### REVIEW



# **ABSTRACT**

Psoriasis varies widely in its clinical expression, from a single fingernail pit to widespread disfiguring skin lesions and disabling arthritis. Treatments are divided into five levels, providing a framework for approaching this disease according to severity and recalcitrance to previous treatment. Powerful immunosuppressive drugs are showing some success in treating severe cases.

# **KEY POINTS**

Flare-ups of psoriasis can be triggered by trauma, cold weather, infections, drugs, and a compromised immune system.

Topical treatments, especially corticosteroids, are most commonly used, but newer vitamin  $D_3$  analogs (eg, calcipotriene) and retinoids (eg, tazarotene) may be more effective.

Phototherapy (ultraviolet B or the combination of psoralen and ultraviolet A) is highly effective for moderate to severe psoriasis.

Systemic therapy with acitretin, methotrexate, or cyclosporine is reserved for the most recalcitrant or severe cases of psoriasis.

Consider referring to a dermatologist if 20% or more of the body surface is involved.

**P** RIMARY CARE PHYSICIANS see 58% of new cases of psoriasis,<sup>1,2</sup> although dermatologists handle 80% of the 1.5 million office and hospital visits for psoriasis each year in the United States.<sup>3</sup> This fact, coupled with the current trend toward managed health care delivery, reinforces the need for primary care clinicians and internists to recognize the various forms of psoriasis and to keep abreast of current therapies and their safe and effective use, and when to refer to a dermatologist, all of which this article reviews.

# GENERAL HALLMARKS OF PSORIASIS

Psoriasis is a single disease with several morphologic expressions and a full range of severity. The form that psoriasis takes in an individual patient likely depends on genetic influences, environmental factors (eg, trauma and climate), associated diseases (especially infections), medications, and immunologic status.

The mean age at onset is 30 years, but the range is the full spectrum of human life. Men and women are affected equally, but women may be affected earlier than men. The severity ranges from a single fingernail pit to skin lesions covering the entire body surface and disabling arthritis.

The most common pattern is symmetric, inflammatory, and papulosquamous. The classic skin lesions—thick, erythematous, itchy patches covered with silvery scales usually confirm the diagnosis, but examination of scales using potassium hydroxide to look for hyphal elements (ie, fungal infection), serologic testing to rule out syphilis, and skin biopsy to rule out other inflammatory skin diseases such as eczema, pityriasis



**FIGURE 1.** The classic fully developed skin lesion of psoriasis vulgaris.

rubra pilaris, drug reactions, and cutaneous T-cell lymphoma.

### The Koebner phenomenon

In some patients, a scratch, burn, or surgical incision leads to a flare-up of psoriasis in the area of the trauma. This effect, known as the Koebner phenomenon or isomorphic response, is more likely in patients with unstable psoriasis.

The Koebner phenomenon also occurs in lichen planus, vitiligo, and other skin diseases. Routine daily trauma may be partly responsible. Certain drugs (eg, lithium, antimalarials, beta-adrenergic blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, interferons) have been associated with an "endogenous Koebner phenomenon," inducing psoriasis or aggravating preexisting disease in some patients.<sup>4</sup> Emotional stress may also cause cutaneous nerve fibers to release peptides, which can evoke inflammation or proliferation, thereby representing another endogenous Koebner phenomenon.<sup>4</sup>

#### Proposed causes of psoriasis

The cause of psoriasis is still not known, but experts agree that the lesions are the result of hyperproliferation and abnormal differentiation of the epidermis.

The primary pathologic process likely lies in the immune system, specifically an aberration in the regulation of interleukin-2, growth factors, or adhesion molecules. Evidence for this theory comes from success in treating severe psoriasis with immunosuppressive drugs used in organ transplantation.<sup>4</sup>

# CLINICAL EXPRESSIONS OF PSORIASIS

### Plaque-type psoriasis

Plaque-type psoriasis, or psoriasis vulgaris, is the most common form, occurring in 75% to 80% of all psoriasis patients. When fully developed, the lesion is a well-demarcated, red-violet, round or oval plaque 1 cm or larger in diameter surmounted by white silvery scales, overlying bony prominences (FIGURE 1). In darkly pigmented patients, lesions are hyperpigmented with various shades of brown or black, especially if the patient scratches or rubs them.

