Guidelines of care for the management of psoriasis and psoriatic arthritis

Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents

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Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. In this fourth of 6 sections of the guidelines of care for psoriasis, we discuss the use of traditional systemic medications for the treatment of patients with psoriasis. Treatment should be tailored to meet individual patients' needs. We will discuss in detail the efficacy and safety, and offer recommendations for the use of the 3 most commonly used, and approved, traditional systemic agents: methotrexate, cyclosporine, and acitretin. We will also briefly discuss the available data for the use of azathioprine, fumaric acid esters, hydroxyurea, leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine in psoriasis. (J Am Acad Dermatol 2009;61:451-85.)

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore these guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

Abbreviations used:

AAD:	American Academy of Dermatology
AST:	aspartate aminotransferase
BUN:	serum urea nitrogen
CBC:	complete blood cell
CSA:	cyclosporine
FDA:	Food and Drug Administration
MMF:	mycophenolate mofetil
PASI:	Psoriasis Area and Severity Index
PPD:	purified protein derivative
PUVA:	psoralen plus ultraviolet A
SCC:	squamous cell carcinoma
TB:	tuberculosis
UV:	ultraviolet

SCOPE

This fourth section will cover the management and treatment of psoriasis with traditional systemic therapies.

METHOD

A work group of recognized psoriasis experts was convened to determine the audience and scope of

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the guideline, and identify clinical questions to structure the primary issues in diagnosis and management discussed in American Academy of Dermatology (AAD) psoriasis guidelines section 1 and 2.[1,2] Work group members completed a disclosure of commercial support.

An evidence-based model was used and evidence was obtained using a search of the MEDLINE database spanning the years 1960 through 2008. Only English-language publications were reviewed.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies.[3] Evidence was graded using a 3-point scale based on the quality of methodology as follows:

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

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

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

In those situations where documented evidence-based data are not available, we have used expert opinion to generate our clinical recommendations. Prior guidelines on psoriasis were also evaluated. This guideline has been developed in accordance with the AAD "Administrative Regulations for Evidence-based Clinical Practice Guidelines," which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

GENERAL PRINCIPLES

In the past, conventional systemic psoriasis therapies—methotrexate, cyclosporine (CSA), and acitretin—were used when psoriasis was too extensive for topical therapy or refractory to topical therapy and phototherapy. Although a minimum body surface area, eg, 10%, has been traditionally used as a prerequisite to starting a systemic therapy for psoriasis, a subset of patients with limited disease have debilitating symptoms. For example, although severe psoriasis of the palms and soles or severe scalp psoriasis affects less than 5% of the body surface area, the significant negative affect on the quality of life of the patient makes a systemic approach to treatment appropriate.

In recent years, biologics have changed the treatment of psoriasis, giving us additional therapeutic options that are potentially less toxic to the liver, kidneys, and bone marrow and are not teratogenic. Nevertheless, traditional systemic therapies continue to play an important role in the treatment of psoriasis with their oral route of administration and low cost (compared with biologics) making them an important treatment option in the appropriate patient.

Methotrexate is the most commonly prescribed traditional systemic therapy worldwide for psoriasis. Detailed guidelines concerning its dosing and monitoring in patients with psoriasis have recently been published by the National Psoriasis Foundation.[4] It is noteworthy that the rheumatology guidelines for the use of methotrexate[5] are less stringent than those in dermatology, especially in the monitoring of hepatotoxicity. The difference in this monitoring may be that patients with psoriasis with more severe disease are more likely to be obese than patients with rheumatoid arthritis, and thus be more prone to have underlying nonalcoholic steatohepatitis. Methotrexate can be dramatically effective with even the most severe cases of psoriasis. The potential role of pharmacogenetic testing to improve our ability to predict the efficacy and safety of methotrexate suggests the possibility of personalizing the use of methotrexate in the years ahead.[6] Methotrexate has been used in combination with all of the approved biologic agents for psoriasis. The greatest experience is with tumor necrosis factor inhibitors. Methotrexate has been used to suppress antibodies against the two monoclonal tumor necrosis factor inhibitors, adalimumab and infliximab.[7] It is not known whether the use of methotrexate and biologics causes additive immunosuppression as this combination has primarily been studied in patients without psoriasis, and the differing baseline risks associated with these diseases make this distinction uncertain.

CSA is one of the most effective treatments available for psoriasis.[8] However, when used in the longer term (3-5 years), a significant proportion of patients will develop some degree of glomerulosclerosis.[9] Published guidelines in the United States therefore limit its use to 1 year,[8]

whereas in the United Kingdom it is allowed for 2 years.[10] In patients with severe flares of psoriasis, CSA frequently induces a rapid remission. Rebound flares of psoriasis after discontinuation of systemic steroids or efalizumab can be prevented or rapidly controlled with CSA[11] or methotrexate.

Of the systemic therapies, acitretin is the least effective as monotherapy and it is therefore often used in conjunction with ultraviolet (UV) B or psoralen plus UVA (PUVA) phototherapy. Studies performed in the 1980s demonstrated that etretinate, the pro-drug of acitretin, is particularly effective in patients with palm and sole psoriasis.[12] Because acitretin is not immunosuppressive, it has also been used in combination with biologic therapies. Acitretin's major side effect is its teratogenicity, and its use is, therefore, limited to male and female patients of nonchildbearing potential. At high doses, it may be associated with significant mucocutaneous effects along with hair loss, and although it can occasionally be dosed at 50 mg daily, most clinicians use doses between 10 and 25 mg per day.

Because of the known organ toxicities of traditional systemic agents, the concept of rotational therapy was developed so that patients could rotate from one agent to the other or to phototherapy or photochemotherapy to minimize total cumulative dose and thereby limit toxicity.[13] With the advent of biologic therapies, and their reduction in incidence of major organ toxicity, rotational therapy is less commonly used.[13]

To minimize the toxicity of any therapy, proper patient selection and appropriate monitoring are crucial. The decision to administer methotrexate, CSA, acitretin, or any other traditional therapy must be individualized. Every patient needs to be carefully evaluated with reference to disease severity, quality of life, and general medical and psychologic status.

METHOTREXATE

Oral methotrexate is an effective treatment for psoriasis being initially used more than 50 years ago. Methotrexate competitively inhibits the enzyme dihydrofolate reductase, thus decreasing the synthesis of folate cofactors needed to produce nucleic acids. Because the effects of methotrexate are most dramatic on rapidly dividing cells, it was originally thought that its beneficial effects in psoriasis were a result of the inhibition of epidermal proliferation.[14] However, it is now known that there is little effect on epidermal cells, but there is significant inhibition of the proliferation of lymphoid tissue at concentrations of methotrexate that are typically achieved with low-dose weekly methotrexate.[15] These findings support the concept that the therapeutic effect of low-dose methotrexate in psoriasis is a result of its effects on the immune system.[16] Methotrexate was approved by the Food and Drug Administration (FDA) in 1972 for the treatment of severe, recalcitrant, disabling psoriasis. Because methotrexate was introduced before the acceptance of randomized clinical trials as the standard by which to judge drug efficacy, there are no large high-quality studies demonstrating its safety and efficacy, and clinical experience with methotrexate is much greater than the documentation of its safety and efficacy in clinical studies. For these reasons, methotrexate guidelines, which were originally written in 1972[17] and have since been updated on numerous occasions (most recently in 2009[4]), provide expert-based standards for the use of methotrexate in the treatment of psoriasis.

Efficacy

Three well-designed studies that evaluated the efficacy of methotrexate were recently performed. Heydendael et al[18] compared the efficacy and safety of methotrexate with CSA in a study that randomized 88 patients to receive either medication without a placebo group. The primary end point of Psoriasis Area and Severity Index (PASI) 75 at 16 weeks was 60% for methotrexate and 71% for CSA (no statistical difference). Twelve of 44 patients in the methotrexate group dropped out because of elevated liver function test results (it should be noted that no folic acid supplementation was given in this study), whereas only one patient in the CSA group dropped out (because of elevated bilirubin).[18] Flytstrom et al[19] compared methotrexate with CSA in the treatment of 84 patients with psoriasis in a 12-week study that also did not include a placebo arm. These authors used a different end point, namely a mean PASI change from baseline, which was 72% for CSA compared with 58% for methotrexate. Although CSA was statistically more effective than methotrexate, 12 patients in the CSA group and 4 patients in the methotrexate group dropped out secondary to laboratory abnormalities and withdrawn consents before initiation of treatment.[19] Saurat et al[20] performed the first double-blind, placebo-controlled study of methotrexate, designed to compare the safety and efficacy of adalimumab, methotrexate, and placebo in 250 patients. After 16 weeks of treatment, PASI 75 improvement was 19% for placebo, 36% for methotrexate, and 80% for adalimumab. For those patients in the methotrexate arm of the study, methotrexate was initiated at a low weekly dosage of 7.5 mg for 2 weeks, followed by 10 mg weekly for 2 weeks, and then 15 mg for 4 weeks. Thereafter, an increase in the dosage of methotrexate was permitted depending on the response and the presence or absence of

toxicities. After 8 weeks, if patients in the methotrexate arm had achieved a PASI 50 response, no further increase in methotrexate dosage was allowed. After 16 weeks, when the mean methotrexate dose was 19 mg, these patients were crossed over to receive adalimumab; it should be noted that patients in the methotrexate arm were still showing clinical improvement at the time of crossover, suggesting that the results of this study may have underestimated the efficacy of methotrexate.[20] Furthermore, the placebo response rate of 19% is dramatically higher than is seen in a clinical trial of this type, raising doubt about the validity of this study.

Dosage

Methotrexate is generally given as a single weekly oral dose, given as a tablet or occasionally as a carefully measured parenteral solution given orally (0.1 mL of a 25 mg/mL multidose vial is equivalent to a 2.5-mg oral tablet). The parenteral solution of methotrexate is less costly than tablets. Intramuscular administration is helpful when there is gastrointestinal intolerance to oral dosing or if there are concerns regarding patient compliance. Subcutaneous injection is equally effective and can be self-administered at home. Doses are usually started at low levels to minimize side effects and then gradually increased to achieve efficacy. Many practitioners give a single test dose of 2.5 or 5 mg to evaluate for significant bone-marrow suppression in susceptible patients. Although there are no established maximum or minimum dosages of methotrexate, weekly dosages usually range from 7.5 to 25 mg. All dosing schedules should be adjusted to the individual patient and the dosage raised or reduced to obtain or maintain adequate disease control or minimize side effects. After an increase in methotrexate dose, it may take up to 4 weeks for a clinical response to occur. Some patients can be gradually tapered off treatment and restarted when the psoriasis recurs. It is important to minimize the total cumulative dose of methotrexate while maintaining disease control and medication tolerance.

Folate supplementation

Although the majority of experts recommend that all patients treated with methotrexate receive folate supplementation (1-5 mg/d given daily except the day of methotrexate), others will add folate only if a patient develops gastrointestinal side effects or early bone-marrow toxicity as manifested by an increased mean corpuscular volume. In patients who develop bone-marrow toxicity or gastrointestinal side effects while on folate, increasing the dose of folate may be helpful. Although a literature review of these data, largely derived from the rheumatoid arthritis literature, suggests that low-dose folate supplementation may reduce the hematologic, gastrointestinal, and hepatic side effects of methotrexate without decreasing the efficacy,[21] one small controlled study in patients with psoriasis using folic acid at 5 mg daily suggested that there may be a slight decrease in efficacy.[22] However, the methodology of this latter study has been questioned.[23] The optimal dosage of folic acid is still to be determined.

