



# Update on the epidemiology and systemic treatment of psoriasis

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Recent epidemiological observations reveal that the prevalence of psoriasis increases more rapidly in young women compared with young men, and that the prevalence of psoriasis may decrease in the elderly. Emerging evidence suggests that some potentially modifiable exposures, such as smoking, stress and obesity, may increase a patient's risk of developing psoriasis. The evolving literature suggests that psoriasis is associated with multiple other diseases, including cancer, cardiovascular disease, diabetes and psychiatric disease, and that psoriasis itself may be an independent risk factor for developing atherosclerosis and myocardial infarction. The treatment of moderate-to-severe psoriasis is undergoing a revolution with the advent of biological therapies that target the immunopathogenesis of psoriasis, such as tumor necrosis factor- $\alpha$  and T-cell function. The pharmacokinetics, pharmacodynamics, efficacy and safety profiles vary among biologicals and, therefore, drug and patient factors are important in selecting the optimum therapy. In this article, we focus on recent developments in the epidemiology and systemic treatment of psoriasis.

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Psoriasis is a common chronic inflammatory disease of the skin and joints. The etiology is unknown, but it is believed to be caused by an interaction between genetic and environmental factors, resulting in increased antigen presentation, T-helper (Th)-1 cytokine production and T-cell activity. Psoriasis can cause significant reductions in health-related quality-of-life and is associated with substantial healthcare costs [1,2]. The last 20 years have witnessed tremendous advances in our knowledge about psoriasis. In this article, we focus on recent developments in the epidemiology and systemic treatment of psoriasis.

## Epidemiology

### Incidence

Incidence is defined as the proportion of individuals who develop a disease within a specified time period. In the general population of Rochester (MN, USA), the overall annual crude incidence rate of psoriasis was found to be 57.6 per 100,000 individuals using medical records linkage data [3]. The incidence was slightly higher in women compared with men

and the highest overall incidence occurred in patients 60–69 years of age. These findings may underestimate the incidence of psoriasis since patients with new-onset mild disease may not seek medical care. The incidence (onset) of psoriasis is believed to have a bimodal distribution, occurring more often in early adult life (late second decade into third decade) and then again in later adult life (sixth and seventh decades). One plausible explanation is that there are in fact two clinical presentations of psoriasis, Type I and Type II, which affect younger and older populations, respectively [4–8]. Patients with Type I psoriasis tend to have a higher association with the human leukocyte antigen (HLA)-*Cw6* allele [8] and a more severe disease manifestation, as well as a greater number of relatives affected than those with a Type II phenotype.

### Prevalence

Prevalence is defined as the proportion of individuals in a population who have the disease of interest in a specified time period. Studies of the prevalence of psoriasis have varied in their

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definition of prevalence (i.e., point prevalence vs lifetime prevalence), the definition of psoriasis (e.g., self report vs physician diagnosis), the population studied, as well as sampling techniques. These differences may influence results and worldwide epidemiological studies have estimated the prevalence of psoriasis to be anywhere from 0.6 to 4.8% [9–29].

The prevalence of psoriasis varies based on the geographical region sampled, with psoriasis being more prevalent in cooler climates [30,31]. The prevalence of psoriasis also varies based on ethnicity [32]. For example, in a US population-based study, the prevalence of psoriasis among African-Americans was found to be lower (1.3%) than in Caucasians (2.5%) [25]. These observations suggest that both genetic and environmental factors influence the development of psoriasis.

Recent studies indicate novel impacts of gender and age on the prevalence of psoriasis. Psoriasis appears to be more prevalent in young female patients compared with young male patients (<20 years of age) [8,9]. Psoriasis is now believed to be a Th1 cell autoimmune disease, which may suggest a susceptibility to the development of psoriasis at an earlier age in female patients. In addition, recent population-based studies from Spain [17], the UK [9] and Norway [31] indicate that the prevalence of psoriasis decreases with age. These data suggest that psoriasis may go into remission in the elderly. Alternatively, elderly psoriasis patients may be at higher risk of mortality due to associated comorbidities, health behaviors (such as smoking), the effects of treatment or, possibly, the disease itself [33,34].

#### Psoriasis risk factors & associated behaviours

A risk factor is an exposure or characteristic that increases an individual's chance for developing a certain outcome (e.g., disease) and, by definition, the association is not explained by confounding or bias.

#### Genetics

Family history (genetics) is the strongest risk factor for the development of psoriasis. It is estimated that 40% of patients with psoriasis or psoriatic arthritis have a first-degree relative with the disease [35]. When both parents are affected, psoriasis develops in as many as 50% of siblings, but this number falls to 16% when only one parent is affected and 8% when neither parent is affected but there is an affected sibling [36]. Interestingly, men with psoriasis appear to be more likely to have affected offspring than women with psoriasis, suggesting genomic imprinting; an epigenetic effect that causes differential expression of a gene depending on the gender of the transmitting parent [37].

#### Infection

Bacterial and viral infections may be linked to psoriasis. At this time, large-scale, analytical, epidemiological studies looking at the association between onset of plaque psoriasis and infection are lacking [38]. However, it is well accepted that there is an association between the onset and flaring of guttate psoriasis and streptococcal pharyngitis [32,39,40] with a plausible biological mechanism of sequence similarities between streptococcal M peptides

and human keratins [41]. One case-control study confirmed this association and found an increased odds ratio (OR) of 7.8 (95% confidence interval [CI]: 1.8–32.5) for a recent history of acute pharyngitis, with no distinction between viral and bacterial etiology, in patients with guttate psoriasis [42]. There is also an association between severe psoriasis and HIV infection [39,43] where it is thought that HIV may act as a superantigen in the activation of T cells [43].

