

**CLINICAL REVIEW**

# Psoriasis Vulgaris: An Evidence-Based Guide for Primary Care

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**Psoriasis vulgaris is a chronic, sometimes debilitating, inflammatory disorder with multiple pathways of pathogenesis that can be associated with metabolic and cardiovascular disease. This article aims to be a comprehensive, literature-based review of the epidemiology, genetic factors, clinical diagnosis, treatments, and pharmacology for psoriasis as derived from articles published in PubMed. Levels of evidence and recommendations were made according to the strength of recommendation taxonomy. This article is divided into 2 sections: the first is clinical and diagnostic, the second is therapeutic. This review serves as a practical, evidence-based, and unbiased guide for primary care practitioners. (J Am Board Fam Med 2013;26:787–801.)**

**Keywords:** Dermatology, Primary Health Care, Psoriasis, Skin Diseases

Psoriasis is a chronic inflammatory disease that affects up to 5% of the world's population.<sup>1</sup> Current estimates put the prevalence of psoriasis at up to 7.5 million cases in the United States. It is more common in whites and those who live farther from the equator, and it is equally common in men and women.<sup>2</sup> Psoriasis is more common with certain human leukocyte antigen (HLA) subtypes, but these cannot be distinguished histologically or clinically and there is no apparent difference in the response to therapy.<sup>2</sup> Psoriasis can generally be divided into 2 types: Type 1 psoriasis shows a strong family history for the disease, demonstrates an association with HLA-CW6,<sup>3</sup> and usually presents before 40 years of age.<sup>2</sup> Type 2 is not familial in presentation, has no association with HLA-CW6,<sup>3</sup> and usually presents after 40 years of age.<sup>2</sup>

## Methods

The literature published in PubMed from 2000 to 2012 was searched using the following key words: *psoriasis, treatments, clinical trials, and reviews*. Abstracts were included only if they were clinically relevant; the articles were downloaded as portable document files. The first author (EAK) performed the literature search, captured and processed the articles, and determined the strength of recommendation taxonomy (SORT) criteria with level of evidence (1–3).<sup>4</sup>

## Diagnostics

Table 1 describes the pathogenesis of psoriasis, and Table 2 lists risk factors and comorbidities that can contribute to the development of moderate or severe psoriasis. The diagnosis of psoriasis can be determined clinically (Table 3) and histologically, if needed. Before treatment for psoriasis can be initiated, the grading and severity must be determined (Table 4).

## Topical Treatments

### **Topical Corticosteroids (SORT Criteria Recommendation A, Level of Evidence 1)**

#### *Dosing and Side Effects*

Choosing the strength of topical steroids and vehicle of administration is important in order to obtain the most benefit with the least potential for side

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**Table 1. Pathogenesis of Psoriasis**

Pathway	Producer	Action in Psoriasis
TNF- $\alpha$ (over expressed in psoriasis) <sup>5</sup>	Macrophages, T cells, mast cells, granulocytes, natural killer cells, fibroblasts, neurons, keratinocytes, and smooth muscle cells <sup>5</sup>	Increases the release of cytokines by lymphocytes and chemokines by macrophages <sup>6</sup> Increases expression of adhesion molecules attracting neutrophils and macrophages to the lesions by activation of the vascular endothelium <sup>6</sup> Induces keratinocyte and endothelial cell neovascularization stimulating the inflammatory process <sup>6</sup>
IL-12/23 (upregulated in psoriasis) <sup>7</sup>		IL-12 promotes the differentiation of naive CD4+ T lymphocytes to Th1 cells. <sup>7</sup> IL-12 triggers the specialization of CD4 and CD8 T lymphocytes by major histocompatibility complex class I and II, respectively, via antigen-presenting cells, which convert CD4+ cells into Th cells and CD8+ into cytotoxic T cells. <sup>6</sup> As a result, TNF- $\alpha$ , IL-2, interferon- $\gamma$ , and other cytokines are produced. <sup>6</sup>
Th17	Th17 cells produce IL-17, a potent proinflammatory cytokine	IL-17 directly perpetuates further inflammation of the keratinocyte, but it also indirectly stimulates production of IL-6. <sup>8</sup>

IL, interleukin; Th, T helper; TNF, tumor necrosis factor.

effects. It is possible to treat the majority of patients if a physician has a good grasp on the use of just 3 classes of steroids: superhigh potency (class I), mid/high potency (class III), and low potency (class VI). Steroids should be used with caution on the face,

groin, axilla, and breasts because these areas are more sensitive to topical steroid penetration and can develop striae.<sup>15</sup> The usual dosage for topical steroids is twice per day for 2 weeks, but this can range depending on the severity and location of the psoriasis and the strength of the steroid used. For example, a superpotent steroid limited to <5% body surface area can be used twice daily for up to 2 weeks on the body but avoiding the face and intertriginous regions. Atrophy, telangiectasia, and striae<sup>15</sup> are always a concern, especially when topical steroids are used for long periods of time or used on the groin, axilla, or under occlusion.

**Table 2. Risk Factors and Comorbidities for Moderate to Severe and Severe Psoriasis<sup>2,5,9,10</sup>**

- Psoriatic arthritis (25% of psoriatics develop PsA<sup>2</sup>)
- Genetic predisposition to autoimmune disease
- TNF- $\alpha$  deregulation
- Elevated C-reactive protein increases risk of diseases like Crohn's, multiple sclerosis, cardiovascular disease (myocardial infarction and stroke), depression, and lymphoma (compared to the nonaffected age- and sex-matched population)\*
- More likely to smoke
- Have HTN
- Have diabetes, obesity, and hypercholesterolemia
- Even when corrected for above risk factors (hypercholesterolemia, diabetes, HTN, and obesity), patients with severe psoriasis have an elevated incidence of myocardial infarction compared with age-matched patients without psoriasis<sup>2,11</sup>
- Control of HTN, cholesterol, weight, and diabetes can assist in decreasing psoriasis burden and frequency of flares<sup>2</sup>
- Moderate to severe psoriasis is associated with depression, suicide,<sup>9</sup> and rarely lymphoma<sup>10</sup>; this risk increases with disease burden

\*Because of this baseline elevation in inflammatory markers, especially in patients with moderate to severe plaque psoriasis, risk for certain diseases like multiple sclerosis,<sup>12</sup> lymphoma,<sup>13</sup> and myocardial infarction may be elevated even further with use of a TNF- $\alpha$  blocker.<sup>2,10</sup> On the other hand, patients with moderate to severe psoriasis with depression and suicidal ideation who are placed on etanercept, a TNF- $\alpha$  blocker, may improve both their psoriasis and their depression.<sup>9,14</sup>  
TNF, tumor necrosis factor; HTN, hypertension.

