustekinumab 90 mg at weeks 12 and 16 (Group 2). As a result of a change in study protocol, most doses of ustekinumab were 63 mg rather than 90 mg. At week 12, patients in Group 1 exhibited significantly greater reductions in disease severity as assessed by American College of Rheumatology (ACR) response criteria.

For Lucas, it is clear that monotherapy with ustekinumab was ineffective at managing his joint symptoms (the symptoms presented while on therapy). Although methotrexate is an effective treatment for psoriatic arthritis and is commonly used in combination with biologic agents, there are no studies examining the safety and efficacy of ustekinumab used in

Table 2. CASPAR criteria for psoriatic arthritis.⁴⁵

Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006;54(8):2665-2673. Used with permission of John Wiley and Sons.

Diagnostic criteria include inflammatory articular disease plus three (or more) of the following:

1. Current psoriasis,* a history of psoriasis, or a family history of psoriasis
2. Onycholysis, pitting, and hyperkeratosis of the nails
3. Negative for rheumatoid factor
4. Current dactylitis (ie, swelling of an entire digit), or rheumatologist-documented dactylitis in the past
5. Radiographic evidence of juxtaarticular new bone formation

*If patient has current psoriasis, only one additional criteria is required for the diagnosis of psoriatic arthritis.

combination with methotrexate. Concomitant methotrexate therapy was permitted in the phase 2 study discussed above and used by approximately 20% of subjects in each arm, but a subanalysis of combination efficacy results is unavailable.⁴⁷ Patients receiving ustekinumab plus methotrexate were more likely to report adverse events than were those receiving ustekinumab monotherapy (67% vs 59% at week 12), but the nature of these events is not reported and similar differences were observed between the subjects receiving placebo with and without methotrexate.⁴⁷

Stephanie: Loss of Efficacy on an Anti-TNF Agent

Initial History, Presentation, and Treatment

Stephanie, a 30-year-old white female, presented with severe, recalcitrant psoriasis and joint pain. She had previously been successfully treated with methotrexate for 3 to 4 years. She had also purchased a home UVB unit and utilized it two to three times per week. Despite an increased dose of methotrexate (to 20 mg/week) and continued use of home phototherapy, the patient exhibited worsening psoriasis, and her local primary care physician suggested she see a dermatologist. The patient resided in a remote area, necessitating flights across the state to visit the closest dermatologist.

Stephanie traveled to the dermatologist who prescribed etanercept 100 mg/week (an off-label dose) and discontinued methotrexate. She responded with diminished pain and joint stiffness but exhibited only about 50% improvement in her skin lesions. After 3 months, the dermatologist was unsure how to proceed given the patient's suboptimal response. Taking into account the patient's childbearing potential, particularly in light of her recent marriage, and considering her prior long-term use of methotrexate, the dermatologist did not deem it appropriate to place her back on methotrexate.

Long-Term Methotrexate Use and Nonresponse to a TNF Inhibitor

As observed in this patient, the combination of methotrexate and UVB therapy can be an effective treatment for psoriasis and may be associated with a reduced risk of dose-related toxicity by allowing for decreased dosages and duration of each therapy.⁶ Methotrexate has been used for the treatment of psoriasis for more than half of a century. Despite decades of clinical experience, evidence-based data supporting its safety,

efficacy, and mechanism of action are relatively recent.³ Guidelines regarding the use of methotrexate were updated by both the AAD and NPF in 2009.^{3,48}

Safety concerns regarding methotrexate are largely focused on the drug's potential to cause myelosuppression, hepatotoxicity, and pulmonary fibrosis.⁴⁸ Prior to initiation of therapy with methotrexate, a complete history and physical is indicated. Signs and symptoms of renal, hepatic, or infectious disease should be carefully followed up, as these are potential contraindications to therapy with the agent.⁴⁸ A summary of the recommended baseline assessments for patients in whom methotrexate is being considered is presented in Table 3. In patients with significant hepatic disease, a liver biopsy should be considered to further assess liver function.⁴⁸ Follow-up monitoring of liver function varies based on the patient's risk of hepatotoxicity; alcohol consumption, abnormal liver chemistry studies, history of liver disease, diabetes, obesity, lack of concomitant folate supplementation, hyperlipidemia, and exposure to other hepatotoxic agents are all considered risk factors for the development of hepatotoxicity from methotrexate.⁴⁸

Table 3. Baseline and monitoring evaluations for patients with psoriasis on methotrexate.⁴⁸

Baseline	Follow-Up Monitoring
CBC	CBC every 2–4 weeks for a “few months” and 1–3 months thereafter
Renal function tests	
Liver function tests	Renal function tests every 2–3 months
PPD	
Hepatitis B/C profile (if indicated)	Liver function tests monthly x6 months then every 1–2 months thereafter for low-risk patients with additional monitoring as indicated
Pregnancy test (if indicated)	
HIV screening (if indicated)	
	Consider liver biopsy in high-risk patients

