



EDUCATIONAL OBJECTIVE: Readers will manage psoriasis on the basis of its type and severity

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Psoriasis: Evolving treatment for a complex disease

ABSTRACT

The cutaneous manifestations of psoriasis can vary in morphology and severity, and therapy should be tailored accordingly. Biologic agents are important new options for treating patients with the most severe forms of the disease. All physicians should be aware that severe psoriasis may increase cardiovascular morbidity and the risk of death, and preventive strategies for patients with severe disease should be considered.

KEY POINTS

Studies in the past 10 years have uncovered a link between psoriasis, metabolic syndrome, and cardiovascular disease. Interestingly, the risk grows less with age; patients at greatest risk are young men with severe psoriasis.

The most common presentation of psoriasis is plaque psoriasis. However, there are several other clinical variations of psoriasis, each of which has a distinct response to treatment and may be associated with significant systemic symptoms.

Tumor necrosis factor inhibitors should be considered first-line in the treatment of psoriatic arthritis.

Phototherapy and systemic medications including methotrexate, acitretin (Soriatane), cyclosporine (Gengraf, Neoral, Sandimmune), and biologic agents are the most effective treatments for moderate-to-severe psoriasis.

MUCH HAS CHANGED in our understanding of psoriasis over the past decade, which is having a major effect on its treatment.

Although topical corticosteroids and phototherapy remain mainstays of treatment, a variety of biologic agents have given new hope to those with the most severe forms of the disease. We are also beginning to understand that patients with psoriasis are at greater risk of cardiovascular disease, though the exact nature of that risk and how we should respond remains unclear. Finally, genome-wide association studies are just beginning to unravel the genetic basis of psoriasis.

In this paper, we review the epidemiology and impact of psoriasis, current views of its pathogenesis, its varied clinical forms, and its treatment.

PSORIASIS IMPOSES A GREAT BURDEN

Psoriasis is common, with a reported prevalence ranging from approximately 2%¹ to 4.7%.² It can manifest at any age, but it is most common in two age groups, ie, 20 to 30 years and 50 to 60 years.

For the patient, the burden is great, affecting physical, psychological, and occupational well-being. In fact, patients with psoriasis report quality-of-life impairment equal to or worse than that in patients with cancer or heart disease.^{3,4} Notably, functional disability secondary to psoriatic arthritis has been reported in up to 19% of psoriatic arthritis patients, and this negatively affects quality of life.⁵

In 2004, the annual direct medical costs of psoriasis in the United States were estimated to exceed \$1 billion. Its indirect costs, measured as missed days and loss of productivity at

work, are estimated to exceed the direct costs by \$15 billion annually.^{6,7}

Linked to cardiovascular and other diseases

Studies in the past 10 years have uncovered a link between psoriasis, metabolic syndrome, and cardiovascular disease.^{8–13} Specifically, patients with severe psoriasis are at higher risk of myocardial infarction and cardiovascular death than control patients. Interestingly, the risk decreases with age; patients at greatest risk are young men with severe psoriasis.^{8–10}

In a large cohort study in the United Kingdom⁷ comparing patients with and without psoriasis, the hazard ratio for cardiovascular death in patients with severe psoriasis was 1.57 (95% confidence interval 1.26–1.96). This translated to 3.5 excess deaths per 1,000 patient-years. These patients were also at higher risk of death from malignancies, chronic lower respiratory disease, diabetes, dementia, infection, kidney disease, and unknown causes.

How much of the risk is due to psoriasis itself, its treatments, associated behaviors, or other factors requires more study. However, some evidence points to the dysregulation of the immune system, notably chronic elevation of pro-inflammatory cytokines.

Psoriasis and its comorbid conditions are thought to arise from chronically elevated levels of cytokines such as tumor necrosis factor alpha (TNF-alpha), interleukin 1 beta (IL-1 beta), and IL-17. These cytokines impair insulin signaling, deregulate lipid metabolism, and increase atherosclerotic changes in the coronary, cerebral, and peripheral arteries. In addition, several other diseases that involve the immune system occur more frequently with psoriasis, including Crohn disease, ulcerative colitis, lymphoma, obesity, and type 2 diabetes.^{1,8,14–18}

In view of the prevalence of these comorbid conditions and the risks they pose, primary care physicians should consider screening patients with severe psoriasis for metabolic disorders and cardiovascular risk factors and promptly begin preventive therapies.¹⁹ Unfortunately, to date, there are no consensus guidelines as to the appropriate screening tests or secondary cardiovascular preventive measures for patients with severe psoriasis.