#### Stress

A case-control study in outpatient clinics in Italy found that patients with new onset psoriasis were more likely to report a stressful life event in the year preceding disease onset compared with patients seen for other dermatological conditions (OR: 2.2; 95% CI: 1.4–3.4) even when controlling for age, sex, marital status, hospitalization, education level, body mass index (BMI), smoking and alcohol habits [44]. Results of a descriptive study found that 71% of members of the Nordic psoriasis association and 66% of patients seen in a dermatology clinic reported their psoriasis was exacerbated by stress [45]. These findings were not corroborated in a study of patients hospitalized for psoriasis [46]. One limitation inherent to studies that evaluate stress as a risk factor is that they may be subject to recall bias and, therefore, the association between psoriasis and stress may be spurious.

#### Body mass index

Several studies have implicated an association between psoriasis and obesity. In a case-control study of recent onset psoriasis, obesity was found to be a risk factor for the development of psoriasis and the risk of psoriasis was directly related to BMI with an OR of 1.6 (95% CI: 1.1–2.1) for overweight subjects (BMI: 26–29) and 1.9 (95% CI: 1.2–2.8) for obese subjects (BMI > 29). This association persisted after controlling for age, marital status, hospitalization, education, smoking and alcohol intake [44]. A large population-based, cross-sectional study, demonstrated an increased OR for obesity in patients with mild (OR: 1.27; 95% CI: 1.24–1.31) and severe psoriasis (OR: 1.79; 95% CI: 1.55–2.05) [34]. Other investigators have suggested that patients with psoriasis may become obese over time, based on patient recall of body mass prior to the onset of psoriasis [47]. Although most investigators agree that there is an association between obesity and psoriasis, whether or not this is a true risk factor and whether obesity may influence psoriasis severity requires further study.

#### Smoking/alcohol

Smoking was established as a possible risk factor for chronic plaque psoriasis based on a case-control study, which found an overall increased risk for the development of psoriasis in current (OR: 1.7; 95% CI: 1.1–3.0) and former (OR: 1.9; 95% CI: 1.3–2.7) smokers [44]. A plausible biological mechanism for this association exists in that nicotine has been shown to activate dendritic and T cells, as well as increase the secretion of proinflammatory Th1 cytokines and accelerate keratinocyte

differentiation [48–52]. Studies from numerous countries (Italy, the UK, China, Finland and the USA) have found an increased prevalence of smoking in patients with psoriasis with ORs varying from 1.7 to 3.7 [34,47,53–56]. In a hospital-based, cross-sectional study, smoking more than 20 cigarettes daily (vs less than 10) was associated with a greater than two-fold increased odds of clinically more severe psoriasis (OR: 2.2; 95% CI: 1.2–4.1) after controlling for several potential confounders [57]. A strong link between smoking and palmoplantar pustular psoriasis has also been described (OR for smoking and pustular psoriasis: 5.3; 95% CI: 2.1–13.0) [44,58].

Several case-control studies have evaluated alcohol intake as a risk factor for psoriasis and have yielded inconsistent findings [30,55,59,60]. Although alcohol consumption may not be a risk factor in the onset of psoriasis, several prevalence studies have demonstrated an association between alcohol consumption and psoriasis with positive findings being more consistently demonstrated in male psoriasis patients [53,61–66]. There was also a significant positive relationship between the affected body surface area (BSA) of psoriasis patients and average alcohol intake during the year preceding the examination [55]. Additional studies have established that alcohol use may decrease medication adherence in psoriasis patients and, therefore, the association of alcohol intake and psoriasis severity may in part be owing to decreased compliance with treatment regimens in those who drink alcohol [67].

#### Comorbidities

Recent studies have focused on the association of psoriasis with other major comorbidities. These studies are informative in that they provide insight into the burden of psoriasis, as well as demonstrate a need for clinicians to be more comprehensive in the evaluation and treatment of patients with psoriasis.

#### Cancer

The immunological nature of psoriasis, as well as therapies that are immunosuppressive or mutagenic, may predispose patients with psoriasis to an increased risk of cancer. A higher incidence of nonmelanoma skin cancer (NMSC) has been reported in psoriasis patients and there are conflicting findings regarding internal cancers, such as lung, breast, colon and prostate cancers [68–74]. Lymphoma has been of special interest since inflammatory conditions may be associated with a higher risk of lymphoproliferative diseases. Studies of the risk of internal lymphoma in psoriasis patients have yielded inconsistent results [69–73,75–84]. The largest study to date found no increased risk of non-Hodgkin's lymphoma, but did observe an increased risk of Hodgkin's lymphoma and a markedly increased relative risk for cutaneous T cell lymphoma (CTCL) [85]. The association of psoriasis with CTCL may be owing to misdiagnosis of early CTCL as psoriasis or may be related to chronic lymphoproliferation leading to CTCL [85]. Recently, the results of 30 years of follow-up of psoriasis patients treated with psoralen and long-wave ultraviolet radiation (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 [IRR]: 4.39; 95% CI: 1.59–12.06) [86]. Increased rates of lymphoma were also observed in other patient categories created by the author (e.g., PUVA patients who received more than 300 UVB treatments, patients with skin types 1 or 2, patients who received more than 200 PUVA treatments), but these were not statistically significant, possibly owing to limitations of statistical power. In addition, there may have been under ascertainment of lymphoma outcomes in the PUVA cohort study since there was a significant degree of loss to follow-up and a significant percentage of lymphomas were only identified by searching the national death index [86].