The dermatologist's concerns regarding re-initiation of methotrexate therapy for Stephanie were based on both her prior long-term use of the agent and her potential for pregnancy. Although the risk of cumulative toxicities may be reduced by switching agents,⁴⁸ current guidelines suggest that treatment with methotrexate can be continued as needed, provided no signs of toxicity are observed with regular monitoring.³ Methotrexate is contraindicated in pregnancy (category X) and should only be used by sexually active women with reproductive



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capacity if adequate contraception is used.³ Methotrexate has been associated with numerous fetal abnormalities including skeletal, cardiac, and neurologic defects. The developing embryo is believed to be particularly susceptible to the effects of methotrexate at weeks 6 to 8 of development.^{3,48}

Stephanie's primary lack of response to etanercept, as evidenced by inadequate improvement of her symptoms, is not uncommon. In a study of 32 patients started on etanercept as first-line biologic therapy for psoriasis, 11 (34%) did not respond to therapy (though the precise definition of "response" was not provided). When asked to rank the therapeutic options for patients exhibiting primary failure to a TNF inhibitor, a consensus panel of dermatology experts agreed that switching to another anti-TNF agent was their top option.⁹ The addition of methotrexate and switching to an anti-IL-12/23 agent represented their second and third options, respectively. These rankings mirrored those for secondary failure of a TNF inhibitor (discussed above).⁹

Consultation and Treatment Recommendations

Stephanie sought out dermatologists with extensive experience in treating psoriasis and was eventually seen by a university-based dermatology clinic. A class I (ultra-high potency) topical steroid with occlusion was prescribed for the treatment of excoriated psoriatic plaques on her lower legs. It was also suggested that she be switched from etanercept to adalimumab. Following her review of the patient education materials and attaining insurance approval for the medication, but prior to her first dose, Stephanie learned that she was pregnant. She elected not to use any therapy except occasional home UVB throughout her pregnancy. Stephanie remained reasonably comfortable, but not clear, during the pregnancy and for 2 to 3 months postpartum.

While the biologic agents are categorized as category B, wherever possible they should be withdrawn preconception, unless other therapeutic options such as phototherapy and topical corticosteroids have been exhausted and the patient was apprised of the potential risks.

Pregnancy and Psoriasis Treatment

Data regarding the safety of biologic agents during pregnancy are extremely limited. As per their prescribing information, adalimumab, infliximab, etanercept, alefacept, and ustekinumab are classified as pregnancy category B.^{15,24,25,35,49} Postmarketing data from the FDA, as reported by Carter et al, suggests a potential association between TNF antagonists and birth defects that can be part of the VACTERL association (ie, vertebral abnormalities, anal atresia, cardiac defects, tracheoesophageal abnormalities, renal defects, and limb abnormalities).⁵⁰ It is worth noting, however, that Koren and Inoue's interpretation of these data have shed doubt on such an association, let alone the possible causality of birth defects.⁵¹

Much of the limited data that are available regarding the safety of biologics during pregnancy comes from patients with rheumatologic and gastrointestinal illnesses.⁵² A recent publication described the first report of pregnancy in a psoriasis patient receiving adalimumab.⁵² The 34-year-old patient received adalimumab for the first 5 weeks of gestation and delivered a low-birth-weight neonate. At 1-year follow-up, the infant had normal development.⁵² Adverse pregnancy outcomes among women with psoriasis can be influenced by factors other than medications. A recent study demonstrated that pregnant women with psoriasis are more likely than controls to be overweight, smoke, have coexisting depression, and fail to take prenatal vitamins prior to conception.⁵³

The safety of anti-TNF agents for women who are breastfeeding also remains unclear. A recent review of the limited data available suggests that infliximab is likely safe to administer to a patient who is breastfeeding, as it is not detectable in breast milk.⁵⁴ Etanercept can appear in breast milk, but its oral bioavailability is unknown.⁵⁴ It is generally accepted that both NB- and BB-UVB therapies are safe for use by women that are pregnant or breastfeeding.⁶ Targeted therapy with an excimer laser is also believed to be safe for pregnant patients.⁶ Consensus opinion from a panel of dermatology experts ranked NB-UVB therapy as the top therapeutic option for women planning to become pregnant, those that are pregnant (in any trimester), and those that are breastfeeding.⁹

Postpartum Treatment

Approximately 3 months after delivery of a healthy, full-term infant, with Stephanie's psoriasis returning to prepregnancy levels, the decision was again made to initiate therapy with

adalimumab 40 mg every other week. Given the difficulties associated with in-person follow-up for this particular patient, management of her care was aided by the use of e-mail correspondence and photos. She was seen back at the clinic 6 weeks after starting therapy with adalimumab. As was the case with etanercept, the patient's joint pain responded well to therapy, but only 50% improvement in skin lesions was observed. Stephanie continued adalimumab therapy with the understanding that the maximal benefit may not have occurred at 6 weeks. Topical therapies were also employed, as were home UVB treatments (3–5 times per week). NSAIDs were used to control breakthrough joint pain. Although 75% clearance was attained, the patient continued to have stubborn pruritic plaques.