Toxicity

Common and generally minor toxicities of methotrexate include nausea, anorexia, stomatitis, and fatigue that most often occur at the time of methotrexate administration. These effects may be minimized by administering methotrexate by intramuscular or subcutaneous injection, splitting the dose, folate supplementation, or by administering the dose with food or at bedtime. The major toxicities that are of greatest concern in patients treated with methotrexate are myelosuppression, hepatotoxicity, and pulmonary fibrosis. Of 164 possible methotrexate-associated fatalities, 67 were caused by myelosuppression, 30 were caused by pulmonary fibrosis, and 8 were caused by hepatotoxicity.[24] Pulmonary fibrosis is one of the more severe manifestations of methotrexate toxicity and must be ruled out in patients presenting with new pulmonary symptoms such as cough; however, this complication is much less common in patients with psoriasis than in patients with rheumatoid arthritis.[25-27]

Because methotrexate has not been studied in large double-blind placebo-controlled trials of the type that have been routinely used to determine the safety and efficacy of the biologic agents, less common adverse effects have not been carefully evaluated. Recent reports suggest that treatment with methotrexate may be associated with some of the risks similar to those of the biologic agents, although to date these reports have occurred almost exclusively in patients with rheumatoid arthritis.[28-31] Hepatitis, reactivation of tuberculosis (TB), and lymphoma, especially the B-cell type that is commonly associated with Epstein-Barr virus infection, have all been reported in patients being treated with methotrexate.[23-26] These observations suggest that practitioners need to maintain a high index of suspicion for these infections in patients being treated with methotrexate.

Hematologic

The major risk factors for hematologic toxicity are advanced age, renal impairment, the absence of folate supplementation, drug interactions, and

Table I. Risk factors for hematologic toxicity from methotrexate

- Renal insufficiency
- Advanced age
- Lack of folate supplementation
- Methotrexate dosing errors
- Drug interactions
- Hypoalbuminemia
- Greater than moderate alcohol intake

Adapted with permission from Kalb et al.[4]

medication errors (Table I). Most of the literature concerning myelosuppression with methotrexate derives from the experience in patients with rheumatoid arthritis. Although the relative risk of myelosuppression in patients with psoriasis compared with patients with rheumatoid arthritis is unknown, the literature suggests that significant myelosuppression is rare in appropriately monitored patients with psoriasis who have no risk factors for hematologic toxicity.

The practice of using a single test dose of methotrexate derives from the desire to ensure that severe myelosuppression does not occur. The test dose is typically 2.5 or 5 mg with a complete blood cell (CBC) count evaluated 5 to 6 days later, to ensure that myelosuppression has not occurred before increasing to the full weekly dosage. Although the use of a test dose does not guarantee that patients will not experience myelosuppression, it is mandatory in patients with a decreased glomerular filtration rate or other significant risk factors for hematologic toxicity.[32]

Pancytopenia can rarely occur with the use of low-dose weekly methotrexate, even after single doses of methotrexate.[33-35] It can occur at any time during treatment; in all cases, however, there were identified risk factors, particularly impaired renal function, medication errors, or use of concomitant medications, especially sulfonamide-based.[32,36] As pancytopenia may occur as long as 4 to 6 weeks after increasing the methotrexate dosage, more frequent monitoring is suggested with dosage increases.

Hepatotoxicity

Hepatotoxicity is a well-known side effect of methotrexate. Recent studies, however, demonstrated that hepatic fibrosis and cirrhosis are considerably less common than initially reported.[37,38] Rheumatologists traditionally deem the liver biopsy as unnecessary, particularly in healthy patients. Thus, dermatology guidelines are stricter as hepatic toxicity is greater in patients with psoriasis than in patients with rheumatoid arthritis.[27]

Table II. Risk factors for hepatotoxicity from methotrexate

- History of or current greater than moderate alcohol consumption (methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy; the exact amount of alcohol that leads to risk is unknown and differs from person to person)
- Persistent abnormal liver chemistry study findings
- History of liver disease including chronic hepatitis B or C
- Family history of inheritable liver disease
- Diabetes mellitus
- Obesity
- History of significant exposure to hepatotoxic drugs or chemicals
- Hyperlipidemia

Adapted with permission from Kalb et al.[4]

The pathologic features of methotrexate-induced liver toxicity resemble nonalcoholic steatohepatitis, the pattern of liver histology observed in people who are obese, hyperlipidemic, or diabetic. Methotrexate likely aggravates preexisting nonalcoholic steatohepatitis, suggesting that patients with psoriasis at greatest risk while receiving methotrexate are those with diabetes, with obesity, or who collectively meet the criteria for metabolic syndrome in addition to those who drink alcohol.[39,40] Recent studies suggest that when evaluating patients for methotrexate treatment, risk factors including alcohol intake, obesity, hyperlipidemia, diabetes, previous exposure to liver toxins, and hepatitis need to be considered.[40,41]

Recently updated methotrexate guidelines from the National Psoriasis Foundation[4] suggest that patients be divided into two groups, those with risk factors for hepatotoxicity from methotrexate (Table II) and those without. Patients with no risk factors for methotrexate-induced hepatotoxicity should be judged by the American College of Rheumatology criteria for monitoring methotrexate. These criteria include an evaluation of liver chemistries every 1 to 3 months with the need for a liver biopsy only if 5 of 9 aspartate aminotransferase (AST) levels are elevated during a 12-month period or if there is a decline in the albumin (in patients with normal nutritional status) below normal in the setting of well-controlled disease (Table III). This approach has been validated in patients with rheumatoid arthritis and has also demonstrated a decrease in the number of liver biopsies.[42] Furthermore, data suggest that 3.5 to 4.0 g instead of 1.0 to 1.5 g of cumulative methotrexate may be a more appropriate time frame for the first liver biopsy in patients without preexisting risk factors for hepatotoxicity.[39,43,44] In patients with

Table III. Monitoring for hepatotoxicity in patients with no risk factors for hepatotoxicity

- No baseline liver biopsy
- Monitor LFT results monthly for the first 6 mo and then every 1-3 mo thereafter
  - → For elevations <2-fold upper limit of normal: repeat in 2-4 wk
  - → For elevations >2-fold but <3-fold upper limit of normal: closely monitor, repeat in 2-4 wk, and decrease dose as needed
  - → For persistent elevations in 5/9 AST levels during a 12-mo period or if there is a decline in the serum albumin below the normal range with normal nutritional status, in a patient with well-controlled disease, a liver biopsy should be performed
- Consider liver biopsy after 3.5-4.0 g total cumulative dosage

  or
- Consider switching to another agent or discontinuing therapy after 3.5-4.0 g total cumulative dosage

  or
- Consider continuing to follow up according to above guidelines without biopsy

Adapted with permission from Kalb et al.[4]
AST, Aspartate aminotransferase; *LFT*, liver function test.

Table IV. Monitoring for hepatotoxicity in patients with risk factors for hepatotoxicity

- Consider the use of a different systemic agent
- Consider delayed baseline liver biopsy (after 2-6 mo of therapy to establish medication efficacy and tolerability)
- Repeated liver biopsies after approximately 1-1.5 g of methotrexate

Adapted with permission from Kalb et al.[4]

normal liver chemistry results, history, and physical examination findings, the decision about whether or not to undergo a liver biopsy should be made on an individual basis. Choices for patients who have accumulated 3.5 to 4.0 g of methotrexate (whether from continuous or intermittent methotrexate dosing) include performing a liver biopsy, switching to another therapy, or following the above guidelines and continuing to monitor without a biopsy unless 5 of 9 AST levels are elevated. If the first liver biopsy specimen reveals normal results, repeated liver biopsy would be dictated by the guidelines in Table III.

Patients with one or more risk factors for hepatotoxicity need be followed up with the more stringent guidelines (Table IV). If the risk-benefit analysis for a patient with such risk factors favors the use of methotrexate, then this patient should have a liver biopsy performed at or near the beginning of methotrexate therapy. As some patients will discontinue methotrexate within 2 to 6 months because of adverse effects or lack of clinical effectiveness, it is sensible to postpone the early treatment liver biopsy until after this initial period. There is little to no evidence to suggest that a several-month period of methotrexate treatment will cause clinically significant liver disease. In patients with risk factors for liver disease, a repeated biopsy should be performed at a cumulative dose of 1.0 to 1.5 g. In patients with persistent significant abnormalities in liver chemistry values, a liver biopsy is also indicated. The liver biopsy in these patients at higher risk should be repeated with every additional 1.0 to 1.5 g of methotrexate.

Serum assays for liver fibrosis are now widely accepted and recommended in Europe as a means of eliminating or decreasing the need for liver biopsies. Measurement of the amino-terminal peptide of pro-collagen III is the most used marker. One study using the amino-terminal peptide of pro-collagen III assay demonstrated a 7-fold reduction in the number of liver biopsies by the use of this assay.[45] The amino-terminal peptide of pro-collagen III assay is generally not available in the United States. New developments such as magnetic resonance elastography[46] and the enhanced liver fibrosis panel[47] could likewise further reduce the need for liver biopsies in the future. FibroSpect, II (Prometheus Laboratories, San Diego, CA) and FibroSure (LabCorp, Burlington, NC) tests for liver fibrosis, although unproven to aid in the diagnosis of methotrexate-induced fibrosis, are available in the United States and could be considered as possible alternatives for patients in whom liver biopsy is technically difficult or contraindicated.

Pregnancy

Methotrexate is an abortifacient and a teratogen. It is FDA pregnancy category X and is contraindicated in women attempting to conceive. Methotrexate-induced fetal abnormalities include cardiac, skeletal, and central nervous system defects.[48] Women of childbearing potential who are sexually active and are being treated with methotrexate must use contraception. Although the critical period of methotrexate

exposure is thought to be between 6 to 8 weeks after conception, fetal abnormalities have been reported at all times of exposure to methotrexate. Conversely, numerous first-trimester pregnancies with exposure to large doses of methotrexate (primarily for the treatment of leukemia) have resulted in live births with no congenital or developmental problems.[49] Because methotrexate is widely distributed in maternal tissues and may persist in the liver for up to 3 months after exposure,[50] it is appropriate for women to wait 3 months after discontinuing methotrexate before attempting to conceive a child.

Male fertility

Methotrexate is not mutagenic but spermatogenesis studies in rats suggest that it may be toxic to cells undergoing division.[51] In human beings, there is controversy regarding the effect of methotrexate on spermatogenesis[52]; the teratogenicity of methotrexate in fetus fathered by men who are on methotrexate is unclear because of a lack of data. Although some studies suggest that methotrexate treatment may result in severe, yet reversible, oligospermia despite normal hormone levels,[53] other studies reveal no changes in spermatogenesis and sperm counts.[54,55] One cycle of spermatogenesis requires 74 days thus it is appropriate for male patients to wait 3 months after discontinuing methotrexate before attempting to conceive a child to allow for the methotrexate effects to be eliminated.