### Vehicles

Topical steroid compounds come in various vehicles, which can determine the area of application, level of efficacy, and possible side effects. Lotions are water-based, weakest in strength, and evaporate. Shampoos may be used for psoriasis on the scalp but limited contact time limits efficacy, making solutions and sprays more effective for the scalp. Gels are alcohol-based, evaporate quickly, and sting but are equipotent with ointments and solutions. Many patients prefer gels because they are easy to apply and do not stain clothing. Ointments are petrolatum-based, typically the most potent, and usually do not irritate, making them the best option for sensitive skin. Foams contain alcohol and therefore evaporate quickly, which make them appropriate for application in the hair or for patients (especially men) who prefer this clean type of vehicle. Creams are lipid-based and do not evap-

**Table 3. Diagnosis of Psoriasis\*: Clinical Appearance and Types**

Presentation	Features	Additional Features	Location	Treatment(s)
Plaque (psoriasis vulgaris is most common)	Well-demarcated papule or plaque with silvery scale and punctuate bleeding when peeled (Auspitz's sign)	Koebner's phenomenon, which is the development of psoriasis in areas of trauma <sup>16</sup>	Knees, elbows, trunk (extensor surfaces), nape of neck, postauricular, lumbosacral area, scalp, feet, hands, penis <sup>16</sup>	Topical and/or systemic, depending on severity and recalcitrance Intralesional steroids for local recalcitrant disease
Nail	Proximal nail matrix produces defects in keratinization that are translated as the nail grows out from the cuticle in the form of pits <1 mm in diameter Psoriasis of the nail bed results in oil spots. Patients also get splinter hemorrhages. <sup>17</sup>	Subungual hyperkeratosis (onycholysis) starts as the free nail separates from the nail bed and can be demarcated by a yellow band; this allows for material from the nail bed to accumulate under the nail. <sup>16,17</sup> Consider possible future development of PsA.	Fingernails and/or toenails	Intralesional steroids, CsA <sup>18</sup>
Inverse (uncommon)	Painful, well-demarcated, symmetric, erythematous papules and plaques that may become macerated, often eroded, or secondarily infected because of location <sup>19</sup>		Intertriginous regions of the body: inframammary, neck, axillary, inguinal crease, and intergluteal	Topical
Erythrodermic	>90% Involvement of BSA Acute: develops over days, can be severe and even life threatening because of greater stress on the heart and other metabolic resources of the body Chronic: develops more slowly over months to years	Acute form can result in hospitalization and can be life threatening if severe because of loss of fluids (electrolytes, water, proteins) and unstable body temperature <sup>20</sup>	Widespread	Systemic (accretin, <sup>18</sup> MTX, CsA <sup>18</sup> )
Pustular (generalized type; rare; 4 types)	Erythema and sterile pustules sometimes in preexisting plaques or in annular lesions	Some can have metabolic disturbances. <sup>19</sup> Causes include pregnancy, rapid steroid taper, infections, hypocalcemia, or topical local irritants <sup>19</sup>	Widespread in flexures	Systemic (acitretin <sup>18</sup> ) or biological
Palmar/plantar pustular	Vesicles lead to pain and/or significant itch in involved areas.	Typically recalcitrant because of the thickness of the skin of the palms and soles, limiting penetration of topical treatments and trauma to hands and feet, causing the Koebner phenomenon	Hands/feet	UV light (PUVA/UVB), acitretin, <sup>18</sup> CsA <sup>18</sup>
Guttate	Abrupt eruption of psoriasis that is characterized by 2- to 5-mm teardrop-shaped papules.	Preceded by a streptococcal infection or drug-induced (carbamazepine, $\alpha$ -interferon, antimalarials, abrupt cessation of systemic corticosteroids, lithium, $\beta$ -blockers) <sup>2</sup>	Trunk and extremities	With UV light and withdrawal of offending drugs or resolution of streptococcal disease, some patients have resolution. Some patients will go on to have psoriasis later in life, with most developing plaque-type psoriasis.

\*Psoriasis is a disease that is diagnosed clinically, but if the condition fails to respond to therapy or lesions do not appear classic, a biopsy or dermatology referral may be warranted.  
CsA, cyclosporin A; MTX, methotrexate; PsA, psoriatic arthritis; UV, ultraviolet; PUVA/UVB, psoralen + ultraviolet A/ultraviolet B; BSA, body surface area.

**Table 4. Psoriasis: Severity Grading<sup>19</sup>**

Psoriasis	BSA* (%)	Treatment Required
Mild	<5	Topical
Moderate to severe <sup>†</sup>	5–10	Topical and systemic
Severe	>10	Systemic

\*To determine a patient's body surface area (BSA) of plaque involvement, the doctor would use the patient's own palmar handprint as a guide while they perform their examination. The surface area for each handprint is equal to 0.8% of the total BSA for men,<sup>21</sup> 0.7% for women, and 0.94% for children.<sup>22</sup>

<sup>†</sup>Severe disease: significant involvement of the palms/soles, face or intertriginous areas as these may be significantly debilitating.

orate as quickly but may sting with application. In general, anything that is not petrolatum-based will almost definitely temporarily burn on the skin that is excoriated or not intact. Most lotions are not true lotions but more along the line of alcohol-based solutions.