#### Cardiovascular & metabolic disease

Epidemiological studies in Sweden, Germany and the USA have demonstrated an association between psoriasis and cardiovascular disease (CVD) [87–89]. Mallbris and colleagues found that a Swedish cohort of patients with a history of hospital admission for psoriasis had an overall increased risk of CVD mortality of 50% compared with the general population (standardized mortality ratio [SMR]: 1.52; 95% CI: 1.44–1.60) [89]. However, this finding was not supported by Stern and colleagues who found no evidence of increased cardiovascular mortality in psoriasis patients receiving PUVA treatment compared with the general population (SMR: 0.83; 95% CI: 0.7–1.0) [90]. These studies are limited in that they are of highly selected patient populations, utilized an external comparison group, which can introduce bias, and did not control for other cardiac risk factors, which may confound the relationship between psoriasis and CVD. In addition to smoking and obesity, several studies suggest that cardiovascular risk factors, such as diabetes, hypertension and hyperlipidemia, are more prevalent in psoriasis patients [11,87,88,91–96]. In particular, diabetes has shown a strong association with severe psoriasis (OR: 1.62; 95% CI: 1.3–2.01) independent of other risk factors for diabetes, such as obesity [34]. Although evolving evidence suggests that psoriasis is associated with a variety of cardiovascular risk factors, recent studies suggest that psoriasis itself is an independent risk factor for developing coronary artery disease and myocardial infarction (MI), possibly owing to shared immunological pathways that function abnormally in both diseases [33,97]. For example, severe psoriasis confers a similar independent risk of MI to diabetes and the relative risk is higher in younger psoriasis patients and declines towards baseline in patients aged 70 years or older [33].

#### Psychiatric disease

Multiple studies, the majority of which are descriptive, have examined psychological characteristics of patients with psoriasis [98–100]. A wide range of problems have been described, such as depression, anxiety, obsessive behavior, sexual dysfunction and suicidal ideation [101–106], and the clinical severity of the psoriasis may not reflect the degree of emotional impairment. A study comparing 50 patients with psoriasis in outpatient

clinics with 50 healthy controls found that patients with psoriasis had a higher average score in the Beck Depression Inventory (BDI) (16.96 vs 5.48, respectively;  $p < 0.01$ ) [107]. Suicidal ideation was found to be present in 7.2% of patients hospitalized for psoriasis, 2.5% of psoriasis outpatients and 2.4–3.3% of general medical patients, suggesting that patients with more severe disease may suffer greater emotional impairment [98]. Psychological distress may also impair response to psoriasis therapies. For example, in a cohort of psoriasis patients treated with PUVA, pathological 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 [108].

#### *Psoriatic arthritis*

Joint diseases are common among patients with psoriasis [109]. Psoriatic arthritis is defined as a rheumatoid factor-negative inflammatory arthritis associated with psoriasis [110]. The prevalence of psoriatic arthritis varies greatly by skin severity [111,112]. Population-based studies, which are broadly representative of all patients with psoriasis, have found the prevalence of psoriatic arthritis in patients with psoriasis to be 6.25% in Olmstead County (MN, USA) and 11% in the continental US population, whereas studies in psoriasis patients from referral centers and advocacy groups (which are skewed towards patients with more extensive skin disease compared with the general population) have found prevalences of psoriatic arthritis of approximately 30% [109,111,113].

In the majority of patients, psoriatic arthritis tends to appear several years after the onset of skin lesions; however, it can precede the skin disease in approximately 13–17% of cases [114]. Nail lesions may help to identify those patients with psoriasis who are at higher risk of developing arthritis as these lesions occur in 80–90% of patients with psoriatic arthritis compared with 46% in those with psoriasis uncomplicated by arthritis [115]. Although the severity of skin psoriasis predicts the prevalence of psoriatic arthritis, it does not reliably correlate with the severity of psoriatic arthritis symptoms and signs [115]. Broadly representative, population-based studies suggest that the incidence of structural damage in psoriatic arthritis is low (<10%) and that the disease does not impact on mortality [113]. Studies from tertiary-care centers, which are skewed towards patients with more severe disease, have demonstrated a higher risk of mortality for patients with psoriatic arthritis and have found higher overall frequencies of destructive joint changes [114,116]. Several HLA types have been associated with psoriatic arthritis, suggesting a genetic predisposition to developing this disease [35,117,118].

#### *Systemic treatment*

Traditional systemic therapies for psoriasis include phototherapy (broad-band UVB, narrow-band UVB, PUVA), methotrexate, cyclosporine, and acitretin. Although generally well tolerated, oral therapies for psoriasis are limited by a variety of side effects that are relatively common and occur in more than 5% of patients [119]. For example, a recent study

demonstrated that 30% of psoriasis patients discontinue methotrexate therapy within 1 year, mainly owing to drug intolerance [120]. In addition, there is concern regarding long-term exposure to oral medications owing to the potential of damage to the liver (methotrexate), kidneys (cyclosporine), bone (acitretin) or skin (psoralen). As a result, these therapies are used in only approximately 5% of patients with psoriasis [9,21]. The treatment of psoriasis is currently undergoing a revolution with the advent of biological therapies, which target specific aspects of the immune system involved in psoriasis, such as cytokines (e.g., tumor necrosis factor [TNF]- $\alpha$  targeted by adalimumab, etanercept and infliximab) and T-cell function (e.g., alefacept and efalizumab). Biologicals are generally well tolerated and appear to be associated with very low risks of organ damage and serious side effects (TABLE 1).