A VICIOUS CIRCLE OF INFLAMMATION AND KERATINOCYTE PROLIFERATION

The hallmark of plaque psoriasis is chronic inflammation in the skin, leading to keratinocyte proliferation.

External and internal triggers that have been identified include cutaneous injury (eg, sunburn, drug rash, viral exanthems), infections (eg, streptococcal), hypocalcemia, pregnancy, psychogenic stress, drugs (eg, lithium, interferon, beta-blockers, and antimalarials), alcohol, smoking, and obesity.^{20–23}

As reviewed by Nestle et al,²⁴ the initiation of lesion formation is still poorly understood but is thought to occur when a trigger (physical trauma, bacterial product, cellular stress) causes DNA to be released from keratinocytes. DNA forms a complex with the antimicrobial protein LL-37 and activates plasmacytoid dendritic cells (PDCs) via toll-like receptor 9. Activated PDCs release type I interferons, which in turn activate myeloid dendritic cells. Myeloid dendritic cells release IL-20 locally, which speeds keratinocyte proliferation.

A subset of myeloid dendritic cells leaves the dermis and migrates to local lymph nodes, where they release IL-23 and activate naive T cells. T helper 1 (Th1) and Th17 cells are recruited to the lesions and begin producing numerous cytokines, including interferon gamma, IL-17, and IL-22. This cytokine milieu increases keratinocyte proliferation and causes the keratinocytes to secrete antimicrobial proteins (LL-37, beta defensins), chemokines, and S100 proteins. These soluble factors have three main functions: stimulation of dendritic cells to release more IL-23, recruitment of neutrophils to the epidermis, and activation of dermal fibroblasts.

This cycle of keratinocytes activating dendritic cells, dendritic cells activating T cells, and T cells activating keratinocytes appears to be the main force maintaining the disease.²⁴ It is unclear, however, whether this applies to all forms of psoriasis or only to plaque psoriasis.

Genetic factors discovered

In recent years, genome-wide association studies have identified at least 10 psoriasis-susceptibility loci that involve functioning of the immune system.²⁵ These genes include those

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FIGURE 1. Well-demarcated erythematous, scaly plaques characteristic of plaque psoriasis on the elbow.

of the major histocompatibility complex, cytokines, receptors, and beta-defensins.

Of specific interest, polymorphisms in the IL-12/IL-13 receptor, the p40 subunit of IL-12 and IL-23, and the p19 subunit of IL-23 strongly associate with psoriasis, supporting their critical role in the disease process and providing targets for medical therapy.²⁶

■ PSORIASIS HAS SEVERAL CLINICAL PHENOTYPES

Psoriasis has several clinical variants, each with a distinct clinical course and response to treatment.²⁷ Moreover, many patients present with more than one variant.

Plaque psoriasis

Plaque psoriasis (FIGURE 1) accounts for more than 80% of cases. It is characterized by well-



FIGURE 2. Patient with inverse psoriasis of the axilla.

PHOTO COURTESY OF JOSEPH C. ENGLISH III, MD.

demarcated, scaly, pink-to-red plaques of various sizes with a relatively symmetric distribution. Involvement of the extensor surfaces such as the elbows and knees and of the scalp, trunk, and intergluteal cleft is common.

Plaques can persist for several months to years, even in the same location, and only about 5% of patients report complete remission for up to 5 years.

Inverse psoriasis

Involvement of the skin folds, including the axillary, genital, perineal, intergluteal, and inframammary regions with pink-to-red plaques with minimal scale is the main clinical feature of inverse psoriasis (FIGURE 2). Absence of satellite pustules clinically distinguishes it from candidiasis.

Guttate psoriasis

Guttate psoriasis (named for its droplet-shaped lesions) presents abruptly with 1-mm to 10-mm pink papules with associated fine scale over the trunk and extremities (FIGURE 3). This variant occurs in fewer than 2% of patients with psoriasis, who are usually younger than 30 years. It is often preceded 2 to 3 weeks

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FIGURE 3. Guttate psoriasis with characteristic erythematous, scaly papules and small plaques on the back.

PHOTO COURTESY OF LAURA K. FERRIS, MD, PhD.