#### *Classes and Compounds*

Class I (superhigh potency) topical steroids includes clobetasol propionate, betamethasone dipropionate augmented, and halobetasol propionate. Class III (mid/high potency) includes triamcinolone acetonide 0.1%, fluticasone propionate, amcinonide, fluocinonide. Class VI (low potency) topical steroids are alclometasone dipropionate and desonide. Some pharmacies can “compound” these steroids in combination with CeraVe (Valeant Pharmaceuticals North America, Bridgewater, NJ) or Cetaphil (Galderma Laboratories, Fort Worth, TX), usually as 1:1. CeraVe and Cetaphil are preferred over Aquaphor or Eucerin (Beiersdorf, Inc., Wilton, CT) because the latter contain lanolin, which can have chemicals like cetostearyl alcohol and potassium sorbate added during their chemical preparation and cause irritation and allergies in those who are susceptible to it, precipitating a Koebner phenomenon.<sup>23</sup>

#### **Vitamin D Analog Preparations (SORT Criteria Recommendation A, Level of Evidence 1)**

Vitamin D analogs inhibit keratinocyte proliferation through increased differentiation of cells and inhibit the accumulation of inflammatory cells.<sup>3</sup> Vitamin D analogs can be used alone or in combination with topical steroids (compounded by the pharmacy) or alternating with topical steroids (applied by the patient), acitretin, cyclosporin A (CsA),

or phototherapy. Calcipotriene 0.005% cream, ointment, and scalp solution 0.005% are available for use twice a day. Calcipotriene is also available combined with betamethasone dipropionate 0.064% in an ointment and suspension. The maximum dose for these is 100 g/week. Calcitriol 3 µg/g ointment is also available, to be applied twice daily. The maximum exposure to this drug is 200 g/week because of the risk of hypercalcemia and hypercalciuria. Vitamin D analogs can be applied 2 hours after ultraviolet (UV) light therapy, but they should not be applied before UV therapy since they are inactivated by UV light.<sup>24</sup> The most common reaction is irritation at the site of application, which limits its use on the face and intertriginous areas. A Cochrane review published in 2011 showed that the compounded vitamin D analog calcipotriene and betamethasone dipropionate was more effective for long-term treatment of mild to moderate psoriasis than using either drug alone.<sup>25</sup>

#### **Topical Calcineurin Inhibitor (SORT Criteria Recommendation A, Level of Evidence 2)**

The topical calcineurin inhibitors tacrolimus 0.1% ointment and pimecrolimus 1.0% cream are available. They are applied twice daily and mostly used for disease on the face and intertriginous areas, for inverse psoriasis, or used anywhere on the body as a steroid-sparing or maintenance therapy.<sup>26,27</sup> There has been no evidence of skin atrophy or absorption by the body.<sup>3</sup> It is important for the primary care physician (PCP) to become familiar with the “black box” warning from the US Food and Drug Administration as well as articles refuting the use of these inhibitors, which found 20 case reports of lymphoma and 10 cases of skin neoplasms worldwide after treatment with these drugs, but no causal relationships were verified.<sup>28</sup> These preparations are off-label, generally safe, and are recommended for use in children >2 years old.

#### **Ultraviolet Light (SORT Criteria Recommendation B, Level of Evidence 2)**

Using UV light is probably one of the safest and oldest modalities for the treatment of psoriasis. Historically, the combination of dead sea salts, which are rich in anti-inflammatory mediators, with irradiation, called heliotherapy, was and is useful for the treatment of many skin and rheumatic conditions.<sup>29</sup> In general, UV light works by decreasing keratinocyte proliferation and has anti-

inflammatory properties.<sup>3</sup> As an anecdote, the recommendation for patients with psoriasis who are using natural light should try to achieve only 5 to 10 minutes spent unprotected in the mid-day sun 3 times per week. Some PCPs who see a large number of dermatologic cases may own a light box or send patients to a hospital-based light therapy center. UV light therapy can be used in combination with certain systemic (eg, methotrexate and acitretin) and topical medications (eg, topical steroids or calcipotriene); however, timing of the application of topical steroids and tapering the dose of UV therapy to avoid burning are factors to consider. The current consensus is that narrowband UVB light is better than broadband UVB light and is considered first-line treatment for extensive plaque psoriasis, especially if the plaques are thin and the patient is young.<sup>30–32</sup> UV therapy is also effective for psoriasis of the palms and soles or guttate psoriasis. Although treatments vary, doses of UV therapy generally are administered 3 times per week for a minimum of 3 months.<sup>30</sup> Psoralen plus UVA is useful for psoriasis of the hands and feet, in cases where narrowband UVB light fails, or for plaques that are too thick for light to penetrate.<sup>33</sup> The risks of UV use are burning and skin cancer risk, but these are more common with the use of Psoralen plus UVA, so routine full skin examinations are recommended.<sup>30</sup>

***Intralesional Corticosteroid Triamcinolone Acetonide 2.5 to 10 mg/mL (SORT Criteria Recommendation C, Level of Evidence 3)***

Intralesional injections are an effective method to deliver a small amount of corticosteroid to an area of psoriasis. In the case of nail psoriasis, injecting the proximal nail fold to target the proximal nail matrix reduces nail inflammation.<sup>34</sup> Using a fine-gauge insulin needle that will not pop off is recommended. The decision of whether to use anesthesia depends on the patient; however, injecting the deep proximal nail fold or the nail bed to target subungual hyperkeratosis or onycholysis will require initial anesthesia block.<sup>34</sup> In mild psoriatic disease, where 1 or 2 plaques are resistant to topical treatments, for example, intralesional steroids may play a role. Skin atrophy is a concern with this modality; to avoid this, the lowest effective dose of triamcinolone acetonide (3–5 mg/mL) should be used.

These procedures are painful for the patient, especially injection of the nail bed. Injections should be limited to no more than 6 to 8 weeks apart and given only if necessary.