The most commonly involved areas are the elbows, knees, scalp, sacrum, umbilicus, intergluteal cleft, and genitalia, and all of these areas should be examined: any one of them may be the solitary site.

### Guttate psoriasis

Guttate psoriasis, named for its droplet-shaped lesions (FIGURE 2), accounts for about 18% of all cases, more commonly among children and young adults.<sup>5</sup> Guttate lesions range in diameter from 0.1 to 1.0 cm and are not as indurated or scaly as the lesions of plaque-type psoriasis. They predominate on the trunk and proximal areas of the extremities and are likely to involve the face.

Guttate psoriasis may be the initial manifestation of psoriasis, or it may represent an acute flare of preexisting chronic plaque-type psoriasis. Patients frequently have a history of upper respiratory tract infection, laryngitis, or tonsillitis.

Streptococci and guttate psoriasis. Some cases of acute guttate flares are believed to have been precipitated by infection with groups A, C, and G streptococci.<sup>6</sup> Leung et al<sup>7</sup> showed that acute guttate psoriasis following streptococcal throat infection in 10 patients was the result of streptococcal exotoxin C, which acts as a superantigen and activates CD4+ and CD8+ T cells in the lesions and the areas around them. Researchers hypothesize that these T cells persist in the skin of patients who go on to develop chronic plaque-type psoriasis, because the T cells mistakenly recognize skin autoantigens such as keratins and carbohydrates as bacterial antigens.

The cause of psoriasis likely lies in the genome and the immune system

### **Pustular** psoriasis

Pustular psoriasis accounts for perhaps 1.7% of cases.<sup>4</sup> It is characterized by sterile pustules either localized to the palms and soles or generalized. The average age at onset is 50 years.

Localized pustular psoriasis. The eruption is chronic and recurring and is recognizable by yellowish pustules on a background of redness and scaling on the palm (thenar and hypothenar eminences) or on the instep of the sole and side of the heel (FIGURE 3), or on both areas. Lesions are observed in all stages of development, including vesicles, vesicopustules, frank pustules, and dried brown maculopapules. There is a female predominance.

Generalized (von Zumbusch) pustular psoriasis may develop de novo or from preexisting plaque-type psoriasis and is characterized by fiery-red, irregular patches with round, arcuate, serpiginous borders, over which are seen tens of thousands of 1-mm to 2-mm superficial pustules (FIGURE 4). These tend to occur in flexural or skin-fold areas (armpits, groin, under the breasts) but may occur anywhere. The pustules coalesce into lakes of pus, desquamate, and form new pustules as the border moves in waves every 24 to 72 hours. Most patients have fever, leukocytosis, hypocalcemia, and hypoalbuminemia. The incidence is equal in men and women.

Ryan and Baker<sup>8</sup> reported that 37 (24%) of 155 patients had their first attack of generalized pustular psoriasis within 1 month of either starting or stopping systemic corticosteroids, and they concluded that the steroids provoked the attacks. Other precipitating factors included infection and other drugs. Methotrexate was less effective in patients who previously received systemic corticosteroids.

Ohkawara et al<sup>9</sup> recently reviewed 208 cases of recurrent generalized pustular psoriasis and found that cases in patients with preceding plaque-type psoriasis were more likely to have been triggered by corticosteroids, whereas cases in patients without a history of psoriasis were more likely to have been triggered by infection.

### Erythrodermic psoriasis

Exfoliative dermatitis or psoriatic erythroder-



**FIGURE 2.** Guttate psoriasis on the upper back representing an acute flare of preexisting chronic psoriasis of the lower back and buttocks.



