

Guidelines of care for the management of psoriasis and psoriatic arthritis

Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics

Work Group: Alan Menter, MD, Chair,^a Alice Gottlieb, MD, PhD,^b Steven R. Feldman, MD, PhD,^c Abby S. Van Voorhees, MD,^d Craig L. Leonardi, MD,^e Kenneth B. Gordon, MD,^f Mark Lebwohl, MD,^g John Y. M. Koo, MD,^h Craig A. Elmets, MD,ⁱ Neil J. Korman, MD, PhD,^j Karl R. Beutner, MD, PhD,^k and Reva Bhushan, PhD^l

Dallas, Texas; Boston, Massachusetts; Winston-Salem, North Carolina; Philadelphia, Pennsylvania; Saint Louis, Missouri; Chicago and Schaumburg, Illinois; New York, New York; San Francisco and Palo Alto, California; Birmingham, Alabama; and Cleveland, Ohio

Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. In this first of 5 sections of the guidelines of care for psoriasis, we discuss the classification of psoriasis; associated comorbidities including autoimmune diseases, cardiovascular risk, psychiatric/psychologic issues, and cancer risk; along with assessment tools for skin disease and quality-of-life issues. Finally, we will discuss the safety and efficacy of the biologic treatments used to treat patients with psoriasis. (J Am Acad Dermatol 2008;58:826-50.)

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines do not purport to establish a legal standard of care and should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding

From the Baylor University Medical Center, Dallas^a; Department of Dermatology, Tufts-New England Medical Center, Tufts University School of Medicine, Boston^b; Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem^c; Department of Dermatology, University of Pennsylvania^d; Saint Louis University^e; Division of Dermatology, Evanston Northwestern Healthcare and Department of Dermatology, Northwestern University, Feinberg School of Medicine, Chicago^f; Department of Dermatology, Mount Sinai School of Medicine, New York^g; Department of Dermatology, University of California—San Francisco^h; Department of Dermatology, University of Alabama at Birminghamⁱ; Murdough Family Center For Psoriasis, Department of Dermatology, University Hospitals Case Medical Center, Cleveland^j; Anacor Pharmaceuticals Inc, Palo Alto^k; and American Academy of Dermatology, Schaumburg.^l

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Reprint requests: Reva Bhushan, PhD, 930 E Woodfield Rd, Schaumburg, IL 60173. E-mail: rbhushan@aad.org.

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Abbreviations used:

AAD:	American Academy of Dermatology
BMI:	body mass index
BSA:	body surface area
CHF:	congestive heart failure
CyA:	cyclosporine
FDA:	Food and Drug Administration
IL:	interleukin
LFA:	lymphocyte function associated antigen
MS:	multiple sclerosis
NB:	narrowband
PASI:	Psoriasis Area and Severity Index
PASI-75:	75% improvement in the Psoriasis Area and Severity Index score
PGA:	Physicians Global Assessment
PUVA:	psoralen plus ultraviolet A
QOL:	quality of life
TB:	tuberculosis
TNF:	tumor necrosis factor
UV:	ultraviolet

the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

SCOPE

These guidelines address the treatment of both adult and childhood psoriasis and psoriatic arthritis. This document will include the various treatments of psoriasis including topical modalities, ultraviolet (UV) light therapies, systemic agents, and the

Table I. Eight clinical questions used to structure the primary issues in diagnosis and treatment of patients with psoriasis

Guideline section	Clinical questions
Section 1	<ul style="list-style-type: none"> • How is psoriasis classified? • What are the potential comorbidities of psoriasis? • What tools are used to measure quality of life in psoriasis and how are these tools used in the treatment of patients?
Section 2	<ul style="list-style-type: none"> • What are the safety and efficacy of biologic therapies used to treat psoriasis?
Section 3	<ul style="list-style-type: none"> • Discuss the classification, prognosis, assessment tools, and systemic therapies used in the treatment of patients with psoriatic arthritis.
Section 4	<ul style="list-style-type: none"> • What are the safety and efficacy of topical therapies used to treat psoriasis?
Section 5	<ul style="list-style-type: none"> • What are the safety and efficacy of systemic therapies and phototherapies used to treat psoriasis?
	<ul style="list-style-type: none"> • Describe an overall approach to the treatment of patients with psoriasis with an emphasis on decision-making criteria that enable the clinician to individualize therapy based on disease type, extent, response to previous treatments, quality-of-life issues, and comorbidities.

biologic therapies. In addition, quality of life (QOL) parameters, the type of psoriasis, and the presence of comorbidities such as obesity and other associations of the metabolic syndrome will be reviewed. This guideline will be subdivided into 5 separate documents given the large breadth of material. The first section will give an overview of classification, comorbidities, and assessment tools and cover the biologic treatments for psoriasis. The second section will cover treatments for psoriatic arthritis with an emphasis on the biologics; the third section will cover topical therapies; the fourth section will cover UV light therapy and systemic nonbiologic therapies; and the fifth section will be an overall approach to the treatment of patients with psoriasis with an emphasis on decision-making criteria.

It is important, however, for dermatologists to address psoriasis in its entire scope of manifestations. This guideline will not cover the effectiveness of treatments for the less common subtypes of psoriasis, such as guttate, pustular, inverse, and erythrodermic.

METHOD

A work group of recognized psoriasis experts was convened to determine the audience and scope of the guideline, and identify clinical questions to structure the primary issues in diagnosis and management (Table I). Work group members completed a disclosure of commercial support.

An evidence-based model was used and evidence was obtained using a search of the MEDLINE database spanning the years 1990 through 2007. Only English-language publications were reviewed.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family*

Practice, and *BMJ USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies.¹ Evidence was graded using a 3-point scale based on the quality of methodology as follows:

- I. Good-quality patient-oriented evidence.
- II. Limited-quality patient-oriented evidence.
- III. Other evidence including consensus guidelines, opinion, or case studies.

Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows:

- A. Recommendation based on consistent and good-quality patient-oriented evidence.
- B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C. Recommendation based on consensus, opinion, or case studies.

Prior guidelines on psoriasis were also evaluated.^{2,3} This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/AAD Association "Administrative Regulations for Evidence-based Clinical Practice Guidelines," which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

DEFINITION

Psoriasis vulgaris is a genetic, systemic, inflammatory, chronic disorder, which can be altered by environmental factors. It may be associated with other inflammatory disorders such as psoriatic arthritis, inflammatory bowel disease, and coronary artery disease. It is characterized by scaly, erythematous patches, papules, and plaques that are often pruritic.

INTRODUCTION

Psoriasis is a multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. Psoriatic arthritis is a member of the seronegative spondyloarthropathies. Other conditions that may be associated with psoriasis, psoriatic arthritis, or both include autoimmune diseases such as inflammatory bowel disease, components of the metabolic syndrome such as diabetes, cardiovascular disease, and lymphoma. As physicians who care for the large majority of patients with psoriasis, dermatologists play an important role in identifying the morbidity of all aspects of psoriatic disease.

The major manifestation of psoriasis is chronic inflammation of the skin. It is characterized by disfiguring, scaling, and erythematous plaques that may be painful or often severely pruritic and may cause significant QOL issues. Psoriasis is a chronic disease that waxes and wanes during a patient's lifetime, is often modified by treatment initiation and cessation and has few spontaneous remissions.

CLASSIFICATION OF PSORIASIS

The phenotyping of psoriasis has traditionally been based on historical morphologic descriptions.⁴ Although this phenotyping is very useful for classification purposes, clinical findings in individual patients frequently overlap in more than one category.

Plaque

Plaque psoriasis is the most common form, affecting approximately 80% to 90% of patients. The vast majority of all high-quality and regulatory clinical trials in psoriasis have been conducted on patients with this form of psoriasis. Plaque psoriasis manifests as well-defined, sharply demarcated, erythematous plaques varying in size from 1 cm to several centimeters (Figs 1 and 2). These clinical findings are mirrored histologically by psoriasiform epidermal hyperplasia, parakeratosis with intracorneal neutrophils, hypogranulosis, spongiform pustules, an infiltrate of neutrophils and lymphocytes in the epidermis and dermis, along with an expanded dermal papillary vasculature. Patients may have involvement ranging from only a few plaques to numerous lesions covering almost the entire body surface. The plaques are irregular, round to oval in shape, and most often located on the scalp, trunk, buttocks, and limbs, with a predilection for extensor surfaces such as the elbows and knees. Smaller plaques or papules may coalesce into larger lesions, especially on the legs and trunk. Painful fissuring

within plaques can occur when lesions are present over joint lines or on the palms and soles. Psoriatic plaques typically have a dry, thin, silvery-white or micaceous scale, often modified by regional anatomic differences, and tend to be symmetrically distributed over the body (Fig 1). Approximately 80% of those affected with psoriasis have mild to moderate disease, with 20% having moderate to severe psoriasis affecting more than 5% of the body surface area (BSA) or affecting crucial body areas such as the hands, feet, face, or genitals.^{5,6}

Inverse

Inverse psoriasis is characterized by lesions in the skin folds. Because of the moist nature of these areas, the lesions tend to be erythematous plaques with minimal scale. Common locations include the axillary, genital, perineal, intergluteal, and inframammary areas. Flexural surfaces such as the antecubital fossae can exhibit similar lesions (Fig 1, B).

Erythrodermic

Erythrodermic psoriasis can develop gradually from chronic plaque disease or acutely with little preceding psoriasis. Generalized erythema covering nearly the entire BSA with varying degrees of scaling is seen (Fig 1, E). Altered thermoregulatory properties of erythrodermic skin may lead to chills and hypothermia, and fluid loss may lead to dehydration. Fever and malaise are common.

Pustular

All forms of psoriasis may contain neutrophils in the stratum corneum. When the collections of neutrophils are large enough to be apparent clinically, it is termed "pustular psoriasis." Pustular psoriasis may be generalized or localized. The acute generalized variety (termed the "von Zumbusch variant") is an uncommon, severe form of psoriasis accompanied by fever and toxicity and consists of widespread pustules on an erythematous background (Fig 1, D, and Fig 2, C). Cutaneous lesions characteristic of psoriasis vulgaris may be present before, during, or after an acute pustular episode. There is also a localized pustular variant of psoriasis involving the palms and soles, with or without evidence of classic plaque-type disease.

