

Update on the Natural History and Systemic Treatment of Psoriasis

Stephen K. Richardson, MD^a, Joel M. Gelfand, MD, MSCE^{b,*}

^aFlorida State University College of Medicine/Dermatology Associates of Tallahassee, 1714 Mahan Center Boulevard, Tallahassee, FL 32308, USA

^bDepartment of Dermatology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 3600 Spruce Street, 2 Maloney Building, Philadelphia, PA 19104, USA

EDITORIAL COMMENTS

Dr. Richardson and Dr. Gelfand deliver a scientific overview of the fast-moving advances in our understanding and treatment of psoriasis. Scaling, red, itchy, burning, and fissured skin are all visually disturbing components of the “heartbreak of psoriasis.” In a series of studies, Dr. Gelfand and his collaborators have redefined psoriasis as a systemic disease with adverse impacts on the heart, brain, endocrine system, and, indeed, life itself. Recognition that it is an independent risk factor for myocardial infarction, stroke, diabetes, lymphoma, and mortality will assist physicians in educating and promoting preventative care for affected patients. At the same time, a revolution in our ability to treat severe disease with an ever-increasing array of innovative agents has occurred. Whether these targeted drugs modify the risks while providing relief of the skin signs is a story waiting to unfold. I think you will enjoy this outstanding article!

William D. James, MD

Pсориаз is a common inflammatory disease of the skin and joints. Its cause remains unknown; however, it has been linked to complex interactions between predisposing genes and the environment. The pathophysiology of psoriasis is characterized by epidermal hyperproliferation, enhanced antigen presentation, helper T-cell (Th)1 and Th17 cytokine production, T-cell expansion, and angiogenesis. Tremendous advances in our understanding of this disorder has led to the development of novel therapeutics and the Food and Drug Administration (FDA) approval of more systemic agents for its treatment in the last 5 years than in the previous 50 years combined. Our improved

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*Corresponding author. *E-mail address:* joel.gelfand@uphs.upenn.edu (J.M. Gelfand).

understanding of the pathogenesis of psoriasis has led to epidemiologic studies that have contributed to further characterization of its natural history. In this article, the authors focus on specific advances in our understanding of the pathogenesis, natural history, and systemic treatment of psoriasis, which are of major clinical relevance to the clinician.

KEY ADVANCES IN THE PATHOGENESIS OF PSORIASIS

The biologic basis of psoriasis informs its natural history and treatment options. Here, the authors briefly review key discoveries in the pathogenesis of psoriasis relevant to the clinician and refer the reader to several comprehensive reviews for a more detailed discussion [1–4]. Psoriasis was initially believed to be a primary disorder of keratinocytes; however, advances in molecular biology and immunology proved its cause to be much more complex. In 1995, Gottlieb and colleagues [5–7] demonstrated that psoriasis could be treated successfully with the lymphocyte-selective toxin DAB389-IL-2, a discovery that heralded a new era in our approach to treating psoriasis, one focused on developing therapeutics to inhibit immunologic targets. It is now believed that the clinical phenotype of psoriatic skin arises from the interplay between inflammatory cytokines and cells that make up the cutaneous microenvironment (ie, lymphocytes, antigen-presenting cells [APCs], endothelial cells, and keratinocytes).

Lymphocytes are believed to play a central role in the pathogenesis of psoriasis; recent work has demonstrated how various lymphocyte subsets contribute to this disorder. In particular, Th1 lymphocytes have been identified as a primary source of inflammatory cytokine production in psoriatic skin; regulatory T cells, which normally suppress effector T-cell activity, are dysfunctional in the blood and skin of patients who have psoriasis; and recently identified Th17 cells produce the cytokine interleukin (IL)-17, which is critical to the establishment and maintenance of autoimmunity, and IL-22, which is primarily involved in the process of epidermal differentiation and hyperproliferation. APCs (ie, plasmacytoid and myeloid dendritic cells) and endothelial cells lining the dermal microvasculature have also been shown to play a role in psoriatic disease. In particular, dermal dendritic cells have been shown to contribute to the production of Th1 cytokines and the recruitment of inflammatory cells into psoriatic plaques. The production of IL-20 and IL-23 by myeloid dendritic cells has been reported to promote keratinocyte proliferation, up-regulate inflammatory gene products, and stimulate T-cell activation, all of which contribute to psoriatic lesions [8,9]. Endothelial cells play a critical role in recruiting inflammatory cells through their expression of E-selectin, which enhances the homing of cutaneous lymphocyte-associated antigen-positive T cells into the skin. Angiogenesis is stimulated by the inflammatory process and studies demonstrate that circulating levels of vascular endothelial growth factor correlate with psoriasis activity [10].

Whether psoriasis reflects an abnormal response to an unidentified antigen or a reaction to the aberrant production of endogenous/exogenous immune cell activators remains uncertain. However, it is clear that the response of keratinocytes to locally produced cytokines underlies the formation of

cutaneous lesions. In addition, keratinocytes have been shown to produce their own cytokines, such as IL-6 and transforming growth factor-alpha, which may act in concert to promote their own proliferation in an autocrine fashion [11].

Underlying its immunopathogenesis is a complex role for genetics in promoting psoriasis disease susceptibility. More than 20 genetic loci containing varying numbers of genes, many of which have no known function, have been associated with psoriasis susceptibility. The strongest association was identified on a locus within the class I major histocompatibility complex on chromosome 6p21, known as PSORS1. This region is believed to account for 35% to 50% of psoriasis heritability. The PSORS1 locus contains fewer than 10 genes, 3 of which have been strongly implicated in psoriatic disease: human leukocyte antigen-C, CCHCR1, and CDSN. The HLA-Cw6 allele is present in up to 85% of individuals who develop psoriasis under the age of 40; these patients typically have more severe disease than individuals who develop psoriasis at a later time in life. Only 15% of individuals who develop psoriasis over the age of 40 express the HLA-Cw6 allele. Although much progress has been made toward dissecting the genetic components of this disease, few genes have been definitively implicated in its pathogenesis, and genetic testing is not clinically useful. For example, only 10% of individuals who express the HLA-Cw6 allele go on to develop psoriasis [12].