PEDIATRIC USE

Methotrexate is FDA-approved for the treatment of psoriasis in adults and for juvenile rheumatoid arthritis. Although there are only a few reports on the use of methotrexate for the treatment of pediatric psoriasis,[56] the use of methotrexate in children for several different dermatologic and rheumatologic conditions has been recently reviewed.[57] In general, low-dose weekly methotrexate is well tolerated in children. Primary side effects seen in children include abnormal liver function test results, stomatitis, and gastrointestinal irritation. When interpreting the data for the use of methotrexate in children, it is important to be aware that the majority of the published studies derived from the rheumatology literature where patients are often treated with concomitant oral corticosteroids. These authors suggested that most pediatric patients can be monitored for hepatotoxicity according to the rheumatologic liver biopsy guidelines recommended for adults without risk factors.

Drug interactions

Numerous medications may interact with methotrexate by a variety of mechanisms that can result in elevated drug levels, thereby increasing the risk for methotrexate toxicity (Table V). After absorption, methotrexate binds to serum albumin. Salicylates, sulfonamides, diphenylhydantoin, and antibiotics including penicillin, minocycline, chloramphenicol, and trimethoprim may decrease the binding of methotrexate to albumin leading to increased serum levels of methotrexate. Several other medications including colchicine, CSA, probenecid, salicylates, and sulfonamides may lead to decreased renal tubular excretion leading to decreased renal elimination of methotrexate and increased serum levels.

Given the hepatotoxicity of methotrexate, caution should be used when prescribing this drug to patients taking other potentially hepatotoxic agents including alcohol, statins, leflunomide, retinoids, azathioprine, and minocycline.

Although some nonsteroidal anti-inflammatory drugs may lead to elevation of serum methotrexate levels, including ibuprofen, salicylates, and naproxen[58] other nonsteroidal anti-inflammatory drugs such as ketoprofen, flurbiprofen, piroxicam, and meloxicam,[59,60] as well as lumiracoxib, rofecoxib (which is no longer available), and celecoxib[61-63] do not. Other interactions can occur with methotrexate with most of the clinically relevant contraindications being summarized in Table VI.

Table V. Medications that may increase methotrexate toxicity

Nonsteroidal anti-inflammatory drugs	Antibiotics	Others
Salicylates	Trimethoprim/ sulfamethoxazole	Barbiturates
Naproxen	Sulfonamides	Colchicine
Ibuprofen	Penicillins	Dipyridamole
Indomethacin	Minocycline	Ethanol
Phenylbutazone	Ciprofloxacin	Phenytoin
		Sulfonylureas
		Furosemide
		Thiazide-diuretics

Adapted with permission from Kalb et al.[4]

INITIATION AND MONITORING

Before initiating therapy with methotrexate, patients should have a thorough history and physical examination, reviewing alcohol intake, possible exposure to hepatitis B or C, and family history of liver disease. Laboratory tests, including a CBC count with differential, creatinine, liver function tests including albumin and bilirubin should be obtained for baseline levels. Screening for hepatitis B and C should be

Table VI. Relative contraindications for the use of methotrexate

- Abnormalities in renal function may require a marked reduction in the dose as 85% of methotrexate is renally excreted
- Abnormalities in liver function—LFT results should be followed up and all elevations require careful monitoring
- Hepatitis, active or recurrent
- Greater than moderate alcohol consumption—although there are few data to support specific limits on alcohol consumption, some physicians require patients to completely refrain from alcohol whereas others allow daily alcohol intake; a history of alcoholism is particularly worrisome if there is baseline liver damage
- Concomitant use of hepatotoxic drugs—more frequent monitoring of LFT results should be considered
- Active infectious disease, particularly chronic infections that are likely to be worsened by immunosuppressive effects of methotrexate (eg, active untreated tuberculosis or acquired immunodeficiency syndrome); methotrexate should be withheld during acute infections
- Current use of other immunosuppressive agents
- Conception should be avoided during methotrexate treatment and afterward for at least 3 mo in men and 3 ovulatory cycles in women
- Recent vaccination with a live vaccine
- Obesity (body mass index > 30)
- Diabetes mellitus
- Unreliable patient

Adapted with permission from Kalb et al.[4]
LFT, Liver function test.

considered when there is evidence of viral hepatitis such as elevated liver function test results.

In regard to testing for TB, some experts recommend a baseline purified protein derivative (PPD) test or other screening test for latent TB, particularly if the patient's history indicates risk. Although some argue that this is not the standard of care, the Centers for Disease Control and Prevention World Wide Web site recommendations for TB suggest that patients on immunosuppressive drugs should be considered for a pretreatment PPD.[64] The National Psoriasis Foundation consensus statement also recommends screening for latent TB infection in all patients with psoriasis who will be treated with systemic or biologic immunosuppressive agents.[65]

Pretreatment liver biopsy should only be performed in patients who have abnormal liver function test results, chronic hepatitis, and a history of greater than moderate alcohol intake defined as one drink/d for female patients or anyone older than 65 years and two drinks/d for men younger than 65 years.[66] A chest radiograph is important for patients with underlying pulmonary disease. Contraception issues, as discussed earlier, should be addressed.

Ongoing laboratory studies should include a CBC count every 2 to 4 weeks for the first few months, then every 1 to 3 months, depending on leukocyte count and patient's stability. Some suggest that laboratory studies be performed on the fifth to sixth day of the weekly methotrexate cycle, to detect the leukopenia nadir, and because liver chemistry values may be elevated 1 to 2 days after a dose of methotrexate. Patients with risk factors for hematologic toxicity (Table I) need closer monitoring, particularly at the onset of therapy and after increasing the dosage of methotrexate. Patients with significant renal impairment are at risk even after single doses of methotrexate, and these patients require careful monitoring by obtaining blood counts before the second dose. A significant reduction in leukocyte or platelet counts necessitates reduction or temporary discontinuation of methotrexate therapy. Folinic acid (leucovorin) is the antidote for the hematologic toxic effects of methotrexate. When an overdose of methotrexate is suspected or there a worrisome decrement in the leukocyte, platelet, or red cell count, folinic acid (at 10 mg/m^2) should be administered. Because the effectiveness of folinic acid in counteracting the hematologic toxicity of methotrexate decreases as the time interval between methotrexate administration and folinic acid treatment increases, folinic acid should be given immediately with subsequent doses given every 6 hours.[4] The frequency of blood count monitoring may be slowly decreased over time as long as there is no toxicity or changes in the medical history. Serum urea nitrogen (BUN) and creatinine should be obtained at 2- to 3-month intervals. For those patients with normal values, who may be at risk for decreased renal function, such as the elderly or those with a decreased muscle mass, a glomerular filtration rate should be calculated. Liver chemistries including alanine aminotransferase, AST, alkaline phosphatase, and serum albumin levels should be performed every 4 weeks (more frequent liver chemistry monitoring should be performed in lieu of an initial liver biopsy for patients with hepatic risk factors) (Table II). More frequent liver chemistry

Table VII. Recommendations for methotrexate

- Indication: severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy
- Dosing: methotrexate is administered as a weekly single oral dose
  - Doses can be increased gradually until an optimal response is achieved; total dose should not ordinarily exceed 30 mg/wk; doses should be reduced to the lowest possible amount of drug needed to achieve adequate control of psoriasis with concomitant topical therapy
  - A test dose of 2.5-5 mg is recommended
- Duration of dosing
  - Treatment can be continued for as long as is necessary provided there are no meaningful signs of liver or bone-marrow toxicity with adequate monitoring; folic acid supplementation 1-5 mg daily by mouth, except for the day of methotrexate dosing, reduces the frequency of side effects
- Therapeutic results
  - In the only placebo-controlled trial of methotrexate for psoriasis, 36% of patients treated with 7.5 mg/wk orally, increased as needed up to 25 mg/wk, reached PASI 75 after 16 wk
- Absolute contraindications
  - Pregnancy
  - Nursing mothers
  - Alcoholism
  - Alcoholic liver disease or other chronic liver disease
  - Immunodeficiency syndromes
  - Bone-marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
  - Hypersensitivity to methotrexate
- Relative contraindications
  - Abnormalities in renal function
  - Abnormalities in liver function
  - Active infection
  - Obesity
  - Diabetes mellitus
- Toxicity
  - Elevated LFT results
  - Minor elevations of LFT results are common; if elevation exceeds 2× normal, must check more frequently; if exceeds 3× normal, consider dose reduction; if exceeds 5× normal, discontinue
  - Anemia, aplastic anemia, leukopenia, thrombocytopenia
  - Interstitial pneumonitis
  - Ulcerative stomatitis
  - Nausea, vomiting, diarrhea
  - Malaise or fatigue
  - Chills and fever
  - Dizziness
  - Decreased resistance to infection
  - GI ulceration and bleeding
  - Photosensitivity (''radiation recall'')
  - Alopecia
- Drug interactions
  - Hepatotoxic drugs: eg, barbiturates
  - Acitretin has been used successfully in combination with methotrexate despite the potential for hepatotoxicity from both medications
  - Drugs that interfere with renal secretion of methotrexate: eg, sulfamethoxazole, NSAIDs, and penicillins
  - Folic acid antagonists: eg, trimethoprim
- Liver biopsy
  - Patients at low risk—at baseline, not necessary
  - First biopsy: 3.5-4 g; subsequent biopsies to be considered after 1.5 g
  - Patients at high risk including history of diabetes, obesity, abnormal LFT results, excessive EtOh ingestion, chronic liver disease, family history of heritable liver disease
  - Consider baseline biopsy or at 6 mo with subsequent biopsies after 1-1.5 g
- Baseline monitoring
  - History and physical examination
  - CBC and platelet counts

Continued

Table VII. Cont'd

- BUN, creatinine, and LFTs
- Liver biopsy is only indicated in patients with a history of significant liver disease
- Pregnancy test and test for HIV in selected patients
- Consider PPD
- Consider chest radiograph if patient has underlying pulmonary disease

- Ongoing monitoring
  - CBC and platelet counts at varying intervals (initially every 2-4 wk for first few months and then every 1-3 mo depending on dosage adjustments, symptoms, and previous CBC count results)
  - LFTs at monthly intervals, BUN, creatinine every 2-3 mo depending on dosage adjustments, symptoms, and previous blood test results
  - Pregnancy test if indicated
  - Consider liver biopsy in patients at high risk including history of diabetes, obesity, abnormal LFT results, excessive EtOh ingestion, chronic liver disease, family history of heritable liver disease
  - For those without risk factors, consider liver biopsy in patients with cumulative doses of more than 3.5-4 g methotrexate
  - For patients without risk factors, consider repeated liver biopsies after each subsequent 1.5-g dosage, based on LFT results, risk factors (eg, diabetes and obesity) or in consultation with a hepatologist
  - The aminoterminal peptide of procollagen III is used in Europe (but is generally not available in the United States) as a test for hepatic fibrosis, reducing the need for frequent liver biopsies
- Pregnancy: category X; men and women considering conception should be off methotrexate for 3 mo before attempting to conceive; should pregnancy ensue before this time period, consider genetic counseling
- Nursing: mothers receiving methotrexate should not breast-feed
- Pediatric use: methotrexate is approved for the treatment of juvenile rheumatoid arthritis; low-dose methotrexate has been used effectively and safely in children for a variety of dermatologic and rheumatologic disorders
- Psoriatic arthritis: although there are only two small controlled trials evaluating methotrexate for psoriatic arthritis that are inadequately powered to assess clinical benefit,[176,177] methotrexate is often used as the primary agent to treat psoriatic arthritis

BUN, Serum urea nitrogen; *CBC*, complete blood cell; *EtOh*, alcohol; *GI*, gastrointestinal; *LFT*, liver function test; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *PASI*, Psoriasis Area and Severity Index; *PPD*, purified protein derivative.

monitoring is also indicated when the dosage is increased or if the patient is taking concomitant hepatotoxic medications. If a significant persistent abnormality in liver chemistry develops, methotrexate therapy should be withheld for 1 to 2 weeks and then liver chemistry tests should be repeated, with liver chemistry values likely to return to normal in 1 to 2 weeks. If significantly abnormal liver chemistry values persist for 2 to 3 months, a liver biopsy should be considered if continuation of methotrexate therapy is desired. The extent of fibrosis on liver biopsy specimen dictates whether methotrexate may be continued. It is prudent to discontinue methotrexate if a patient refuses to undergo a liver biopsy. More frequent monitoring of both laboratory studies and liver histology is necessary if other hepatotoxic medications are used along with methotrexate. (Please see above section on hepatotoxicity for guidance on the use of liver biopsies in the monitoring of patients being treated with methotrexate.)