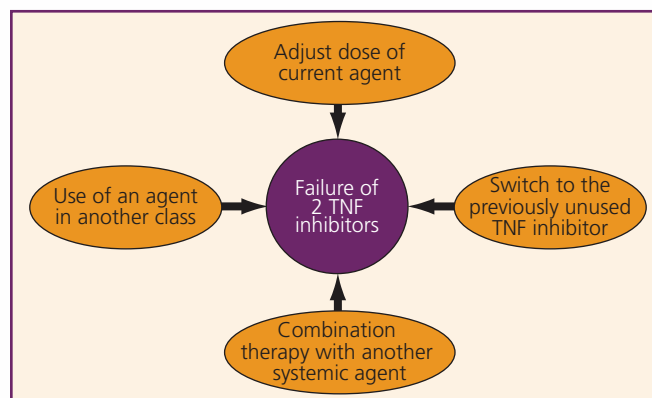
Stephanie was not pleased with her response and contacted the treating physician to discuss ustekinumab as an option. Since Stephanie lived too far away for the visits to the dermatologist for ustekinumab injection, a home-health care nursing agency was contacted to administer the injections. While ustekinumab represented a potential treatment option, the treating physician noted the current lack of evidence for ustekinumab as a psoriatic arthritis treatment. Instead, treatment with methotrexate 7.5 mg weekly was begun, in addition to continuation of adalimumab 40 mg every other week. At the time, it was felt that methotrexate represented a generally safe option given the length of time since Stephanie was last treated with it (ie, 3–4 years), and the fact that the patient was otherwise healthy, did not drink or smoke, and was not sexually active (she was separated from her husband at the time).

Treatment Options Following Failure With a Second TNF Inhibitor

As discussed, a trial of therapy with a second TNF inhibitor is a rational treatment option in patients exhibiting inadequate response to etanercept. This patient's lack of response to a second TNF blocker made the case particularly challenging for the treating physician. Only a limited number of therapeutic options were available (Figure 2). There is evidence that weekly dosing of adalimumab 40 mg is associated with greater efficacy than every-other-week dosing.⁵⁵ In an open-label extension study of adalimumab, of patients not achieving at least PASI 50 on a 40-mg-every-other-week regimen, 38% exhibited a PASI 75 response following escalation to a weekly dosing regimen.⁵⁵ Although this dosing regimen is approved for the treatment of rheumatoid arthritis, it is not approved for the management of

psoriasis or psoriatic arthritis²⁵ and therefore will frequently not be covered by payors. Furthermore, the safety of such a regimen has not been systematically investigated in patients with psoriasis. The potential to switch therapy to another TNF inhibitor (in this case, infliximab), was also considered. Unlike other TNF agents, however, infliximab is administered via intravenous infusion and patients require close monitoring.²⁴ Given Stephanie's remote location, this strategy was dismissed and the decision to add methotrexate was made.

Figure 2. Therapeutic options for the treatment of a patient exhibiting inadequate response to two anti-TNF agents.



Given the relative lack of data available supporting the use of ustekinumab for the treatment of psoriatic arthritis,⁴⁷ the treating clinician's hesitation to use it in Stephanie's case is understandable. With additional clinical experience, the role of ustekinumab for the treatment of psoriatic arthritis and its use in combination therapy regimens will likely become clearer. It is important to note that the response to therapy for psoriasis and psoriatic arthritis do not necessarily correlate in an individual patient.

Conclusion

The cases presented in this *Biologic Bulletin* highlight a number of therapeutic challenges faced by dermatology clinicians who treat patients who have moderate to severe psoriasis. In these instances, the selection of a management regimen was not supported by strong clinical data nor covered by current treatment guidelines. Instead, as is often the case, clinicians had to rely on sparse evidence and clinical experience. Treatment decisions were influenced by patients' access to care, geographic location, insurance coverage, and personal preferences, factors virtually impossible to incorporate into a study design. Moreover, it is clear that there is no single strategy that can be applied universally, and patients' individual clinical and personal



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circumstances must be taken into account. It is essential that treatment decisions consider the needs of the patient, especially those relating to quality of life. Although these cases illustrate the

need for continued study of the safety and efficacy of psoriasis treatments, they also underscore the importance of clinicians sharing personal insights into their psoriasis management strategies.

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