FIGURE 4. Erythematous plaques studded with pustules and red-brown macules on the acral surface of the foot in palmoplantar pustulosis.

PHOTO COURTESY OF JOSEPH C. ENGLISH III, MD.

earlier by an upper respiratory tract infection with group A beta-hemolytic streptococci.

Erythrodermic psoriasis

Approximately 1% to 2.25% of all patients with psoriasis develop this severe form, affecting more than 75% of the body surface area. It presents as generalized erythema, which is the most prominent feature, and it is often associated with superficial desquamation, hair loss, nail dystrophy, and systemic symptoms such as fever, chills, malaise, or high-output cardiac failure. There may be a history of preceding characteristic psoriatic plaques, recent withdrawal of treatment (usually corticosteroids), phototoxicity, or infection.

Conversely, approximately 25% of all patients with erythroderma have underlying psoriasis.²⁸

Pustular psoriasis

Pustular psoriasis (**FIGURE 4**) is uncommon. The predominant lesions are large collections of neutrophils in the stratum corneum that clinically present as sterile pustules. The pustules may be localized within or at the edge of existing psoriatic plaques or may present as a generalized eruption.

There are several forms of pustular psoriasis, including generalized pustular psoriasis, annular pustular psoriasis, impetigo herpetiformis (pustular psoriasis of pregnancy), and palmoplantar pustulosis. However, there is some evidence to suggest that palmoplantar pustulosis may be distinct from psoriasis.²⁹

Several triggers have been identified, including pregnancy, rapid tapering of medications, hypocalcemia, infection, or topical irritants.

Generalized pustular psoriasis, annular pustular psoriasis, and impetigo herpetiformis often present in association with fever and other systemic symptoms and, if left untreated, can result in life-threatening complications including bacterial superinfection, sepsis, dehydration, and, in rare cases, acute respiratory distress secondary to aseptic pneumonitis.³⁰

Placental insufficiency resulting in stillbirth or neonatal death and other fetal abnormalities can occur in severe pustular psoriasis of pregnancy.³¹

Psoriatic arthritis

Psoriatic arthritis is a seronegative inflammatory spondyloarthropathy that can result in erosive arthritis in up to 57% of cases and functional disability in up to 19%.³² Although rare in the general population, it affects approximately 6% to 10% of psoriasis patients and up to 40% of patients with severe psoriasis.³³ In 70% of cases, psoriasis precedes the onset of arthritis by about 10 years, and approximately 10% to 15% of patients simultaneously present with psoriasis and arthritis or develop arthritis before skin involvement.^{5,34}

Patients complain of joint discomfort that is most prominent after periods of prolonged rest. Patterns of involvement are extremely variable but have been reported as an asymmetric oligoarthritis (involving four or fewer joints) or polyarthritis (involving more than four joints) in most patients. A rheumatoid arthritis-like presentation with a symmetric polyarthropathy involving the small and medium-sized joints has also been reported, making it difficult to clinically distinguish this from rheumatoid arthritis.

A distal interphalangeal-predominant pattern is reported in 5% to 10% of patients. Axial disease resembling ankylosing spondylitis occurs only in 5% of patients. Arthritis mutilans, characterized by severe, rapidly progressive joint inflammation, joint destruction, and deformity, occurs rarely. Enthesitis, ie, inflammation at the point of attachment of tendons or ligaments to bone, is present in up to 42% of patients.^{5,35}

Nail disease

Nail psoriasis occurs in 35% to 50% of patients and can be seen with all forms of psoriasis.¹ Involvement of the nail matrix can result in nail pitting and leukonychia. Oil spots, subungual hyperkeratosis, and distal onycholysis are the result of disease involvement of the nail bed (FIGURE 5). Up to 90% of patients with psoriatic arthritis have nail changes, especially patients with enthesitis.³⁶

Disease severity also varies

Disease severity also differs among patients. An estimated 80% of patients have mild to moderate disease and 20% have moderate to severe disease, which includes disease involv-



FIGURE 5. Nail pitting and onycholysis with surrounding psoriatic plaques along the perionychium and proximal nail fold.