Guttate

Guttate psoriasis is characterized by dew-drop-like, 1- to 10-mm, salmon-pink papules, usually with a fine scale. This variant of psoriasis, common in individuals younger than 30 years, is found primarily on the trunk and the proximal extremities and occurs in less than 2% of patients with psoriasis. A history of

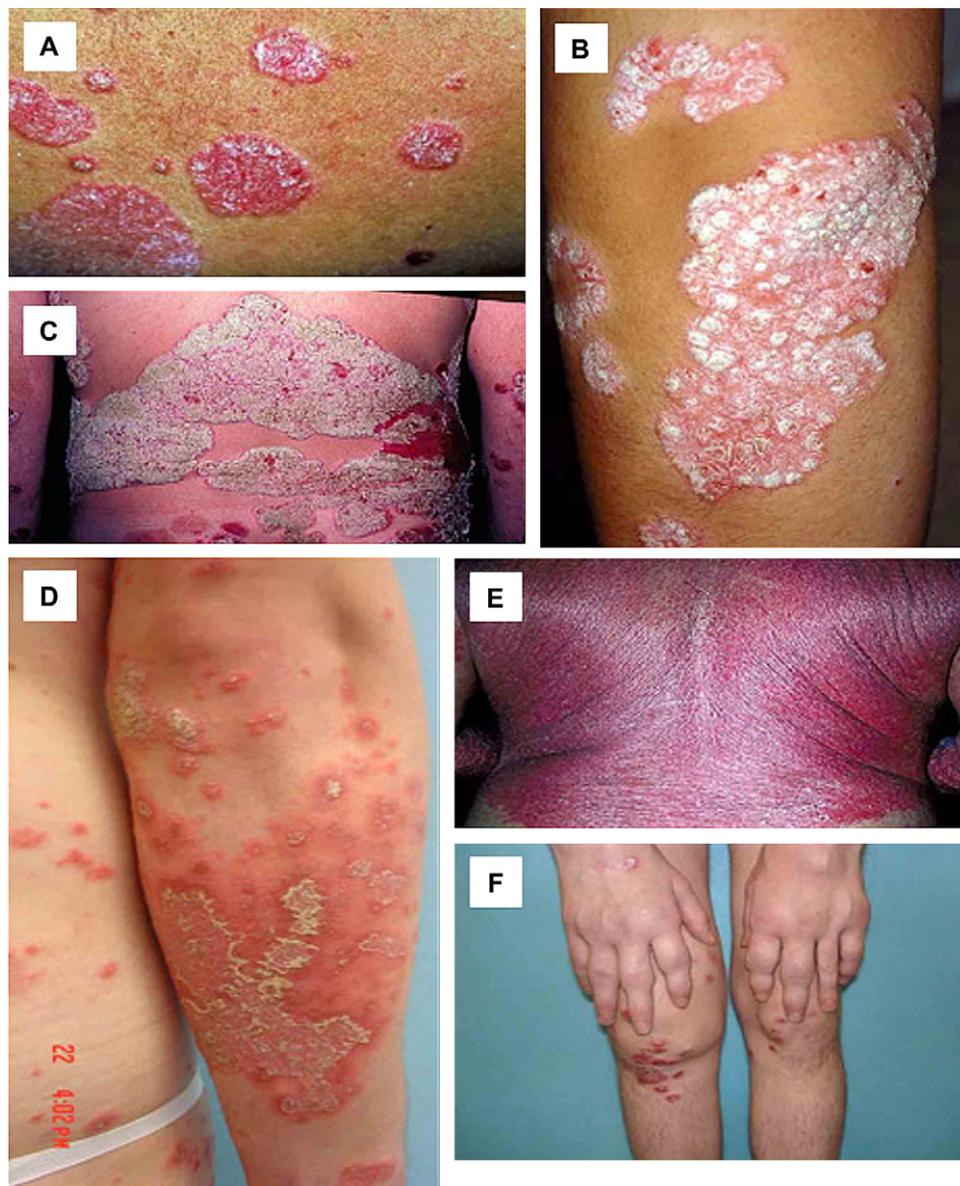


Fig 1. Photographs of patients with psoriasis. **A**, Small plaque psoriasis. **B**, Localized thick plaque type psoriasis. **C**, Large plaque psoriasis. **D**, Inflammatory localized psoriasis. **E**, Erythrodermic psoriasis. **F**, Psoriasis and psoriatic arthritis.

upper respiratory infection with group A beta-hemolytic streptococci often precedes guttate psoriasis, especially in younger patients, by 2 to 3 weeks. This sudden appearance of papular lesions may be either the first manifestation of psoriasis in a previously unaffected individual or an acute exacerbation of long-standing plaque psoriasis (Fig 2, D).

Nail disease (psoriatic onychodystrophy)

Nail psoriasis can occur in all psoriasis subtypes. Fingernails are involved in approximately 50% of all patients who are psoriatic and toenails in 35% of patients. These changes include pitting, onycholysis, subungual hyperkeratosis, and the oil-drop sign

(Fig 3). Up to 90% of patients with psoriatic arthritis may have nail changes. Psoriasis of the nails is a significant therapeutic challenge.

Psoriatic arthritis

Psoriatic arthritis is an inflammatory arthropathy associated with psoriasis that will be discussed at length in Section 2 of the guidelines (Fig 1, F).

COMORBIDITIES ASSOCIATED WITH PSORIASIS

Although psoriasis has been previously thought to be a disease solely affecting primarily the skin and

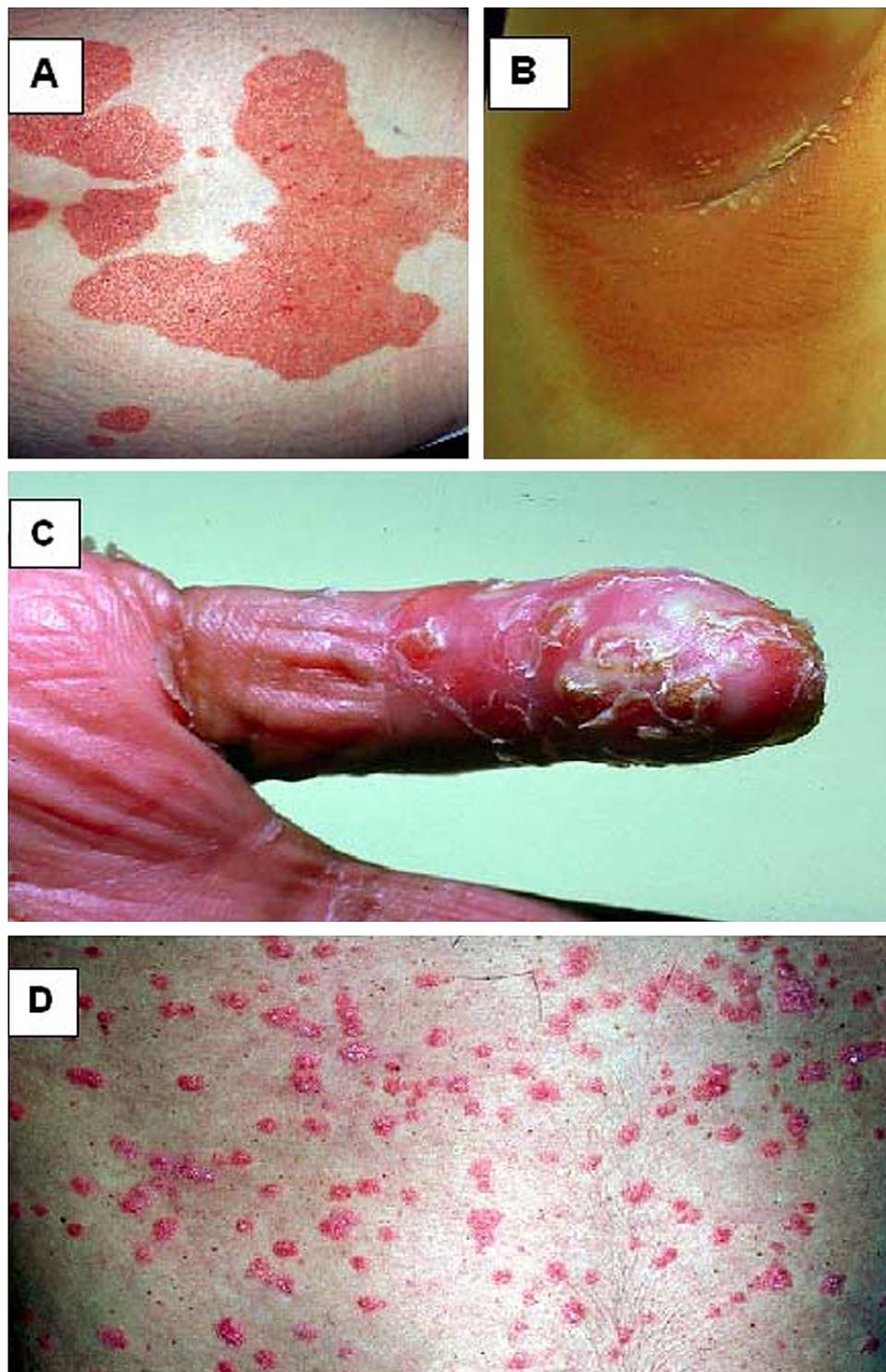


Fig 2. Photographs of patients with psoriasis. **A**, Thin plaque type psoriasis. **B**, Inverse type psoriasis. **C**, Pustular type psoriasis. **D**, Guttate type psoriasis.

the joints, our understanding of the comorbidities that may be associated with this disease has grown significantly. Recent evidence has even suggested an increased overall risk of mortality in patients with severe psoriasis.⁷

MEDICAL COMORBIDITIES

Autoimmune diseases

Some of the comorbidities associated with psoriasis have been attributed to shared or closely linked genetic susceptibility traits. For example, the

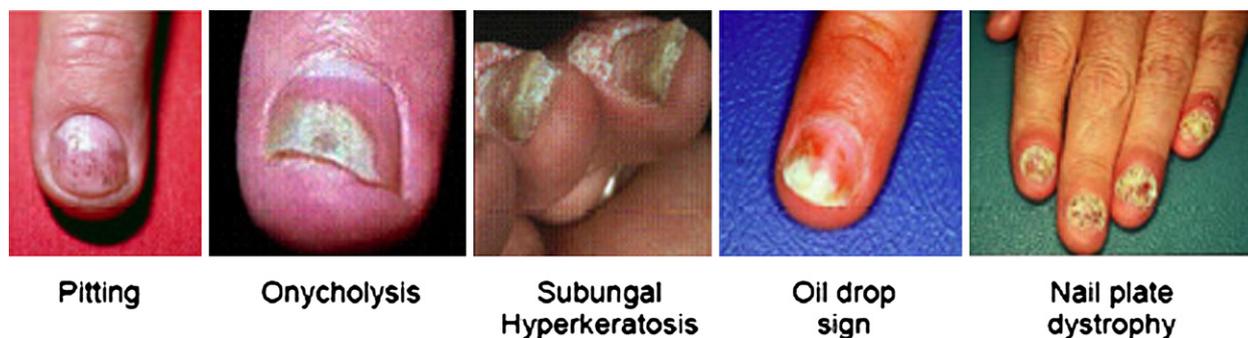


Fig 3. Photographs of patients with nail psoriasis.