KEY ADVANCES IN THE NATURAL HISTORY OF PSORIASIS

Recent studies have broadened our knowledge of how genetics and environmental factors may lead to psoriasis and how the pathophysiology of psoriasis or its associated psychosocial behaviors and treatments may lead to adverse health outcomes (Fig. 1).

What are the risk factors for developing psoriasis?

Genetics are believed to play a key role in the development of psoriasis. It is estimated that approximately 40% of individuals suffering from psoriasis or psoriatic arthritis (PsA) have a first-degree relative who has the disease [13]. In addition, concordance rates as high as 70% have been reported among identical twins [14]. Given the strong genetic component of psoriasis, patients who have psoriasis are often concerned about the heritability of the disease. Family studies indicate that if both parents have psoriasis then the offspring have a 50% chance of developing the disease; if only one parent has psoriasis then the risk for a child to develop psoriasis is 16%. If neither parent is affected but a child develops psoriasis then his/her siblings have an 8% risk for developing the disease. Men have a higher risk for transmitting psoriasis to offspring than women, likely because of genomic imprinting, which is an epigenetic effect that causes differential expression of a gene depending on the gender of the transmitting parent [15].

Because genetics are immutable, modifiable environmental risk factors for psoriasis are of special interest. Data from analytic epidemiologic studies (eg, case-control and nested cohort studies) with appropriate control for

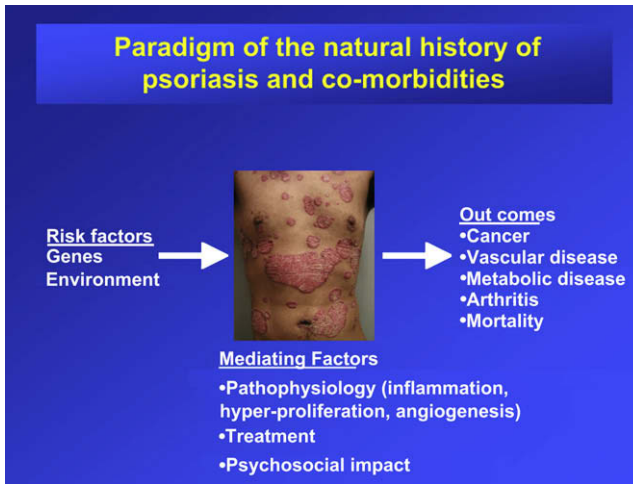


Fig. 1. The relationship among risk factors for developing psoriasis, mediating factors associated with the disease, and the risk for various health outcomes is complex. Obesity and smoking have recently been demonstrated to increase the risk for developing psoriasis. Increasingly, epidemiologic studies are controlling for these factors to determine which outcomes are directly related to having psoriasis, as opposed to being mediated by confounding factors such as smoking and obesity.

confounding variables have recently identified smoking and obesity as risk factors for the development of psoriasis. A large cohort study of more than 78,000 nurses from the United States demonstrated a “dose–response” relationship for obesity and smoking on the risk for developing incident psoriasis [16,17]. Similarly, a cohort study from the General Practice Research Database in the United Kingdom of almost 4000 incident cases of psoriasis confirmed that current smoking and obesity are independent risk factors for developing psoriasis. Finally, in a case-control study of 560 psoriasis patients seen by dermatologists, smoking and obesity were also found to be independent risk factors for the development of psoriasis [18]. The consistency of the findings across different study populations and study designs, and the dose–response relationships observed, strongly support the validity of these associations. Both smoking and obesity trigger Th1–mediated immunologic pathways, suggesting a plausible biologic explanation for these associations [19].

Clinical implications of risk factors for psoriasis

The importance of family history in the risk for developing psoriasis necessitates that clinicians be knowledgeable on counseling patients regarding the risk for their offspring to develop the disease. Furthermore, the identification of obesity and smoking as consistent and reproducible risk factors for the development of psoriasis may provide an opportunity for prevention of this chronic disease through behavior modification. For example, in the nurses’

cohort study, it was estimated that 30% of new psoriasis cases were due to being overweight (body mass index >25) [16]. Future studies are necessary to determine if maintenance of ideal body weight and avoidance of smoking will truly lower one's risk for developing psoriasis. Until such data are available, it is prudent to recommend weight management and smoking avoidance to individuals at greatest risk for developing the disease (eg, those who have a positive family history).

Which major comorbidities are patients who have psoriasis at increased risk for developing?

Patients who have psoriasis may be at increased risk for developing other diseases because of shared genetic pathways, common immune mechanisms, treatment-related toxicities, psoriasis-associated behaviors such as smoking and excess alcohol use, and the associated psychosocial burden of the disease (see Fig. 1). For example, psoriasis patients have an increased prevalence of Crohn's disease, which may be because of shared genetic loci; the psoriasis susceptibility loci, PSORS8, has been shown to overlap with a Crohn's disease locus on chromosome 16q [20,21]. Moreover, chronic Th1 inflammation, central to the pathophysiology of psoriasis, can also lead to seemingly diverse conditions such as insulin resistance, atherosclerosis, and thrombosis [22]. Therapies for psoriasis frequently are immunosuppressive, which could lead to a higher risk for infections and cancer. Similarly, psoriasis is associated with smoking, excess alcohol use, mood disorders, and decrements in income, all of which could lead to adverse health outcomes [23,24]. More recent epidemiologic research has focused on determining which health outcomes in patients who have psoriasis may be direct consequences of the disease itself.

Psoriatic arthritis

Patients who have psoriasis are at significant risk for developing PsA. The frequency of PsA appears to be strongly related to the degree of skin severity. For example, a population-based study indicated that the prevalence of PsA in patients who have less than 1% body surface area (BSA), 1% to 2% BSA, 3% to 10% BSA, and more than 10% BSA was 6%, 14%, 18%, and 56%, respectively [25]. Similarly, nail involvement is another clinical predictor of PsA. For example, nail lesions are seen in 80% to 90% of patients who have concomitant PsA compared with 46% among those who have psoriasis uncomplicated by arthritis [26]. Skin disease occurs concurrently or before the development of PsA in more than 80% of cases. Studies of PsA from rheumatology referral centers indicate that the disease can be progressive and can be associated with permanent disability and excess mortality [27,28]. Studies of PsA in the general population and in the dermatology setting indicate that the disease may be less disabling and require fewer treatments of symptom management [29,30]. Having multiple joints involved at baseline and having elevated markers of systemic inflammation (eg, erythrocyte sedimentation rate, C-reactive protein)

predict a more aggressive course for PsA, whereas severity of skin disease is a poor predictor of the severity of joint disease or its progression [25,30].