PHOTO COURTESY OF JOSEPH C. ENGLISH III, MD.

ing more than 5% of the body surface or involvement of the face, hands, feet, or genitalia.¹

The Psoriasis Area and Severity Index (PASI) is an objective measure used in clinical trials. It incorporates the amount of redness, scaling, and induration of each psoriatic lesion over the body surface involved. A 75% improvement in the PASI score (PASI-75) is regarded as clinically significant.³⁷

■ PSORIASIS IS DIAGNOSED CLINICALLY

In most cases, the diagnosis of psoriasis is made clinically and is straightforward. However, in more difficult cases, biopsy may be needed. In particular:

- The plaques of psoriasis may be confused with squamous cell carcinoma in situ, der-

A 75% improvement in the PASI score is regarded as clinically significant

matophyte infection, or cutaneous T-cell lymphoma, especially if they are treatment-resistant.

- Guttate psoriasis may be difficult to distinguish from pityriasis rosea.
- Erythrodermic psoriasis must be distinguished from other causes of erythroderma, including Sézary syndrome, pityriasis rubra pilaris, and drug reactions.
- Intertrigo, candidiasis, extramammary Paget disease, squamous cell carcinoma, and contact dermatitis all may mimic inverse psoriasis.
- Palmoplantar pustulosis may be difficult to differentiate from dyshidrotic eczema.
- Generalized pustular psoriasis should be distinguished from a pustular drug eruption (acute generalized exanthematous pustular drug eruption or acute generalized exanthematous pustulosis), impetigo, candidiasis, or an autoimmune blistering disorder such as pemphigus.

■ TREATMENT OF LIMITED DISEASE

Topical corticosteroids

A topical corticosteroid, either by itself or combined with a steroid-sparing agent, is the first-line therapy for patients with limited disease. The potency required for treatment should be based on the extent of disease and on the location, the choice of vehicle, and the patient's preference and age.

Several double-blind studies have assessed the efficacy of various topical corticosteroids in treating psoriasis. In general, super-potent (class I) and potent (class II) topical corticosteroids are more efficacious than mild or moderate corticosteroids.³⁸ Class I and class II steroids include agents such as clobetasol propionate 0.05% (Temovate), betamethasone dipropionate 0.05% (Diprolene), fluocinonide 0.05% (Lidex), and desoximetasone 0.25% (Topicort).

Use of class I steroids should be limited to an initial treatment course of twice-daily application for 2 to 4 weeks in an effort to avoid some of the local toxicities such as skin atrophy, telangiectasia, and striae. Decreasing class I topical steroid use to 1 to 2 times per week with the gradual introduction of a steroid-sparing agent following the initial 2 to 4 weeks of treatment is advised.

Steroid-sparing agents

Steroid-sparing agents include vitamin D analogues, retinoids, and tacrolimus ointment (Protopic).

Vitamin D analogues and retinoids are thought to decrease keratinocyte proliferation and enhance keratinocyte differentiation.³⁹ The vitamin D analogues are also considered first-line topical agents and include calcipotriol (Dovonex), calcipotriene (Dovonex), and calcitriol (Vectical). To prevent hypercalcemia, use of more than 100 g of vitamin D analogues per week should be avoided.³⁹

Treatment of inverse psoriasis and scalp psoriasis may be challenging

The areas affected in inverse psoriasis, such as the genitalia and axillae, are more prone to side effects when potent topical steroids are used because of increased absorption and occlusion in these areas. Agents that minimize irritation and toxicity in sensitive areas, such as topical tacrolimus, less-potent topical steroids, or calcitriol, can be used.³⁹

For scalp psoriasis, alternative vehicles such as shampoos, gels, solutions, oils, sprays, and foams have improved patient compliance and efficacy of treatment.⁴⁰

■ PHOTOTHERAPY FOR SEVERE DISEASE

Narrow-band ultraviolet B

Narrow-band ultraviolet B, ie, light confined to wavelengths of 311 to 313 nm, is a first-line treatment for moderate to severe psoriasis, either as monotherapy or in combination with other treatments. It is an especially attractive option in patients who are on medications or who have comorbidities that may preclude treatment with other systemic agents.

The mechanism of action may be via immunosuppressive effects on Langerhans cells, alteration of cytokines and adhesion molecules that lead to an increase in Th2 cells, and induction of apoptosis of T lymphocytes. Additionally, ultraviolet light affects the proliferation and differentiation of keratinocytes.⁴¹

Dosing is based on skin type, and treatment usually involves two or three visits per week for a total of 15 to 20 treatments, with

Steroid-sparing agents include vitamin D analogues, topical retinoids, and tacrolimus ointment

additional therapy for maintenance. Adding acitretin (Soriatane), with close monitoring of aspartate aminotransferase and alanine aminotransferase levels and the patient's lipid panel, can be considered in treatment-resistant cases.⁴²

Psoralen combined with ultraviolet A

Psoralen combined with ultraviolet A is another option. It can be considered if narrow-band ultraviolet B treatment fails. It is also useful for dark-skinned patients and those with thicker plaques because ultraviolet A penetrates deeper than ultraviolet B. Oral or topical treatment with psoralen is followed by ultraviolet A treatment.