It is important to note that there are rare circumstances in which oral corticosteroids are prescribed for psoriasis. In all cases, the benefits should outweigh the risks. Abrupt discontinuation can precipitate an erythrodermic reaction, a flare-up of pustular psoriasis, or simply a significant rebound flare of classic psoriasis.

***Anthralin (SORT Criteria Recommendation C, Level of Evidence 3)***

Anthralin is a man-made version of a natural substance found in goa powder, which is from the araroba tree and functions by slowing the growth of keratinocytes. It can be used with caution in both children and adults because it can cause contact dermatitis if left on too long or if rubbed in the eyes or on the genital area.<sup>35</sup> Anthralin is usually left on for 5 to 20 minutes then washed off to avoid brown discoloration of clothing. Anthralin can be compounded with salicylic acid for stability.<sup>35</sup>

**Systemic Treatments**

Systemic treatments used to treat psoriasis are summarized in Table 5.

***Biological Drugs (SORT Criteria Recommendation A, Level of Evidence 1)***

*Screening before Administration of Biologic Therapy*

Before starting a patient on any biologic drug, much needs to be assessed by a history and physical examination, laboratory tests have to be analyzed (see Tables 6 and 7), and a closer follow-up must be considered. Though mostly well tolerated without significant side effects and because of the extensive follow-up required with their use, many PCPs will use biologics, working in conjunction with dermatologists who are familiar with their use. Drug allergies and current medications (dermatological and others) should be assessed, looking for those medicines that may increase immunosuppression or may exacerbate the psoriasis.<sup>2</sup> In addition, a patient's medical history should be carefully evaluated and medicine regime reconciled to ensure that if the patient were to start taking a biologic drug, there would be as few interactions as possible. For example, reports of hypoglycemia in patients taking

**Table 5. Summary of Systemic Drugs for Psoriasis Using Strength of Recommendation Taxonomy (SORT)<sup>4</sup>**

Drug	Mechanism of Action	Dosing	FDA-Approved Indication	SORT Level	Level of Evidence	Studies
<b>Biologics</b>						
Etanercept	Soluble dimeric fusion protein that links the p75 TNF- $\alpha$ receptor to the Fc portion of IgG1, decreasing its activity <sup>33</sup>	SC injection of 50 mg twice/week for 3 months, followed by 50 mg weekly <sup>33</sup>	Moderate to severe plaque psoriasis and PsA <sup>36</sup>	A	1	Amgen-Pfizer has >3 years of clinical data for this drug; early studies for rheumatoid arthritis have shown that 25 mg SC twice/week over 2 years not only has good clinical responses but also provides better mental health and less bone damage. <sup>37</sup> This response reverted to baseline once etanercept was discontinued and improved when use of the drug resumed. <sup>37</sup> Later, as these studies were conducted in patient cohorts with PsA and psoriasis, similar positive results were found: psoriatic skin plaques improved, structural damage halted, and inflammatory markers decreased, and the patients reported feeling better both physically and mentally. <sup>37</sup>
Adalimumab	Recombinant human Ig monoclonal antibody neutralizes the biological function of TNF- $\alpha$ by blocking its interaction with the p55 and p75 cell-surface TNF- $\alpha$ receptors <sup>8,8</sup>	SC injection at a dosage of 80 mg at week 0, followed by 40 mg every 2 weeks beginning at week 2 <sup>33</sup>	Moderate to severe plaque psoriasis and PsA	A	1	Three major trials assessed the efficacy of adalimumab. <sup>39</sup> After week 16 in each of these trials, approximately 80% of patients experienced a PASI 75* response.
Infliximab	Chimeric monoclonal antibody (75% human, 25% murine) in which the Fc portion is human IgG1 and the Fab portion is primarily of murine origin. <sup>40</sup> Neutralizes soluble TNF- $\alpha$ and blocks membrane TNF- $\alpha$ . <sup>41</sup>	The drug is administered intravenously every 8 weeks following an initial loading dose	Moderate to severe psoriasis  PsA (Preg Cat B)	A	1	Three major trials assessed efficacy of infliximab. <sup>42-44</sup> After maintenance phase (through week 50), patients remained at PASI 75. Anti-infliximab antibodies commonly develop after prolonged therapy and can result in decreased drug efficacy or in some cases a severe infusion reaction with respiratory compromise. <sup>45</sup>
Ustekinumab	Human monoclonal antibody that blocks IL-12 and IL-23, binding the p40 subunit, which activates T cells in psoriasis. <sup>7</sup>	45 mg for patients weighing $\leq 100$ kg; <sup>33</sup> 90 mg for patients weighing >100 kg <sup>33</sup> SC at weeks 0 and 4, repeated every 12 weeks <sup>33</sup>	Moderate to severe plaque psoriasis	A	1	Two phase III clinical trials showing that about two-thirds of patients achieved a PASI 75 response after 12 weeks of treatment. <sup>46,47*</sup>