Cardiovascular and metabolic disease

Studies from the early 1970s first identified that patients who have psoriasis have higher frequencies of atherosclerotic disease and thrombotic complications [31]. More recently, studies have indicated that patients who have severe psoriasis have excess rates of cardiovascular disease that is not accounted for by traditional cardiovascular risk factors (obesity, hypertension, diabetes, hyperlipidemia, and smoking). For example, Gelfand and colleagues [32] demonstrated in a large observational cohort study that patients who have mild and severe psoriasis (identified by treatment patterns) have an increased risk for myocardial infarction and that the adjusted relative risk for myocardial infarction is greatest in younger patients who have severe disease. Similarly, Ludwig and colleagues [33] demonstrated that the prevalence and severity of coronary artery disease in 32 well-characterized patients who had severe psoriasis was greater than matched controls, even when controlling for major cardiovascular risk factors.

The prevalence of obesity, diabetes, and metabolic syndrome has been shown to be increased in psoriasis patients in the general population and in referral centers [34]. At least one study has demonstrated a higher prevalence of diabetes in patients who have psoriasis independent of traditional diabetes risk factors such as age, gender, obesity, hypertension, and hyperlipidemia, indicating that the disease itself, or possibly its chronic treatments, may predispose to the development of diabetes [19].

Cancer

The immunologic nature of psoriasis, and therapies that are immunosuppressive or mutagenic, may predispose patients who have psoriasis to an increased risk for cancer. A higher incidence of nonmelanoma skin cancer has been reported in psoriasis patients and findings regarding internal cancers such as lung, breast, colon, and prostate are conflicting [35–41]. Lymphoma has been of special interest because inflammatory conditions may be associated with a higher risk for lymphoproliferative disease. Studies of the risk for internal lymphoma in psoriasis patients have yielded inconsistent results. The largest study to date found no increased risk for non-Hodgkin's lymphoma, but did observe an increased risk for Hodgkin's lymphoma and a markedly increased relative risk for cutaneous T-cell lymphoma (CTCL) [42]. This association of psoriasis with CTCL may be due to misdiagnosis of early CTCL as psoriasis or may be related to chronic lymphoproliferation leading to CTCL [42]. Recently, the results of 30 years of follow-up of psoriasis patients treated with psoralen-UV-A (PUVA) found that patients who received PUVA and were exposed to high levels of methotrexate (≥ 36 months) had an increased incidence of lymphoma compared with the general population (incidence rate ratio 4.39, 95% CI 1.59–12.06) [43]. Increased rates of lymphoma were also observed in other patient categories created by the investigator (eg, PUVA patients who received >300 UV-B treatments, patients who had skin types 1 or 2, patients who received >200 PUVA treatments), but these were

not statistically significant, possibly because of limitations of statistical power or incomplete capture of outcomes.

Psychiatric disease

Multiple studies, most of which are descriptive, have examined psychologic characteristics of patients who have psoriasis [44–46]. A wide range of problems have been described, such as depression, anxiety, obsessive behavior, sexual dysfunction, and suicidal ideation [47–52]. A study comparing 50 patients who had psoriasis in outpatient clinics to 50 healthy controls found that patients who had psoriasis had a higher average Beck Depression Inventory score (16.96 versus 5.48, respectively, $P < .01$) [53]. Suicidal ideation was found to be present in 7.2% of patients hospitalized for psoriasis, in 2.5% of psoriasis outpatients, and in 2.4% to 3.3% of general medical patients, suggesting that patients who have more severe disease may suffer greater emotional impairment [44]. Psychologic distress may also impair response to psoriasis therapies. For example, in a cohort of psoriasis patients treated with PUVA, pathologic or high-level worry was a significant predictor of time taken for PUVA to clear psoriasis, whereas clinical severity of psoriasis, skin phenotype, alcohol intake, anxiety, and depression were not [54].

Clinical implications of comorbidities in psoriasis

The emerging data on comorbidities in psoriasis have important clinical implications for the care of these patients. First, the dermatologist must play a central role in the initial diagnosis of PsA, given that the skin disease typically precedes the onset of joint disease. Early diagnosis of PsA may lead to improved joint function and a decreased risk for future disability. Second, given the high prevalence of concomitant PsA in patients who have extensive psoriasis, dermatologists should consider joint symptoms when selecting a therapy to treat the skin disease. For example, methotrexate and tumor necrosis factor (TNF) inhibitors are considered disease-modifying antirheumatic drugs that may prevent joint destruction in patients who have PsA. Data from controlled clinical trials indicate that etanercept decreases fatigue symptoms in psoriasis patients who have concomitant PsA and also may improve symptoms suggestive of depression [55]. Furthermore, the broad evidence of elevated cardiovascular risk associated with psoriasis has resulted in new consensus statements suggesting that dermatologists play a role by either screening for cardiovascular risk factors in patients who have psoriasis or by encouraging the patient to follow up with his/her primary care physician for appropriate screenings and interventions aimed at lowering cardiovascular risk [56]. The importance of optimizing medical care for patients who have psoriasis is emphasized by recent studies indicating that severe psoriasis patients die 3 to 4 years earlier than patients who do not have psoriasis, a finding similar to estimates of years of life lost because of severe hypertension [57]. Finally, the mental health status of patients who have psoriasis should be assessed because mood disorders such as depression and anxiety are highly prevalent in this patient population and also may impair response to treatment.

KEY ADVANCES IN THE TREATMENT OF PSORIASIS

What are the current food and drug administration–approved systemic biologics available for the treatment of moderate/severe plaque psoriasis? What are their associated risks and benefits?

