Biologics are rapidly gaining acceptance as a second-line therapy for psoriasis and psoriatic arthritis. Although these agents are expensive, many health plans are allowing increased access to them, which is a testament to their efficacy and relative safety. Patients with psoriasis who take biologics—which are immune-modulating agents—may present to the ED with complications arising from their use. The most common adverse event associated with all of these agents is an injection-site reaction manifesting as bruising, itching, and/or erythema. However, the potential for more serious adverse sequelae should be duly noted. Biologics have been linked to an increased risk for infection, including reactivation of tuberculosis. Fortunately, associated infection is uncommon, but the risk is highlighted by black box warning labels on all tumor necrosis factor (TNF)–blocking agents. A patient taking a biologic who develops any potentially serious infection must discontinue the agent’s use until the infection has resolved. Furthermore, patients taking biologics should not receive live vaccines (eg, varicella, mumps, measles, typhoid, yellow fever) or live attenuated vaccines, including intranasal influenza and herpes zoster vaccines.

Recent postmarket surveillance identified three cases of progressive multifocal leukoencephalopathy (PML) occurring in patients who received the T-cell inhibitor efalizumab. PML is a fatal demyelinating disorder caused by polyomavirus JC. The infected patients had received the drug for more than 3 years. In April 2009, the drug’s manufacturer voluntarily withdrew this biologic from the US market.

In August 2009, the FDA mandated that prescribing information for all TNF-blocking agents document additional cases of cancer, including leukemia, in adults, adolescents, and children taking these medications. Because these agents had been prescribed
for illnesses linked to immune system dysfunction (eg, juvenile idiopathic arthritis) and the affected patients had likely been exposed to other immunosuppressive therapies, definitive causality has not been established.

With increased use of biologics, other untoward consequences may emerge; thus, vigilant evaluation of patients who receive these medications is necessary. When a patient with psoriasis presents to the ED, careful scrutiny of his or her current treatment regimen is warranted. If an infection requires treatment with an antibiotic, the patient should be counseled to stop taking the biologic therapy. Although risk of infection may be higher in patients taking biologics than in the general population, serious opportunistic infections, such as tuberculosis and histoplasmosis, have rarely been associated with anti-TNF agents.

**PSORIASIS EPIDEMIOLOGY AND VARIANTS**

Psoriasis is a common inflammatory disorder that affects up to 2% of the population.\(^6\) Until recently, experts believed that the condition was confined exclusively to the skin and joints; however, a number of studies published in the past few years have shown that psoriasis is a multisystem disease. Associated comorbidities include cardiovascular disease,\(^9\) obesity,\(^10\) hypertension and diabetes,\(^11\) and the metabolic syndrome.\(^12\) Psoriasis negatively impacts quality of life and markedly increases the incidence of impaired self-image, low self-esteem, and depression.\(^13,14\)

Several variants of psoriasis are defined morphologically. The most common type is plaque psoriasis, which is found in nearly 90% of patients with the disorder.\(^6\) Psoriatic plaques have sharply demarcated borders, erythema, and a whitish, adherent scale (Figure 1). Common areas of involvement include the scalp, knees, elbows, and buttocks. Less frequently encountered variants include guttate, pustular, and erythrodermic subtypes; two of these subtypes are discussed in the case studies (on pages 8 and 9). Psoriatic arthritis affects up to 30% of psoriasis patients; it usually develops between ages 30 and 50 years.\(^15\) The course is variable and, at the extreme, may cause joint distortion, destruction, and marked functional impairment.

**TREATMENT**

The advent of biologic therapy has greatly changed the course of psoriasis treatment. A more detailed discussion on conventional (“prebiologic”) therapies for psoriasis was published in this journal in 1999.\(^16\) Conventional treatment includes topical modalities such as corticosteroids and vitamin A and D derivatives, as well as phototherapy. Many cases of mild to moderate psoriasis respond adequately to such treatment.

Patients whose condition does not respond well to these treatments—especially those with more extensive psoriasis—are candidates for conventional systemic therapies, including acitretin, cyclosporine, and methotrexate.\(^17\) All are FDA approved for treatment of psoriasis and are administered orally (methotrexate may be administered subcutaneously as well). In addition, they are all associated with varying degrees of success in the management of difficult cases.

Of course, initiation and continuation of systemic therapy must involve a risk-versus-benefit analysis: Acitretin is teratogenic, incurring an FDA pregnancy category X rating, and can raise levels of triglycerides; cyclosporine may impair renal function; and methotrexate may induce leukopenia, pulmonary fibrosis and, rarely, cirrhosis; it, too, has an FDA pregnancy category X rating.