#### *TNF- $\alpha$ antagonists*

TNF- $\alpha$  is a pro-inflammatory cytokine associated with Th1 immune responses and plays a critical role in cell-mediated immunity through enhancing the activity of antigen-presenting cells, cytolytic T cells and natural killer cells, while, at the same time, suppressing the maturation and proliferation of Th2 cells (which are involved in atopy and allergic reactivity as well as the response to some parasites). Overproduction of TNF- $\alpha$  in patients with psoriasis and psoriatic arthritis can lead to tissue disruption, joint injury, and keratinocyte hyperproliferation [121]. High levels of TNF- $\alpha$  in psoriatic lesions and psoriatic arthritis synovial fluid, as well as correlations between disease severity and TNF- $\alpha$  levels, provide a strong rationale for the role of this cytokine in psoriasis [122]. Three types of TNF- $\alpha$  antagonists are commercially available and all have demonstrated efficacy for psoriasis and psoriatic arthritis.

#### *Adalimumab*

Adalimumab is a fully humanized, recombinant immunoglobulin (Ig)G1 monoclonal antibody that is specific for human TNF- $\alpha$ . It is approved by the US FDA for treatment of ankylosing spondylitis, rheumatoid arthritis (RA) and, more recently, psoriatic arthritis. Adalimumab binds and neutralizes TNF- $\alpha$ , thereby blocking the binding and activation of p55 and p75 receptors. In a controlled trial, patients were randomized into three groups to receive a loading dose of 80 mg at week 0 followed by either 40 mg of subcutaneous adalimumab weekly (starting at week 2) or 40 mg of adalimumab every other week (starting at week 1) versus placebo. After 12 weeks, 80% of patients treated with 40 mg of adalimumab weekly and 53% of patients taking 40 mg of adalimumab every other week compared with 4% of patients taking placebo achieved 75% improvement in the Psoriasis Area and Severity Index score (PASI 75) ( $p < 0.001$ ) [123].

#### *Etanercept*

Etanercept is a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of the p75 human TNF receptor and the human constant (Fc) portion of human IgG<sub>1</sub>

Table 1. Overview of biologicals for psoriasis.

Drug	Molecular structure	Pharmacodynamic and pharmacokinetics	Dosing	PASI 75 summary	Required screening tests and lab monitoring per US FDA	Suggested additional considerations for screening and periodic monitoring
Adalimumab* (Humira®)	Fully humanized, recombinant IgG <sub>1</sub> monoclonal antibody, which is specific for human TNF- $\alpha$ .	Binds soluble and transmembrane TNF- $\alpha$ , inhibiting activation of TNF- $\alpha$ receptors. Mediates lysis of TNF-producing cells. Half-life: 10–20 days	40 mg SC every other week <sup>†</sup>	ADEPT 2006 [123] At week 12 PBO 4% 80 mg at week 0, then 40 mg EOW starting at week 1 53% 80 mg at week 0, 1 then 40 mg QW starting at week 2 80%	Screen for latent tuberculosis infection. Evaluate patients at risk for hepatitis B for previous HBV infection prior to beginning therapy	HIV in those at risk. Blood count and liver function tests. History and physical exam as necessary to detect symptoms of infection, cancer, congestive heart failure, demyelination. Baseline chest X-ray in those at risk for fungal infections. Annual screening for tuberculosis. Update vaccinations
Etanercept (Enbrel®)	Recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of the p75 human TNF receptor and the Fc portion of human IgG1 antibody	Binds primarily soluble TNF- $\alpha$ and blocks its interaction with TNF receptor. Also binds and blocks the activity of lymphotoxin- $\alpha$ . Half-life: 4–12.5 days	50 mg SC weekly for 12 weeks, followed by 50 mg SC given once weekly <sup>†</sup>	Gottlieb 2003 [124] At week 12 PBO 2% 25 mg SC BW 30% Leonardi 2003 [126] At week 12 PBO 4% 25 mg SC BW 34% 50 mg SC BW 49% Papp 2005 [125] At week 12 PBO 3% 25 mg SC BW 34% 50 mg SC BW 49%	Evaluate patients at risk for hepatitis B for previous HBV infection prior to beginning therapy	HIV in those at risk. Screen for latent tuberculosis infection. Blood count and liver function tests. History and physical exam as necessary to detect symptoms of infection, cancer, congestive heart failure, demyelination. Baseline chest X-ray in those at risk for fungal infections. Annual screening for tuberculosis. Update vaccinations
Infliximab (Remicade®)	Chimeric human and murine IgG 1K monoclonal antibody against TNF- $\alpha$	Binds soluble and transmembrane TNF- $\alpha$ , inhibiting activation of TNF- $\alpha$ receptors. Blocks assembly of TNF. Mediates lysis of TNF-producing cells. Half-life: 8–9.5 days	5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks <sup>†</sup>	Reich 2005 [127] At week 10, PBO 3% 5 mg/kg IV (at weeks 0,2,6) 80%	Screen for latent tuberculosis infection. Evaluate patients at risk for hepatitis B for previous HBV infection prior to beginning therapy. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury	HIV in those at risk. Blood count and liver-function tests. History and physical exam as necessary to detect symptoms of infection, cancer, congestive heart failure, demyelination. Baseline chest X-ray in those at risk for fungal infections. Annual screening for tuberculosis. Update vaccinations

\*FDA approved dosing for psoriatic arthritis. Psoriasis dosing to be determined.

<sup>†</sup>TNF inhibitors have also been studied extensively in combination with methotrexate in the rheumatoid arthritis population.

<sup>§</sup>Note that PASI75 was for throughout the study period and not at week 12 only. Therefore, this estimate probably overestimates the efficacy at week 12.