The therapeutic paradigm for treating psoriasis with systemic agents continues to evolve. Recent consensus statements suggest that indications for systemic psoriasis treatment or phototherapy are psoriasis affecting greater than or equal to 5% BSA, psoriasis affecting vulnerable areas (eg, palmar-plantar), psoriasis with concomitant PsA, pustular, erythrodermic, and guttate psoriasis variants, and psoriasis unresponsive to topical medications in which significant physical, social, or emotional impairments are involved [58]. Traditional therapies include methotrexate, acitretin, cyclosporine, phototherapy (including laser devices), and PUVA. In this article, the authors focus on recently approved biologic therapies for psoriasis. A biologic therapy is a compound engineered from living organisms. Biologics for psoriasis vary in structure (eg, humanized versus chimeric, antibody versus fusion protein), target (eg, cytokines versus T cells), route of administration, safety, efficacy, and monitoring requirements. TNF inhibitors were first approved for use in 1998 and have been studied extensively in clinical trials across multiple diseases and in long-term cohort studies in multiple populations involving tens of thousands of patients. By comparison, T-cell inhibitors for psoriasis have been studied predominantly in psoriasis patients, and no large, long-term, cohort studies of these drugs have been published. A summary of relevant characteristics of biologics is shown in Tables 1 and 2.

The tumor necrosis factor inhibitors

TNF- α is a 17-kD polypeptide that plays a central role in the regulation of innate immune responses. It is involved in stimulating the production of inflammatory cytokines, inducing the expression of cell surface adhesion molecules, enhancing the phagocytic/bactericidal properties of macrophages, and activating apoptotic pathways on association with membrane-bound forms of its receptors, TNF-R1 (p55) and TNF-R2 (p75). These receptors also exist in soluble forms, which regulate TNF- α bioavailability in the circulation.

TNF- α is produced by various cells, ranging from lymphocytes and monocytes, to keratinocytes, mast cells, and APCs in the skin. It is believed to contribute to the pathogenesis of psoriasis through its ability to promote immune cell trafficking to the skin and induce keratinocyte proliferation [59–61]. At present, three anti-TNF therapeutics are available for the treatment of autoimmune conditions: the fusion protein, etanercept, and two recombinant monoclonal antibodies (infliximab and adalimumab). Specific characteristics and safety issues of special interest with regard to these agents are now discussed.

Adalimumab. Adalimumab is a recombinant human monoclonal antibody that blocks the interaction between TNF- α and its p55/p75 cell surface receptor. It differs from infliximab in that it is fully human, which theoretically may decrease the risk for autoantibody formation against it. Nevertheless, neutralizing antibodies

Table 1
Overview of biologic dosing and efficacy

Biologic	Structure	Target	Dosing	Pharmacokinetics	PASI 75 ^a
Adalimumab	Human monoclonal antibody	Soluble and membrane-bound TNF- α	80 mg SC followed by 40 mg SC 1wk later, then 40 mg SC qow	Half-life: 10–20 d	68% at wk 12 [95,134]
Alefacept	Fusion protein	LFA-3	15 mg IM qwk for 12 wk	Half-life: 11.25 d	33% during 14-wk study period
Efalizumab	Humanized monoclonal antibody	LFA-1	0.7 mg/kg SC followed by 1 mg/kg qwk	Half-life: 6.21 d	27% at wk 12
Etanercept	Fusion protein	Soluble TNF- α , lymphotoxin- α	50 mg SC biw for 12wk, then 50 mg SC qwk	Half-life: 4–12.5 d	34% at wk 12 (based on 25-mg SC biw dosing); 49% at wk 12 (based on 50-mg biw dosing)
Infliximab	Chimeric monoclonal antibody	Soluble and membrane-bound TNF- α	5 mg/kg IV at wk 0, 2, and 6, then q8wk	Half-life: 8–9.5 d	80% at wk 10

Data from Thomson PDR. Physician's Desk Reference. 61st edition. Montvale, New Jersey: 2007.

Abbreviations: biw, 2 times per week; IV, intravenous; IM, intramuscular; LFA, leukocyte function-associated antigen; PASI, psoriasis area and severity index; q8wk, every 8 weeks; qow, every other week; qwk, every week; SC, subcutaneous; TB, tuberculosis.

^a Data from Kurd SK, et al. Update on the epidemiology and systemic treatment of psoriasis. Expert Rev Clin Immunol 2007;3(2):171–85.

Table 2
Overview of biologic monitoring and safety

Biologic	FDA-required screening and monitoring ^a	Common adverse effects (>5%)	Uncommon adverse effects (0.1%–5%)	Rare adverse effects (<0.1%)	Black box warnings
Adalimumab	Screen for latent TB Evaluate patients at risk for HBV or who had prior HBV infection	Injection site reaction; +ANA; upper respiratory infection; headache; nausea; elevated alk phos, cholesterol	Neutralizing antibodies; serious infection	TB; malignancy; lupus-like syndrome; hypersensitivity; hepatitis B reactivation; demyelination; congestive heart failure; pancytopenia	Infection (TB, sepsis, fungal, and opportunistic)
Alefacept	Measure CD4 count before and during treatment Evaluate for signs/symptoms of liver injury	Lymphopenia	LFT elevation; serious infection	Malignancy; hypersensitivity	None
Efalizumab	Measure platelet count before and during treatment (monthly with treatment initiation, then q 3 mo with ongoing treatment) Follow for worsening psoriasis during or on discontinuation of treatment	Flu-like symptoms; mild psoriasis flare; lymphocytosis	Severe psoriasis flare; serious infection; thrombocytopenia; arthritis; hypersensitivity; LFT elevation	Malignancies; hemolytic anemia; pancytopenia; interstitial pneumonia; toxic epidermal necrolysis; aseptic meningitis	Risk of serious infections leading to hospitalizations or death, including bacterial sepsis, viral meningitis, invasive fungal disease, opportunistic infections, and progressive multifocal leukoencephalopathy resulting from JC virus infection. Warning issued October, 2008.