CONTRAINDICATIONS

Methotrexate is absolutely contraindicated in pregnancy or nursing and in patients with cirrhosis or who have significant anemia, leukopenia, or thrombocytopenia. Relative contraindications to the use of methotrexate for the treatment of psoriasis are numerous and are included in Table VI. Methotrexate should not be used in combination with trimethoprim/sulfamethoxazole (Septra [Hoffmann-La Roche Inc, Roche, Nutley, NJ], Bactrim [Monarch Pharmaceuticals Inc, Bristol, TN]) because of increased methotrexate toxicity. Although the combination is contraindicated in official labeling, methotrexate can be used in combination with acitretin when necessary with appropriate hepatic monitoring.[67] Recommendations for the use of methotrexate are shown in Table VII. The strength of recommendations for the treatment of psoriasis using methotrexate is shown in Table VIII.

CYCLOSPORINE

CSA is a highly effective and rapidly acting systemic agent for the treatment of psoriasis. Discovered in 1970 and originally used as an immunosuppressive agent in organ transplantation, it was first shown to be effective for psoriasis in 1979.[68] CSA induces immunosuppression by inhibiting the first phase of T-cell activation. It binds to cyclophillin,

Table VIII. The strength of recommendations for the treatment of psoriasis using traditional systemic therapies

Agent	Strength of recommendation	Level of evidence	References
Methotrexate*	B	II	18-20
Cyclosporine*	B	II	18,71-75,77,78
Acitretin*	B	II	108,110-113,115,117,118,121
Azathioprine	C	III	149,150
Fumaric acid esters†	B	I	152,153
Hydroxyurea	C	III	159-161
Leflunomide‡	B	II	163
Mycophenolate mofetil	C	III	166,167
Sulfasalazine‡	B	II	168
Tacrolimus‡	B	II	172
6-Thioguanine	C	III	173-175

The reader is advised not to use this table alone for decision making regarding the choice of traditional systemic therapies.
*Although methotrexate, cyclosporine, and acitretin are all Food and Drug Administration approved for the treatment of psoriasis and have been used for many years by dermatologists with good to excellent results, the quality of the evidence supporting their use is as listed.
†The fumaric acid esters studies are well-designed placebo-controlled trials but because this treatment is not approved in the United States, it has been given strength of recommendation of B with a level I of evidence.
‡Although there are placebo-controlled trials evaluating the use of leflunomide, sulfasalazine, and tacrolimus in the treatment of psoriasis requiring systemic therapy, the quality of the evidence supporting their use is not very convincing.

with the resulting CSA/cyclophillin complex binding to and inhibiting the enzyme calcineurin, leading to blockade of signal transduction pathways that are dependent on the transcription factor, nuclear factor of activated T cells. This blockade leads to lower levels of multiple inflammatory cytokines including interleukin-2 and interferon gamma, thus inhibiting T-cell activation.[69,70] Despite the recent development of multiple new therapeutic modalities, CSA remains an important option in treating psoriasis. CSA is very useful in crisis management, as a bridge to other therapies, and in the rapid treatment of psoriasis unresponsive to other modalities, ie, as interventional therapy.

EFFICACY

Numerous clinical trials have demonstrated the efficacy of CSA in psoriasis. The original studies evaluating CSA's efficacy in psoriasis provided evidence that psoriasis is a T-cell–driven immunologic disorder rather than a disorder of altered keratinocyte growth and differentiation. CSA given at 2.5 to 5 mg/kg/d for 12 to 16 weeks leads to rapid and dramatic improvement in psoriasis in up to 80% to 90% of patients.[71-75] When dosed at 3 mg/kg/d, CSA leads to a PASI 75 response in 50% to 70% of patients and a PASI 90 response in 30% to 50% of patients.[76]

Short-term treatment with CSA is an attractive method of treatment with minimal toxicities in healthy patients. In an open, multicentered, randomized trial of up to 12 weeks of intermittent courses of CSA either tapered or abruptly stopped in the treatment of psoriasis during the course of 1 year, 400 patients were randomized to two groups: abrupt discontinuation of CSA or gradual tapering by 1 mg/kg/d weekly until cessation. Relapsed patients were retreated with CSA.[74] In all, 400, 259, 117, and 26 patients required 1, 2, 3, and 4 additional treatment courses, respectively. The median time to relapse was 109 days in the patients who abruptly stopped CSA and 113 days for patients who were tapered off therapy; a statistically significant difference of unclear clinical significance. Short, intermittent courses of CSA were generally well tolerated, however, 8% of patients discontinued the study because of adverse events, including those related to increased creatinine and hypertension.

Several studies have evaluated the efficacy of long-term CSA in the treatment of psoriasis. In a study of 217 patients treated for 6 to 30 months with CSA at 1.25, 2.5, or 5.0 mg/kg/d, 12.5% of patients were successfully maintained on 1.25 mg/kg/d without loss of efficacy.[77] In another study of 181 patients with severe disease initially treated with an induction phase of CSA, 86% of responders were treated with a 6-month maintenance phase in which they were assigned to either CSA 3.0, 1.5, or 0 mg/kg/d. In all, 42% of the patients on 3 mg/kg/d of CSA relapsed compared with 84% of those who were given placebo.[78]

DOSAGE

Although the package insert suggests dosing CSA based on ideal body weight,[79] we have found that obese patients often require dosing based on their

actual weight. CSA microemulsion is considered to have a superior pharmacokinetic profile to the regular preparation. CSA should be administered at a consistent time of the day and in relation to meals to decrease the intraindividual blood level variations. The CSA solution can be mixed with milk or orange juice but not with grapefruit juice, because this can increase plasma CSA concentrations by inhibiting the cytochrome P450 metabolism of CSA. The initial daily dose of CSA is 2.5 to 3 mg/kg in two divided doses. It is generally recommended to maintain this stable dose for 4 weeks, and then increase the dosage at increments of 0.5 mg/kg/d until disease control is achieved. Although the package insert recommends that the maximal daily dosage should be 4 mg/kg/d,[79] the customary maximum psoriasis dose is 5 mg/kg/d. Another approach to dosing of CSA used in patients with more severe disease is to initiate treatment at the highest dosage, typically 5 mg/kg/d, with stepwise decreases after adequate disease control is achieved.

TOXICITY

CSA's most serious side effects are nephrotoxicity and hypertension. These two toxicities are thought to be mediated by CSA's vasoconstrictive effects on renal arterioles.[80] Although reversible changes in the kidney may be related to this vascular effect, long-term therapy frequently leads to permanent scarring with subsequent loss of renal function.[81] Because of these concerns, CSA is a drug that requires careful patient selection and subsequent monitoring to be used safely. Therefore, a careful assessment of psoriasis disease severity is critical when assessing the risk-benefit ratio of treatment with CSA.

Patients with psoriasis taking CSA may be at increased risk of developing cutaneous squamous cell carcinomas (SCCs) particularly those with a history of more than 200 PUVA treatments.[80] A history of treatment with PUVA puts patients at significantly greater risk for the development of nonmelanoma skin cancers when using CSA. For example, the risk of SCC in patients with a history of PUVA and any use of CSA is similar to the risk of SCC in patients with psoriasis who have received greater than 200 PUVA treatments.[82] The incidence of internal malignancies in patients with psoriasis treated with CSA was not significantly increased as compared with the general population (patients with <2 years of treatment with CSA [standard incidence ratio 1.2; 95% confidence interval 0.7-1.9], patients with >2 years of treatment with CSA [standard incidence ratio 1.7; 95% confidence interval 0.7-3.5])[83]; however, this study did not have appropriate statistical power to rule out a potentially important increased risk in internal malignancies.[83]

Elevation of serum triglycerides (>750 mg/dL) may occur as many as in 15% of patients with psoriasis treated with CSA,[79] whereas hypercholesterolemia (>300 mg/dL) occurs in less than 3% of patients.[79] Importantly, these changes in lipid levels are reversible after CSA is discontinued.

Testing for TB should be considered before initiating treatment with CSA. A TB skin test result with greater than 5 mm of induration is considered positive and is the test used most frequently. A newer, more specific test for latent TB infection is the QuantiFERON TB Gold test (Cellestis, Carnegie, Victoria, Australia), which measures whole blood interferon gamma. This is especially useful in patients with a history of BCG immunization.[65]

Nephrotoxicity

Patients must be carefully monitored for nephrotoxicity with monthly serum creatinine levels and yearly glomerular filtration rates in patients who are maintained on therapy for greater than 1 year.[84] The package insert recommends that patients with elevations of serum creatinine greater than 25% of baseline on two occasions (separated by 2 weeks) should have a 25% to 50% decrease in their dosage of CSA. After lowering the dosage of CSA, the serum creatinine should be followed up every other week for 1 month. If the creatinine level does not decrease to within 25% of the patient's baseline creatinine level, the CSA dose should be decreased by another 25% to 50%. If after these changes, the creatinine continues to remain greater than 25% above baseline, CSA should be discontinued. This cutoff of 25% above baseline for decreasing the CSA dosage is lower than the more commonly used 30% cutoff in clinical practice. Furthermore, many experts use a stepwise dose reduction of approximately 1 mg/kg/d in place of a percentage of the initial dose.

The length of CSA treatment correlates with the development of nephrotoxicity. It is the opinion of the authors that intermittent treatment with 12-week courses of CSA significantly reduces the risk of renal toxicity compared with ongoing therapy. In all, 19% to 24% of patients on short-term treatment will develop nephrotoxicity, largely reversible on cessation of CSA.[74,75,85] Patients treated continuously for more than 2 years have a significantly higher risk of developing irreversible renal damage.[9,86,87] In one study, elevations of creatinine greater than 30% of baseline were found in 71% of patients who had been treated with CSA for an average of 4.5 years. In the majority of these patients, creatinine levels

stabilized but did not return to baseline levels after the CSA dosage was decreased.[9,86]

Hypertension

Hypertension is another common side effect of CSA therapy that often resolves in patients treated with short courses of CSA. CSA-induced hypertension occurs more commonly in older patients.[9] Patients who develop hypertension (measured on two separate occasions) and who have no history of hypertension should have their CSA dose reduced by 25% to 50%. If the blood pressure does not normalize after lowering the dose on several occasions, the package insert recommends stopping CSA. Another approach, advocated by Griffiths et al,[10] is to continue CSA as long as the hypertension is appropriately treated and monitored. Calcium channel blockers are the preferred treatment for CSA-induced hypertension because of their effect on smooth muscle vasodilation, with isradipine and amlodipine preferred because neither agent alters CSA levels. Other options for treating hypertension include beta blockers and angiotensin-converting enzyme inhibitors. The use of thiazide diuretics should be avoided as they can lead to increased nephrotoxicity when combined with CSA.[88] Potassium-sparing diuretics should also not be used as they act synergistically with CSA to cause hyperkalemia.