*Continued*

**Table 5. Continued**

Drug	Mechanism of Action	Dosing	FDA-Approved Indication	SORT Level	Level of Evidence	Studies
Systemic						
Acitretin	Oral retinoid inhibits induction of helper T lymphocytes via IL-6 by modulating gene expression, <sup>33</sup> which functions to regulate the keratinocyte turnover in psoriasis. <sup>18</sup>	Used in conjunction with phototherapy or topical steroids/vitamin D analog for plaque psoriasis at the lowest effective dose. Start at doses of 10–25 mg/day and increase dose every 2 weeks until xerosis (dry skin) to cheilitis (or dry lips) appear; may take about 3 months to see a therapeutic response. <sup>18</sup>	Severe psoriasis, palmoplantar pustulosis, nail psoriasis, generalized pustular psoriasis <sup>18</sup>	A	1	After 12 weeks of therapy, the percentage reduction in the PASI score was 54%, 76%, and 54% for the groups taking acitretin 25, 35, and 50 mg/day, respectively. <sup>48</sup> A PASI 75 response was achieved in 47%, 69%, and 53% patients in the acitretin 25, 35, and 50 mg/day groups, respectively. <sup>48</sup>
MTX	Folic acid analog that irreversibly inhibits dihydrofolate reductase in the eukaryotic cell, decreasing DNA and protein synthesis, which prevents epidermal hyperproliferation. Also decreases DNA in activated T lymphocytes by inhibiting aminimidazole carboxamide ribocucleotide, an enzyme involved in purine metabolism. <sup>2</sup>	Single weekly dose or in 3 doses: 1 dose every 12 hours over 36 hours, or once weekly, starting at 5 to 10 mg and adjusting the dosage upward at 4-week intervals to a therapeutic dose between 15 and 25 mg/week, with a maximum dose of 25 mg/week. <sup>18,33</sup> Low-dose folic acid (1–5 mg) is administered in 3 doses over 36 hours, starting 12–36 hours after the last MTX dose to avoid megaloblastic anemia with few reductions in efficacy. <sup>18,33,49</sup> Or, can be given daily, except the day(s) the MTX is taken.	Severe plaque psoriasis, erythrodermic, pustular, and other off-label uses <sup>50</sup>	A	1	92.7% of patients achieve a PASI 75 response after 12 weeks of high-dose MTX. <sup>51</sup>
Cyclosporine	Binds to cyclophilins and forms a complex, blocking differentiation and activation of T cells by inhibiting calcineurin, thus preventing the production of IL-2 and its receptor. It also inhibits keratinocyte hyperproliferation. <sup>18</sup>	In the absence of comorbidities (obesity and older age) it is weight-based and dosed at 3 mg/kg/day; it is usually divided into 2 doses. <sup>18</sup> Alternative dosing is 2.5 mg/kg/day in 1 or 2 divided doses for patients with stable moderate to severe psoriasis and 4.0–6.0 mg/kg/day in 1 or 2 divided doses for patients with severe or recalcitrant psoriasis. <sup>52</sup> The goal is the lowest effective dose possible. Taking CsA before meals may result in better absorption and bioavailability of the drug, translating into a reduced disease burden. <sup>52</sup>	Severe, recalcitrant, or disabling psoriasis, <sup>53</sup> as well as pustular, erythrodermic, and nail psoriasis <sup>52</sup>	B	2	PASI 75 responses in up to 97% of treated patients have been reported. <sup>54</sup>

\*Psoriasis Area and Severity Index (PASI) 75 score is reported here because it is a good tool used in clinical trials to determine treatment efficacy and response. A PASI 75 response indicates a 75% reduction in psoriasis lesions. Note that, because of its complexity, PASI is, in general, not calculated outside of the research setting; body surface area is another way to monitor treatment progress.

CsA, cyclosporine; Ig, immunoglobulin; IL-, interleukin; MTX, methotrexate; PsA, psoriatic arthritis; SC, subcutaneous; TNF, tumor necrosis factor; FDA, U.S. Food and Drug Administration.

**Table 6. Exclusions for Biological Drugs**

Latent TB dx without proper tx <sup>36,55,56*</sup>
Blood dyscrasia
Wegener's granulomatosis <sup>36,55</sup>
Recent illness
Immunosuppressive disease
Ustekinumab only for drug-induced psoriasis, any history of malignancy (except for basal or squamous cell carcinoma skin cancer and cervical cancer in situ treated at least 5 years before the initiation of ustekinumab), and a history of active TB (latent, treated TB can receive treatment) <sup>7</sup>
History of hepatitis, positive hepatitis B (which can be reactivated in chronic carriers, thus, the need for the vaccination), or active or untreated hepatitis C
Multiple sclerosis (except for ustekinumab)
Any demyelinating disorder <sup>7,36,55</sup>

\*Patients diagnosed with tuberculosis (TB) who have received at least 2 months of treatment can receive a tumor necrosis factor (TNF)- $\alpha$  inhibitor with close supervision and a multidisciplinary approach. TNF- $\alpha$  modulates granuloma homeostasis and contains latent disease.<sup>57</sup> In patients with a history of latent TB, indurations on PPD of >5 mm, even with history of BCG vaccination, is considered positive and exclusionary without proper treatment for TB.<sup>36,55</sup> The risk of TB reactivation is lower with etanercept, a TNF- $\alpha$ , than with other monoclonal antibody inhibitors.<sup>58</sup>

etanercept warrant a reduction of antidiabetic dosing and monitoring of glucose logs by PCPs for some of these patients.<sup>36</sup> Because some patients who have plaque psoriasis have untreated antistreptolysin O titers from guttate psoriasis (that developed into plaque psoriasis), it always is a good idea to check an antistreptolysin O titer for every patient with new psoriasis.

**Table 7. Biologics Screening and Monitoring<sup>7,59</sup>**

Biological	Screen Lab	Follow Labs Every 2 to 6 Months	Vaccine/Frequency	PPD/Frequency
Etanercept	CBC with differential CMP ANA (optional)	CBC with differential CMP	Flu (standard for age)	At baseline + Annual
Adalimumab	CBC with differential CMP ANA (optional)	CBC with differential CMP	Flu (standard for age)	At baseline + Annual
Infliximab	CBC with differential CMP ANA (optional)	CBC with differential CMP	Flu (standard for age)	At baseline + Annual
Ustekinumab	CBC with differential CMP ANA (optional)	CBC with differential CMP	Flu (standard for age)	At baseline + Annual

CBC, complete blood count; CMP, complete metabolic panel; ANA, anti-nuclear antibody; PPD, purified protein derivative; Flu, inactivated influenza vaccine (avoid live vaccines).