Etanercept	Evaluate patients at risk for HBV or who had prior HBV infection Screen for latent TB	Injection site reaction; +ANA	Serious infection	TB; malignancy; lupus-like syndrome; hypersensitivity; hepatitis B reactivation; demyelination; congestive heart failure; pancytopenia	Infection (bacterial, sepsis, and TB)
Infliximab	Screen for latent TB Evaluate patients at risk for HBV or who had prior HBV infection Evaluate for signs/symptoms of liver injury	Infusion reaction; +ANA; elevated liver function tests; neutralizing antibodies	Hypersensitivity; serious infection	Severe hepatic injury; TB; malignancy; lupus-like syndrome; hypersensitivity; hepatitis B reactivation; demyelination; congestive heart failure; pancytopenia	Infection (TB, sepsis, fungal, and opportunistic) Hepatosplenic T-cell lymphoma

Abbreviations: alk phos, alkaline phosphatase; +ANA, antinuclear antibodies; FDA, Food and Drug Administration; HBV, hepatitis B virus ; LFTs, liver function tests; q, every; TB, tuberculosis.

^a Note that published guidelines suggest that latent TB be screened for before initiating therapy with all TNF inhibitors; many practitioners screen for latent TB before starting any biologic and then annually if the patient continues on the drug. Practitioners vary in their monitoring practices for biologics, but most monitor complete blood count and liver function tests periodically during treatment.

may develop to adalimumab in patients treated with this biologic [62]. In January 2008, adalimumab received FDA approval for the treatment of adult patients who have moderate-to-severe plaque psoriasis and are candidates for systemic therapy or phototherapy, or among whom other systemic therapies may not be appropriate. It is also approved for the treatment of PsA, rheumatoid arthritis (RA) juvenile idiopathic arthritis, ankylosing spondylitis, and Crohn's disease. The half-life of adalimumab ranges from 10 to 20 days, and it achieves a peak concentration approximately 130 hours after administration, with an absolute bioavailability of 64%. For the treatment of psoriasis, adalimumab is administered as a subcutaneous injection with an initial 80-mg dose, followed by a 40-mg dose 1 week later. Subsequent maintenance doses of 40 mg should be administered every other week thereafter [63].

Infliximab. Infliximab is a chimeric recombinant monoclonal antibody consisting of a human immunoglobulin (Ig)G1 constant region fused to a murine variable region that recognizes and binds to human TNF- α . It is FDA approved for the treatment of PsA, RA, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and chronic severe plaque psoriasis. Serum concentrations vary and are directly related to the administered dose. Infliximab concentrations of greater than 0.1 mg/kg are detected in most patients up to 14 weeks after treatment [60]. The serum half-life of infliximab ranges from 8 to 9.5 days. It is administered intravenously over a 2- to 3-hour period at an infusion dose of 5 mg/kg. Treatments are recommended at 2 weeks, 6 weeks, and 8 weeks after the initial dose. It may then be dosed every 8 weeks thereafter. Among the biologics, infliximab provides the most rapid onset of clinical improvement among patients who have moderate-to-severe psoriasis, with approximately 80% of patients achieving a psoriasis area and severity index (PASI) 75 by treatment week 10 [64]. When used as a monotherapy, however, treatment efficacy has been observed to decrease over time [65]. This loss of efficacy has been attributed to increased metabolism of the drug, possibly secondary to the generation of neutralizing autoantibodies. The development of neutralizing antibodies is associated with an increased risk for infusion reactions [65]. Such reactions may be serious; thus, strategies to reduce the incidence of neutralizing antibodies should be considered. It has been suggested that combining infliximab therapy with methotrexate may decrease the development of neutralizing antibodies and loss of efficacy, as was reported among patients who had Crohn's disease [65]. Furthermore, intermittent dosing of infliximab for psoriasis is similarly associated with an increased risk for neutralizing antibody formation and loss of efficacy over time; thus, intermittent dosing is discouraged [66]. Although infliximab acts quickly, it requires intravenous administration in a medical setting, and thus is not as convenient as self-administered medications.

Etanercept. Etanercept is a recombinant dimer of human soluble TNF-R2 (p75), consisting of the extracellular ligand-binding portion of p75 fused to a human IgG1Fc region; it exhibits a higher affinity (\sim 50 fold) for TNF- α than its

endogenous soluble counterpart. Unique among the TNF inhibitors, etanercept also binds lymphotoxin- α (TNF- β), a member of the TNF family of cytokines. Etanercept reversibly binds to TNF- α in the circulation, thus competitively inhibiting its ability to associate with its endogenous receptors. Etanercept is FDA approved for the treatment of PsA, RA, ankylosing spondylitis, and moderate-to-severe plaque psoriasis. It has a serum half-life of between 4 and 25 days, achieving peak plasma concentrations approximately 48 hours after dosing [67]. The bioavailability of subcutaneous etanercept is approximately 58% [68]. Etanercept is self-administered by the patient as a 50-mg subcutaneous injection, typically twice weekly for the first 12 weeks, then weekly thereafter. Etanercept efficacy may be affected by patient weight, particularly in those who are extremely obese (body mass index >40) [69].

Tumor necrosis factor inhibitors: comparisons

Although etanercept effectively neutralizes soluble forms of TNF- α , it exhibits minimal affinity for membrane-bound forms and is incapable of inducing complement fixation and the apoptosis of cells. In contrast, the antibody-based therapeutics (infliximab and adalimumab) inhibit soluble and membrane-bound forms of TNF- α . Their association with membrane-bound forms accounts for their ability to induce apoptosis of targeted cells by way of complement fixation and antibody-dependent cell-mediated cytotoxicity [70,71]. Etanercept also differs from antibody-based therapies with regard to its affinity for TNF. Unlike infliximab and adalimumab, etanercept sheds approximately 50% of soluble TNF within 10 minutes of binding [71], whereas the antibody-based therapeutics exhibit irreversible high affinity binding to both soluble and membrane-bound TNF. With regard to pharmacokinetics, the subcutaneous dosing of etanercept and adalimumab allows for more uniform serum concentration-time profiles at steady state, whereas the intravenous infusion of infliximab accounts for elevated peak-to-trough ratios [72].