In the past, hypertension was defined as a blood pressure of either greater than 140/90 mm Hg or greater than 160/90 mm Hg and this level was used as a reference point in the early studies of CSA. According to the 2003 guidelines published by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[89] prehypertension is defined as 120 to 139/80 to 89 mm Hg, stage 1 hypertension is 140 to 159/90 to 99 mm Hg, and stage 2 hypertension is above 160/100 mm Hg. As all stages of hypertension or prehypertension put patients at increased risk for the development of cardiovascular disease, the decision of when to initiate treatment for hypertension and when to discontinue treatment with CSA will depend on the individual situation. Thus, careful, regular, and correct monitoring of blood pressure in all patients undergoing CSA therapy is essential as elevations in blood pressure frequently pre-date changes in serum creatinine.[90]

Other toxicities

The most common cutaneous side effect of CSA is hypertrichosis, occurring in about 6% of patients,[8] usually a more significant issue in women with darker hair.[91] Headache occurs in 15% of patients treated with CSA, paresthesia in 7%, and musculoskeletal pain in 5%.[8] Rare incidences of pseudotumor cerebri in young patients taking concomitant tetracyclines for acne have been noted. Other neurologic side effects include tremor, asthenia, and fatigue.[91] Psychiatric side effects have also been reported.[8] Patients with a history of seizures should be made aware that CSA can lower the seizure threshold.[8] Gingival hypertrophy, commonly seen in patients with transplantation treated with CSA, occurs rarely in patients with psoriasis. Pulmonary and respiratory symptoms including cough, rhinitis, and dyspnea occur in about 5% of patients.[8] Gastrointestinal side effects include abdominal pain, which may resolve after a few days, nausea, vomiting, and diarrhea.[91] As hypomagnesemia and hyperuricemia may occur, magnesium and uric acid levels should be monitored at regular intervals.

Pregnancy

The majority of the information about CSA's safety during pregnancy derives from studies of patients treated with CSA for the prevention of organ transplant rejection. In these studies, CSA was given along with systemic steroids, azathioprine, or mycophenolate mofetil (MMF) and some series include patients treated with tacrolimus rather than CSA. In one study of 67 pregnancies after renal transplantation, preterm labor occurred in more than 40% of the pregnancies and fetal growth retardation in nearly 20%. Perinatal mortality occurred in approximately 10% of patients. Pregnancy outcome was better in those cases in which the mother was not treated with CSA. Prematurity and low birth weight have also been reported in pregnancies after liver transplantation.[92] In these studies, the pregnancy-related complications are unlikely to be solely attributable to CSA, as these patients had many complications and comorbidities of organ transplantation and they were also being treated with many other medications.

There have been no specific birth defects linked to CSA in registries of patients with transplantation.[93] However, in one series of 61 pregnancies in 53 patients treated with CSA plus other drugs, a single infant was born with a club foot and another infant was born with a large facial hemangioma.[94]

Because CSA is nephrotoxic, its effect on kidney function in children of women treated with CSA during pregnancy is important to assess. Animal studies suggest some concern that has not been borne out by the limited human experience. Rabbit kits exposed to 10 mg/kg/d of CSA from day 14 to day 18 of gestation were born with renal dysfunction,

Table IX. Medications that may interfere with cyclosporine

Medications that increase cyclosporine levels
Antifungals: ketoconazole, itraconazole, fluconazole, vorinconazole
Diuretics: furosemide, thiazides, carbonic anhydrase inhibitors
Calcium channel antagonists: diltiazem, nicardipine, verapamil
Corticosteroids: high-dose methylprednisolone
Antiemetics: metoclopramide
Antibiotics: macrolides, fluoroquinolones
Antiarrhythmics: amiodarone
Antimalarials: hydroxychloquine, chloroquine
Anti-HIV drugs: ritonavir, indinavir, saquinavir, nelfinavir
SSRIs: fluoxetine, sertraline
Medications that decrease cyclosporine levels
Antibiotics: nafcillin, rifabutin, rifampin, rifapentine
Antiepileptics: carbamazepine, phenytoin, phenobarbital, valproic acid
Somatostatin analogues: octreotide
Tuberculostatics: rifampicin
Retinoids: bexarotene
St John wort: Hypericum perforatum
Others: octreotide, ticlopidine, bosentan
Medications that may increase the risk of renal toxicity
NSAIDs: diclofenac, naproxen, sulindac, indomethacin
Antifungals: amphotericin-B, ketoconazole
Antibiotics: ciprofloxacin, vancomycin, gentamycin, tobramycin, trimethoprim
Alkylating agents: melphalan
Others: H2 histamine antagonists, tacrolimus
Medications whose levels increase when taken concomitantly with cyclosporine
Calcium channel blockers: diltiazem, nicardipine, verapimil
Erectile dysfunction drugs: sildenafil, tadalafil, vardenafil
Statins: atorvastatin, lovastatin, simvastatin
Benzodiazepines: midazolam, triazolam
Others: prednisolone, digoxin, colchicine, digoxin, diclofenac, bosentan

It is strongly recommended that an up-to-date pharmaceutical reference be consulted whenever concomitant medication is used during cyclosporine therapy.
NSAIDS, Nonsteroidal anti-inflammatory drugs; *SSRI*, selective serotonin reuptake inhibitor.

hypertension that worsened with age, and progressive chronic renal insufficiency in adulthood.[95] However, children exposed in utero to CSA have shown no evidence of renal damage as they grow.[96]

The FDA has ranked CSA as pregnancy category C; ie, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Although CSA does not appear to have mutagenic or teratogenic effects, increased prenatal and postnatal mortality and reduced fetal weight have been found in animal studies and there has been an increased risk of premature birth in babies exposed to CSA in utero.[97]

PEDIATRIC USE

CSA is FDA-approved for the treatment of psoriasis in adults. Although there is limited literature on the use of CSA for the treatment of pediatric psoriasis,[98-100] a recent review of its use in children with several different dermatologic and rheumatologic conditions suggests that the side effect profile of CSA in children is similar to that seen in adults.[57]

DRUG INTERACTIONS

CSA is metabolized by the cytochrome P450 3A4 system. Macrolides, antifungals, and calcium channel blockers thus increase CSA levels, whereas anticonvulsants, rifamycins, and griseofulvin decrease CSA levels. Foods that contain grapefruit juice increase levels of CSA by inhibiting cytochrome P450 enzymes in the intestinal wall, whereas St John Wort may decrease CSA concentrations. In patients who have severe liver disease, CSA metabolism may be decreased, leading to higher drug levels. Although heavy alcohol intake increases CSA levels, mild to moderate alcohol consumption has little effect.[101]

CSA is also an inhibitor of cytochrome P450 3A4 with levels of other interacting drugs such as calcium channel blockers, erectile dysfunction drugs, and statins being increased. Reports of serious rhabdomyolysis occurring in patients who are concurrently treated with CSA together with a Statin have been described.[102] Certain drugs potentiate the renal toxicity of CSA including aminoglycosides and nonsteroidal anti-inflammatory drugs and these should be restricted as should medications that elevate potassium levels. Many other interactions can occur with CSA and some of the most clinically relevant contraindications are summarized in Table IX. Given the long list of possible drug interactions, a thorough drug history must be obtained from all patients before initiating treatment with CSA and patients should be educated regarding the introduction of new drugs while taking CSA.

INITIATION AND MONITORING

Before initiating therapy with CSA, patients should have a thorough history and physical examination, reviewing possible exposure to TB and hepatitis B or C, and family history of kidney disease. A thorough history and physical examination with blood pressure documentation should be obtained before starting CSA therapy.[8,10] Because of the critical importance of accurate measurement of baseline renal function, serum

creatinine should be measured on two separate occasions. Some even suggest 3 separate measurements of creatinine taking the average of the 3 as the baseline creatinine level. Other laboratory studies should include BUN, urinalysis, CBC count, magnesium, potassium, uric acid, lipids, liver enzymes, and bilirubin. Patients should be evaluated for factors that might increase their risk of nephrotoxicity including obesity,[87] increased age,[9] concomitant use of nephrotoxic drugs (Table IX), and diabetes. It is important to discuss appropriate contraception (see prior section on pregnancy and cyclosporine).

Appropriate monitoring for patients on CSA is important for the prevention of adverse events. After starting CSA, patients should be monitored with every-other-week blood pressure, BUN, and creatinine measurements, along with monthly levels of CBC count, uric acid, potassium, lipids, liver enzymes, serum bilirubin, and magnesium. After 3 months of every-other-week monitoring of blood pressure, BUN, and creatinine, monthly monitoring of these parameters can be instituted. Although the package insert recommends every-other-week monitoring of blood pressure, BUN, and creatinine for the first 3 months, many authors transition to monthly monitoring of these parameters after 6 to 8 weeks provided there are no ongoing abnormalities.[8,10,91]

Monitoring of CSA blood levels is generally unnecessary in the doses used to treat patients with psoriasis.[103] However, patients who are taking greater than 3 mg/kg/d of CSA over the long term, are being treated with other medications that may alter CSA metabolism, or have liver disease that might put them at risk for unpredictable drug metabolism, may require monitoring of CSA blood levels.

Although practitioners should attempt to avoid long-term continuous CSA treatment, it may occasionally be the only option available for patients with severe, recalcitrant disease, necessitating a nephrology consultation to assist with management of CSA-associated nephrotoxicity. Elevations of serum creatinine should be managed as described above with decreased dosage and re-evaluations. In addition, most other laboratory studies should be obtained monthly.

Vaccinations given concomitantly with CSA may be less effective. Studies in patients with transplantation taking CSA have shown inconsistent effectiveness of the influenza vaccine.[104-106] Because of the immunosuppression in patients treated with CSA, killed vaccines may prevent severe infection and their administration appears to be safe.

CONTRAINDICATIONS

Hypersensitivity to CSA, a history of systemic malignancy (except for nonmelanoma skin cancer), uncontrolled hypertension, renal insufficiency, prior treatment with PUVA, and uncontrolled infections are all contraindications for use of CSA. Live vaccinations are contraindicated during CSA therapy. CSA should be used with extreme caution in the elderly, immunodeficient, and obese population; in patients who have previously received PUVA therapy; and in pregnancy. Furthermore, care should be taken when using other medications that may interact with CSA.[8] Recommendations for the use of CSA are shown in Table X. The strength of recommendations for the treatment of psoriasis using CSA is shown in Table VIII.

RETINOIDS

The oral retinoids are vitamin-A derivatives that have been used to treat psoriasis since the early 1980s. Although their exact mechanism of action in the treatment of psoriasis is not completely understood, retinoids are known to modulate epidermal proliferation and differentiation and to have immunomodulatory and anti-inflammatory activity. Etretinate was the first retinoid introduced for the treatment of severe psoriasis and replaced in 1988 by acitretin, the active metabolite of etretinate.