*Vaccines*

Since patients taking these therapies may not receive live or live-attenuated vaccines (measles, mumps, rubella; oral polio vaccine; varicella zoster vaccine [VZV]; Bacillus Calmette-Guérin; yellow fever; and influenza [nasal]), ensuring that these patients are up to date with their age-appropriate vaccines is important. Annual inactivated influenza and pneumococcal (at least one dose, if necessary)<sup>60</sup> vaccines should be given since these biologic drugs can lower the immune system's ability to fight infection. Vaccination for hepatitis A and B also are recommended before beginning a biologic. It usually takes 2 to 6 weeks for the body to produce a significant amount of antibodies after immunization.<sup>59</sup>

*Other Risks*

**Lymphoma and Leukemia.** Lupus-like symptoms (butterfly sun-sensitive rash, oral ulcers, etc.) can be a side effect of using tumor necrosis factor (TNF)- $\alpha$  inhibitors.<sup>36,55</sup> Some biological drugs also increase antinuclear antibody titers, so establishing a baseline antinuclear antibody titer is optional.<sup>59</sup> Biological drugs can also increase the risk of cancer, mostly lymphoma<sup>10</sup> and leukemia<sup>36,55</sup>; however, it is uncertain whether it is the psoriasis or the initiation TNF- $\alpha$  blocking treatment that is the causative factor.<sup>5</sup> According to some studies, many of the original clinical trials conducted using adalimumab and etanercept in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing



spondylitis, Crohn's disease, and psoriasis showed a 3-fold higher rate of lymphoma compared with the general US population.<sup>36,55,57</sup> However, when meta-analyses of these randomized controlled trials were considered, most of the patients who populated the original trials were from cohorts with rheumatoid arthritis and Crohn's disease, which usually combined biological therapies with additional immunosuppressive agents, therefore introducing selection bias and confounding.<sup>61</sup> In the absence of TNF- $\alpha$  blocking therapy, patients with moderate to severe rheumatoid arthritis, for example, have a 5- to 25-fold increased risk of developing lymphoma.<sup>57</sup> It is therefore unclear whether the increases in the rate of lymphoma observed in these trials were related to TNF- $\alpha$  blocking therapy.

**Congestive Heart Failure/Cardiac Events.** Because signs and symptoms of congestive heart failure can worsen while taking a biologic drug like a TNF- $\alpha$  inhibitor, physicians should monitor these patients carefully and weigh the risk-to-benefit ratio.<sup>55</sup> Major adverse cardiovascular events have been seen with the use of interleukin-12/23 inhibitors, namely briakinumab, which was pulled from clinical trials.<sup>62,63</sup> Ustekinumab data also show some events, but further research is needed to clarify the role that these drugs may play in risk of major adverse cardiovascular events and the mechanism by which they may occur.<sup>64</sup> The rate of major adverse cardiac events in patients taking ustekinumab was no greater than rates in both the general population and a population with psoriasis.<sup>7</sup> Ustekinumab can cause reversible posterior leukoencephalopathy syndrome, which presents as a persistent headache, seizures, sudden vision changes, and mental and mood changes,<sup>7</sup> so establishing a neurological history and physical examination at baseline is important.

#### **Reactivation of Varicella Zoster**

While the risk of potential reactivation of VZV is very low when a patient is taking a biologic drug,<sup>65,66</sup> the risk increases when this patient is also taking oral prednisone for a comorbidity. Reactivation of VZV can lead to a potentially serious neurological complication,<sup>67,68</sup> and VZV vasculopathies in immunocompromised patients have been described in the literature.<sup>69</sup> In these cases the patient should be closely monitored for and edu-

cated about any signs or symptoms of stroke or transient ischemic attack and administration of VZV intravenous immunoglobulin should be considered.

#### *Basic Pharmacology of Biologicals*

The half-life of etanercept is 4 days, that of adalimumab is 10 to 20 days, infliximab is 8 to 9.5 days, and ustekinumab is 14.9 to 45.6 days<sup>5</sup>; the time required for any of these drugs to be removed from the body once they are discontinued is approximately 4 to 5 half-lives.<sup>70</sup> Once a patient begins taking a biologic drug, it's important to closely follow them for drug-related adverse events. Reasons to stop a biologic drug are serious infection; severe persistent neurological symptoms such as headache, eye pain, loss of vision in one eye, or numbness; Guillain-Barré syndrome; lymph node swelling; unintended weight loss; malaise; easy bruising; bleeding; pallor; or serious allergic reaction such as anaphylaxis or angioedema.<sup>36,55</sup>

#### *Indications and Dosing*

Because of the significant cost of biologics, more traditional medications should be tried first, if possible, and biologics used only when those fail or there is a contraindication to oral systemic therapy.<sup>71</sup>

#### **Acitretin (SORT Criteria Recommendation A, Level of Evidence 1)**

This drug should be completely avoided in women of childbearing age because it is teratogenic and category X. Although acitretin may take 2 months to be eliminated from the body, when alcohol is consumed, etretinate, its metabolite, can have a half-life of up to 168 days.<sup>72</sup> It is recommended that women abstain from consuming alcohol in any form while taking the drug and for at least 2 months after it is discontinued because the amount of metabolite is directly proportional to the amount of alcohol ingested.<sup>72</sup> In fact, the teratogenic effects can occur for up to 2 to 3 years after acitretin discontinued in a patient who has consumed alcohol.<sup>33,72</sup> Because of this, it is advised that if prescribing this for women of childbearing age, they must (1) have 2 negative urine or serum pregnancy tests before receiving their first dose of acitretin; (2) have monthly pregnancy tests before receiving their acitretin prescriptions; (3) simultaneously use 2 effective forms of birth control for at least 1 month before starting the drug, during the therapy,

and for at least 3 years after discontinuing the therapy; and (4) receive counseling about the risk of birth control failure and risk of birth defects and abstain from every form of alcohol while taking the drug and for at least 2 months after the drug has been discontinued.<sup>72</sup>