**FIGURE 3.** Localized pustular psoriasis of the soles.

ma accounts for only 1% to 2% of all cases of psoriasis, making it the least common form.

Erythroderma in general is defined as a scaling pruritic, inflammatory process of the skin that involves all or almost all of the body surface. Erythrodermic psoriasis (FIGURE 6) usually develops gradually or acutely during the

Streptococcal infection may precipitate flare-ups of guttate psoriasis

# PSORIASIS CAMISA



**FIGURE 4.** Generalized pustular psoriasis of von Zumbusch showing waves of annular pinpoint pustules followed by desquamation.

course of chronic plaque-type psoriasis, but it may be the first manifestation of psoriasis, even in children. The mean age at onset is about 50 years. Male patients outnumber female patients. Sterile pustules may develop in some areas of erythrodermic psoriasis. In patients with the most unstable cases (ie, those with inflammation), generalized pustular psoriasis may develop. Concomitant psoriatic arthropathy is common.

Precipitating factors for erythrodermic psoriasis include systemic illnesses, emotional stress, and alcoholism, but the most important ones seem to be related to treatment, especially the inappropriate or excessive use of potent topical, oral, and intramuscular corticosteroids.<sup>10</sup>

Patients are at risk for *Staphylococcus aureus* septicemia owing to their compromised skin barrier and, in some, because of immuno-suppressive drugs.<sup>11</sup>

#### Nail psoriasis

Up to 50% of patients with psoriasis have involvement of the nails; in patients with psoriatic arthritis the incidence is more than 80%.<sup>12</sup>

Fingernails are affected more often than toenails. Pitting of the nail plate is the most common manifestation. The pits tend to be large, deep, and randomly dispersed on the nail plate. Small red spots in the lunula or yellow-brown spots (the "oil droplet" sign) in the nail bed correspond to early guttate lesions of psoriasis there. The nail plate may thicken, with dispersed deep pitting and ridging, which causes crumbling. The distal nail plate may separate from the nail bed (onycholysis). Splinter hemorrhages are very common after minor trauma.

Link with arthropathy. The severity of skin and nail involvement does not correlate with the severity of joint disease in patients with psoriatic arthritis. However, psoriatic involvement of the fingernail is significantly associated with arthropathy of the adjacent distal interphalangeal joint. Whereas the most frequent fingernail change is pitting, subungual hyperkeratosis is the most common toenail change in psoriatic arthritis.

## SORIASIS THERAPY: AN OVERVIEW

Treatments for psoriasis are divided into five levels (TABLE 1).<sup>4</sup> The choice of treatment depends on the severity and response in the individual patient.

#### Level 1: Topical treatments

Emollients (bland lubricants) should be tried first, followed by keratolytic lotions. Topical corticosteroids and calcipotriene ointment or cream can be used by internists for psoriasis involving less than 20% of the body surface area. Most nondermatologists would probably not use anthralin, crude coal tar, or tazarotene, as these are inelegant (messy, inconvenient to use, and with a bad odor) and have a high irritation potential; coal tar gels, often available over the counter, are more elegant though less efficacious.

### Level 2: Phototherapy

All forms of phototherapy are highly effective (80% to 100%) at clearing skin, but some maintenance is necessary. Disadvantages are the requirement for specialty care, the need for office visits two or three times a week, expense, maintenance therapy, theoretical short-term risks of sunburn, and long-term risk of skin cancer.

Beyond natural sunlight and tanning beds, phototherapy is given by dermatologists in the office or clinic and is reserved for patients with widespread lesions involving 20% or more of the body surface area. Specialized equipment and training is necessary for delivery of phototherapy.