EFFICACY

The efficacy of acitretin is dose dependent. The results of several clinical trials suggest that acitretin monotherapy is somewhat less effective than other traditional systemic agents; however, head-to-head trials would be necessary to confirm these conclusions. In patients with chronic plaque psoriasis, various different dosages have been used in clinical trials.[107-114] Of patients treated with 50 mg/d of acitretin over 8 weeks of treatment, 23% achieved PASI 75.[115] In another study, after 12 weeks of treatment with acitretin, the mean PASI improvement was between 70% and 75%.[116] In another study, 59 patients were treated with 20 mg per day of acitretin with dose increases of 10 mg every 2 weeks up to a final dose of 70 mg. Clearance or marked improvement was achieved by 41% of the patients; however, 36% of patients dropped out of the study, mostly because of retinoid-related adverse events.[117] Acitretin may be used as an effective maintenance therapy. Thus, after 6 and 12 months of continuous treatment, 75% and 88%, respectively, of patients with chronic plaque psoriasis reached PASI 50.[118]

In patients with pustular psoriasis, rapid and impressive responses may be seen with acitretin. In

Table X. Recommendations for cyclosporine

- Indication: adult, nonimmunocompromised patients with severe, recalcitrant psoriasis
  - Severe is defined by the FDA as extensive or disabling plaque psoriasis
  - Recalcitrant is defined by the FDA as those patients who have failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated
  - Some guidelines suggest use of cyclosporine in moderate to severe psoriasis
  - Efficacy observed in erythrodermic psoriasis, generalized pustular psoriasis, and palmoplantar psoriasis
- Dosing: 2.5-5.0 mg/kg/d in two divided doses/d
  - Dose adjustments downward (by 0.5-1.0 mg/kg) when clearance is achieved or when hypertension or decreased renal function test results are observed
- Duration of dosing
  - Optimally used as interventional therapy; may be repeated at intervals after a rest period
  - US approval: 1 y continuous treatment; non-US approval: 2 y continuous treatment
- Short-term results
  - At 3 and 5 mg/kg/d, 36% and 65%, respectively, achieved a clear or almost clear result after 8 wk
  - After 8-16 wk, 50%-70% of patients achieve PASI 75
- Long-term results
  - Not recommended because of toxicities
  - Rapid relapse after abrupt discontinuation of cyclosporine
- Contraindications
  - Concomitant PUVA or UVB, methotrexate or other immunosuppressive agents, coal tar, history of >200 PUVA treatments or radiation therapy
  - Abnormal renal function
  - Uncontrolled hypertension
  - Malignancy
  - Hypersensitivity to cyclosporine
  - Avoid live vaccinations
  - Caution with major infection and poorly controlled diabetes
- Toxicity
  - Renal impairment
    - Acute
    - Chronic (increasing glomerular fibrosis with increasing duration of treatment with higher dosages)
  - Hypertension
  - Malignancies
    - Cutaneous
    - Lymphoproliferative
  - Headache, tremor, paresthesia
  - Hypertrichosis
  - Gingival hyperplasia
  - Worsening acne
  - Nausea/vomiting/diarrhea
  - Myalgias
  - Flu-like symptoms
  - Lethargy
  - Hypertriglyceridemia
  - Hypomagnesemia
  - Hyperkalemia
  - Hyperbilirubinemia
  - Increased risk of infection
  - May increase risk of cancer
- Drug interactions (see Table VIII)
  - Inducers/inhibitors of cytochrome P450 3A4
  - St John Wort decreases cyclosporine concentration
  - Cyclosporine may reduce clearance of digoxin, colchicine, prednisolone, statins (increased risk of rhabdomyolysis)
  - Potassium-sparing diuretics cause hyperkalemia
  - Thiazide diuretics increase nephrotoxicity
  - Killed vaccines may have decreased efficacy
  - Live vaccination is contraindicated

Continued

Table X. Cont'd

- Grapefruit juice
- NSAIDs

- Baseline monitoring
  - History and physical examination
  - Blood pressure × 2
  - BUN and Cr × 2
  - Urinalysis
  - Consider PPD
  - LFTs, CBC count, lipid profile, magnesium, uric acid, and potassium
  - Pregnancy test if indicated
- Ongoing monitoring
  - Every other week during initial 3 mo, thereafter at 1-mo intervals: blood pressure, BUN, and Cr
  - Monthly CBC count, LFTs, lipid profile, magnesium, uric acid, and potassium
  - Pregnancy testing if indicated
- Pregnancy: category C; lower birth weight and shorter duration of pregnancy reported in patients with transplantation; appears not to be teratogenic in patients with transplantation
- Nursing: mothers receiving cyclosporine should not breast-feed
- Pediatric use: transplantation recipients as young as 1 y have been treated with no unusual adverse events; although safety and efficacy of cyclosporine for children < 18 y with psoriasis has not been established, it may be considered in this patient population with severe psoriasis
- Psoriatic arthritis: there are studies demonstrating the efficacy of cyclosporine for psoriatic arthritis[178,179]

BUN, Serum urea nitrogen; *CBC*, complete blood cell; *Cr*, creatinine; *FDA*, Food and Drug Administration; *LFT*, liver function test; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *PASI*, Psoriasis Area and Severity Index; *PUVA*, psoralen plus ultraviolet A; *UV*, ultraviolet.

generalized pustular psoriasis, acitretin has been shown to be effective in 84% of patients.[119] Patients with erythrodermic psoriasis can be successfully treated with etretinate, the pro-drug of acitretin.[120] Because of a lack of significant immunosuppression, acitretin is generally considered effective and the treatment of choice in HIV-positive patients with severe psoriasis.[121]

DOSAGE

Acitretin response is relatively slow with a 3- to 6-month period required to achieve a maximal response. Appropriate dosing must take into account the balance among safety, tolerability, and efficacy as many patients may not tolerate the higher dosages of acitretin to achieve optimal efficacy. For these reasons, the combination of retinoids and UV light therapy may be considered where feasible and appropriate.

SAFETY

Several potential adverse effects have been associated with acitretin but these can generally be minimized by appropriate patient selection, careful dosing, and monitoring. Teratogenicity is the most important safety issue. Acitretin is FDA pregnancy category X (highly unsafe during pregnancy, with the risk of use outweighing any possible benefit). The use of any dose of acitretin during pregnancy may lead to numerous malformations, including cardiovascular, ocular, auditory, central nervous system, craniofacial, and skeletal, with the greatest risk occurring between the third and sixth weeks of gestation.[122] Although the half-life of acitretin is 49 hours, acitretin may transform either spontaneously, or as a result of alcohol ingestion, into etretinate, which has a half-life of 168 days. Based on this long half-life, it can take up to 3 years for etretinate to be eliminated from the body. The minimum amount of alcohol consumption for this conversion to take place is not known and inadvertent exposure to alcohol-containing products is difficult to avoid. For these reasons, acitretin is contraindicated in women who plan to become pregnant or who fail to use adequate contraception for 3 years after discontinuing acitretin. Under almost every circumstance, acitretin should not be used in women of childbearing potential.

Mucocutaneous side effects of acitretin occur in almost all patients to varying degrees and may include cheilitis, dryness of the eyes, nasal and oral mucosa, epistaxis, xerosis, brittle nails, hair loss, and burning or sticky skin. A less commonly seen cutaneous side effect is "retinoid dermatitis," in which erythematous scaly patches with very superficial fissuring of skin may occur; this may mimic "unstable psoriasis." Periungual pyogenic granulomas may occur during long-term use of acitretin.[112,123]

The most common laboratory abnormality seen in patients treated with acitretin is hyperlipidemia, with

as many as 25% to 50% of patients experiencing increases in serum triglycerides.[124] Rare cases of pancreatitis, including fatal fulminant pancreatitis have been reported.[125] Patients who are maintained on acitretin over long periods of time and whose triglycerides are chronically elevated may be at increased risk for atherosclerosis and may warrant therapy with triglyceride-lowering therapy.[126] The risk for developing hyperlipidemia is increased in the setting of diabetes mellitus, obesity, and increased alcohol intake.[127] Lifestyle change to prevent/reduce hyperlipidemia should be encouraged in patients with psoriasis who are being treated with oral retinoids.

Elevations of transaminases occur in 13% to 16% of patients treated with acitretin.[123] A liver biopsy study did not reveal a significant risk for liver toxicity in patients treated with acitretin.[128] Severe increases of liver function test results are rare, but may indicate toxic hepatitis induced by acitretin.[129] Diffuse idiopathic hyperostosis has rarely been reported as a side effect of systemic retinoids. It is characterized by degenerative spondylosis, arthritis of the vertebral articulations, and syndesmophytes of the vertebral spine, and extra spinal bones with bone spur formation.[130] Occasionally severe hyperostosis may also be induced.[131] Whether or not acitretin induces osteoporosis has been the subject of controversy,[132,133] with the risk possibly highest in those receiving high-dose retinoids for long time periods.

Pseudotumor cerebri-like symptoms and signs have been observed during acitretin usage. Decreased color vision and impairment of night vision may also occur. Although muscle and joint symptoms may occur during acitretin treatment, they are seldom a significant problem.

DRUG INTERACTIONS

Drug interactions may be relevant, particularly drugs that interfere with cytochrome P450 metabolism, such as CSA and drugs that compete for plasma protein binding such as phenytoin. Acitretin has been reported to potentiate the glucose-lowering effect of glibenclamide. Because of the risk of hypervitaminosis A, concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided.

COMBINATION TREATMENT

Enhanced clinical response and a possible reduction of side effects are the goals of combination therapy. Combination regimens of traditional treatments were reviewed in 2004.[134] A consensus conference on the treatment of acitretin in combination with UVB or PUVA determined that the combination enhances efficacy and limits the treatment frequency, duration, and cumulative doses, resulting in a more effective, better-tolerated, more convenient, and perhaps safer treatment.[135] Broadband UVB in combination with acitretin is highly effective as compared with monotherapy with acitretin.[136-139] This combination also increased safety as lower cumulative UVB exposure and lower doses of acitretin were needed to achieve clinical improvement. A 74% improvement in psoriasis severity score was shown in patients treated with acitretin 50 mg/d plus broadband UVB as compared with 35% with broadband UVB only, or to 42% with acitretin only.[138] Another study showed a similar efficacy with acitretin (35 mg/d) for 4 weeks followed by a combination of broadband UVB plus acitretin (25 mg/d), with the median cumulative dose of broadband UVB to achieve 75% improvement being 41% lower for the combination as compared with UVB monotherapy.[139] The preferred schedule is acitretin monotherapy for 2 weeks followed by the addition of phototherapy. In patients already receiving UVB phototherapy but having a suboptimal response, acitretin dosed at 25 mg/d may be added.[128] In this scenario, it is prudent to decrease the UVB dose by 30% to 50% for 1 week to minimize the propensity of UVB-induced erythema in skin exposed to oral retinoids. The UVB dose can then be increased gradually as tolerated by the patient.

The combination of narrowband UVB and acitretin is highly effective in patients whose psoriasis is difficult to control, resulting in an improvement of at least 75% of the severity score in 72.5% of such patients.[140]

The combination of acitretin and PUVA is more effective compared with monotherapy with either acitretin or PUVA alone.[141-143] The efficacy of this combination is also evident from the reduced cumulative UVA dosage and the reduced number of PUVA sessions, implying an increased safety as compared with PUVA monotherapy. In theory, the anticancer potential of oral retinoids may also add to their safety.[144-147] As with UVB therapy, acitretin is given for 14 days before instituting PUVA treatment. When PUVA monotherapy appears to be insufficient, acitretin can be added with appropriate reduction of the UVA dose by 30% to 50%.