Aside from their shared ability to inhibit TNF function, differences between etanercept and the antibody-based therapeutics with regard to their effects on cytokine production by Th1 cells have been revealed by recent laboratory studies. More specifically, results from cell culture experiments found that TNF inhibition by infliximab led to strong suppression of genes mediating Th1 cytokine production (eg, interferon [IFN]- γ), whereas a similar effect was not appreciated among etanercept-treated cells [73].

Given the importance of Th1 cytokines such as IFN- γ in promoting cell-mediated immune responses, their suppression by infliximab may account for the increased reactivation of *Mycobacterium tuberculosis* reported among patients [73]. This characteristic, however, may prove beneficial in the setting of certain autoimmune disorders characterized by enhanced Th1 cytokine production, such as inflammatory bowel disease. In particular, antibody-based TNF inhibitors have proved efficacious in the management of Crohn's disease, a Th1-mediated disorder, whereas etanercept has not proved effective in this setting [74–76]. Differences in the pharmacokinetic and pharmacodynamic

profiles of the TNF inhibitors may also contribute to differences in their clinical efficacy and safety in the management of specific disease states.

Tumor necrosis factor inhibitors: adverse effects/safety

Given their immunosuppressive properties, patients should be screened for signs of infection or malignancy before the initiation of therapy and during the course of treatment. The TNF inhibitors are contraindicated among patients who have active, chronic, or localized infections. In addition, they should not be administered to patients receiving the IL-1 receptor antagonist anakinra because this substantially increases the risk for infection.

Relative contraindications to treatment include a personal history of congestive heart failure or a family history of demyelinating disease (eg, multiple sclerosis). Injection site and infusion reactions are the most common side effects reported among patients receiving anti-TNF- α therapy. Other adverse effects include a potentially increased risk for infection, lymphoma, demyelinating disease, congestive heart failure, and autoantibody formation. In particular, infliximab at doses greater than 5 mg/kg is contraindicated in patients who have moderate-to-severe congestive heart failure because studies suggest that it may increase the risk for mortality in this patient population [77,78]. Adalimumab, infliximab, and etanercept are all pregnancy category B medications and are metabolized by proteolysis.

Consideration should be given to vaccination against common serious infections such as pneumonia and influenza before the initiation of therapy whenever possible because treatment during therapy, although likely efficacious, may result in decreased antibody titer responses against vaccination antigens [79,80]. Live vaccines are generally contraindicated during treatment with TNF inhibitors. The authors now discuss additional safety issues related to the use of these medications, which are of special interest.

Safety issues related to malignancy

Theoretic concern exists that TNF inhibitors may increase the risk for malignancy, such as lymphoma. Observational cohort studies of TNF inhibitors for the treatment of RA have reported an increased risk for lymphoma among treated patients [81,82]. Whether this finding represents a disease-associated predisposition for lymphoma or a drug/treatment-associated phenomenon remains to be determined. Studies that have controlled for the severity of RA have not found an increased risk for lymphoma in RA patients treated with TNF inhibitors [83]. A meta-analysis of randomized, controlled trials involving the use of infliximab and adalimumab for the treatment of RA reported an increased risk for solid organ malignancies, of which 35% were skin cancers, among patients [84]. Observational studies in patients who have RA have also found a modest increased risk for nonmelanoma skin cancer in patients treated with TNF inhibitors [85]. An increased risk for solid organ cancer was also reported among patients receiving etanercept and cyclophosphamide concurrently for the treatment of Wegener's granulomatosis in a randomized, controlled trial [86]. Thus, one should consider avoiding the concurrent use of TNF inhibitors with cyclophosphamide [86]. The

applicability of malignancy risk associated with TNF inhibitors in the psoriasis population is not clear because psoriasis patients are generally treated with monotherapy, whereas the patients treated with TNF inhibitors for RA are commonly treated with concomitant immunosuppressives, which could alter the safety profile of these drugs.

Safety issues related to viral hepatitis and tuberculosis

Among psoriasis and RA patients who have concomitant hepatitis C virus (HCV) infection, no exacerbation of liver disease was reported in the setting of anti-TNF- α therapy (ie, etanercept, adalimumab, infliximab) [87–89]. In fact, TNF- α inhibition may be beneficial in the management of HCV infection because excess TNF is believed to contribute to the hepatic inflammation and fibrosis characteristic of this condition. A recent retrospective survey and prospective trial reported no substantial change in liver transaminases or HCV load among RA patients who underwent treatment with etanercept or infliximab for their arthritis [90]. Furthermore, a randomized controlled trial demonstrated that etanercept may be useful as adjuvant therapy (eg, in addition to IFN- α -2b and ribavirin) for HCV infection [91].

Patients who are chronically infected with hepatitis B virus (HBV) require special attention when being treated with anti-TNF- α therapy. More specifically, HBV reactivation and associated fatalities have been reported among patients treated with TNF- α inhibitors (ie, infliximab) [92]. Thus, consideration should be given to screening prospective treatment subjects for HBV if they are at risk for chronic HBV infection (see www.cdc.gov/ncidod/diseases/hepatitis/b/Bserology.htm). If the patient is chronically infected with HBV, then therapies that are not immunosuppressive or hepatotoxic are preferred. In situations in which TNF inhibitors must be used in a patient who has chronic HBV infection, close monitoring should occur. Additionally, concomitant treatment of HBV may be considered. For example, a small case series reported no changes in serum transaminases or viral load among chronic HBV patients receiving concomitant TNF inhibitor therapy and lamivudine [93].

The risk for tuberculosis (TB) among patients on TNF inhibitor therapy appears to be greatest among those receiving antibody-based therapeutics (ie, infliximab and adalimumab), as opposed to receptor-based therapy (ie, etanercept). Infliximab has been associated with a 4- to 20-fold increased risk for TB infection [94]. Checking a purified protein derivative (tuberculin) (PPD) is recommended, based on consensus guidelines, before initiation of treatment with all TNF inhibitors because all three may increase the risk for reactivation of latent TB [95]. Patients should also be monitored for signs/symptoms of active TB during treatment. If active disease is detected, further anti-TNF therapy should be withheld until the infection is effectively treated or resolved. If a patient tests positive for latent disease, treatment of latent TB should be initiated according to standard guidelines and TNF-inhibitor therapy may be considered [96,97].