ADEPT: Adalimumab Effectiveness in Psoriatic arthritis Trial; APC: Antigen-presenting cell; BW: Biweekly; EOW: Every other week; Fc: Fragment crystallizable; ICAM: Intracellular adhesion molecule; IV: Intravenous; HBV: Hepatitis B virus; IM: Intramuscular; LFA: Leukocyte function antigen; PASI 75: 75% improvement on the Psoriasis Area and Severity Index; PBO: Placebo; QW: Every week; TNF: Tumor necrosis factor.

Table 1. Overview of biologicals for psoriasis (cont.).

Drug	Molecular structure	Pharmacodynamic and pharmacokinetics	Dosing	PASI 75 summary	Required screening tests and lab monitoring per US FDA	Suggested additional considerations for screening and periodic monitoring
Alefacept (Amevive <sup>®</sup> )	Dimeric fusion protein consisting of the CD2-binding portion of LFA-3 linked to the constant portion of a human IgG <sub>1</sub> antibody	Binds CD2 on activated T cells, blocking activation by inhibiting costimulatory signals delivered by LFA-3 on APCs. Half-life: 11.25 days after IV administration	15 mg IM once weekly. Usual duration of treatment is 12 weeks	Lebwohl 2003 [157] Received treatment for 12 weeks PBO 13% 15 mg IM OW 33% <sup>§</sup>	Baseline CD4 <sup>+</sup> T-lymphocyte count. During treatment, CD4 <sup>+</sup> lymphocyte counts every 2 wks (withhold dosing if CD4 <sup>+</sup> counts are <250 cells/ $\mu$ l and monitor weekly. Do not re-treat with alefacept if below 250 for 1 month) Patients with signs of symptoms of liver injury should be fully evaluated	HIV in those at risk. Screen for latent tuberculosis infection. Liver function tests. Baseline chest X-ray in those at risk for fungal infections. History and physical exam as necessary to detect symptoms of infection, cancer and arthritis. Update vaccinations
Efalizumab (Raptiva <sup>®</sup> )	Recombinant humanized monoclonal antibody which binds to CD11a, a subunit of LFA-1 on lymphocytes	Inhibits the interaction of LFA-1 and ICAM-1 on APCs and vascular endothelial cells, blocking T-cell activation and decreasing trafficking into skin. Half-life: 6.21 days	0.7 mg/kg followed by weekly doses of 1 mg/kg (max: 200 mg/dose) at week 1	Gordon 2003 [164] At week 12 PBO 4% Conditioning dose of 0.7 mg/kg (wk 0), then 1 mg/kg SC OW at week 1 27%	Platelet count at baseline and then every month during treatment (every 3 months with continued therapy). Patients should be closely observed for psoriasis worsening upon discontinuation of efalizumab, including nonresponders	HIV in those at risk. Screen for latent tuberculosis infection. Complete blood count when checking platelets. Baseline chest X-ray in those at risk for fungal infections. History and physical exam as necessary to detect symptoms of infection, cancer and arthritis. Update vaccinations prior to initiating efalizumab

\*FDA approved dosing for psoriatic arthritis. Psoriasis dosing to be determined.

<sup>†</sup>TNF inhibitors have also been studied extensively in combination with methotrexate in the rheumatoid arthritis population.

<sup>‡</sup>Note that PASI75 was for throughout the study period and not at week 12 only. Therefore, this estimate probably overestimates the efficacy at week 12.

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antibody, which together exhibit higher affinity for TNF- $\alpha$  than the naturally occurring TNF receptors. Etanercept is approved for treatment of ankylosing spondylitis, RA, juvenile RA (ages 4–17 years), psoriasis and psoriatic arthritis. Two large-scale Phase III trials have evaluated the safety and efficacy of etanercept in the treatment of psoriasis [124,125]. In a randomized, placebo-controlled clinical trial, PASI 75 at week 12 was achieved by 4% of the placebo group, 34% of the 25-mg subcutaneous biweekly and 49% of the 50-mg subcutaneous biweekly group [126].

#### *Infliximab*

Infliximab is a chimeric IgG 1K monoclonal antibody against TNF- $\alpha$  that possesses the Fc region and a murine variable region. Infliximab is approved by the FDA for treatment of ankylosing spondylitis, Crohn's disease, RA, ulcerative colitis and, recently, for the treatment of psoriatic arthritis and psoriasis. In Phase III trials, 80% of patients treated with 5 mg/kg intravenous infliximab at weeks 0, 2 and 6, then every 8 weeks, versus 3% of those receiving placebo achieved PASI 75 by week 10 ( $p < 0.001$ ) [127]. However, at week 50, only 61% of the infliximab-treated patients had a 75% reduction in PASI scores owing in part to the development of neutralizing antibodies [127]. For example, among patients who achieved PASI 75 at week 10, 39% ( $n = 20$ ) who were positive for antibodies to infliximab maintained this response through to week 50 compared with 81% ( $n = 106$ ) and 96% ( $n = 22$ ) of antibody-negative and inconclusive patients, respectively [127].