incidence of Crohn's disease and ulcerative colitis is 3.8 to 7.5 times greater in patients with psoriasis than in the general population.⁸ Although individual susceptibility to all 3 of these diseases has been localized to a similar region of chromosome 16, multiple other genetic loci are found in each condition.⁹ Other studies suggest a possible link between multiple sclerosis (MS) and psoriasis as psoriasis occurs more commonly in families of patients with MS compared with control subjects.¹⁰ Furthermore, in this study, families with more than one case of MS had the highest likelihood of having a family member with psoriasis, supporting a genetic relationship between these two diseases.¹⁰

Cardiovascular disease

There is an increased risk of cardiovascular disease in patients with psoriasis. Several factors are believed to contribute to the increased risk for cardiovascular disease in these patients.¹¹ Patients with psoriasis are more frequently overweight, have an increased incidence of diabetes, have an increased incidence of hypertension, and have an atherogenic lipoprotein profile at the onset of psoriasis with significantly higher very low-density lipoprotein cholesterol levels and high-density lipoprotein levels.¹¹⁻¹⁶ Epidemiologic analysis of the United Kingdom General Practice Database, which contains data on more than 130,000 patients with psoriasis aged 20 to 90 years, has determined that patients with psoriasis have a higher than normal incidence of myocardial infarction.¹¹ Even after correcting for the heart disease risk factors of smoking, diabetes, obesity, hypertension, and hyperlipidemia, the probability of myocardial infarction is higher in patients who are psoriatic than in nonaffected individuals (the relative risk being particularly elevated in younger patients with more severe psoriasis). Patients with both rheumatoid arthritis and systemic lupus erythematosus also have an increased incidence of coronary heart disease,¹⁷ suggesting that the chronic inflammatory process found in all of these diseases may

play a role in the promotion of coronary heart disease. Preliminary studies suggest that therapy of both rheumatoid arthritis and psoriasis with methotrexate¹⁸ and rheumatoid arthritis with tumor necrosis factor (TNF) inhibitors¹⁹ can decrease the cardiovascular mortality.

Metabolic syndrome

The combination of obesity, impaired glucose regulation, hypertriglyceridemia, reduced high-density lipoprotein, and hypertension is known as the metabolic syndrome. Patients with the metabolic syndrome are at a significantly increased risk of developing cardiovascular morbidity and mortality. Although the prevalence of metabolic syndrome is elevated in most westernized countries, a recent study of hospitalized patients demonstrates that the prevalence of metabolic syndrome in hospitalized patients with psoriasis is significantly elevated when compared with hospitalized patients who do not have psoriasis.²⁰

Lymphoma, melanoma, and nonmelanoma skin cancer

The question of whether patients with psoriasis are at greater risk of developing lymphoma than the general population is an area of ongoing controversy. One study of more than 2700 patients with psoriasis followed up for nearly 4 years showed an almost 3-fold increased relative risk of developing any type of lymphoma compared with a control group, after accounting for sex and age.²¹ Although medications with a known risk of lymphoma had only been used in 1.55% of patients in this study, they cannot be completely eliminated as a potential confounding factor. In addition, the patients in this study were all older than 65 years, and it is unknown whether these findings would hold true for a younger cohort. A more recent retrospective study of 150,000 patients of all ages with psoriasis also demonstrates an increased risk of lymphoma, but suggests that the relative risk for all lymphomas is lower at 1.34. In this study, there was a significantly

increased risk of developing cutaneous T-cell lymphoma (relative risk of 10.75), or Hodgkin's lymphoma (relative risk of 3.18) in patients with severe psoriasis.²²

Although many²³ but not all²⁴ studies reveal that the risk of melanoma and nonmelanoma skin cancer in patients with psoriasis is equivalent to that of the general population, there are subpopulations in which there is an increased risk of skin cancer. Caucasian individuals who have received more than 250 psoralen plus UVA (PUVA) treatments have a 14-fold higher risk of cutaneous squamous cell carcinoma than patients who have received fewer treatments.^{25,26} There is also evidence that Caucasians with extensive PUVA exposure have an increased risk of melanoma, although this is not universally accepted and has not been demonstrated in the non-Caucasian population.^{27,28}

PSYCHIATRIC/PSYCHOLOGIC COMORBIDITIES

Depression/suicide

Psoriasis is associated with lack of self-esteem and increased prevalence of mood disorders including depression.²⁹ The prevalence of depression in patients with psoriasis may be as high as 60%.³⁰ Depression may be severe enough that some patients will contemplate suicide. In one study of 217 patients with psoriasis, almost 10% reported a wish to be dead and 5% reported active suicidal ideation.³¹ Treatments for psoriasis may affect depression. One study demonstrated that patients with psoriasis treated with etanercept had a significant decrease in their depression scores when compared with control subjects. However, clinically diagnosed depression was an exclusionary criterion for entry into this study.³² Therefore, treatment of psoriasis with etanercept lessened symptoms of depression in patients without overt clinical depression.³² Increased rates of depression in patients with psoriasis may be another factor leading to increased risk of cardiovascular disease. Although there is some suggestive evidence that treatment of depression with selective serotonin reuptake inhibitors may reduce cardiovascular events, conclusive evidence is lacking.³³

Psychologic and emotional burden of psoriasis

Psoriasis can have a substantial psychologic and emotional impact on an individual, which is not always related to the extent of skin disease. There are elevated rates of various psychopathologies among patients with psoriasis including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation.³⁴ Because the clinical severity of psoriasis

may not reflect the degree of emotional impact of the disease, it is important that clinicians consider the psychosocial aspects of this illness.

BEHAVIORS CONTRIBUTING TO MEDICAL AND PSYCHIATRIC COMORBIDITIES

Smoking

In 2004, the prevalence of smoking among US adults was 21%. Smoking increases the risk of hypertension, peripheral vascular disease, stroke, and myocardial infarction.

An increased prevalence of smoking among patients with psoriasis has been observed in numerous countries including Finland, Italy, the United Kingdom, Norway, China, and the United States.³⁵⁻³⁷ Data from the Utah Psoriasis Initiative, which included more than 800 subjects, reveals that 37% of patients with psoriasis were smokers versus 13% smokers in the general population. Among patients with psoriasis who smoke, 78% started smoking before the onset of their psoriasis and 22% of patients starting after onset.¹² Both the Italian studies and the Nurses Health Study II clearly establish smoking as a risk factor for incident psoriasis.^{36,38} The increased prevalence of smoking in patients with psoriasis may also contribute to an elevation in cardiovascular risk.

Alcohol

The prevalence of psoriasis is increased among patients who abuse alcohol.³⁹ However, conflicting evidence exists as to whether increased alcohol intake in patients with psoriasis is a factor in the pathogenesis or whether having a chronic disorder such as psoriasis leads to greater intake of alcohol. For example, one study of 144 patients with psoriasis demonstrated that alcohol consumption in the previous 12 months was linked to the onset of psoriasis. This study suggests that psoriasis may lead to sustained alcohol abuse and that alcohol intake may perpetuate psoriasis.⁴⁰ In contrast, another study of 55 patients showed no association between alcohol consumption and the onset of psoriasis.⁴¹ Support of increasing alcohol abuse as a postdiagnosis condition was found in a case-control study of 60 twins discordant for psoriasis. In this study, no difference in alcohol consumption between discordant twins, either monozygotic or dizygotic, was discovered.⁴² In summary, alcohol consumption is more prevalent in patients with psoriasis, and it may also increase the severity of psoriasis.

Obesity

Obesity has become an epidemic within the United States. A body mass index (BMI) of more than 30 is defined as obese with overweight being

defined as a BMI between 25 and 30. In the United States, 65% of people older than 20 years are either overweight or obese. Obesity has serious health consequences including hypertension, vascular disease, and type 2 diabetes mellitus. Psoriasis was first associated with obesity in several large, European epidemiologic studies. Studies from the United States also show an elevated BMI in patients with psoriasis. These analyses of BMI compared subjects with and without psoriasis while controlling for age, sex, and race. Analysis of data from the Utah Psoriasis Initiative revealed that patients with psoriasis had a significantly higher BMI than control subjects in the general Utah population.¹² The Nurses Health Study II, which contains prospective data from 78,626 women followed up during a 14-year period, indicates that obesity and weight gain are strong risk factors for the development of psoriasis in women.⁴³ In this study, multiple measures of obesity, including BMI, waist and hip circumference, waist-hip ratio, and change in adiposity as assessed by weight gain since the age of 18 years, were substantial risk factors for the development of psoriasis. Multivariate analysis demonstrated that the relative risk of developing psoriasis was highest in those with the highest BMIs. In contrast, a low BMI (<21) was associated with a lower risk of psoriasis, further supporting these findings. Furthermore, the average weights of patients with psoriasis in the large clinical trials of the biologic agents have been in the 90- to 95-kg range⁴⁴⁻⁴⁷ (although these clinical trials all enrolled more men than women) whereas the average body weight for the US population from the NHANES database from 1999 to 2002 was 86 kg.⁴⁸ An association between psoriasis and elevated BMI appears to be yet another factor that predisposes individuals with psoriasis to cardiovascular disease.⁴⁹