In patients who have received of PUVA treatment, subsequent therapy with CSA increases the risk for developing SCCs.[80] On the other hand, acitretin, when combined with PUVA therapy, considerably decreases the incidence of SCC.[148]

INITIATION AND MONITORING

Before initiating therapy with acitretin, patients should have a thorough history and physical examination. Pretreatment laboratory studies should include pregnancy testing; lipid studies to evaluate for hypertriglyceridemia and hypercholesterolemia; and liver and renal function tests. If, despite acitretin's teratogenicity, it is considered for use in a woman of childbearing potential, then baseline and monthly pregnancy testing is appropriate.

Monitoring for patients on acitretin is important for the prevention of adverse events. After starting acitretin, patients should be monitored with every-other-week lipid profiles and liver enzymes. After 8 weeks of every-other-week monitoring, monitoring of lipid profiles and liver enzymes every 6 to 12 weeks can be instituted. CBC count and renal function test results should be obtained every 3 months. Recommendations for the use of acitretin are shown in Table XI. The strength of recommendations for the treatment of psoriasis using acitretin is shown in Table VIII.

SECOND TIER SYSTEMIC AGENTS

Although methotrexate, CSA, and acitretin are the traditional systemic therapies used in the treatment of psoriasis, it is occasionally necessary to consider treatment with alternative agents because of treatment-resistant disease or multiple intolerable adverse events. In these clinical scenarios, it may be reasonable to consider therapy with other systemic agents. The level of evidence supporting the use of these agents is of lesser quality than the more commonly used agents.

AZATHIOPRINE

Azathioprine, a purine analogue that blocks purine synthesis, is a commonly used immunosuppressive agent. Approved for use in renal transplantation and rheumatoid arthritis, azathioprine has been used off label for many years in the treatment of the autoimmune blistering diseases and atopic dermatitis. Although there are no randomized trials for azathioprine in psoriasis, a few reports suggest beneficial results. The largest study was an open-label one that included 29 patients dosed at 100 to 300 mg of azathioprine daily. Of 29 patients, 19 benefited, with 13 of 19 patients showing greater than 75% improvement and 6 of 19 showing greater than 50% improvement, although the scale used to measure improvement was not specified.[149] In another open-label study of 10 patients with severe psoriasis treated with azathioprine, 5 of 10 showed at least 25% improvement with the scale used to measure improvement again not specified.[150]

Adverse effects of azathioprine may include leukopenia, anemia, thrombocytopenia, or pancytopenia. As 1 in 300 patients have an inherited deficiency in thiopurine methyltransferase that leads to an increased risk of developing myelotoxicity, thiopurine methyltransferase levels should be measured before commencing therapy. Liver toxicity manifested by elevations in serum transaminases and alkaline phosphatase can occur. Gastrointestinal symptoms including nausea, vomiting, and diarrhea are relatively common and pancreatitis has rarely been reported. The dosage of azathioprine ranges from 0.5 up to 3 mg/kg, and is determined by the results of thiopurine methyltransferase testing. Azathioprine works slowly with its onset of action generally requiring at least 6 to 8 weeks. Recommendations for the use of azathioprine are shown in Table XII. The British guidelines for the use of azathioprine, published in 2004, could also be considered.[151] The strength of recommendations for the treatment of psoriasis using azathioprine is shown in Table VIII.

FUMARIC ACID ESTERS

Fumaric acid esters (also known as fumarates) are a mixture of dimethylfumarate along with monoethylfumarate salts. Although fumarates are commonly used in Northern Europe, particularly in German-speaking countries and the Netherlands, for the treatment of patients with moderate to severe psoriasis, they are not approved in the United States. Fumarates appear to function by inhibiting T lymphocytes and shifting the cytokine profile from a T-helper 1 to a T-helper 2 phenotype. Several well-designed randomized studies of fumarates demonstrate mean PASI improvement rates of between 50% and 80% after 12 to 16 weeks of treatment when dosed initially at one pill daily of Fumaderm (containing 120 mg of dimethylfumarate, 87 mg of calcium monoethylfumarate, 5 mg of magnesium monoethylfumarate, and 3 mg of zinc monoethylfumarate) and escalated as tolerated up to 6 pills daily.[152-155]

The most common adverse effect of the fumarates are gastrointestinal symptoms, including gastric and esophageal pain as well as nausea and vomiting, which may occur in over two thirds of patients.[156] These effects can be mitigated by initiating therapy with fumarates at a low dose and gradually increasing the dose. About one third of patients develop flushing that tends to subside with ongoing therapy. A mild lymphopenia is almost always present but appears to be of little consequence.[157] Serious, but reversible renal side effects have been sporadically reported,[158] but these events are not believed to be related to

Table XI. Recommendations for acitretin

- Indication: FDA approved for adults with severe plaque type psoriasis
- Dosing: 10-50 mg/d given as a single dose
  - Lower doses ($\leq$25 mg/d) often used to minimize side effects, especially in combination regimens
  - When acitretin is added to UV, light dose should be reduced by 30%-50%
- Short-term results
  - Efficacy rates not well defined but are high, based on studies of high dosages that are poorly tolerated
  - Efficacy rates when used in combination with phototherapy are higher
- Long-term results
  - Not reported
- Contraindications
  - Acitretin is a potent teratogen and must be avoided in women of childbearing potential
  - Severely impaired liver or kidney function
  - Chronic abnormally elevated blood lipid values
- Toxicity
  - Cheilitis
  - Alopecia
  - Xerosis, pruritus
  - Xerophthalmia, night blindness
  - Dry mouth
  - Paronychia
  - Paresthesias
  - Headache, pseudotumor cerebri
  - Nausea, abdominal pain
  - Joint pain
  - Myalgia
  - Hypertriglyceridemia
  - Abnormal LFT results
- Drug interactions
  - Etretinate can be formed with concurrent ingestion of acitretin and ethanol
  - Acitretin may potentiate glucose-lowering effect of glibenclamide
  - May interfere with the contraceptive effect of microdosed progestin minipill[180]
  - Acitretin and methotrexate can both cause hepatotoxicity, therefore they should be combined with caution
  - Acitretin may reduce the protein binding of phenytoin
  - Acitretin and tetracyclines can both increase intracranial pressure; their combined use should be avoided
  - Concomitant administration of vitamin A and other oral retinoids with acitretin should be avoided
- Baseline monitoring
  - History and physical examination
  - Lipid profile, CBC count, LFTs, renal function tests
  - Pregnancy test if indicated
- Ongoing monitoring
  - LFTs, lipid profile at 2-wk intervals for the first 8 wk, then every 6-12 wk
  - CBC count, renal function tests every 3 mo
  - Pregnancy test if indicated
- Pregnancy: category X
- Nursing: mothers receiving acitretin should not breast-feed
- Pediatric use: the safety and efficacy of acitretin in children with psoriasis is not established; high-dose, long-term oral retinoid use has been associated with ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses, decreases in bone mineral density, and premature epiphyseal closure
- Psoriatic arthritis: generally thought to be ineffective for psoriatic arthritis

CBC, Complete blood cell; *FDA*, Food and Drug Administration; *LFT*, liver function test; *UV*, ultraviolet.

fumarates and have not been observed in any of the controlled trials. Recommendations for the use of fumaric acid esters are shown in Table XIII. The strength of recommendations for the treatment of psoriasis using fumaric acid esters is shown in Table VIII.

HYDROXYUREA

Hydroxyurea is an antimetabolite used in the treatment of certain cancers and hematologic conditions. It has been used in the treatment of psoriasis for more than 30 years and is thought to work by inhibiting DNA replication. Although there are no

Table XII. Recommendations for azathioprine

- Indication: there is no FDA-approved use for psoriasis
- Dosing
  - TPMT levels are generally used to guide dosing
  - One suggested daily schedule guided by results of TPMT values[181]
  - TPMT <5.0 U do not use azathioprine
  - TPMT 5-13.7 U 0.5 mg/kg max dose
  - TPMT 13.7-19.0 U 1.5 mg/kg max dose
  - TPMT >19.0 U 2.5 mg/kg max dose
  - Alternatively, start at 0.5 mg/kg, and monitor for cytopenia; if no cytopenia, can increase dose by 0.5 mg/kg/d after 6-8 wk if necessary and increase by 0.5 mg/kg/d every 4 wks thereafter as needed; generally dosed at 75-150 mg/d
- Efficacy
  - In one study 19/29 patients had >75% improvement but in another smaller study 5/10 patients had >25% improvement
- Contraindications
  - Absolute
    - Allergy to azathioprine
    - Pregnancy or attempting pregnancy
    - Clinically significant active infection
  - Relative
    - Concurrent use of allopurinol
    - Prior treatment with cyclophosphamide or chlorambucil
- Toxicity
  - Bone-marrow suppression
  - Malignancies
  - Cutaneous (SCCs)
  - Lymphoproliferative
  - Increased risk of infections
  - GI: nausea, vomiting, diarrhea
  - Hypersensitivity syndrome
  - Pancreatitis
  - Hepatitis
- Drug interactions
  - Allopurinol—increased risk of pancytopenia (if using concurrently, lower azathioprine dose by 75%)
  - Captopril—may increase risk of anemia and leukopenia
  - Warfarin—may need an increased dose of warfarin
  - Pancuronium—may need an increased dose of this for adequate paralysis
  - Cotrimoxazole—increased risk of hematologic toxicity
  - Rifampicin—decreases azathioprine efficacy, also hepatotoxic
  - Clozapine—increased risk of agranulocytosis
- Baseline monitoring
  - History and physical examination
  - LFTs, CBC count/diff, serum chemistry profile, urinalysis, PPD, hepatitis B and C screen
  - Pregnancy test if indicated
- Ongoing monitoring
  - CBC count/diff twice/mo for the first 2 mo, monthly for the next 2 mo, every 2 mo thereafter
  - LFTs monthly for the first 3 mo then every 2 mo thereafter
  - Biannual physical examination focusing on lymph node examination and skin cancer examination (SCCs in particular)
  - Pregnancy testing if indicated
- Pregnancy/nursing: pregnancy category D
  - Pregnancy and breast-feeding should be avoided during treatment with azathioprine, and patients (including male) must use adequate contraception
- Pediatric use: no data
- Psoriatic arthritis: a small observational cohort study suggests that azathioprine may be of value in psoriatic arthritis[182]

CBC, Complete blood cell; *diff*, differential; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *LFT*, liver function test; *max*, maximum; *PPD*, purified protein derivative; *SCC*, squamous cell carcinoma; *TPMT*, thiopurine methyltransferase.