#### *Comparison of TNF inhibitors*

Although all three drugs inhibit TNF- $\alpha$ , they are structurally diverse and have differing pharmacodynamic and pharmacokinetic profiles. For example, all three biologicals bind TNF- $\alpha$ , but only etanercept binds lymphotoxin- $\alpha$ , a member of the TNF family [128]. Infliximab and adalimumab bind to both soluble and membrane-bound TNF, whereas etanercept binds primarily to soluble TNF [129]. Infliximab binds TNF quickly and irreversibly, whereas etanercept sheds approximately 50% of soluble TNF within 10 min of binding [130]. In addition, infliximab blocks TNF activity by interfering with its assembly [131]. Infliximab and adalimumab may also have a greater propensity to cause lymphocyte apoptosis compared with etanercept, as they can lyse cells with membrane-bound TNF through complement activation and/or antibody-dependent cell-mediated cytotoxicity [130]. In terms of pharmacokinetics, the subcutaneous administration of adalimumab and etanercept leads to smooth and uniform concentration time profiles at steady state, whereas the intravenous dosing of infliximab results in very high peak:trough ratios [132]. The half-lives of these biologicals are 8–9.5 days for infliximab, 10–20 days for adalimumab and 4–12.5 days for etanercept. The pharmacodynamic and pharmacokinetic differences among TNF inhibitors may result in differing safety and efficacy profiles. For example, infliximab appears to be more efficacious than etanercept in granulomatous diseases, such as

Crohn's, sarcoidosis and Wegener's granulomatosis [130]. However, infliximab may be associated with a higher risk of granulomatous infections [133].

#### *Cautions & contraindications for prescribing TNF-inhibitors*

TNF inhibitors are immunosuppressive and, therefore, patients should be screened carefully for signs and symptoms of malignancy and infection prior to initiating and during the course of treatment. Product labeling suggests screening for latent tuberculosis (TB) infection with a tuberculin skin test prior to initiating therapy with infliximab and adalimumab. However, published guidelines suggest TB screening for all three TNF inhibitors [134]. Physicians should also monitor patients for signs and symptoms of active TB, including patients who tested negative for latent TB infection during treatment with TNF inhibitors [135,136]. For example, in a recent trial of infliximab for psoriasis, two patients who tested negative for latent TB developed active TB during the study [137]. If the patient has active TB, TNF inhibitor therapy should be withheld until the active infection is treated and resolved. If the patient has latent TB (positive tuberculin skin test and normal chest x-ray), latent TB therapy should be instituted according to current guidelines and TNF-inhibitor therapy can then be considered [138]. TNF inhibitors are associated with serious infections, including pneumonia, sepsis, TB, histoplasmosis and coccidioidomycosis. A meta-analysis by Bongartz and colleagues of RA patients treated with infliximab or adalimumab within randomized controlled trials, suggests that the use of these agents results in one excess serious infection for every 59 patients treated for a period of 3–12 months [139]. A recent cohort study from France found a relative risk of pneumonia due to legionella of 16.5–21 in patients treated with TNF inhibitors for conditions other than psoriasis [140]. The generalizability of these studies to the psoriasis population is unclear as patients with serious infections were often treated with TNF inhibitors in combination with other immune suppressants. The use of etanercept with the interleukin-1 receptor antagonist Anakinra has been associated with an increased risk of serious infections and, therefore, Anakinra is contraindicated with any TNF inhibitor.

To lower the risk of infection associated with TNF inhibitors, one may consider vaccination against common serious infections, such as pneumonia and influenza. TNF inhibitors may lower the titer response to immunizations and it is recommended that patients be current with immunizations prior to initiation of therapy. Nevertheless, it appears that vaccination against influenza and pneumococcus is likely to be efficacious in patients being treated with TNF inhibitors, although it is possible that vaccine-associated titers may be reduced [141,142]. It is important to note that live vaccines have generally been contraindicated during treatment with TNF inhibitors.

TNF inhibitors should be used with caution in patients with a history of congestive heart failure (CHF) and infliximab at doses over 5 mg/kg is contraindicated in patients with moderate-to-severe CHF as studies suggest that it may increase mortality in this patient population [135,143]. Infliximab may be associated

with liver-function test abnormalities, which, in rare cases, have indicated liver failure. In addition, all three TNF- $\alpha$  antagonists have been associated with reactivation of hepatitis B in patients who are chronic carriers and some of these cases have been fatal [136,144]. Therefore, one may consider monitoring liver-function tests during TNF therapy and screening patients for hepatitis B if the patient is at risk of hepatitis B infection. In patients with chronic active hepatitis B infection, use of lamivudine during TNF inhibitor therapy may improve safety; however, careful monitoring is necessary in this setting [145].

There is theoretical concern that TNF inhibitors may increase the risk of certain malignancies, such as lymphoma [139,146,147]. Observational cohort studies have indicated a potential increased risk of lymphoid malignancies in RA patients treated with infliximab or etanercept [146,147]. It is not certain whether the excess risk of malignancy is due to the drug or the underlying disease itself as RA and psoriasis may independently confer a greater risk of lymphoma. An increased risk of solid organ malignancies in RA patients treated with infliximab or adalimumab compared with control patients was observed in a meta-analysis of randomized, controlled trials [139]. Limitations of this study include a longer observation time for the treatment group compared with the control group, and the inclusion of skin cancers as evidence of solid organ malignancies (which comprised over 35% of cancers). Etanercept was associated with an increased risk of solid organ cancer when administered concurrently with cyclophosphamide in a randomized, controlled trial for Wegener's granulomatosis and, therefore, TNF inhibitors should not be used concurrently with cyclophosphamide [148].

TNF inhibitors have been associated with rare cases of new onset and exacerbation of existing demyelinating disease (e.g., multiple sclerosis), as well as the development of anti-nuclear antibodies and anti-double-stranded DNA antibodies. The clinical significance of this is unknown and, rarely, TNF inhibitors have been associated with lupus-like syndromes and vasculitis. In addition to the development of autoantibodies, anti-infliximab neutralizing antibodies have been reported among patients treated with infliximab for a variety of indications [127,149,150]. In a randomized, double blind, placebo-controlled study, 20–27% of psoriasis patients treated with 3 or 5 mg/kg intravenous infliximab at weeks 0, 2 and 6 developed neutralizing antibodies by week 26 [151]. The generation of neutralizing antibodies to infliximab is associated with an increased risk of infusion reactions (e.g., anaphylaxis) and with decreased efficacy [152]. Concomitant treatment with methotrexate, as well as regular (as opposed to intermittent) dosing, reduces the incidence of neutralizing antibodies [149].