Over the past 2 decades, knowledge regarding the pathogenesis of psoriasis has increased considerably. The understanding of psoriasis as a disease of immune dysregulation has led to the introduction of a new class of drugs called biologics that target specific aspects of the immune system. Biologic agents are proteins that are produced by recombinant DNA technology or extracted from animal cells. All must be administered by injection. Three subsets of biologics are used in clinical practice: T-cell–depleting agents, TNF blockers, and interleukin inhibitors.
PSORIASIS IMMUNOLOGY
A brief overview of the immunology involved in psoriasis helps illustrate the mechanism of action of the biologics. Psoriasis is a T-cell–mediated disorder that involves a recently discovered T-cell pathway: Th17. The cytokine interleukin 23 (IL-23) plays a critical role in the proliferation of Th17 cells, a process that produces several interleukins, as well as TNF-α. By interrupting key components of this pathway, biologics improve the physical stigmata of psoriasis. This article reviews FDA-approved agents, including one that demonstrated superior efficacy in phase III clinical trials.

T-CELL–DEPLETING BIOLOGIC
Alefacept is a human recombinant fusion protein that binds to CD2 on T cells and natural killer cells, decreasing both activation and production of psoriasis-inducing pathogenic cells. The agent, which received FDA approval as a treatment for psoriasis in 2003, is given as 15 mg IM once weekly for 12 weeks, followed by at least 12 weeks off treatment.

CASE 1. PUSTULAR PSORIASIS
A 60-year-old man presents to the ED with a generalized eruption accompanied by low-grade fever and chills. He gives a 45-year history of plaque psoriasis, for which he has received multiple systemic therapies, including methotrexate, cyclosporine, and acitretin. Most recently, efalizumab was started on a weekly basis, but this was discontinued one month before the current presentation due to limited efficacy.

Examination reveals an obese patient with a generalized dermatitis characterized by scaling, erythematous patches, and multiple pustules (Figure 2). The initial differential diagnosis included sepsis, and the patient was started on IV antibiotic therapy. Blood and skin bacterial cultures revealed no growth. In consultation with a dermatologist, oral therapy with acitretin was prescribed, along with topical steroids. The patient’s condition markedly improved within 10 days.

Discussion
The von Zumbusch variety of pustular psoriasis arises acutely and may be triggered by a number of factors, including systemic steroid use, pregnancy, emotional stress, and infection. Pustular psoriasis following discontinuation of efalizumab has been documented in the literature. It is characterized by the appearance of widespread areas of erythematous skin containing multiple sterile pustules (Figure 3). Constitutional signs and symptoms include malaise, fever, chills, and headache. Elevations in white blood cell count and erythrocyte sedimentation rate accompany the condition. Dehydration may require hospital admission. The differential diagnosis for pustular psoriasis includes septicemia and subcorneal pustular dermatosis.

FIGURE 2. Pustular psoriasis.

FIGURE 3. Pustular psoriasis.
PSORIASIS

CASE 2. ERYTHRODERMA
A 54-year-old man presents to the ED with a diffuse erythematous rash of 1 week's duration. He also reports malaise and chills. He gives a history of severe plaque psoriasis that has been poorly controlled in the past with methotrexate, cyclosporine, and acitretin. PUVA therapy (oral psoralen plus ultraviolet light) did result in clearing but was discontinued due to inconvenience, and the biologic etanercept was started. This therapy resulted in initial improvement, but the patient had a flare after several months, at which time the biologic adalimumab was commenced. Three weeks later, the patient developed a generalized dermatitis (Figure 4).

After consultation with a dermatologist, IM triamcinolone was administered, along with a potent topical steroid. This resulted in clearing of the erythroderma but also a recurrence of widespread plaque psoriasis that persisted for months. Then, shortly after receiving FDA approval, ustekinumab was administered; after the second dose, the patient's condition improved by roughly 75%.

Discussion
Generalized erythroderma is characterized by widespread cutaneous redness and scaling. This condition may be associated with pruritus, tachycardia, and fever. Individuals with erythrodermic psoriasis are at greater risk for sepsis, pneumonia, and congestive heart failure. The condition may be secondary to underlying atopic dermatitis or a malignancy such as mycosis fungoides. Drugs such as carbamazepine and penicillin are often implicated. Oral prednisone is generally avoided as treatment for psoriasis, as its withdrawal may precipitate this condition. TNF inhibitors have rarely been associated with serious skin reactions.

Both etanercept and adalimumab are subcutaneously administered TNF inhibitors that are classified as biologics. TNF plays a key role in the pathogenesis of psoriasis. The most frequent cutaneous adverse reaction associated with these medications is mild to moderate erythema and swelling at the injection site.

Paradoxically, use of anti-TNF agents may infrequently flare psoriasis; this patient's erythroderma was temporally related to initiation of adalimumab therapy. Adalimumab use was discontinued, and improvement was noted following a short course of oral systemic steroids. To date, the patient's psoriasis has been most difficult to control.

FIGURE 4. Erythrodermic psoriasis.

after which another course may be considered. A significant percentage of patients who respond to this therapy remain in remission for a median of 10 months.6

When statistically compared with other treatments, alefacept has demonstrated decreased efficacy as monotherapy.6 Thus, alefacept is often combined with other therapies, such as ultraviolet light and, for patients with psoriatic arthritis, methotrexate.