QOL

Psoriasis causes psychosocial morbidity and decrement in occupational function.^{50,51} In a large study of more than 300 university-based patients with psoriasis, the physical and mental disability experienced by patients with psoriasis was comparable or in excess of that found in patients with other chronic illnesses such as cancer, arthritis, hypertension, heart disease, diabetes, and depression as measured by the SF-36 Health Survey Form.⁵² QOL measures are an important adjunct to skin lesion assessments to properly assess the full effect of an illness such as psoriasis that is not life-threatening. Dermatology-specific, but not psoriasis-specific, instruments such as the Dermatology Life Quality Index or SKINDEX are very useful to assess the QOL impact of psoriasis, but may have a limited correlation with the actual

severity of a specific skin disease such as psoriasis.⁵³ The Psoriasis QOL 12-item instrument discriminates among patients with psoriasis and varying degrees of disease severity and reliably captures clinical changes from topical or systemic treatments.⁵⁴⁻⁵⁶ Psoriasis clinical trial entry criteria have traditionally been based purely on the extent and character of the skin lesions. However, clinical decision making must incorporate the impact of the skin lesions on patients' lives.^{57,58} This involves assessing both the burden of disease and the severity of the skin lesions. An instrument incorporating the Psoriasis QOL 12-item instrument with the physician's rating of severity by BSA measurement, the Koo-Menter Psoriasis Instrument, was designed to help physicians perform a comprehensive and quantitative evaluation of patients with psoriasis including physical severity, QOL impact, and arthritis issues, to help the physician properly characterize all relevant aspects of disease severity.⁵⁷ Another tool that attempts to capture several relevant aspects of psoriatic disease severity is the Salford index.⁵⁹ Treatments that are effective for psoriasis skin lesions also improve patients' QOL.⁶⁰⁻⁶⁶ The specific characteristics of psoriasis treatments may directly impact patients' QOL, requiring treatment to be tailored to the specific patient's situation and preferences.⁶⁷ The QOL impact of psoriasis may be large even in patients with small areas of involvement.^{6,68} For example, psoriasis of the palms and soles tends to have more impact than far more extensive involvement on the trunk.^{69,70} Thus, patients with these types of psoriasis may be considered candidates for systemic treatment.^{58,71}

PATHOGENESIS

Psoriasis is a complex genetic disease of dysregulated inflammation, although the mechanism of inheritance has not been completely defined. To date, at least 8 chromosomal loci have been identified for which statistically significant evidence for linkage to psoriasis has been observed (these loci are known as PSORS I-VIII). Detailed genetic mapping studies demonstrate that the HLA-Cw6 allele, also known as PSORS1, is the major susceptibility gene for psoriasis.⁷² In addition, a number of environmental factors play an important role in the pathogenesis of psoriasis including drugs, skin trauma (Koebner's phenomenon), infection, and stress.

Evidence suggesting that psoriasis involves immunologic mechanisms includes the efficacy of immunosuppressive drugs such as methotrexate, cyclosporine (CyA), immune-targeting biologic agents, immunotoxins (denileukin diftitox), and TNF-blocking biologics in treating psoriasis, and

exacerbation of psoriasis by certain cytokine therapies such as interferons alfa, beta, and gamma; interleukin (IL)-2; granulocyte colony-stimulating factor; and bacterial superantigens such as streptococcal antigens. Resolution of psoriasis is associated with decreased lesional infiltration of T cells, dermal dendritic cells, Langerhans cells, and neutrophils, and decreased expression of TNF- α -, interferon- γ -, and IL-12/23-dependent genes. In addition, there are altered levels of chemokines and integrins affecting migration of T cells, dermal dendritic cells, macrophages, and neutrophils into the plaques. Thus, psoriasis is an immune-mediated organ-specific (skin, and/or joints) inflammatory disease in which intralesional inflammation primes basal stem keratinocytes to hyperproliferate and perpetuate the disease process.

EVALUATION OF PSORIASIS TREATMENT

Assessment tools used to evaluate psoriasis

Most large double-blind, placebo-controlled clinical trials of psoriasis treatments include patients with chronic stable plaque psoriasis but exclude other less common types of psoriasis including those involving the palms and soles, scalp, and intertriginous areas. Similarly, erythrodermic and pustular psoriasis have been excluded. These areas of involvement and types of psoriasis should be considered in evaluating severity of disease because the impact of these types of psoriasis may be quite substantial.

The Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is a measure of overall psoriasis severity and coverage that assesses BSA and erythema, induration, and scaling.⁷³ It is commonly used in clinical trials for psoriasis treatments but is rarely used in clinical practice. Typically, the PASI score is calculated before, during, and after a treatment to determine how well psoriasis responds to the treatment under test. A decrease in the PASI score supports claims of efficacy. The vast majority of clinical trials of biologics compare the study drug with a placebo rather than other effective treatments making it difficult to compare the efficacy of the various systemic and biologic treatments for psoriasis. A 75% improvement in the PASI score (PASI-75) is predominantly used to document the effectiveness of individual therapies in clinical trials of patients with extensive psoriasis. The PASI is considered by the authors to be less sensitive in patients with lower BSA involvement (<10%).

Other measurement tools

Measures such as the Physicians Global Assessment (PGA) and target plaque scores, together

with percent of BSA involvement are other commonly used assessment tools for patients, particularly for those with milder disease. After PASI, the PGA is the tool most often used to measure psoriasis severity. When using the PGA, the investigator assigns a single estimate of the patients overall severity of disease; usually a 7-point scale from clear to severe is used. Efforts to improve quantitative psoriasis assessment continue, eg, the Lattice System-PGA, where 1% of BSA is approximately equal to the patient's open handprint (from wrist to tips of fingers) with fingers tucked together and the thumb tucked to the side.⁷⁴ In clinical practice, the physician generally uses subjective qualitative assessment of the severity of a patient's psoriasis by combining objective assessment of the BSA involvement, disease location, thickness, and symptoms, presence or absence of psoriatic arthritis with the subjective assessment of the physical, financial, and emotional impact of the disease on the patient's life.

GENERAL RECOMMENDATIONS FOR THE TREATMENT OF PSORIASIS

(Points 1-6 will be discussed in detail in future sections of the guidelines and point 7 will be discussed in detail below [Fig 4].)

1. Topical treatments are appropriate for patients who are candidates for localized therapy but may not be practical as monotherapy for most patients who are candidates for systemic and/or phototherapy,⁷⁵ where traditional systemic treatments, including methotrexate, CyA, narrowband (NB) and broadband UVB, PUVA, oral retinoids, and the newer biologic agents are prescribed.

2. UVB is safe, effective, and cost-effective. NB UVB is more effective than broadband UVB. Up to 20 to 25 NB UVB treatments, given 2 to 3 times a week, are usually required for significant improvement. Treatment can be offered in the office or at home; home UVB reduces the inconvenience of patients having to travel a long distance for treatment. Other forms of UV exposure, including sun exposure, may offer benefit in select patients.

3. PUVA therapy is very effective in the majority of patients, with potential for long remissions. However, long-term PUVA treatment in Caucasians is associated with an increased risk of squamous cell carcinoma and possibly malignant melanoma. PUVA induces photoaging and other skin changes including lentigenes. Ingestion of psoralen may also produce nausea. Oral psoralen is contraindicated in pregnancy. NB-UVB therapy avoids some of the adverse side effects of PUVA, while being slightly less effective than PUVA.

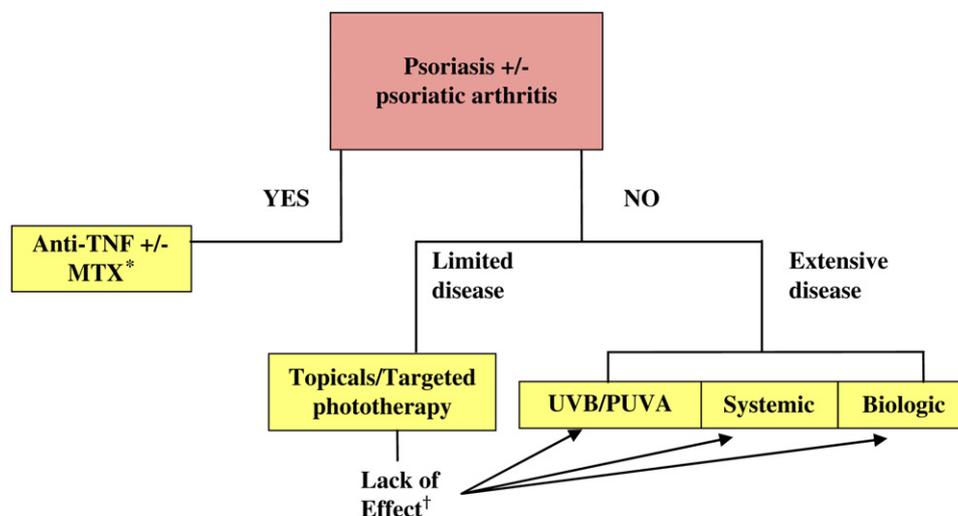


Fig 4. Decision tree. *Patients with nondeforming psoriatic arthritis without any radiographic changes, loss of range of motion, or interference with tasks of daily living should not automatically be treated with tumor necrosis factor (*TNF*) inhibitors. It would be reasonable to treat these patients with nonsteroidal anti-inflammatory agent or to consult rheumatologist for therapeutic options. †Patients with limited skin disease should not automatically be treated with systemic treatment if they do not improve, because treatment with systemic therapy may carry more risk than the disease itself. *MTX*, Methotrexate; *PUVA*, psoralen plus ultraviolet (*UV*)-A.

4. Methotrexate, although effective in the majority of patients, has the potential for hepatotoxicity and is contraindicated in the following clinical scenarios: pregnancy; individuals with renal impairment, hepatitis, or cirrhosis; alcoholics; unreliable patients; and patients with leukemia or thrombocytopenia. In addition, drug interactions are common. Methotrexate is an immunosuppressive agent. In patients treated with methotrexate, drug interactions are common with resultant bone-marrow suppression a concern. Methotrexate may induce pneumonitis. Methotrexate is a teratogen, an abortifacient, and decreases sperm count. Prior guidelines suggest a liver biopsy after 1.5-g cumulative dose.⁷⁶

5. CyA, another immunosuppressive medication, works rapidly and is effective in the majority of patients. However, impaired renal function, hypertension, concerns about lymphoma, and a potential increase in cutaneous malignancies are known adverse effects after long-term treatment with CyA. CyA is thus best used interventionally in short-term courses of 3 to 4 months. There are also numerous potential drug interactions with CyA. Guidelines exist for reducing the CyA dose in patients who develop hypertension or elevations in creatinine.

6. Acitretin is an effective systemic agent for the treatment of psoriasis that is not immunosuppressive. Because it is teratogenic and should not be used in women who are pregnant, breast-feeding, or may become pregnant within 3 years of discontinuing acitretin, its use is substantially limited in female

patients of childbearing potential. Mucocutaneous side effects are frequent. Dyslipidemia may also ensue and require dose reduction or treatment with lipid-lowering agents. Hepatotoxicity rarely arises during therapy. Acitretin is frequently used in combination therapy with UVB or PUVA.

7. Biologic agents are proteins that can be extracted from animal tissue or produced by recombinant DNA technology and possess pharmacologic activity. Five biologic agents are currently Food and Drug Administration (FDA) approved for psoriasis. Their safety and efficacy are discussed in detail in the following section.