Up to 50% of psoriasis patients have nail involvement

# PSORIASIS CAMISA

# TABLE 1

# **Treatments for psoriasis**

Level 1: Topical therapies Emollients Keratolytics Salicylic acid Lactic acid Urea Calcipotriene Anthralin (usually short contact) Corticosteroids Topical Hydrocolloid occlusive dressing Intralesional injections Coal tar Tazarotene

Level 2: Phototherapies

Natural sunlight Ultraviolet B light Ultraviolet B light + coal tar (Goeckerman regimen) Ultraviolet B light + anthralin (Ingram regimen) Ultraviolet B monochromatic light (311 nm) Ultraviolet A light

Phototherapy is highly effective at clearing the skin

# Level 3: Systemic therapies

## (high efficacy, high toxicity)

Psoralen + ultraviolet A light Psoralen + ultraviolet A light + ultraviolet B light Acitretin (may be combined with ultraviolet B light or with psoralen + ultraviolet A light) Methotrexate Cyclosporine

Level 4: Systemic therapy (moderate efficacy, low to moderate toxicity)\* Sulfasalazine Hydroxyurea Calcitriol Antibiotics

Level 5: Innovative systemic therapy (moderate efficacy, high toxicity)\* Azathioprine 6-Thioguanine Mycophenolate mofetil Tacrolimus

\*Not approved for psoriasis treatment by the US Food and Drug Administration

#### Level 3: Systemic treatments

Systemic treatments are more effective than level 2 treatments but are often more expensive and have greater potential for toxicity. (In general, topical therapies are less toxic than phototherapies, which are less toxic than systemic therapies.) Systemic treatments are generally prescribed only by a dermatologist.

### Levels 4 and 5: Experimental treatments

Treatments in level 4 and level 5 are not approved by the US Food and Drug Administration. Level 4 treatments are weakly to moderately effective but are less toxic than level 5 treatments, which are reserved for the most severe and recalcitrant cases, including arthropathy.

### When to refer to a dermatologist

Consider referring to a dermatologist if 20% or more of the body surface area is involved; the disease fails to respond to emollients, keratolytics, topical steroids, calcipotriene, natural sunlight, or tanning treatment bed; or for any form of pustular or erythrodermic psoriasis. Whenever possible, avoid using systemic steroids in psoriatic patients.

### Management of severe psoriasis

The management of patients with psoriatic erythroderma or pustular psoriasis includes admission to the hospital for evaluation, supportive care, and conservative treatment until the patient is stable enough to receive aggressive, conventional antipsoriatic therapy.

Severe psoriasis can usually be controlled eventually with the standard regimen of ultraviolet B light plus coal tar, or with psoralenultraviolet A light therapy, acitretin, methotrexate, or cyclosporine. The disease reverts back to its previous state (either plaque-type psoriasis or clear). Systemic and potent topical corticosteroids are to be avoided. A minority of patients remain unstable and have repeated episodes of erythroderma or pustulation during their lifetime.

Treating localized pustular psoriasis. Recalcitrance to therapy is the rule for localized pustular psoriasis of the palms and soles. Topical keratolytics, corticosteroids, tars, and ultraviolet B light are generally ineffective, and systemic agents such as methotrexate give inconsistent results. The most effective treatment reported to date with the largest number of patients is the aromatic retinoid acitretin, 30 to 50 mg per day by mouth, either alone or combined with psoralen-ultraviolet A therapy.<sup>13</sup> Long-term maintenance therapy is then required to prevent relapse.

Nail psoriasis. No topical therapy is successful for nail bed psoriasis. However, injections of triamcinolone acetonide suspension 5 mg/cc diluted with 1% lidocaine into the proximal and lateral nail folds<sup>4</sup> may be effective. This procedure is usually done in a dermatologist's office. The disadvantages are that it is painful for the patient and tedious for the clinician. The injections must be repeated at monthly intervals until the desired effect is obtained, and then at some less frequent interval for maintenance.

While the best systemic medication for nail psoriasis is probably methotrexate, most clinicians would not use it for nail psoriasis alone unless the psoriasis was disabling or destructive.