### *Monitoring*

A careful history and physical examination is important to identify those at risk for or with a family history of hyperlipidemia; a medicine reconciliation is useful to note potential drug interactions. Monitoring parameters include complete metabolic and lipid panels at baseline, complete blood count with differential, and urinalysis.<sup>73</sup> Lipids can be checked every 1 to 2 weeks once treatment is started until they stabilize, which is usually in 4 to 8 weeks, especially in patients with a personal or family history of hyperlipidemia.<sup>73</sup> In those without a significant history of or baseline hyperlipidemia, checking the lipid panel each month for 3 to 6 months is recommended,<sup>73</sup> especially to monitor for acute pancreatitis, which is rare.<sup>73</sup> Triglyceride levels >600 mg/dL or cholesterol levels >300 mg/dL warrant a discontinuation of acitretin and close monitoring of lipids until they return to baseline.<sup>73</sup> Sometimes, a fenofibrate is recommended for hypertriglyceridemia. Mild elevations in transaminases are rarely seen 2 to 8 weeks after the start of acitretin, but these are transient and just require monitoring.<sup>73</sup> Checking the following laboratory values monthly for the first 3 to 6 months then every 3 months in cases of chronic acitretin therapy is recommended: complete blood count with differential, lipid and complete metabolic panels, and urinalysis. Common adverse reactions are xerostomia (dry mouth), cheilitis, alopecia, xerosis, and sunburn/sensitivity (especially if combined with phototherapy). Because elevated intracerebral pressure can also be an adverse event with acitretin, concomitant medications that have this adverse reaction (eg, tetracyclines) are contraindicated. Finally, because acitretin is a vitamin A derivative, any vitamin A supplementation should be avoided. Skeletal radiograph monitoring is not required.<sup>18</sup>

### ***Methotrexate (SORT Criteria Recommendation A, Level of Evidence 1)***

After a full history and physical examination, reconciling additional medications is important because of potential interactions with various drugs,

including all salicylates, nonsteroidal anti-inflammatory drugs, trimethoprim/sulfamethoxazole, sulfonamides, and tetracyclines, to name a few.<sup>50</sup> Although it has oral, intramuscular, and intravenous routes of administration, oral administration is most common in the primary care setting. Methotrexate (MTX) should not be given to anyone planning to consume alcohol or women who are pregnant or lactating. Risks versus benefits should be discussed because of possible adverse effects; continuous monitoring is required with this drug. About 80% of patients with psoriasis who are treated with MTX respond usually within the first 4 weeks.<sup>50</sup> In addition, for those couples planning on having a family, it is advised that men taking MTX should be off the drug for 3 months and women should discontinue for 1 menstrual cycle and have a negative pregnancy test at each visit.<sup>49,50</sup>

### ***Monitoring***

Before starting a patient on MTX, a complete blood count with differential is required at baseline. This helps establish a baseline to follow for any possible MTX-induced pancytopenia.<sup>50</sup> A complete metabolic panel will examine for poor renal function, low albumin, and liver function at baseline, the first 2 of which can be potential sources of pancytopenia because of increased levels of the free drug.<sup>50</sup> In patients with renal disease, the dose of MTX can be adjusted according to the patient's creatinine clearance (as calculated using the Cockcroft-Gault formula<sup>49</sup>). Testing for human immunodeficiency virus, tuberculosis, and hepatitis B and C is important before starting MTX<sup>49</sup> because it is an immunosuppressive drug. Not only can MTX induce pancytopenia and hepatotoxicity, it can also cause pulmonary fibrosis.<sup>49</sup> If pulmonary symptoms develop, a chest radiograph is warranted.<sup>49</sup>

Once a patient is taking MTX, it is important to monitor for leukocytopenia or thrombocytopenia with a complete blood count with differential 7 to 14 days after starting or increasing the dose, every 2 to 4 weeks for the first few months, then every 1 to 3 months until stable.<sup>49</sup> Leukocytopenia or thrombocytopenia are most likely to occur 7 to 10 days after initiating MTX and clinically serious cases can usually be corrected by 20 mg folinic acid (intravenous).<sup>49</sup> Patients who are at highest risk of MTX-induced pancytopenia, and therefore require close monitoring, are those who have renal insufficiency, the elderly, those at risk for drug interac-

tions or taking multiple medications, those with hypoalbuminemia, or those who are not taking folate.<sup>49</sup> A basic metabolic panel for renal function is required every 2 to 3 months for patients taking MTX; for patients with impaired renal function, glomerular filtration rate needs to be calculated and monitored.<sup>49</sup>

The newest guidelines divide those patients who are at low risk of developing hepatic fibrosis from those who are at highest risk. Patients are considered to have hepatic fibrosis risk factors if they have diabetes mellitus type 2, are obese, consume excess alcohol, have hepatitis B or hepatitis C virus, and/or are exposed to hepatotoxic drugs.<sup>33</sup> In these patients pretreatment biopsies may be warranted and may be repeated after the patient has reached a 1.0-g total cumulative dose.<sup>41</sup> It is important to obtain the blood sample at least 5 days after the last dose of MTX because the drug can erroneously elevate the results of liver function tests.<sup>49</sup> Liver function tests showing minor elevations (less than twice the upper limit of normal) can be repeated in 2 to 4 weeks.<sup>49</sup> Any abnormality (>3-fold the upper limit of normal) in liver function testing necessitates a temporary reduction of MTX and repeat of tests within 2 to 4 weeks.<sup>49</sup> If there are persistent elevations in serum aspartate aminotransferase and hypoalbuminemia for 12 months, a liver biopsy should be considered before the patient reaches the 1.5- to 2.0-g cumulative dose mark.<sup>41,49</sup> Whether MTX treatment should be initiated in high-risk patients or those with any of the risk factors for hepatic fibrosis should be decided on a case-by-case basis.<sup>49</sup> If MTX is considered in these patients, a baseline liver biopsy is advisable; however, because some of these patients will discontinue MTX after 2 to 6 months because of adverse events or lack of efficacy, delaying a liver biopsy may also be advisable.<sup>49</sup> Low-risk patients require a liver biopsy every time they reach the 1.5- to 2.0-g total cumulative dose.<sup>41</sup> Recommendations to continue or discontinue MTX based on liver biopsy are based on the results of Roenigk et al.<sup>74</sup> Whereas liver biopsy remains the gold standard, it is fraught with risk; a liver ultrasound (transient elastography) offers the ability to determine whether the liver is fibrosed, but studies can be limited, especially if the patient is overweight, has increased abdominal girth, or has a diagnosis of nonalcoholic steatohepatitis.<sup>75</sup>