TREATMENT OF PSORIASIS WITH BIOLOGICS

General recommendations for all patients who will be treated with biologics including T-cell inhibitors and TNF inhibitors

When planning to initiate treatment of a patient with psoriasis with a biologic it is important to obtain an age appropriate history and physical examination along with an updated medication list. In addition, it is also important to obtain a reliable set of baseline laboratory studies that will allow the clinician to detect and be aware of any underlying conditions or risk factors. This is particularly important because after patients have been initiated on a biologic treatment, they are likely to be treated with other biologics or systemic therapies and it may be useful to have reliable baseline laboratory studies. A recent

consensus statement from the Medical Board of the National Psoriasis Foundation addresses the appropriate monitoring of patients with psoriasis who are being treated with biologics.⁷⁷ This consensus statement points out that although there is no specific guideline or single way of taking care of any patient, there are some tests that many dermatologists obtain in patients with psoriasis before commencing systemic therapies including biologics. These include a chemistry screen with liver function tests, complete blood cell count including platelet count, a hepatitis panel, and tuberculosis (TB) testing all obtained at baseline and with variable frequencies thereafter. Although there are relatively minimal data on the use of the biologics during pregnancy, 4 of the 5 agents are pregnancy category B, whereas efalizumab is pregnancy category C. All of the data for the biologics are based on studies in adults aged 18 years and older, with little data on the use of biologics for psoriasis in children younger than 18 years, with the exception of one study evaluating the safety and efficacy of etanercept in this age group (see below subsection on pediatric psoriasis within section on etanercept). While being treated with biologics, patients need to be periodically re-evaluated for the development of new symptoms including infection and malignancy. Treatment with biologics is contraindicated in patients with active, serious infections. If patients develop serious infections (usually defined as an infection that requires antibiotic therapy) while being treated with a biologic agent, it is prudent to hold the biologic until the infection has resolved.

Because biologic therapies target the immune system, it is important to use all approaches to prevent infection, including vaccinations. However, it is also possible that biologic therapies may impair the immunologic response to vaccinations. In one small study, efalizumab given before primary immunization reduced the secondary immune response to the immunizing agent.⁷⁸ In contrast, patients treated with alefacept had normal immune responses to tetanus toxoid and to primary vaccination with a neo-antigen.⁷⁹ Most studies evaluating the immune response to vaccinations in patients treated with TNF blockers show adequate but attenuated immune responses to pneumococcal or influenza vaccination.⁸⁰⁻⁸⁵

When developing recommendations for the use of vaccinations in patients with psoriasis being treated with biologics, it is reasonable to evaluate the standard of care in organ transplantation where standard vaccinations, including pneumococcal, hepatitis A and B, influenza, and tetanus-diphtheria are recommended before initiation of immunosuppressive

therapy and transplantation.⁸⁶ Once immunosuppressive therapy has begun, patients are advised to avoid vaccination with live vaccines (including varicella; mumps, measles, and rubella; oral typhoid; yellow fever) and live-attenuated vaccines (including intranasal influenza and the herpes zoster vaccine).^{87,88} Package inserts for several of the biologics carry similar information. In patients with juvenile rheumatoid arthritis and Crohn's disease, vaccinations are recommended before starting etanercept⁸⁹ and infliximab,⁹⁰ respectively. In patients with psoriasis who need vaccination, it is preferable to perform these before initiating biologic therapy. Once patients have begun biologic therapies, physicians should consider the advantages and disadvantages of administering killed virus vaccines such as influenza. Administration of live vaccines must be avoided in patients being treated with biologics under all circumstances.

BIOLOGICS THAT TARGET PATHOGENIC T CELLS

Strength of recommendations for treatment of psoriasis using biologics that target pathogenic T cells are shown in Table II.

Alefacept: efficacy

Alefacept is a recombinant dimeric fusion protein that consists of the extracellular CD2-binding portion of lymphocyte function-associated antigen (LFA)-3 linked to the Fc portion of human IgG1.⁹¹⁻⁹³ Alefacept binds to CD2 on memory-effector T lymphocytes, thereby inhibiting the activation and reducing the number of these cells. The effects of alefacept in inducing in vitro apoptosis and selectively decreasing circulating CD45RO cells suggest disease-remitting properties of this agent.^{91,94} Alefacept is approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic agents or phototherapy. Alefacept does not interfere with the primary and secondary responses to a newly encountered antigen and acquired immune response to recall antigen.⁷⁹ In the pivotal phase III trials of alefacept given intramuscularly and dosed at 15 mg/wk, 21% of patients achieved at least PASI-75 at week 14, 2 weeks after cessation of the 12-week alefacept dosing period. Patients treated with alefacept who achieve at least a 50% improvement in their PASI score also demonstrate a statistically significant improvement in their Dermatology Life Quality Index compared with placebo.^{61,91,92,95-100} Although the primary end point for the alefacept studies was specified as 14 weeks, 2 weeks after the 12-week course of therapy, the maximum response to alefacept generally occurred

6 to 8 weeks after the last intramuscular shot of the 12-week course.^{97,98,100} Although some patients do not respond to this medication, patients who do respond to alefacept can achieve additional benefit from successive 12-week treatment courses. A proportion of patients who respond to alefacept by achieving PASI-75 or greater from baseline maintained a 50% or greater reduction in PASI for a median duration of 10 months.⁹¹

Currently, there is no way to predict which patients will improve significantly with alefacept although investigation looking for predictive markers is ongoing.¹⁰¹ A baseline CD4 lymphocyte count should be performed before treatment and according to label repeated every other week.¹⁰² Dosing of alefacept should be withheld whenever the CD4 count decreases below 250 cells/mL and dosing should be discontinued if the CD4 count remains below 250 cells/mL for 4 consecutive weeks.¹⁰²

Precautions

Alefacept therapy is not indicated for patients with a CD4 T-lymphocyte count below normal or in those who are infected with HIV because of the potential for acceleration of disease progression as a result of CD4 T-lymphocyte count reduction induced by alefacept. Caution should be exercised in patients who are at risk for or have a history of malignancy or infection, especially clinically significant infections. Alefacept is pregnancy category B.¹⁰² Recommendations for alefacept are listed in Table III.

Efalizumab: efficacy

Efalizumab is a recombinant humanized monoclonal IgG₁ antibody directed against the CD11a subunit of LFA-1 that blocks LFA-1-mediated T-cell adhesion. Blockade of LFA-1 interferes with T-lymphocyte activation, trafficking through blood vessels into inflamed skin and T-lymphocyte reactivation.¹⁰³⁻¹⁰⁶ Efalizumab is approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic agents or phototherapy. Efalizumab is administered subcutaneously by the patient. The recommended dose is 0.7 mg/kg for the initiation dose followed by weekly 1-mg/kg doses thereafter.⁷⁸ The results of several phase III trials demonstrate that after 12 weeks of treatment with efalizumab, between 27% and 39% of patients will have PASI-75.^{64,103-105,107-115} After 24 weeks of continuous efalizumab therapy, 44% of patients achieved PASI-75. Efalizumab maintains, and in some patients continues to improve, efficacy during long-term therapy.^{104,110} In a 3-year, open-label, nonrandomized trial of efalizumab

Table II. The strength of recommendations for the treatment of psoriasis using biologics that target pathogenic T cells

Recommendation	Strength of recommendation	Level of evidence	References
Alefacept	A	I	91-93, 95-100
Efalizumab	A	I	64, 103-105, 107-116

responder patients eligible for maintenance therapy, which allowed for the concomitant use of UV phototherapy and topical corticosteroids, intent-to-treat analysis revealed that 44% to 50% of patients achieved and maintained at least PASI-75 from 6 months up to 36 months of ongoing efalizumab therapy.^{108,109} Efalizumab has also been shown to be effective for hand and foot psoriasis in a phase IV, randomized placebo-controlled trial.¹¹⁶

Precautions

Dose-related headache, fever, nausea, and vomiting have been reported after initial dosing of efalizumab.^{103,107,115} This may be minimized by the use of a lower, conditioning dose of 0.7 mg/kg of efalizumab for the first weekly injection of efalizumab. Some clinicians will premedicate patients with acetaminophen before the first few doses of efalizumab but these symptoms typically resolve spontaneously after 3 weeks of treatment.

Efalizumab is not effective in treating psoriatic arthritis¹¹⁷ and psoriatic arthritis may develop or recur in a small percentage of patients during efalizumab treatment of psoriasis. An advisory group report concludes that rebound on discontinuation of efalizumab occurs in 14% of patients and particularly in patients unresponsive to efalizumab treatment.^{111,112,118} Flares during therapy with efalizumab, which may result in skin disease that is worse than at baseline, may occur in both responder and nonresponder patients. Treatment of these patients is controversial; some physicians will add methotrexate or CyA and continue with efalizumab, whereas others will immediately transition patients to another systemic drug. Because of this risk, physicians should strongly consider transitioning to another systemic agent when discontinuing efalizumab. Although the lymphocyte count increases in the blood and decreases in the skin in patients treated with efalizumab as a result of the drug decreasing migration of T cells out of the blood into the skin, this effect wears off rapidly. Because patients may rarely develop thrombocytopenia or hemolytic anemia during treatment with efalizumab and pancytopenia

Table III. Recommendations for alefacept

-
- Indication: moderate to severe psoriasis
 - Dosing: 15 mg every wk given as an intramuscular injection for 12 wk, with a 12-wk follow-up nontreatment period
 - Short-term results:
21% of patients achieved a PASI-75 at wk 14
 - Long-term results:
Associated with long remissions in a subset of responders
Prior response to alefacept is a likely marker of future treatment response; thus, patients responding to the first course of therapy may be treated long-term with repeated 12-wk courses of alefacept—at a minimum of 24-wk intervals
 - Toxicity: excellent safety profile in clinical trials
 - Baseline monitoring: CD4 count
 - Ongoing monitoring: biweekly CD4 count required; hold dose for counts <250
 - Pregnancy category: B
 - Contraindications: HIV infection
-

PASI-75, 75% Improvement in the Psoriasis Area and Severity Index score.