Alefactept is well tolerated and has not been linked to opportunistic infections, reactivation of tuberculosis, or other serious adverse events. A baseline CD4 count should be obtained prior to treatment, and testing should be repeated at frequent intervals. Therapy should be withheld and weekly monitoring should be instituted if the CD4 count dips below
250 cells/mL. Alefacept is an FDA pregnancy category B drug.

TNF INHIBITOR BIOLOGICS

Adalimumab, etanercept, golimumab, and infliximab are TNF-α inhibitors. TNF-α levels are elevated in both the skin and the serum of patients with psoriasis and decline with successful treatment. Although significant adverse events are fortunately uncommon, all TNF-α inhibitors have been associated with serious bacterial and fungal infections, and all patients require purified protein derivative (PPD) testing prior to commencement of therapy, with yearly PPD testing recommended thereafter. Although hepatitis C has been treated with biologics, hepatitis B may be exacerbated by this therapy; thus, prior screening for this disease, too, is often advised.

TNF antagonists have been reported to exacerbate severe congestive heart failure as well as demyelinating diseases, such as multiple sclerosis; patients with these conditions are not candidates for treatment with these agents. TNF inhibitors have an FDA pregnancy category B rating.

Adalimumab

Adalimumab received FDA approval for the treatment of moderate to severe plaque psoriasis in 2008; it had been approved in 2002 to treat rheumatoid arthritis. Additional indications include psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, and juvenile idiopathic arthritis. It is the first fully human anti–TNF-α monoclonal antibody.

Adalimumab is administered with an 80-mg SC loading dose, followed by a 40-mg dose 1 week later and every other week thereafter. Significant improvement is typical with this medication and is often noted within 4 weeks. Continuous-dose therapy is recommended.

Etanercept

A fusion protein that binds to soluble TNF, etanercept received FDA approval for the treatment of moderate to severe psoriasis in 2004. This agent was already approved for severe psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis. Data comparisons of tuberculosis incidence in patients taking biologics indicate that etanercept has a better safety profile than do adalimumab and infliximab.

Etanercept is initiated at a dose of 50 mg SC twice weekly for 3 months, followed by weekly maintenance dosing of 50 mg. As with adalimumab, treatment is continuous. As with other TNF inhibitors, loss of efficacy over time may occur in a small subset of patients.

Golimumab

A human monoclonal antibody that blocks TNF, golimumab received FDA approval in 2009 for the treatment of psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis. It has demonstrated a high rate of clearance for skin disease, and the manufacturer has stated that it will be seeking FDA approval for golimumab for the treatment of psoriasis.

Golimumab is administered once monthly as a 50-mg SC injection. As with other TNF inhibitors, this agent may be used concomitantly with methotrexate. Long-term safety data are not available.

Infliximab

Infliximab is a biologically engineered, part-human, part-mouse antibody that binds TNF molecules. The agent is approved for the treatment of psoriatic and rheumatoid arthritis, psoriasis, ankylosing spondylitis, Crohn’s disease, and ulcerative colitis. Adequate response in patients with psoriasis is common and often rapid.

Infliximab dosage is weight based (5 mg/kg), and the agent is administered by IV infusion at weeks 0, 2, and 6 and at 8-week intervals thereafter, depending on patient response. Clinical response is best maintained with continuous, as opposed to interrupted, therapy. Efficacy may wane over time, possibly as a result of circulating antibodies.

INTERLEUKIN INHIBITORS

IL-12 and IL-23 are naturally occurring proteins involved in the activation of T cells. Expression of these cytokines is increased in psoriatic lesions.

Ustekinumab

Ustekinumab is a first-in-class human monoclonal antibody targeting IL-12 and IL-23. It is given by SC injection. The FDA approved the agent in September 2009 for the treatment of moderate to severe psoriasis in adult patients. A high degree of lesion clearance was achieved and maintained with two loading doses followed by a 12-week dosing sched-
The recommended starting dose is 45 mg for patients weighing less than 220 lb (100 kg), and 90 mg for those weighing more. Another dose is given 4 weeks later, then every 12 weeks thereafter. The agent must be administered in a physician’s office.

**ABT-874**

Phase III testing of ABT-874 began in 2007. This compound, like ustekinumab, is a monoclonal antibody directed against IL-12 and IL-23. Both agents demonstrate clear or near-clear efficacy in more than 70% of patients, and neither has been associated with serious adverse events to date.23,24

**CONCLUSION**

Advances in the understanding of the pathogenesis and pathophysiology of psoriasis have led to the development of targeted therapies that dampen the aberrant immune response at the heart of this disorder and, as a result, may markedly improve patients’ quality of life. Biologics have revolutionized therapy for psoriasis and are associated with an extremely low rate of serious adverse events25; however, emergency physicians should be aware of such risks. In addition, as a relatively new class of therapeutic agents, they merit intensive postmarket surveillance. □

**REFERENCES**