The duration of remission is much longer with psoralen plus ultraviolet A than with narrow-band ultraviolet B. However, this treatment carries a significant risk of cutaneous squamous cell carcinoma and melanoma, especially in light-skinned people and those who receive high doses of ultraviolet A (200 or more treatments) or cyclosporine.^{40,41,43-46} Long-term effects include photoaging, lentiginosities, and telangiectasias. As a consequence of these well-established side effects, this treatment is used less frequently.

Cautions with phototherapy

Careful screening and caution should be used in patients who have:

- Fair skin that tends to burn easily
- A history of arsenic intake or treatment with ionizing radiation
- A history of use of photosensitizing medications (fluoroquinolone antibiotics, doxycycline, hydrochlorothiazide)
- A history of melanoma or atypical nevi
- Multiple risk factors for melanoma
- A history of nonmelanoma skin cancer
- Immunosuppression due to organ transplantation.

ORAL THERAPIES FOR SEVERE PSORIASIS

Patients who have severe psoriasis—ie, affecting more than 5% of the body surface or debilitating disease affecting the palms, soles, or genitalia—are best managed with systemic medications, especially if they do not have access to phototherapy.²⁰

Methotrexate

In 1972, the US Food and Drug Administration (FDA) approved methotrexate for treating severe psoriasis.⁴² In studies of methotrexate at doses of 15 to 20 mg weekly, 36% to 68% of patients with severe plaque psoriasis achieved a PASI-75 score.^{40,42,47}

Dosages of methotrexate for treating severe psoriasis range from 7.5 to 25 mg once a week. Patients should also receive a folate supplement of 1 to 5 mg every day except the day they take methotrexate. The folate is to protect against gastrointestinal side effects, bone marrow suppression, and hepatic toxicity associated with methotrexate.

Other side effects of methotrexate include pulmonary fibrosis and stomatitis. Pregnancy, nursing, alcoholism, chronic liver disease, immunodeficiency syndromes, bone-marrow hypoplasia, leukopenia, thrombocytopenia, anemia, and hypersensitivity to methotrexate are all contraindications to methotrexate use.

The National Psoriasis Foundation, in its 2009 guidelines for the use of methotrexate in treating psoriasis,⁴⁸ recommends obtaining a complete blood cell count with platelets, blood urea nitrogen, creatinine, and liver function tests at baseline and at 1- to 3-month intervals thereafter.

Liver biopsies were previously recommended for patients receiving methotrexate long-term when the cumulative dose of therapy reached 1.5 g. However, given the invasive nature of the liver biopsy procedure and the low incidence of methotrexate-induced hepatotoxicity, this recommendation has been revised.

For patients with no significant risk factors for hepatic toxicity (eg, obesity, diabetes, hyperlipidemia, hepatitis, or history of or current alcohol consumption) and normal liver function tests, liver biopsy should be considered when a cumulative methotrexate dose of 3.5 to 4.0 g is reached. Alternatively, one may choose to continue to monitor the patient without liver biopsy or to switch to another medication, if possible.^{42,48}

Patients at high risk should be monitored more carefully, and liver biopsy should be considered soon after starting methotrexate and repeated after every 1.0 to 1.5 g.⁴⁸

No reliable noninvasive measures to eval-

All retinoids, including acitretin, are in pregnancy category X and should therefore be avoided during pregnancy

uate for liver fibrosis are routinely available in the United States. Serial measurements of serum type III procollagen aminopeptide have been reported to correlate with the risk of developing liver fibrosis; however, this test is readily available only in Europe.⁴⁹

Cyclosporine

Cyclosporine (Gengraf, Neoral, Sandimmune) is very effective for treating psoriasis, especially erythrodermic psoriasis. It is often used only short-term or as a bridge to other maintenance therapies because it has a rapid onset and because long-term therapy (3 to 5 years) is associated with a risk of glomerulosclerosis.⁵⁰