Patients who have had the BCG vaccine may have a positive PPD even in the absence of infection; thus, alternative screening methods would be

appropriate in this setting, such as QuantiFERON-TB Gold (www.quantiferon.com) or T-SPOT.TB assays. These whole blood tests have higher specificity than the traditional tuberculin skin test, ranging from 96% to 100% among BCG-vaccinated subjects, while having comparable sensitivity [94]. A PPD should not be performed before QuantiFERON-TB Gold or T-SPOT.TB assays because theoretically it can result in a higher risk for false-positive results [98].

It has been estimated that screening for latent TB (risk assessment, tuberculin skin testing, and chest radiograph) before anti-TNF therapy may decrease the rate of TB infection by as much as 90% [99]. Although TB screening, and subsequent treatment in positive cases, reduces the incidence of disease reactivation among patients who then receive TNF inhibitor therapy, one study reported the development of TB among 19% of patients who received adequate chemoprophylaxis before anti-TNF therapy [100].

Safety issues related to demyelinating diseases

Occasional reports have been made of new-onset demyelinating events among patients treated with TNF inhibitor therapy. Furthermore, a randomized controlled trial of the TNF inhibitor lenercept for treatment of multiple sclerosis demonstrated that TNF inhibition may lead to a higher rate of disease exacerbations compared with placebo [101]. A definitive link between TNF inhibitor treatment and new-onset demyelinating disease has been raised but remains uncertain. Whether TNF inhibitor therapy unmasks an underlying predisposition for autoimmune neurologic disease, promotes it, or has no direct association with it remains unclear. A recommendation to cease TNF inhibitor use on development of neurologic symptoms, and to avoid use among patients who have pre-existing demyelinating disease, has been made, given rare reports of new-onset demyelinating events among treated patients. It has also been recommended that TNF inhibitor therapy be avoided in patients who have a first-degree relative affected by demyelinating disease [102]. The impact of the T-cell inhibitors used for psoriasis on the risk for demyelination events has not been well characterized; however, such events have been reported to occur in individuals treated with efalizumab [103].

Inhibitors of T-cell activation

Alefacept

Alefacept is a human recombinant dimeric fusion protein consisting of the terminal end of leukocyte function-associated antigen-3 (LFA-3) bound to the Fc portion of human IgG1. Under normal circumstances, endogenous LFA-3, which is expressed on the surface of APCs, is recognized by CD2, which is preferentially expressed at high levels by natural killer cells and effector/memory CD4 and CD8 T cells. The interaction of APC LFA-3 with CD2 on the T-cell surface plays an essential costimulatory role in T-cell activation. By binding to CD2, alefacept inhibits T-cell costimulation and activation [104]. In addition, alefacept may induce the selective apoptosis of effector/memory T cells through its simultaneous binding of CD2 on the T-cell surface and the Fc γ RIII receptor expressed by natural killer cells, which recognizes the Fc portion of

alefacept [105]. Recent data suggest that alefacept may exhibit both agonistic and antagonistic properties with regard to the expression of specific cytokines (ie, the suppression of inflammatory cytokines and induction of IL-8, STAT1, and Mig) [106]. Gene expression patterns specific to responders and nonresponders to alefacept have also been identified [106].

Alefacept is FDA approved for the treatment of adults who have chronic moderate-to-severe plaque psoriasis. After drug administration, peak plasma concentrations of alefacept are achieved between 24 and 192 hours; its elimination half-life is approximately 12 days [107]. Alefacept is administered as a weekly intramuscular injection of 15 mg for 12 consecutive weeks. In a recent international phase 3 trial, a PASI 75 was achieved by 33% of patients receiving alefacept 15 mg intramuscularly weekly and by 13% of placebo-treated patients during the 14-week study period [108]. Recent studies suggest that longer courses of treatment (16 weeks) or repeated courses may lead to enhanced efficacy [109–111]. Although not FDA approved for PsA, recent trials indicate that alefacept may also improve PsA symptoms [112]. It has been used as monotherapy, and in combination with methotrexate, in this setting with promising results [112,113].

In comparison to the TNF inhibitors, alefacept appears to exhibit lower treatment efficacy with a delayed onset of action. Clinical improvement usually occurs late during the treatment course, with maximal responses often noted weeks after the final dose. The potential for long periods of disease remission on cessation of therapy exists; however, this occurs in only a few patients [114]. It is recommended that a CD4+ T-cell count be established at baseline, with subsequent re-evaluation every 2 weeks throughout the 12-week treatment course (therapy should be discontinued if the count falls below 250/uL). Approximately 10% of patients require temporary discontinuation of therapy secondary to dose-dependent lymphopenia [115].

The most common side effects associated with alefacept therapy include injection site reactions, headaches, chills, nausea, and upper respiratory symptoms. Few patients experience lymphopenia, serious infections, malignancies, and elevated serum transaminases. The FDA recommends that alefacept not be administered to patients who have HIV or CD4+ T-cell counts below normal, given the risk for lymphopenia [115]. Alefacept should be used with caution among patients who have a history of systemic malignancy or are at increased risk for infection. Studies addressing the efficacy of influenza and pneumococcal vaccines among treated patients have not been published at this time; however, a study of psoriasis patients exposed to Φ X174 neoantigen and recall antigen tetanus toxoid immunization, after a 12-week treatment course with alefacept, revealed intact CD4+ T-cell-mediated antibody titer responses that were comparable to controls [116]. Large, long-term follow-up studies of alefacept treatment of psoriasis will be necessary to define its safety profile further.

Efalizumab

Efalizumab is a humanized, recombinant, IgG1 monoclonal antibody against the CD11a subunit of leukocyte function-associated antigen-1 (LFA-1).

LFA-1 is endogenously expressed on the surface of T cells. Its ligand, intercellular adhesion molecule-1 (ICAM-1), is expressed on the surface of dermal endothelial cells and APCs. The interaction of LFA-1 with ICAM-1 on the surface of APCs promotes T-cell activation and cytotoxicity [117]. In addition, its recognition of ICAM-1 expressed on the dermal microvasculature promotes the firm adhesion and subsequent migration of lymphocytes into the cutaneous microenvironment. Thus, inhibition of LFA-1 decreases lymphocyte migration to the skin and activation by APCs.