Table IV. Recommendations for efalizumab

-
- Indication: moderate to severe psoriasis
 - Dosing: 0.7 mg/kg first dose followed by 1.0 mg/kg/wk subcutaneously
 - Short-term response: 27% of patients achieve a PASI-75 at 3 mo
 - Long-term response: 44%-50% of patients achieved and maintained a PASI-75 response in a 3-y open-label study that only enrolled responders
 - Toxicities:
Flu-like symptoms frequently occur initially and generally disappear after the third wk of treatment
Thrombocytopenia, hemolytic anemia, pancytopenia, and peripheral demyelination have all been reported
 - Other issues:
Small percentage of patients may develop rebound or flare
Do not discontinue treatment abruptly unless essential
Not effective in psoriatic arthritis; flares and new-onset psoriatic arthritis have been reported in a subset of patients
 - Baseline monitoring: CBC
 - Ongoing monitoring:
CBCs monthly for the first 3 mo and at periodic intervals thereafter
LFT and a periodic history and physical examination are recommended while on treatment
 - Pregnancy category: C
-

CBC, Complete blood cell count; *LFT*, liver function test; *PASI-75*, 75% improvement in the Psoriasis Area and Severity Index score.

Table V. The strength of recommendations for the treatment of psoriasis using tumor necrosis factor inhibitors

Recommendation	Strength of recommendation	Level of evidence	References
Adalimumab	A	I	46, 47, 121, 122
Etanercept	A	I	32, 44, 123-129
Infliximab	A	I	45, 130-136

has also been reported,¹¹⁹ it is recommended that all patients treated with efalizumab have a complete blood cell count including a platelet count every month for the first 3 months and every 3 months afterward. Rare cases of peripheral demyelination

have also been reported.¹²⁰ Caution should be exercised in patients who are at risk for or have a history of malignancy or infection, especially clinically significant infections. Efalizumab may decrease the immune response to other biologically inactive vaccines. Efalizumab is pregnancy category C.⁷⁸ Recommendations for efalizumab are listed in Table IV.

TNF INHIBITORS FOR THE TREATMENT OF PSORIASIS

The potential importance of TNF- α in the pathophysiology of psoriasis is underscored by the observation that there are elevated levels of TNF- α in both the affected skin and serum of patients with psoriasis. These elevated levels have a significant correlation with psoriasis severity as measured by the PASI score. Furthermore, after successful treatment of psoriasis, TNF- α levels are reduced to normal levels.

Table VI. General recommendations for TNF inhibitors

- Anti-TNF agents are contraindicated in patients with active, serious infections
- Tuberculosis testing (PPD) should be performed on all patients who will be treated with TNF inhibitors as there are reports of tuberculosis reactivation in patients treated with this class of drug¹⁷⁷
- Do not use with live vaccines; biologically inactive or recombinant vaccines may be considered, although the immune response of these vaccines could be compromised
- Because there is an association between anti-TNF therapy and demyelinating diseases (ie, MS), TNF inhibitors should not be used in patients with MS or other demyelinating diseases; first-degree relatives of patients with MS have an increased risk of developing MS, with a sibling relative risk of between 18 and 36, evidence strongly suggesting that TNF inhibitors should not be used in first-degree relatives of patients with MS
- Because there have been reports of new onset and worsening of CHF in patients treated with TNF inhibitors, caution should be used when considering TNF inhibitor use in patients with CHF; it is recommended that patients with New York Heart Association class III or IV CHF avoid all use of TNF inhibitors and patients with class I or II CHF undergo echocardiogram testing; if the ejection fraction of these patients is <50%, then TNF inhibitor treatment should potentially be avoided¹⁷⁷
- Hepatitis B reactivation after treatment with TNF inhibitors has been reported; in the appropriate clinical setting, patients should be screened for hepatitis B infection

CHF, Congestive heart failure; MS, multiple sclerosis; PPD, purified protein derivation; TNF, tumor necrosis factor.

EFFICACY OF THE TNF INHIBITORS IN PSORIASIS

The strength of recommendations for the treatment of psoriasis using TNF inhibitors are shown in Table V. The general recommendations for TNF inhibitors are listed in Table VI. The efficacy of the 3 TNF inhibitors in the treatment of psoriasis will be reviewed in alphabetic order.

Adalimumab: efficacy

Adalimumab is the first fully human anti-TNF- α monoclonal antibody. It binds specifically to soluble and membrane-bound TNF- α and blocks TNF- α interactions with the p55 and p75 cell surface TNF receptors.⁴⁶ Adalimumab is currently approved for psoriasis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult rheumatoid arthritis, and Crohn's disease. Adalimumab dosing for psoriasis is 80 mg given subcutaneously the first week, followed by 40 mg subcutaneously given the next week and then every 2 weeks thereafter.^{121,122}

In the phase III studies of adalimumab, 1212 patients were randomized to receive adalimumab (given as 80 mg at week 1, 40 mg at week 2, and then 40 mg every other week) or placebo for the first 15 weeks. At week 16, 71% of patients treated with adalimumab and 7% treated with placebo achieved at least PASI-75. During weeks 33 to 52, the percentage of patients rerandomized to placebo who lost adequate response (defined as 50% improvement in the PASI score and at least a 6-point increase in PASI score from week 33) was 28% compared with 5% of patients treated continuously with adalimumab.⁴⁷

Adalimumab is used continuously, at a dosage of 40 mg every other week. Rebound does not typically

occur when adalimumab is discontinued, however, clearance is better maintained with continuous use and there is loss of efficacy after restart of adalimumab.⁴⁷ Recommendations for adalimumab are listed in Table VII.

Etanercept: efficacy

Etanercept is a recombinant human TNF- α receptor (p75) protein fused with the Fc portion of IgG1 that binds to soluble and membrane-bound TNF- α .^{44,123} Etanercept has demonstrated efficacy in the treatment of several inflammatory diseases and is currently approved for treatment of moderate to severe plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. The dosing of etanercept differs in psoriasis than for its other indications. The approved regimen is 50 mg given subcutaneously twice weekly for the first 12 weeks followed by 50 mg weekly thereafter. Dosing is continuous.⁸⁹ The efficacy of etanercept has been demonstrated in many clinical trials.^{32,44,124-126} At week 12 there was an improvement from baseline of PASI-75 or more in 34% of the etanercept group receiving 25 mg twice weekly and 49% of the etanercept group receiving 50 mg twice weekly, as compared with 4% of the patients in the placebo group ($P < .001$ for both comparisons with the placebo group).^{60,123,127,128} The clinical responses continued to improve with longer treatment. At week 24, there was at least PASI-75 in 44% of those in the 25 mg twice weekly group, and 59% in the 50 mg twice weekly group.¹²⁷ Some patients will show a loss of clinical response after 12 weeks when the weekly dose is reduced from 50 mg twice weekly to 50 mg once weekly.

Table VII. Recommendations for adalimumab

-
- Indications: moderate to severe psoriatic arthritis, moderate to severe psoriasis, adult and juvenile rheumatoid arthritis (as young as age 4 y), ankylosing spondylitis, and Crohn's disease
 - Dosing for psoriasis: 80 mg the first wk, 40 mg the second wk, followed by 40 mg every other wk given subcutaneously
 - Short-term results: 80% of patients achieve PASI-75 at 12 wk
 - Long-term results: 68% of patients achieve PASI-75 at 60 wk
 - Small percentage of patients lose efficacy with continued use
 - Toxicities:
 - Moderately painful injection site reactions are noted
 - Rare reports of serious infections (ie, tuberculosis and opportunistic infections) and malignancies
 - There are rare reports of drug-induced, reversible side effects including lupus without renal or CNS complications, cytopenia, MS, and exacerbation of and new onset of CHF
 - Baseline monitoring:
 - PPD is required
 - LFT, CBC, and hepatitis profile
 - Ongoing monitoring:
 - Periodic history and physical examination are recommended while on treatment
 - Consider a yearly PPD, and periodic CBC and LFT
 - Pregnancy category B
-

CBC, Complete blood cell count; *CHF*, congestive heart failure; *CNS*, central nervous system; *LFT*, liver function test; *MS*, multiple sclerosis; *PASI-75*, 75% improvement in the Psoriasis Area and Severity Index score; *PPD*, purified protein derivation.

Table VIII. Recommendations for etanercept

-
- Indications: moderate to severe psoriasis, moderate to severe psoriatic arthritis, adult and juvenile rheumatoid arthritis (as young as 4 y), and ankylosing spondylitis
 - Dosing: 50 mg twice/wk given subcutaneously for 3 mo followed by 50 mg once/wk
 - Short-term results: 49% of patients given 50 mg twice/wk achieved a PASI-75 at 12 wk; 34% of patients given 25 mg twice/wk achieved a PASI-75 at 12 wk
 - Step-down results: 54% of patients whose dose was decreased from 50 mg twice/wk to 25 mg twice/wk achieved a PASI-75 at 24 wk; 45% of patients whose dose remained at 25 mg twice/wk achieved a PASI-75 at 24 wk
 - Toxicities:
 - Mildly pruritic injection site reactions may occur
 - Rare cases of serious infections (ie, tuberculosis) and malignancies
 - There are also rare cases of drug-induced, reversible side effects including lupus without renal or CNS complications, cytopenia, MS, and exacerbation and new onset of CHF
 - Baseline monitoring:
 - PPD is required
 - LFT and CBC
 - Ongoing monitoring:
 - Periodic history and physical examination are recommended while on treatment
 - Consider yearly PPD, and periodic CBC and LFT
 - Pregnancy category B
 - Contraindications: sepsis
-

CBC, Complete blood cell count; *CHF*, congestive heart failure; *CNS*, central nervous system; *LFT*, liver function test; *MS*, multiple sclerosis; *PASI-75*, 75% improvement in the Psoriasis Area and Severity Index score; *PPD*, purified protein derivation.

In rheumatoid and psoriatic arthritis, TNF inhibitors including etanercept are often used in combination with methotrexate. In psoriasis, all clinical studies have been performed with etanercept as monotherapy. Rebound does not typically occur when etanercept is discontinued.^{123,126,128} An important issue to consider with etanercept, as with other TNF inhibitors, is the potential loss of efficacy over time, possibly related to the development of

antibodies. Recommendations for etanercept are listed in [Table VIII](#).