Cyclosporine works by decreasing T-cell activation by binding cyclophilin, which leads to inhibition of transcription of calcineurin and nuclear factor of activated T cells.⁵¹ Given at doses of 2.5 to 5 mg/kg/day, cyclosporine has been shown to result in rapid improvement in up to 80% to 90% of psoriatic patients.^{52,53}

The initial recommended dose of cyclosporine is usually 2.5 to 3 mg/kg/day in two divided doses, which is maintained for 4 weeks and then increased by 0.5 mg/kg/day until the disease is stable.⁴²

Nephrotoxicity and hypertension are cyclosporine's most serious side effects. Blood urea nitrogen, creatinine, and blood pressure should be monitored at baseline and then twice a month for the first 3 months and once monthly thereafter. Liver function tests, complete blood cell count, lipid profile, magnesium, uric acid, and potassium should also be checked every month.

Cyclosporine also increases the risk of cutaneous squamous cell carcinoma, especially in patients who have received psoralen plus ultraviolet A treatment.⁴²

Patients with hypersensitivity to cyclosporine, a history of chronic infection (eg, tuberculosis, hepatitis B, hepatitis C), renal insufficiency, or a history of systemic malignancy should not receive cyclosporine.

Acitretin

Acitretin, an oral retinoid, has been used for several years to treat psoriasis. Its onset is slow, typically ranging from 3 to 6 months, and its effects are dose-dependent. It is most effec-

tive as a maintenance therapy, usually after the disease has been stabilized by agents such as cyclosporine, or in combination with other treatments such as phototherapy.⁴² Acitretin has been shown to be effective in patients with pustular psoriasis.⁵⁴

Acitretin does not alter the immune system and has not been shown to have significant cumulative toxicities. Serum triglycerides are monitored closely, since acitretin can lead to hypertriglyceridemia.

All retinoids, including acitretin, are in pregnancy category X and should therefore be avoided during pregnancy. Although its half-life is only 49 hours, acitretin may be transformed to etretinate either spontaneously or as a result of alcohol ingestion. Etretinate has a half-life of 168 days and can take up to 3 years to be eliminated from the body. Therefore, acitretin is contraindicated in women who plan to become pregnant or who do not agree to use adequate contraception for 3 years after the drug is discontinued.⁴²

Biologic agents

Advances in our understanding of the pathogenesis of psoriasis have resulted in more specific, targeted therapy.

Alefacept (Amevive) is a human Fc IgG1 receptor fused to the alpha subunit of LFA3. It binds to CD2, blocks costimulatory signaling, and induces apoptosis in activated memory T cells.

Alefacept was the first biologic agent approved by the FDA for the treatment of psoriasis and one of the few biologic agents to induce long-term remission.⁵⁵ However, its use has declined because few patients achieved significant clearance of their psoriasis and its onset of action was much slower than that of other medications.⁵⁶

The currently approved biologic therapies commonly used for moderate to severe psoriasis include the TNF-alpha inhibitors and ustekinumab (Stelara).

The TNF-alpha inhibitors include infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). They are generally well tolerated and highly effective. However, TNF-alpha inhibitors and other biologic agents are contraindicated in patients with serious infection, a personal history or a family

In cases of psoriatic arthritis, evaluation by a rheumatologist is highly recommended

history in a first-degree relative of demyelinating disease, or class III or IV congestive heart failure. Patients should be screened for active infection, including tuberculosis and hepatitis B, since reactivation has been reported following initiation of TNF-alpha inhibitors.¹

Adalimumab is a human monoclonal antibody against TNF-alpha. It binds to soluble and membrane-bound TNF-alpha and prevents it from binding to p55 and p75 cell-surface TNF receptors.

The dosing schedule for adalimumab is 80 mg subcutaneously for the first week, followed by 40 mg subcutaneously the next week, and then 40 mg subcutaneously every 2 weeks thereafter.¹

Etanercept is a recombinant human TNF-alpha receptor (p75) protein fused with the Fc portion of IgG1, which binds to soluble TNF-alpha.⁵⁷ Dosing for etanercept is 50 mg subcutaneously twice weekly for the first 12 weeks, followed by 50 mg weekly thereafter.