#### T-cell inhibitors

##### *Alefacept*

Alefacept is a dimeric fusion protein consisting of the extracellular CD2-binding portion of the human leukocyte function antigen (LFA)-3 linked to the Fc portion of human IgG<sub>1</sub>

antibody. Alefacept binds to CD2 on activated T cells and blocks activation by inhibiting costimulatory signals delivered by LFA-3 on antigen-presenting cells [153]. It also triggers apoptosis of activated memory T cells expressing high levels of CD2 through binding of Fc $\gamma$ R/III IgG receptors on natural killer cells and macrophages [154]. Alefacept has also shown promise in the treatment of psoriatic arthritis, either as monotherapy or in combination with methotrexate; however, additional studies are necessary to determine whether or not alefacept should be indicated for psoriatic arthritis [155,156].

An international Phase III study evaluated the efficacy and safety of weekly intramuscular alefacept treatment in patients with moderate-to-severe chronic plaque psoriasis for 12 weeks with follow-up to week 24 [157]. During the study period, 13% of the placebo group versus 33% of the 15-mg group achieved PASI 75. Of patients in the 15-mg group who achieved at least PASI 75 reduction 2 weeks after the last dose, 71% maintained at least 50% improvement in PASI throughout the 12-week follow-up [157]. Alefacept is typically initiated as a 15-mg intramuscular dose administered weekly for 12 weeks, followed by a 12-week observation period. On the basis of a recent study, improved efficacy may be achieved by increasing the initial treatment course to 16 weeks [158]. Phase III clinical trials have demonstrated increased efficacy of alefacept with successive courses of treatment [159,160].

#### Cautions & contraindications for prescribing alefacept

The main safety concern regarding alefacept therapy is the induction of dose-dependent lymphopenia, specifically CD4<sup>+</sup> T cells (up to 10% of patients require temporary discontinuation) [161]. As a result, monitoring of CD4 T-cell counts is required before initiation of therapy and every 2 weeks during the 12-week treatment. Treatment should be held and T-cell counts monitored weekly if the CD4<sup>+</sup> T-cell count drops below 250 cells/ $\mu$ l. Alefacept should be discontinued if CD4<sup>+</sup> T-cell counts remain below 250 cells/ $\mu$ l for 1 month [161]. The half-life of intramuscular alefacept is 270 h (11.25 days) and therefore, depressed T-cell counts may take time to recover in selected patients. The FDA recommends that alefacept should not be used in patients with HIV or in patients with a CD4<sup>+</sup> T-cell count below normal owing to the possibility of lymphopenia [161]. Alefacept is well tolerated with a limited side-effect profile. Abnormalities in liver-function tests were more frequent in alefacept-treated patients compared with placebo, and serious liver reactions have been reported in the postmarketing arena. Therefore, patients with signs or symptoms of liver injury should be evaluated fully. Alefacept is immunosuppressive and, thus, may theoretically be associated with a higher risk of infections and malignancies. In a study of psoriasis patients treated with intravenous alefacept for 12 weeks, CD4<sup>+</sup> T-cell-mediated antibody responses remain intact as measured by titer responses to neoantigen  $\Phi$ X174 and recall antigen tetanus toxoid immunization and were comparable to controls; however, the efficacy of influenza and pneumococcal vaccines in patients treated with alefacept has not been

published at this time [162]. Long-term follow-up studies are necessary to determine whether or not the immunosuppressive properties of alefacept increase the risk of serious infections and malignancies. Alefacept should be used with caution in patients with a history of systemic malignancy and in patients who are prone to infection.

#### *Efalizumab*

Efalizumab is a recombinant, humanized monoclonal antibody that inhibits the interaction between LFA-1 on lymphocytes and intracellular adhesion molecule (ICAM-1). Blockade of the binding of LFA-1 and ICAM-1 on antigen-presenting cells contributes to inhibition of T-cell activation and reactivation. By inhibiting the same interaction on vascular endothelial cells, efalizumab inhibits T-cell trafficking to the dermis and epidermis [163]. Subcutaneous dosing of efalizumab with an initial 0.7 mg/kg conditioning dose, followed by weekly dosing of 1 mg/kg, is FDA-approved for the treatment of moderate-to-severe plaque psoriasis. Efalizumab is not effective for the treatment of psoriatic arthritis. A Phase III trial assessed the efficacy and safety of efalizumab 1 mg/kg subcutaneous weekly in patients with moderate to severe plaque psoriasis [164]. A total of 27% of efalizumab-treated patients achieved PASI-75 versus 4% of the placebo group ( $p < 0.001$ ).