Pediatric psoriasis

In a study of etanercept treatment for children and adolescents (ages 4-17 years) with plaque psoriasis who were dosed once weekly with 0.8 mg/kg of etanercept (up to a maximum of 50 mg), 57% of patients receiving etanercept achieved PASI-75 as

Table IX. Recommendations for infliximab

-
- Indications: severe psoriasis, moderate to severe psoriatic arthritis, adult rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and Crohn's disease
 - Dosing: 5 mg/kg dose infusion schedule at wk 0, 2, and 6 and then every 6-8 wk; dose and interval of infusions may be adjusted as needed
 - Short-term response: 80% of patients achieved a PASI-75 at wk 10, 50% PASI improvement noted by wk 2
 - Long-term response: 61% of patients achieved a PASI-75 at wk 50
 - Toxicities:
 - Infusion reactions and serum sickness can occur—more commonly in patients who have developed antibodies
 - The incidence of infusion reactions may be reduced by concurrent administration of methotrexate
 - Rare cases of serious infections (ie, tuberculosis) and malignancies including hepatosplenic T-cell lymphoma (in children); there are rare reports of drug-induced, reversible side effects including lupus without renal or CNS complications, cytopenia, MS, and exacerbation of and new onset of CHF
 - Baseline monitoring:
 - PPD is required
 - LFT, CBC, and hepatitis profile
 - Ongoing monitoring:
 - Periodic history and physical examination are recommended while on treatment
 - Consider a yearly PPD, and periodic CBC and LFT
 - Pregnancy category B:
 - Contraindications: infliximab at doses > 5 mg/kg should not be given to patients with New York Heart Association functional class III or IV CHF
-

CBC, Complete blood cell count; CHF, congestive heart failure; CNS, central nervous system; LFT, liver function test; MS, multiple sclerosis; PASI-75, 75% improvement in the Psoriasis Area and Severity Index score; PPD, purified protein derivation.

compared with 11% of those receiving placebo ($P < .001$).¹²⁹

Infliximab: efficacy

Infliximab is a chimeric antibody constructed from murine and human DNA sequences comprising a mouse variable region and human IgG1- α constant region. Infliximab binds to both the soluble and the transmembrane TNF- α molecules, thereby neutralizing the effects of TNF- α .¹³⁰

Infliximab is approved for the treatment of psoriasis and psoriatic arthritis, adult rheumatoid arthritis, ankylosing spondylitis, Crohn's disease in adults and children, and ulcerative colitis. Infliximab is administered intravenously at a dose of 5 mg/kg over 2 to 3 hours at weeks 0, 2, and 6 and then every 8 weeks for psoriasis and psoriatic arthritis.⁹⁰ Patients are less likely to develop antibodies against infliximab (or human antichimeric antibodies) if they are continuously treated with infliximab rather than on an as-needed basis and clinical responses are better maintained with continuous compared with intermittent therapy.^{45,131-135} Approximately 80% of patients achieve PASI-75 at week 10 (after 3 doses of infliximab). Infliximab is remarkable for the rapidity of clinical response. Loss of efficacy over time may also occur with infliximab therapy. Some dermatologists prescribe low-dose methotrexate concurrently with the goal of decreasing the formation of antibodies against infliximab and, hence,

maintaining clinical efficacy over time.⁴⁵ In the pivotal phase III trial of infliximab, although 80% of patients achieved PASI-75 at week 10, by week 50, 61% of patients treated with infliximab (5 mg/kg at 8-week intervals) maintained PASI-75.^{45,136} A 91% improvement in the Dermatology Life Quality Index occurred after 10 weeks of therapy with infliximab.¹³² Recommendations for infliximab are listed in Table IX.

GENERAL SAFETY ISSUES OF THE TNF INHIBITORS

The TNF inhibitors have been available for more than 10 years, predominantly for inflammatory bowel disease and rheumatoid arthritis with more than 1.5 million patients being dosed with the 3 agents. In recent years, the indications for use of TNF inhibitors have expanded to their use in psoriasis and psoriatic arthritis among other diseases. The following discussion about the safety of the TNF inhibitors is derived in large part from observations made from their use in rheumatoid arthritis and inflammatory bowel disease (Table VI). Patients with both rheumatoid arthritis and inflammatory bowel disease are often treated with the combination of TNF inhibitors and an immunosuppressive agent (methotrexate or azathioprine), whereas patients with psoriasis are most often treated with the TNF inhibitors as monotherapy. It, therefore, seems possible that extrapolations regarding the safety of TNF inhibitors derived

from this combination therapy data may overestimate the potential risk of these agents when used as monotherapy in psoriasis. In addition, as discussed, patients with psoriasis may have distinctive comorbidities that distinguish them from patients with either rheumatoid arthritis or Crohn's disease.

Infections: bacterial, viral, and mycobacterial

All of the TNF inhibitors carry the potential for an increased risk of infection with upper respiratory tract infections being the most common. Serious infections are uncommon, with patients with underlying predisposing medical conditions being more at risk. Rare opportunistic infections, including histoplasmosis, listeriosis, coccidioidomycosis, cryptococcosis, aspergillosis, candidiasis, and pneumocystis,¹³⁷⁻¹³⁹ have been reported more often in patients treated with anti-TNF antibodies such as infliximab or adalimumab than in those treated with fusion protein receptor drugs such as etanercept. However, many of these patients were also treated with other immunosuppressive agents, such as methotrexate, systemic corticosteroids, or both. Despite the rarity and sometime subtlety of clinical presentation of these types of potentially serious infections, careful monitoring and early evaluation is critical. In the event of an infection requiring antibiotic therapy, the TNF inhibitor should be withheld and in the event of more serious infections or opportunistic infections, the TNF inhibitor should be discontinued. Treatment with TNF inhibitors should be avoided if possible in patients with chronic, serious, or recurring infections.¹⁴⁰

There are elevated levels of TNF- α in patients with hepatitis C compared with control subjects suggesting that TNF- α may be involved in the pathogenesis of hepatocyte destruction in chronic hepatitis C infection.¹⁴¹ There is one prospective study and one small randomized, double-blind, placebo-controlled study suggesting that anti-TNF therapy may be safe to use in chronic hepatitis C infection.^{142,143} However, these data are preliminary, and one must exercise great caution when considering anti-TNF therapy in patients with concomitant chronic hepatitis C infection. Consultation with liver specialists as indicated may be appropriate when considering the use of anti-TNF therapy in this setting. Interval monitoring of serum aminotransferases and hepatitis C viral load are also recommended in this setting.

TNF- α promotes viral clearance in hepatitis B infection in animals; this is different from its role in hepatitis C where it is thought to promote chronic liver injury. Treatment with infliximab \pm methotrexate can reactivate chronic hepatitis B viral infection, yet concurrent treatment with infliximab \pm

methotrexate with lamivudine can stabilize hepatitis B viral disease activity.¹⁴⁴ Given the lack of prospective randomized controlled trials using TNF- α antagonists in patients with hepatitis B infection, screening patients for hepatitis B before treatment with anti-TNF therapy should be considered in the appropriate clinical setting. There is an FDA warning suggesting that patients who have concurrent hepatitis B infection should not be treated with any of the TNF inhibitors.⁹⁰

TNF- α plays an important role in the host response against TB.^{145,146} Reactivation of TB has been associated with TNF inhibitors and patients undergoing anti-TNF therapy are at higher risk for developing TB. In addition to several case reports of TB reactivation in patients on anti-TNF therapy, registry data from patients with rheumatoid arthritis and postmarketing reports to the FDA have identified numerous cases of TB reactivation associated with all 3 TNF inhibitors. Importantly, there is an increased incidence of extrapulmonary or disseminated cases of TB occurring in patients on anti-TNF therapy. Although there is an increased risk of reactivation of TB with etanercept treatment compared to the general population, it is likely to be less frequent than with infliximab or adalimumab treatment.¹⁴⁷ The FDA recommends TB screening with a purified protein derivation for adalimumab, etanercept, and infliximab. Furthermore, the Centers for Disease Control and Prevention also recommends TB screening with a purified protein derivation for all patients being treated with TNF inhibitors.¹⁴⁸ Patients at increased risk for TB, eg, institutional workers and frequent travelers abroad, must be carefully screened at appropriate intervals.

Neurologic disease

Both peripheral and central demyelinating disorders, including MS, have been reported to not only to develop but also to worsen in patients taking TNF- α antagonists.^{89,149-152} These medications should be avoided in the setting of a personal history of demyelinating conditions. First-degree relatives of patients with MS have an increased risk of MS, with a sibling relative risk of between 18 and 36, evidence strongly suggesting that TNF inhibitors should not be used in first-degree relatives of patients with MS.^{153,154} Although some patients' symptoms of demyelinating disease have abated despite continued TNF inhibition, other reports demonstrate that patients who develop neurologic symptoms suggestive of MS after treatment with a TNF inhibitor resolve after the TNF inhibitor is stopped.¹⁵⁰ Onset of new neurologic symptoms in a patient on TNF- α inhibitors that suggest the development of a demyelinating

disorder should be promptly evaluated by a neurologist while the TNF inhibitor is withheld.

Heart disease

The issue of prescribing TNF- α blockers in patients with congestive heart failure (CHF) is somewhat controversial. Several studies have evaluated the use of etanercept and infliximab in CHF. The etanercept studies were either terminated early as a result of lack of efficacy¹⁵⁵ or showed no benefit on CHF morbidity or mortality¹⁵⁶ whereas one infliximab study revealed an increased mortality caused by CHF in the highest dose group (10 mg/kg). There is, however, preliminary evidence that TNF- α blockade could be of benefit to the failing heart as one report found the incidence of CHF in patients with rheumatoid arthritis on either infliximab or etanercept to be significantly lower than in those not on TNF inhibitors.¹⁵⁷

Moreover, another study demonstrated a dose-dependent improvement in both left ventricular function and CHF in patients being treated with etanercept.¹⁵⁸ We recommend that TNF inhibitors be avoided in patients with severe CHF (New York Heart Association class III or IV) and those with milder CHF should have their TNF inhibitors withdrawn at the onset of new symptoms or worsening of pre-existing CHF.

Drug-induced lupus-like syndromes

The development of or an increase in the levels of circulating antinuclear antibodies may occur in patients taking any of the 3 anti-TNF agents. Although there have been several reported cases of patients who developed signs and symptoms of systemic lupus erythematosus while receiving anti-TNF therapy,¹⁵⁹ this condition may be reversible on cessation of the drug. To date, there have been only anecdotal reports of full-blown systemic lupus erythematosus including renal or central nervous system involvement induced by anti-TNF therapy. There are, likewise, case reports in which treatment with etanercept was associated with disappearance of subacute cutaneous lupus erythematosus.^{160,161} Although clinicians treating patients with anti-TNF agents need to be aware of this entity, it is not necessary to evaluate patients for antinuclear antibodies or to conduct other serologic tests before or during anti-TNF therapy unless clinical symptoms warrant.