## ORAL RETINOID THERAPY FOR PSORIASIS: SPECIAL CONSIDERATIONS

Retinoids are naturally or synthetically derived from vitamin A (retinol) and have anti-inflammatory, antikeratinizing, and antiproliferative effects on the skin. The two aromatic retinoids approved for psoriasis therapy are etretinate and acitretin. The drugs are given orally but may be combined with topical therapy (not tazarotene) or ultraviolet light. The therapeutic results with these drugs have been good to excellent, especially in combination with other conventional treatments.<sup>14,15</sup>

Etretinate accumulates in adipose tissue and is eliminated slowly after discontinuation. Acitretin, the main active metabolite of etretinate, was developed to avoid these problems. However, tests using a new chromatography assay detected *etretinate* in the plasma and subcutaneous fat of a woman 4.3 years after she stopped taking *acitretin*,<sup>16</sup> indicating that acitretin may in fact be esterified in vivo to etretinate. Alcohol consumption and possibly even excess body fat may enhance this reaction.

### Adverse effects of oral retinoids

With the exception of teratogenicity, the side effects of oral retinoids, while numerous, are generally not serious. The most common and frequently troublesome side effects are dryness of the skin and mucous membranes, hair loss, and nail changes. Patients taking etretinate or acitretin for years may develop diffuse idiopathic skeletal hyperostosis-like (dish-like) involvement of the spine. Extraspinal tendon and ligament calcifications are more common. Many of these changes are asymptomatic, and well-established guidelines for monitoring skeletal toxicity are lacking.

A rare idiosyncratic hepatic reaction has been reported in about 1.5% of patients taking etretinate.

Lipid effects. Retinoids cause hyperlipidemia, especially elevations of serum triglyceride and decreases in high-density lipoprotein cholesterol. Experimental evidence supports the hypothesis that retinoids induce increased synthesis of apoprotein B and triglycerides.<sup>17</sup> Fish oil supplements given to patients receiving etretinate or acitretin significantly decrease triglyceride levels in every patient. Gemfibrozil is also useful in patients with hyperlipidemia due to acitretin who are recalcitrant to dietary manipulation and dose reductions.

Use in pregnancy. I usually reserve acitretin for male patients or for women who are not of childbearing age. Fertile women with severe psoriasis who take acitretin must follow strict two-method contraception or abstinence and have monthly pregnancy tests. Now that it is known that acitretin may be converted to etretinate and stored in fat, guidelines recommend that patients abstain from alcohol during treatment and avoid pregnancy during and for 3 years after terminating treatment.

### Tazarotene: A newer, topical retinoid

Tazarotene (Tazorac), a new topical receptorselective retinoid, alleviates psoriasis by normalizing keratinocyte differentiation, inhibiting cell proliferation, and decreasing the expression of inflammatory markers. In a study,<sup>18</sup> tazarotene gel 0.1% applied once daily for 12 weeks produced a 65% improvement in psoriatic plaques compared with a 30% Most systemic therapies for psoriasis are effective for psoriatic arthritis



improvement with vehicle gel (a typical placebo response). Although systemic absorption of tazarotene after topical application is minimal, the product information recommends obtaining a pregnancy test before starting therapy and using effective contraception during therapy.

Up to 80% of patients developed skin irritation while using this agent in studies, and most would probably stop using it unless closely followed. Research is continuing into newer receptor-specific drugs that may eventually bypass irritation and teratogenicity.

# METHOTREXATE THERAPY FOR PSORIASIS: SPECIAL CONSIDERATIONS

Methotrexate, first used for psoriasis in 1958, is the antimetabolite most often prescribed by dermatologists for this disease. Double-blind, controlled studies confirmed the superiority of methotrexate compared with placebo in improving skin manifestations, joint symptoms, and function in psoriatic patients. A good to excellent response (50% to 100% clearing of psoriasis) occurred in 70% of patients with severe disease using a single weekly oral dose of methotrexate (20 to 37.5 mg).<sup>19</sup>

# Adverse effects

The most common adverse effects of methotrexate therapy are nausea, anorexia, fatigue, headache, and alopecia. Oral ulcerations generally do not occur at the doses normally used for psoriasis treatment, and if they do, they indicate toxic serum levels due to drug interactions, dehydration, overdose, or deterioration of renal function. Bone marrow depression is also more likely to occur under these circumstances.