Efalizumab is FDA approved for the treatment of moderate-to-severe plaque psoriasis. Peak plasma concentrations are achieved approximately 2 to 3 days after subcutaneous injection of the drug, with an elimination half-life of approximately 6 days [118]. Treatment is initiated with a 0.7 mg/kg subcutaneous conditioning dose, followed by weekly 1.0 mg/kg subcutaneous injections for an indefinite period of time depending on patient response to therapy.

In a 2003 phase 3 study, 27% of patients who had moderate-to-severe plaque psoriasis achieved a PASI 75 after 12 weeks of treatment with efalizumab at a weekly subcutaneous dose of 1 mg/kg, whereas only 4% of the placebo group achieved a similar result [117]. The most common side effects associated with treatment include flu-like symptoms (on initial dosing), leukocytosis/lymphocytosis, and nonserious infections.

Treated patients have a small risk for hemolytic anemia and thrombocytopenia that is not well understood. It is therefore recommended that treated patients undergo monthly evaluation of their platelet count for the first 3 months, and every 3 months thereafter.

A few patients treated with efalizumab have experienced a flare of their disease or a change in the nature of their psoriasis during treatment [119]. Additionally, some patients may experience worsening of their disease on discontinuation of therapy [103]. It has been estimated that approximately 5% of patients will experience a rebound flare on cessation of therapy [120]. In clinical trials, serious disease flares characterized by inflammatory, pustular, and erythrodermic psoriasis affected 0.7% of patients [121]. Based on a small trial, inflammatory flares associated with efalizumab appear to respond best to cyclosporine or methotrexate, as compared with oral steroids or retinoids [122].

Efalizumab must be used with caution among patients who have a history of systemic malignancy or are at increased risk for infection. The package insert recommends against the administration of acellular, live, and live attenuated vaccines during treatment. Although a decreased response to tetanus booster has been reported among treated patients (with titers still in the protective range), no studies addressing the safety or efficacy of the pneumococcal and influenza vaccine in this setting have been reported to date [123]. Large, long-term follow-up studies of efalizumab treatment of psoriasis will be necessary to define its safety profile further.

What novel biologic agents are currently under investigation?

The discovery of the proinflammatory cytokines, IL-12 and IL-23, in the past 2 decades has led to increasing interest in their potential roles as mediators of

psoriatic disease. Both are involved in the regulation of cell-mediated immune responses. IL-12 is involved in the activation of natural killer cells and has been shown to promote the differentiation of naïve CD4 T-cells into effector/memory cells that secrete Th1 cytokines [124]. IL-23 stimulates the production of TNF, IL-6, IL-17, and IL-22 by a unique subset of Th cells called Th17 cells [125]. The production of IL-17 has been shown to induce the production of inflammatory cytokines by multiple cell types [126] (including macrophages, fibroblasts, and endothelial cells) and is believed to play a pivotal role in sustaining inflammatory responses in multiple autoimmune disorders [127]. IL-22 has been shown to play a role in cutaneous inflammatory processes and may promote psoriatic lesions through its inhibitory effects on keratinocyte differentiation [127].

IL-12 and IL-23 share structural similarity in that both possess an IL-12p40 subunit. Their receptors are also similar in that they share the IL-12R β 1 subunit, which recognizes IL-12p40. Elevated levels of IL-12p40 mRNA have been reported in the skin lesions of psoriasis patients [128]. Several studies have correlated clinical improvement in psoriasis lesions with marked reductions in IL-12 and IL-23 expression levels in affected skin [128], further supporting a pathogenic role for these cytokines in psoriasis. To evaluate the therapeutic efficacy of IL-12/23 blockade on psoriasis, a recombinant human monoclonal antibody against IL-12p40 (CNTO 1275) was recently developed (Centocor Corp., Malvern, PA).

A phase 2 study ustekinumab (CNTO 1275) among patients who had moderate-to-severe plaque psoriasis reported a PASI 75 by week 12 in 52% of patients who received one 45-mg intravenous dose, in 59% of patients who received one 90-mg dose, and in 81% of patients who received four weekly 90-mg doses; compared with 2% who received placebo [129]. Twenty-three percent to 52% of patients achieved a PASI 90, depending on the dose.

In a recently conducted phase 3 study, 67% to 76% of patients receiving ustekinumab achieved a PASI 75 at 12 weeks depending upon the administered dose (45mg versus 90mg at week 0, week 4, then every 12 weeks) [130]. Among partial responders receiving the higher dose, an increase in dosing frequency from every 12 to every 8 weeks was associated with a significant improvement in clinical response. Adverse events among treatment groups were similar. Clinical responses were best sustained among patients receiving maintenance dosing [131].

Another monoclonal antibody against IL-12/23 has been developed (ABT-874; Abbot Laboratories, Abbott Park, IL) and studied in the setting of Crohn's disease and, more recently, psoriasis. A phase 2 trial among Crohn's disease patients receiving subcutaneous ABT-784 for 7 weeks resulted in marked improvements in patient symptom scores, with no serious adverse effects [132]. A phase 2 trial to assess its safety and efficacy in the treatment of moderate-to-severe chronic plaque psoriasis was recently conducted [133]. More than 90% of patients receiving repeated doses of this agent, in varying amounts and duration, achieved a PASI 75 after 12 weeks.

These studies provide early evidence that IL-12/23 monoclonal antibody therapy may offer a safe and efficacious treatment alternative for patients who have moderate-to-severe plaque psoriasis.

SUMMARY

The onset of psoriatic disease and its associated comorbidities involves the interplay among a myriad of genetic and environmental risk factors. As we gain further insight into the immunopathogenesis of psoriasis, we hope it will provide the basis for the development of safer, more efficacious, and more durable therapeutics in the future. Given its enormous toll on patient health and quality of life, steps should be taken to prevent or decrease the risk for psoriasis-associated comorbidities through behavior modification and use of preventative health screenings and treatments. Future studies will need to be performed to determine if successful treatment of psoriasis will lead to a decreased risk for developing psoriasis-associated comorbidities over time.

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