Hepatic disease

In the phase III trial of infliximab, patients treated with monotherapy infliximab had elevated levels of aspartate aminotransferase and alanine

aminotransferase.¹³⁶ After 24 weeks of treatment with infliximab, 6% and 2% of patients in the infliximab group had markedly abnormal increases in alanine aminotransferase and aspartate aminotransferase, respectively (defined as >150 U/L and 100% increase from baseline), compared with none in the placebo group.¹³⁶ In 2004, the FDA issued a warning that hepatic disease, including severe hepatic failure, might complicate infliximab therapy.¹⁶² These cases included patients who were also taking multiple concomitant drugs some of which were known to be hepatotoxic. No similar reports of hepatotoxicity caused by etanercept or adalimumab have been published. Risks associated with viral hepatitis are discussed above.

Lymphoma

The potential risk of lymphoma induction by the TNF inhibitors is a much-debated issue. As discussed previously, patients with psoriasis may have an increased risk of lymphoma (particularly Hodgkin's lymphoma and cutaneous T-cell lymphoma).^{21,22} While a consensus panel of experts reviewing the clinical trial evidence concluded that the overall risk of malignancies including lymphoma was not increased over baseline levels in patients with rheumatoid arthritis being treated with TNF inhibitors,¹⁴⁹ clinical trials are underpowered to evaluate the risk of rare events such as cancer.¹⁶³ However, there have been numerous anecdotal cases of lymphomas reported in patients being treated with TNF inhibitors, and many of these have resolved after discontinuation of the drug.¹⁶⁴ Therefore, one should carefully consider the decision to use TNF antagonist in patients with a history of malignancy, particularly lymphoma.

Melanoma and nonmelanoma skin cancer

The potential risk of melanoma, cutaneous T-cell lymphoma, and nonmelanoma skin cancer in patients treated with the TNF inhibitors has been raised by several case reports.¹⁶⁵⁻¹⁶⁹

A large observational study of patients with rheumatoid arthritis demonstrated an increased risk for the development of nonmelanoma skin cancer (odds ratio 1.5, 95% confidence interval 1.2-1.8) and a trend toward increased risk of melanoma (odds ratio 2.3, 95% confidence interval 0.9-5.4) in patients treated with biologic agents (largely the 3 TNF inhibitors). Importantly, this large study also demonstrated no increased risk of any other types of solid cancers.¹⁷⁰ These findings contrast with the results of a meta-analysis of rheumatoid arthritis studies examining patients treated with adalimumab and infliximab, which revealed an increased risk of solid cancers.¹⁷¹

Hematologic disease

Aplastic anemia, isolated leukopenia, and thrombocytopenia have been reported in individual patients treated with TNF antagonists.^{172,173} These appear to be isolated cases but it is prudent to consider this possibility in patients developing pallor, easy bruising, bleeding, or fever.

Other cutaneous reactions

Leukocytoclastic vasculitis has been reported to occur in patients treated with anti-TNF agents,¹⁷⁴ but most of these reports have been in patients with rheumatoid arthritis, which is itself known to be associated with vasculitis.

Pregnancy

All of the TNF inhibitors are pregnancy category B.

SAFETY ISSUES SPECIFIC FOR INDIVIDUAL TNF AGENTS

Adalimumab

Adalimumab is the newest of the TNF inhibitors, and available safety data are more limited than for etanercept or infliximab. Adalimumab injections can lead to painful injection site reactions in up to 15% of patients. These reactions usually resolve spontaneously within the first 2 months of therapy.

Etanercept

Injection site skin reactions occur in up to 37% of patients treated with etanercept and are mild to moderate, generally not requiring drug discontinuation. Mean duration of reactions is 3 to 5 days; these reactions generally occur in the first month of drug administration and subsequently decrease. The needle cover of the prefilled etanercept syringe contains latex so this formulation should not be used in latex-sensitive patients.

Infliximab

Infusion-related reactions occur in 16% of patients treated with infliximab compared with 6% of patients treated with placebo. Although the majority of the infusion reactions are mild consisting of pruritus or urticaria, some patients will have moderate reactions consisting of chest pain, hypertension, and shortness of breath and only rarely will severe reactions with hypotension and anaphylaxis occur. Infusion reaction risk tends to correlate with the development of human antichimeric antibodies and can usually be managed by slowing the rate of infusion or stopping treatment entirely. Patients who are concurrently treated with an immunosuppressive agent such as methotrexate or azathioprine or at regularly dosed

intervals are likely to have a lowered incidence of infusion reactions.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with infliximab.¹⁷⁵ This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of the patients who have developed hepatosplenic T-cell lymphomas during treatment with infliximab have occurred in adolescent and young adult patients who were also receiving concomitant treatment with azathioprine or 6-mercaptopurine.

IL-12/23 BLOCKADE IN PSORIASIS

The p40 subunit of IL-12 is overexpressed in psoriatic plaques, and preclinical studies implicate IL-12 in the pathogenesis of psoriasis. In a double-blind, placebo-controlled trial, 320 patients with moderate to severe plaque psoriasis were randomized to treatment with IL-12/23 monoclonal antibody (one 45-mg dose, one 90-mg dose, 4 weekly 45-mg doses, or 4 weekly 90-mg doses) or placebo. There was at least PASI-75 at week 12 in 52% of patients who received 45 mg of the IL-12/23 monoclonal antibody, in 59% of those who received 90 mg, in 67% of those who received 4 weekly 45-mg doses, and in 81% of those who received 4 weekly 90-mg doses, as compared with 2% of those who received placebo ($P < .001$ for each comparison).¹⁷⁶ Serious adverse events occurred in 4% of patients who received the monoclonal antibody and in 1% of those who received placebo. This study demonstrates the therapeutic efficacy of an IL-12/23 monoclonal antibody in psoriasis and provides evidence for a role of IL-12/23 in the pathophysiology of psoriasis.

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Conflicts of interest: Alan Menter: MD, Chair Psoriasis Work Group. Dr Menter served on the Advisory Board and was a consultant, investigator and speaker for Abbott Labs, Amgen, and Centocor, receiving grants and honoraria; served on the Advisory Board and was an investigator and consultant for Cephalon and UCB, receiving grants and honoraria; was a consultant, investigator, and speaker for Warner Chilcott and Wyeth, receiving honoraria; served on the Advisory Board and was an investigator for Galderma and Genentech, receiving grants and honoraria; was a

consultant and investigator for Allergan and Astellas, receiving grants and honoraria; as an investigator for Collagenex, CombinatoRx, Dow, Ferndale, Leo, Medicis, Photocure, Pierre Fabre, 3M Pharmaceuticals and XOMA, receiving grants; and was an investigator for Connetics, receiving grants and honorarium.

Alice Gottlieb, MD, PhD: Dr Gottlieb served as a speaker for Amgen Inc and Wyeth Pharmaceuticals; has current consulting/advisory board agreements with Amgen Inc, Centocor, Inc, Wyeth Pharmaceuticals, Celgene Corp, Bristol Myers Squibb Co, Beiersdorf, Inc, Warner Chilcott, Abbott Labs, Roche, Sankyo, Medarex, Kemia, Celera, TEVA, Actelion, UCB, Novo Nordisk, Almirall, Immune Control, RxClinical, Dermipor Ltd, Medacorp, DermiPsor, Can-Fite, Incyte; and has received research/educational grants from Centocor, Amgen, Wyeth, Immune Control, Celgene, Pharmicare, Incyte. All income has been paid to her employer directly.

Steven R. Feldman, MD, PhD: Dr Feldman served on the Advisory Board and was investigator and speaker for Galderma, Stiefel, Warner Chilcott, Abbott Labs and Astellas, receiving grants and honoraria; served on the Advisory Board for Photomedex, receiving stock options; served on the advisory board and was speaker for National Psoriasis Foundation, receiving honoraria; and was an investigator and speaker for Amgen, Centocor and Genentech, receiving grants and honoraria.

Abby S. Van Voorhees, MD: Dr Van Voorhees served on the Advisory Board, was an investigator and speaker for Amgen and Genentech, receiving grants and honoraria; investigator for Astellas, IDEC and Roche, receiving grants; Advisory Board and investigator for Bristol Myers Squibb and Warner Chilcott, receiving grants and honoraria; Advisory Board and was speaker for Abbott Labs and Centocor, receiving honoraria; served on the Advisory Board for Connetics, receiving honoraria; was consultant for Incyte and Xtrac and VGX and has received honoraria from Synta for another function. Dr. van Voorhees' spouse is an employee with Merck receiving a salary, stock and stock options.

Craig L. Leonardi, MD: Dr Leonardi served on the Advisory Board and was consultant, investigator, and speaker for Abbott Labs, Amgen, Centocor, Genentech, receiving honoraria, other financial benefit, and grants for Amgen and Genentech; was speaker for Warner Chilcott receiving honoraria; was on the Advisory Board and was investigator for Serano receiving honoraria and other financial benefit; was investigator for Astellas, Biogen, Bristol Myers, Allergun, Fujisawa, CombinatorRx, and Vitae receiving other financial benefit.

Kenneth B. Gordon, MD: Dr Gordon served on the Advisory Board and was consultant, investigator, and speaker for Abbott Labs, Amgen, and a consultant and investigator for Centocor, receiving grants and honoraria; and was investigator for Genentech, receiving grants.

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speaker for Stiefel, receiving honoraria; was consultant and investigator for Astellas, receiving grants and honoraria; was consultant for Biogen, UCB and Isotechnika, receiving honoraria; was on the Advisory Board and was consultant and investigator for Novartis, receiving grants and honoraria; and had an "other" relationship with PharmaDerm receiving grants and honoraria.

John Y. M. Koo, MD: Dr Koo served on the Advisory Board, was speaker, consultant, and investigator for Amgen, Abbott Labs, Astellas, Warner Chilcott, and Galderma, receiving grants and honoraria; was investigator for Genentech, receiving grants; and was an Advisory Board consultant and investigator for Teikokio, receiving compensation.

Craig A. Elmets, MD: Dr Elmets has served on the Advisory Board and was investigator for Amgen and Abbott Labs, receiving grants and honoraria; was consultant for Astellas, receiving honoraria; and was an investigator for Genentech and Connetics, receiving grants.

Neil J. Korman, MD, PhD: Dr Korman has served on the Advisory Board and was investigator and speaker for Abbott Labs, Genentech and Astellas, receiving grants and honoraria; served on the Advisory Board and was investigator for Centocor, receiving grants and residency/fellowship program funding; and was investigator and speaker for Amgen, receiving grants and honoraria.

Karl R. Beutner, MD, PhD: Chair Clinical Research Committee. Dr Beutner was an employee of Anacor, receiving salary, stock and stock options and had other relationships and received stock from Dow Pharmaceutical Sciences.

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