# Monitoring for liver damage during methotrexate therapy

Hepatotoxicity is the primary clinical concern when planning long-term methotrexate therapy. Mild elevations (less than twice the upper limit of normal) of transaminase levels are to be expected during therapy, but these levels do not correlate with hepatic fibrosis.

Because liver disease is less common in rheumatoid arthritis patients taking methotrexate than in psoriasis patients taking

methotrexate, recommendations for liver biopsy from different organizations differ. For example. the American College of Rheumatology does not recommend liver biopsy during treatment unless 5 of 9 or 6 of 12 aspartate aminotransferase levels in a 12month period are elevated, or unless the serum albumin concentration decreases below normal.<sup>20</sup> Many rheumatologists have adopted the same guidelines for monitoring patients with psoriatic arthritis. On the other hand, 1988 guidelines from the American Academy of Dermatology<sup>21</sup> recommended a liver biopsy at baseline. However, 1998 guidelines from the same organization<sup>22</sup> eliminated this recommendation, unless the patient has significant risk factors. The initial liver biopsy is done after a 1- to 1.5-g cumulative dose and is repeated after 3- and 4-g cumulative doses. Liver biopsy should not be performed in elderly patients, during acute illness, or in patients with limited life expectancy, or if there are medical contraindications to the procedure.

Folic acid. I recommend folic acid supplementation 1 mg/day because it mitigates the gastrointestinal effects of methotrexate (nausea, diarrhea, elevated liver enzymes) without altering its efficacy, and also because it prevents megaloblastic anemia due to folic acid deficiency.<sup>23</sup>

# CYCLOSPORINE THERAPY FOR PSORIASIS: SPECIAL CONSIDERATIONS

Cyclosporine is very effective for psoriasis, but it does not cure it and does not induce remissions that are more durable than those achieved, for example, with psoralen-ultraviolet A therapy. To maintain a prolonged remission, one must continue cyclosporine or change to another systemic therapy. Stopping cyclosporine or giving a suboptimal dose allows skin lesions to recur at a rate and severity consistent with the natural history of an individual's disease.

Cyclosporine interferes directly with T cell activation and communication with antigen-presenting cells by inhibiting the synthesis or expression of interleukin-1, interleukin-2, and interleukin-2 receptor. In psoriatic lesions, cyclosporine also inhibits the epidermal cytokine network. Women of childbearing age taking acitretin must use two birth control methods Since cyclosporine therapy is reserved for severe cases of psoriasis and is usually given by a specialist, a detailed discussion of its use is beyond the scope of this paper. The two most important side effects of cyclosporine, requiring baseline evaluation, constant monitoring, and intervention (medical treatment, dose reduction, or discontinuation of cyclosporine), are nephrotoxicity and hypertension.

## EXPERIMENTAL TREATMENTS FOR PSORIASIS

#### Vitamin D<sub>3</sub> and analogs

Vitamin  $D_3$  (calcitriol) and the synthetic analogs calcipotriene and tacalcitol, all in topical form, are effective for plaque-type psoriasis and are free of any serious toxicity.24 In double-blind studies, patients applied calcipotriene to one side of their body and corticosteroids to the other side. Calcipotriene was equivalent to or better than medium and potent corticosteroid ointments without the risk of skin atrophy or rebound flare-ups upon discontinuation of therapy. In open trials,<sup>25</sup> patients taking oral calcitriol showed dramatic improvement but experienced significant hypercalcemia, hypercalciuria, and nephrotoxicity. No placebo-controlled study of oral calcitriol alone has been performed. However, oral calcitriol had no additive effect compared with placebo when combined with 21 erythemogenic ultraviolet B treatments.<sup>26</sup>

Guidelines differ for liver biopsy during methotrexate treatment

# Hydroxyurea in recalcitrant psoriasis

The antimetabolite hydroxyurea plays a minor role in the treatment of recalcitrant psoriasis. In one trial,<sup>27</sup> 60% percent of patients achieved "complete to near complete clearing" with a starting dose of 1.5 g daily and a maintenance dose ranging from 0.5 to 1.5 g daily. Adverse reactions are common, notably cytopenia and macrocytosis. Hydroxyurea is not effective for pustular or erythrodermic psoriasis or psoriatic arthritis.