### ***Cyclosporine (SORT Criteria Recommendation A, Level of Evidence 2)***

CsA is not contraindicated during pregnancy or lactation because it is a category C drug; however, it is contraindicated in patients with severe renal function, uncontrolled hypertension, and persistent malignancy.<sup>53</sup> During a complete history the patient should be asked about anything that would increase their risk of nephrotoxicity, such as obesity, diabetes mellitus, advanced age, and concomitant use of nephrotoxic drugs.<sup>52</sup> Exercise caution when dealing with patients taking multiple drugs because CsA has numerous drug-drug interactions due to its metabolism by the cytochrome p450 3A4 system or when administering with foods like grapefruit juice.<sup>33,76</sup> During the complete physical examination at baseline and at each monthly visit, patients should be evaluated for skin neoplasms or infections because CsA increases the risk for developing squamous and basal cell carcinomas.<sup>52</sup> In addition, at baseline, all patients initiating CsA should undergo routine age-appropriate cancer screening.<sup>52</sup> Testing for tuberculosis and hepatitis C at baseline is advisable.<sup>52</sup> Because CsA is immunosuppressive, vaccines may be helpful, and booster vaccination may be necessary; however, live vaccines are contraindicated with use of CsA.<sup>52</sup>

### ***Monitoring***

Before starting a patient on CsA, 2 confirmed normal values for serum creatinine and blood pressure should be documented in addition to complete metabolic panels, including liver function testing, bilirubin, potassium, blood urea nitrogen, creatinine, complete blood counts, serum magnesium (which may decrease while taking CsA), uric acid (which is relevant for those at risk for gout), and fasting serum lipids.<sup>52</sup> Despite the recommendations on the package insert, the current consensus now requires monthly monitoring of renal function (creatinine clearance), blood pressure, physical examinations, adverse events, and a basic metabolic panel, including creatinine, blood urea nitrogen, potassium, complete blood count, and magnesium.<sup>52</sup> It is recommended that the Modification of Diet in Renal Disease formula rather than the Cockcroft-Gault equation be used for overweight patients and those >50 years old.<sup>18</sup> After checking fasting serum lipids at the initiation of therapy, these levels can be tested at least every 6 months for evidence of hypercholesterolemia or hypertriglyc-

eridemia.<sup>52</sup> Because of the monthly monitoring or laboratory tests and examinations, obtaining a CsA level is generally not necessary.<sup>52</sup>

Treating patients for more than 1 to 2 years without nephrology consultation is not recommended because of CsA-associated risk of nephrotoxicity.<sup>17,52</sup> Patients taking long-term therapy are also at risk of gingival hyperplasia, so yearly dental examinations are advised.<sup>52</sup> The current recommendations for managing nephrotoxicity are reducing the dose of CsA by 25% to 50% (equivalent to 0.5 to 1.0 mg/kg/day) if serum creatinine levels increase more than 25% to 30% above baseline on 2 occasions (repeated measurements separated by 2 weeks).<sup>52</sup> If serum creatinine fails to return to 10% of the patient's baseline after checking the levels every other week for 1 month, the dose of CsA should be reduced even further by 25% to 50%.<sup>52</sup> Discontinuation of CsA should be considered if serum creatinine remains >10% above the patient's baseline.<sup>52</sup>

For patients with no pre-existing hypertension but who developed hypertension while taking CsA as measured on 2 separate occasions, the PCP can either reduce the dose of CsA by 25% to 50% or treat the hypertension with a calcium channel blocker.<sup>52</sup> For patients with existing hypertension, it is important to closely monitor blood pressure, serum creatinine, compliance, medications, diet, lifestyle, and drug interactions. For example, patients taking angiotensin-converting enzyme inhibitors will need to discontinue and replace them with either calcium channel blockers or  $\beta$ -blockers.<sup>52</sup> Dihydropyridine calcium channel blockers (eg, isradipine and amlodipine) are more effective in reducing blood pressure and they can induce renal arteriolar vasodilation to contrast the vasoconstrictive effects of CsA.<sup>77</sup> Verapamil, diltiazem, and nifedipine can increase the levels of CsA in the blood; nifedipine can cause gingival hyperplasia and should be avoided.<sup>77</sup> Because of their ability to spare potassium and potentiate hyperkalemia with CsA, angiotensin-converting enzyme inhibitors and potassium-sparing diuretics should be avoided.<sup>52</sup>  $\beta$ -Blockers can be used.

## Conclusions

Psoriasis vulgaris is a chronic and sometimes disfiguring and disabling disease. With the growing population, the decrease in health professionals,

and the large number of patients to be seen, it is important that PCPs are equipped with the tools necessary to understand, manage, and effectively treat psoriasis in a short amount of time. Dealing with psoriasis as a complex systemic disease benefits both the provider and the patient. In general, topical therapies can be used for mild psoriasis. For moderate to severe psoriasis, a combination of topical and light or topical and systemic (oral or biologicals) can be used. In these cases, the decision of whether to start oral versus biological therapy may be personal and possibly guided by the patient's finances if the drug is not covered by a patient's insurance. Payment assistance programs such as those provided by the manufacturer for patients taking Enbrel (<http://www.enbrel.com/pay-for-ENBREL.aspx>) and Humira ([https://www.pparx.org/supporters/ViewProgram.php?program\\_id=526](https://www.pparx.org/supporters/ViewProgram.php?program_id=526)) are available. Early intervention and a multidisciplinary approach, managing all aspects of the patient's care and comorbidities, can be the focus of the PCP dealing with this challenging disease.

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