#### Cautions & contraindications for prescribing efalizumab

Initial and periodic assessment (monthly for the first 3 months and then every 3 months with continued treatment) of platelet counts and blood counts are recommended for patients receiving efalizumab, given a small but important risk for thrombocytopenia (platelets  $< 52,000$  cell/ $\mu$ l occurred in 0.3% of patients) and hemolytic anemia [165]. Influenza-like symptoms have been reported among patients after the first few doses, however, these symptoms are rare after the third dose and the incidence can be lowered by starting with a conditioning dose. Exacerbation of psoriasis while on treatment, as well as rebound flares upon abrupt discontinuation of therapy, has also been reported. Serious flares have included the development of inflammatory, pustular and erythrodermic psoriasis and occurred in 0.7% of patients in clinical trials [166]. Patients experiencing serious flare may require management with hospitalization and cyclosporine and methotrexate appear to be more efficacious than systemic steroids or retinoids in managing this complication [167]. Efalizumab is immunosuppressive and, therefore, may theoretically be associated with a higher risk of infections and malignancies. Long-term studies in large numbers of treated patients are necessary to determine whether or not efalizumab is associated with an increased risk of serious infections and malignancy. Efalizumab should be used with caution in patients with a history of systemic malignancy and in patients who are prone to infection. Acellular, live and live attenuated vaccines should not be administered during efalizumab treatment according to product labeling [165]. Efalizumab impairs anti-

body class-switching from IgM to IgG after exposure to bacteriophage  $\Phi$ X174 neoantigen and results in a decreased response to tetanus booster immunization (however, titers in the protective range are developed) [168,169]. There are currently no published data on the safety and efficacy of influenza and pneumococcal vaccination in patients being actively treated with efalizumab.

#### Conclusion

Tremendous advances have been made in our understanding of the epidemiology and treatment of psoriasis. Emerging evidence suggests that potentially modifiable exposures, such as smoking, stress and obesity, may increase the risk of developing psoriasis. In addition, a breadth of studies indicate that psoriasis is associated with a variety of comorbidities and the disease itself may be a risk factor for developing atherosclerosis, MI and, possibly, diabetes. The advent of biological therapies have dramatically expanded the therapeutic options for patients with psoriasis and appear to be better tolerated than traditional oral therapies for psoriasis.

#### Expert commentary

Despite numerous epidemiological studies of psoriasis, there is still a need for population-based observational studies to further identify and confirm modifiable risk factors for developing psoriasis, as well as prospective data on the natural history and determinants of psoriasis remission and flare. Studies of comorbidities in psoriasis patients should focus on which diseases are independently associated with psoriasis, as well as determining the directionality of association. Observational studies and interventional trials will be necessary to determine whether modification of certain risk factors (e.g., smoking, obesity) decreases the risk of psoriasis and/or decreases psoriasis severity and if treatment of psoriasis can prevent the onset of comorbidities, such as psoriatic arthritis and MI. Large, long-term, comparative clinical trials are necessary to best determine which biological therapies are most efficacious, safe and cost-effective in the treatment of moderate-to-severe psoriasis. Although traditional oral therapies are associated with significantly less direct economic costs to payers, patients and physicians often prefer biologicals owing to their better tolerability and perceived long-term safety [170]. When initiating treatment with a biological, TNF inhibitors are considered by some to be a first-line therapy over T-cell inhibitors in patients who do not have contraindications (e.g., history of demyelinating disease, CHF), particularly if the patient has concomitant psoriatic arthritis [171,172]. Etanercept is generally recommended over infliximab unless rapid disease control is necessary (e.g., erythroderma, pustular psoriasis, hospitalized patients). Adalimumab is also an important treatment option; however, it is not yet approved by the FDA for psoriasis. Prior to the initiation of long-term immunosuppressive therapy of psoriasis, patients should have age-appropriate malignancy screening, screening for infections including purified protein

derivative and a chest X-ray in those at risk for fungal infections. Vaccinations should also be updated prior to the initiation of these therapies and influenza and pneumococcal vaccination should be considered. Long-term follow-up studies with appropriate control groups and statistical power are necessary to determine the risk of malignancy and serious infections in patients treated with biologicals.

#### Five-year view

Studies in the next 5 years should focus on better understanding the natural history of chronic plaque psoriasis in order to identify which patients may experience spontaneous remissions and which patients may experience flares of their disease. Large, broadly representative case-control studies can further investigate potential risk factors for developing psoriasis and future intervention trials can determine whether altering modifiable risk factors, such as stress, smoking and obesity, leads to a lower risk of psoriasis or modifies psoriasis severity. Determining the relative importance of psoriasis, its treatments and its associated behaviors on the risk of developing comorbidities, such as CVD, diabetes, cancer and other diseases, will allow us to better counsel patients with psoriasis and interpret long-term safety data on novel therapies for psoriasis. Long-term studies of biologicals in large numbers of patients with psoriasis will provide important data on the efficacy and safety profiles of these agents over time. Comparative randomized control trials of various systemic therapies in psoriasis patients will be important to developing robust, evidence-based guidelines for the treatment of moderate-to-severe psoriasis.

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<http://216.197.104.3/ebderm/newIndex.cfm>  
Centre for Health Evidence.  
[www.cche.net/usersguides/main.asp](http://www.cche.net/usersguides/main.asp)

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#### Key issues

- Psoriasis is a common disease, affecting 0.6–4.8% of the human population.
- Age, gender, geography and ethnicity are important determining factors in the prevalence of psoriasis.
- Family history is the most well-established risk factor for developing psoriasis and emerging evidence suggests that modifiable conditions, such as smoking, stress and obesity, may also be risk factors.
- Psoriasis has been associated with a variety of other comorbidities, such as psoriatic arthritis, cardiovascular disease, cancer, diabetes and psychiatric disease, and may be an independent risk factor for atherosclerosis and myocardial infarction.
- Novel biological therapies that inhibit tumor necrosis factor- $\alpha$  (adalimumab, etanercept, infliximab) or T cells (alefacept, efalizumab) play a key role in the treatment of moderate-to-severe psoriasis.
- Pharmacokinetics, pharmacodynamics, efficacy and safety profiles vary among biologicals and, therefore, drug and patient factors are important in selecting the optimum therapy.

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