#### Thiopurine antimetabolites

Thiopurine antimetabolites—ie, azathioprine, mercaptopurine (6-mercaptopurine, 6-MP), and thioguanine (6-thioguanine, 6-TG)—are used as immunosuppressive and steroid-sparing agents for many diseases. All inhibit DNA synthesis. Azathioprine is metabolized to 6-MP, which is then converted to 6-MP ribotide.

In a study of azathioprine in 29 patients with severe plaque-type psoriasis as well as ery-throderma and pustular variants, 19 (66%) of 29 benefited with 50% to 100% improvement on doses of 75 to 200 mg/day.<sup>28</sup> The main side effects are gastrointestinal and hematologic.

In a study of 6-TG in patients with recalcitrant plaque-type psoriasis, marked improvement occurred in 50% to 70% of patients treated with a pulse-dosing schedule of 120 mg twice weekly to 160 mg thrice weekly.<sup>29</sup> Palmoplantar pustulosis and generalized pustular psoriasis may also respond very well to 6-TG.<sup>30</sup> The response is usually evident within 12 weeks of starting therapy. The chief toxicity of 6-TG is myelosuppression.

### Mycophenolic acid

Mycophenolic acid inhibits de novo synthesis of guanosine nucleotide, thereby selectively suppressing proliferation of T and B lymphocytes.<sup>31</sup> Double-blind placebo-controlled trials confirmed its efficacy in psoriasis (68% decrease in mean severity scores) after 12 weeks, and patients were subsequently treated with 1.6 to 4.8 g/day for 2 years.<sup>32</sup> The main side effects are gastrointestinal and genitourinary. The incidence of herpes zoster was increased. The sponsor discontinued the national clinical trial in 1977.

#### Sulfasalazine

Sulfasalazine is a steroid-sparing agent for inflammatory bowel disease and is also a second-line therapy for rheumatoid arthritis and ankylosing spondylitis. It may have antiinflammatory activity in these diseases and psoriasis by inhibiting 5-lipoxygenase.

In a double-blind study,<sup>33</sup> 17 patients with psoriasis received sulfasalazine 3 to 4 g/day. Of these, 7 had a marked response, 7 had a moderate response, and 3 had a minimal response.

Side effects (anorexia, nausea, vomiting, fatigue, headaches, cutaneous eruptions) are common and, while usually not severe, frequently lead to discontinuation of treatment before any therapeutic benefit can occur. The incidence of drug-induced rash may be as high as 18%.



A lower dose of sulfasalazine than is needed for cutaneous psoriasis may be effective for arthropathy. Two large multicenter doubleblind studies of sulfasalazine at 2 g/day for psoriatic arthritis showed trends favoring a response to sulfasalazine, with decreased pain and decreased erythrocyte sedimentation rate.<sup>34,35</sup>

#### Tacrolimus

The macrolide lactone tacrolimus (Prograf), formerly known as FK506, is an immunosuppressive drug chemically unrelated to cyclosporine that inhibits T lymphocyte activation. The first double-blind trial<sup>36</sup> showed that tacrolimus was effective in improving severe plaque-type psoriasis by 83% after 9 weeks at doses of 0.05 to 0.15 mg/kg/day. Mild hypertension and mild to moderate renal dysfunction developed infrequently. Additional studies with larger numbers of patients treated long-term will be necessary to elucidate optimal dosing schedules and the toxicity profile of systemic tacrolimus. Tacrolimus ointment has proven ineffective in psoriasis.<sup>37</sup>

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