Infliximab is a chimeric antibody composed of a human IgG1 constant region fused to a mouse variable region that binds to both soluble and membrane-bound TNF-alpha.⁵⁸ Infliximab is given as an infusion at a dose of 5 mg/kg over 2 to 3 hours at weeks 0, 2, and 6, and then every 8 weeks thereafter.

Efficacy of TNF inhibitors. There are no specific guidelines for the sequence of initiation of TNF inhibitors because no studies have directly compared the efficacy of these medications. However, response to infliximab is relatively rapid compared with adalimumab and etanercept.

In a phase III clinical trial,⁵⁹ as many as 80% of patients achieved PASI-75 clearance of their psoriasis after three doses of infliximab. Interestingly, only 61% of patients maintained PASI-75 clearance by week 50. This loss of efficacy of infliximab is also reported with other TNF-alpha inhibitors and is thought to be secondary to the development of antibodies to the drugs. For infliximab, this loss of efficacy is less when infliximab is given continuously rather than on an as-needed basis. Simultaneous treatment with methotrexate is also thought to decrease the development of antibodies to infliximab.⁶⁰

Ustekinumab is a monoclonal antibody directed against the common p40 subunit of

IL-12 and IL-23, which have been shown to be at increased levels in psoriatic lesions and important for the pathogenesis of psoriasis.

Between 66% and 76% of patients treated with ustekinumab achieved significant clearance of their disease after 12 weeks of treatment in two large phase III multicenter, randomized, double-blind, placebo-controlled trials.^{61,62}

Dosing of ustekinumab is weight-based. For those weighing less than 100 kg, ustekinumab is given at 45 mg subcutaneously at baseline, at 4 weeks, and every 12 weeks thereafter. The same dosing schedule is used for those weighing more than 100 kg, but the dose is increased to 90 mg.

Guidelines for monitoring patients while on ustekinumab are similar to those for other biologic agents. Information on long-term toxicities is still being collected. However, injection-site reactions, serious infections, malignancies, and a single case of reversible posterior leukoencephalopathy have been reported.²⁰

While biologic agents are significantly more expensive than the conventional therapies discussed above and insurance coverage for these agents varies, they have demonstrated superior efficacy and may be indicated for patients with recalcitrant moderate to severe psoriasis for whom multiple types of treatment have failed.

■ FOR PSORIATIC ARTHRITIS: SYSTEMIC MEDICATIONS

For patients with known or questionable psoriatic arthritis, evaluation by a rheumatologist is highly recommended.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually first-line in the treatment of mild psoriatic arthritis. If after 2 to 3 months of therapy with NSAIDs no benefit is achieved, treatment with methotrexate as monotherapy is a practical consideration because of its low cost. However, methotrexate as a monotherapy has not been shown to prevent radiologic progression of disease.^{5,32}

The TNF-alpha inhibitors have been shown to have similar efficacy when compared among each other in the treatment of psoriatic arthritis.^{32,63} Based on radiologic evidence,

Before starting a TNF-alpha inhibitor, screen for active infection, including tuberculosis and hepatitis B

ustekinumab has not shown to be as efficacious as the TNF-alpha inhibitors for treating psoriatic arthritis. Therefore, TNF inhibitors should be considered first-line in the treatment of psoriatic arthritis.^{21,64}

Few studies have been done on the efficacy or sequence of therapies that should be used in the treatment of psoriatic arthritis. The American Academy of Dermatology's Psoriasis Guidelines of Care recommend adding a TNF-alpha inhibitor or switching to a TNF-alpha inhibitor if no significant improvement is achieved after 12 to 16 weeks of treatment with oral methotrexate.²⁰

■ **FOR ERYTHRODERMIC PSORIASIS: MEDICATIONS THAT ACT PROMPTLY**

The care of erythrodermic psoriatic patients is distinct from that of other psoriatic patients

because of their associated systemic symptoms. Care should be taken to rule out sepsis, as this is a reported trigger of erythrodermic psoriasis.²⁸

Systemic medications with a quick onset, such as oral cyclosporine, are recommended. Infliximab has also been reported to be beneficial because of its rapid onset.²⁸

■ **TREATMENT BASED ON THE TYPE AND THE SEVERITY OF PSORIASIS**

The treatment of psoriasis can be as complex as the disease itself and should be based on the type and the severity of psoriasis. Recognition of the various manifestations of psoriasis is important for effective treatment. However, in patients with moderate to severe psoriasis, atypical presentations, or recalcitrant disease, referral to a specialist is recommended. ■

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