Table XIII. Recommendations for fumaric acid esters

- Indications
  - There is no FDA approved use for psoriasis in the United States; fumaric acid esters are approved in Europe
- Dosing
  - Starting dose: one tablet of Fumaderm; increase over the next 8 wk to a maximum of 6 tablets daily
- Short-term results
  - Multicenter, randomized, double-blind placebo-controlled trial of 100 patients showed that after 16 wk, patients treated with fumarate reached a mean PASI 50 compared with patients given placebo whose PASI was essentially changed
  - Randomized, double-blind controlled trial of 143 patients given either fumarate plus calcipotriol or fumarate alone found that patients given combination therapy reached PASI 50 in 3 wk vs those treated with fumarate alone reaching PASI 50 in 9 wk
- Long-term results
  - Case series of patients treated up to 14 y suggest no increased risk for infections or malignancies; large, long-term follow-up studies are necessary to confirm these observations
- Contraindications
  - Severe liver disease
  - Severe or chronic GI disease
  - Severe or chronic kidney disease
  - Malignancy or a history of malignancy
  - Leukopenia and other hematologic abnormalities
  - Pregnancy
  - Breast-feeding
- Toxicity
  - GI (abdominal cramps, nausea, diarrhea, fullness, and flatulence)
  - Flushing
  - Malaise
  - Fatigue
  - Lymphopenia, leukopenia, eosinophilia
  - Hepatotoxicity and elevated LFT results
  - Increased cholesterol, triglycerides
  - Increased serum creatinine and potassium, and proteinuria
  - Rare case reports of renal disease but none in the controlled trials
- Drug interactions
  - Other fumaric acid derivatives, methotrexate, cyclosporine, immunosuppressive drugs, and cytostatic drugs may potentiate toxicity
  - Drugs known to cause renal dysfunction
- Baseline monitoring
  - History and physical examination
  - CBC and platelet counts
  - Chemistry screen
  - Urinalysis
- Ongoing monitoring
  - CBC and platelet counts every other week for the first 2 mo; monthly until 6 mo, and bimonthly thereafter
  - Serum chemistry and urinalysis every 2 wk for the first month, then monthly for the first 6 mo and bimonthly thereafter
- Pregnancy: not recommended in pregnancy (no FDA pregnancy category because it is not approved in the United States)
- Nursing: there are no data and therefore mothers receiving fumaric acid esters should not breast-feed
- Pediatric use: no data
- Psoriatic arthritis: one small double-blind placebo-controlled trial suggested minimal efficacy as evidenced by decreased joint pain and sedimentation rate[155]

CBC, Complete blood cell; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *LFT*, liver function test; *PASI*, Psoriasis Area and Severity Index.

randomized psoriasis trials for hydroxyurea, several studies suggest that it has a beneficial effect. In a retrospective study, 85 patients received hydroxyurea with no placebo or active control group for a mean duration of 16 months.[159] Although dosing varied according to response, most patients were treated with dosages of 0.5 to 1.5 g/d. In all, 60% of patients achieved complete to near complete clearing.[159] In another nonrandomized study of 31 patients with recalcitrant psoriasis, 75% of patients treated with 1 to

1.5 g/d of hydroxyurea showed at least a 35% reduction in the PASI score and 55% had more than a 70% reduction in the PASI score.[160] A comparative study of methotrexate and hydroxyurea was recently undertaken in 30 patients. Methotrexate treatment (at 15-20 mg/wk) led to a 77% reduction in the mean PASI score whereas hydroxyurea treatment (at the lower dose of 3-4.5 g/wk) led to a 49% reduction in the mean PASI score.[161]

The major adverse effect of hydroxyurea is bone-marrow toxicity causing leukopenia, anemia, thrombocytopenia, or, less commonly, pancytopenia. Most patients display at least mild hematologic abnormalities, especially an asymptomatic macrocytic anemia, and up to one third require dose adjustment.[161] Liver and renal toxicity is rare. Some patients may experience skin pigmentation or diffuse alopecia; but these effects are typically dose dependent and reversible with discontinuation.[160,162] Recommendations for the use of hydroxyurea are shown in Table XIV. The strength of recommendations for the treatment of psoriasis using hydroxyurea is shown in Table VIII.

LEFLUNOMIDE

Leflunomide is a disease-modifying antirheumatic medication that inhibits de novo pyrimidine synthesis. Approved for the treatment of rheumatoid arthritis, it has more recently been studied for the treatment of psoriatic arthritis and psoriasis.

In a large randomized double-blind placebo-controlled trial of 182 patients with both psoriasis and psoriatic arthritis, patients were randomized to placebo or leflunomide at 20 mg daily for 24 weeks. Subjects had a baseline body surface area of psoriasis involvement that was greater than 3% and were allowed concurrent use of low-dose systemic corticosteroids for the treatment of their psoriatic arthritis (15% of the leflunomide-treated group). After 24 weeks of treatment, 17% of the leflunomide-treated subjects achieved a PASI 75 versus 2% of those receiving placebo ($P = .048$) and 59% of the patients treated with leflunomide and 30% of the patients treated with placebo ($P < .001$) were responders by the Psoriatic Arthritis Response Criteria.[163]

Potential toxicities caused by leflunomide are predominantly gastrointestinal irritation (diarrhea, nausea, dyspepsia), but also include elevated liver enzymes, leukopenia, drug eruption, headaches, increased risk of infections,[164] and teratogenicity. In the randomized double-blind placebo-controlled trial of leflunomide for psoriasis and psoriatic arthritis, side effects that occurred at a higher frequency in the leflunomide group than the placebo group included diarrhea, elevated AST levels, lethargy, and leukopenia.[163] Recommendations for the use of leflunomide are shown in Table XV. The strength of recommendations for the treatment of psoriasis using leflunomide is shown in Table VIII.

MYCOPHENOLATE MOFETIL

MMF is an immunosuppressive agent approved for prophylaxis of organ rejection in patients with transplantation. It is the pro-drug of mycophenolic acid, which was originally used to treat psoriasis in the 1970s but was associated with a relatively high incidence of gastrointestinal and infectious adverse effects.[165] Mycophenolic acid acts by interfering with T-cell proliferation. It reversibly blocks the de novo synthesis of guanine nucleotides and thus preferentially affects both B and T lymphocytes. Although there are no randomized trials of MMF in the treatment of psoriasis, it has been used in several uncontrolled studies. An open-label study of 23 patients with moderate to severe psoriasis demonstrated a mean PASI reduction of 47% at 12 weeks of therapy when dosed at 2 to 3 g daily,[166] whereas another smaller open-label study of 11 patients demonstrated a 40% to 70% reduction in PASI in 7 of 11 patients.[167]

In general, MMF is well tolerated, with common side effects including gastrointestinal, hematologic, and genitourinary systems. The most common gastrointestinal symptom is diarrhea, but nausea, vomiting, and abdominal cramps may also occur in up to 35% of patients and usually diminish with ongoing use. Although leukopenia, anemia, and thrombocytopenia have all been reported in patients treated with MMF, these effects are uncommon. Genitourinary effects of MMF may include urgency, frequency, and dysuria. Recommendations for the use of MMF are shown in Table XVI. The strength of recommendations for the treatment of psoriasis using MMF is shown in Table VIII.

SULFASALAZINE

Sulfasalazine is used to treat inflammatory bowel disease and, occasionally, rheumatoid arthritis. Although the mechanism of action of sulfasalazine is unknown, it is thought to function as an anti-inflammatory agent. In the only double-blind, randomized, controlled trial of sulfasalazine in psoriasis, 50 patients with moderate to severe psoriasis were divided into two groups: 50% received sulfasalazine for 8 weeks and the other 50% received placebo.[168] Dosing was escalated (as tolerated) over time, ranging from 1.5 to 4.0 g of daily sulfasalazine in the treatment group. Psoriasis severity was assessed as follows: marked improvement = 60% to 89% change; moderate improvement = 30% to 59% change. After 8

Table XIV. Recommendations for hydroxyurea

- Indication
  - There is no FDA-approved use for psoriasis
- Dosing
  - Initial dose of 500 mg PO twice daily increasing to up to 3 g/d as tolerated
  - Dose of 3-4.5 g/wk has also been used
- Short-term results
  - Efficacy rates vary widely
  - One study showed that 55% of 31 patients had at least a 70% reduction in PASI score (mean treatment time of 36 wk), whereas another study comparing hydroxyurea with methotrexate showed a 48% reduction in PASI score after 12 wk of hydroxyurea
- Long-term results
  - One study found that 60% of 85 patients treated for a mean of 16 mo had a complete or almost complete clearance
- Contraindications
  - Marked bone-marrow depression, including leukopenia, thrombocytopenia, or anemia
- Toxicity
  - Bone-marrow suppression
  - GI symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation)
  - Dermatologic reactions (rash, ulceration, dermatomyositis-like skin changes, alopecia)
  - Dysuria may rarely occur
  - Neurologic disturbances limited to headache, dizziness, disorientation, hallucinations, and convulsions rarely seen
  - Temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine
  - Fever, chills, malaise, edema, asthenia
  - Elevation of hepatic enzymes
  - Pulmonary fibrosis rare
  - Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents
- Drug interactions
  - Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone-marrow depression
  - Hydroxyurea may raise the serum uric acid level; dosage adjustment of uricosuric medication may be necessary
- Baseline monitoring
  - History and physical examination
  - CBC count at baseline and weekly until stable dose is achieved
  - Pregnancy test if indicated
- Ongoing monitoring
  - CBC count at monthly intervals
  - Biannual physical examination focusing on lymph node examination and skin cancer examination (SCCs in particular)
  - Pregnancy test if indicated
- Pregnancy/nursing: pregnancy category D
  - Pregnancy and breast-feeding should be avoided during treatment and patients (including male) must use adequate contraception
- Pediatric use: no data
- Psoriatic arthritis: no data

BUN, Serum urea nitrogen; *CBC*, complete blood cell; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *PASI*, Psoriasis Area and Severity Index; *SCC*, squamous cell carcinoma.

weeks, 26% of the sulfasalazine treated group had dropped out (because of rash or nausea). Of the remaining 17 subjects, 7 had marked improvement and 7 had moderate improvement. The placebo arm had only one subject who showed moderate improvement, with the rest of the group worsening. The statistical analysis was performed per protocol (subjects were required to have tolerated sulfasalazine at 2 g daily for 6 weeks).

Adverse effects with sulfasalazine are generally not serious in nature but occur in as many as 60% of patients.[169] They include gastrointestinal intolerance (nausea, heartburn, vomiting, and diarrhea), malaise, headache, arthralgia, drug fever, and reversible oligospermia.[169] Rare but serious adverse effects may include leukopenia and agranulocytosis. Recommendations for the use of sulfasalazine are shown in Table XVII.

Table XV. Recommendations for leflunomide

- Indication
  - There is no FDA-approved use for psoriasis
- Dosing
  - Loading dose of 100 mg/d for 3 d followed by 20 mg/d long term
- Short-term results
  - In the only randomized controlled trial of 190 patients, 24 wk of leflunomide, dosed as above, led to a PASI 75 of 17% vs placebo response of 8% (P = .048)
- Long-term results
  - Not reported
- Contraindications
  - Patients with hypersensitivity to leflunomide or its metabolites
- Toxicity
  - Most common side effects include nausea, diarrhea, loss of appetite, weight loss, headache, dizziness
  - Less frequent adverse reactions may include severe liver injury, including fatal outcome; most cases of severe liver injury occur within 6 mo of therapy and in patients with multiple risk factors for hepatotoxicity
  - Rare reports of pancytopenia, agranulocytosis, and thrombocytopenia in patients receiving leflunomide; this occurs in patients who have been treated with methotrexate or other immunosuppressive agents, or who had recently discontinued these
- Drug interactions
  - Coadministration of leflunomide with methotrexate demonstrates no pharmacokinetic interaction between the two drugs but can lead to an increased risk of hepatotoxicity
  - When leflunomide is given with rifampin, leflunomide levels are increased
- Baseline monitoring
  - History and physical examination
  - CBC count/diff and LFTs
  - Pregnancy test if indicated
- Ongoing monitoring
  - Monthly CBC count with differential and LFTs for the first 6 mo and then every 6-8 wk
  - Pregnancy testing if indicated
- Pregnancy: category X
- Nursing: leflunomide should not be used by nursing mothers
- Pediatric use: no data
- Psoriatic arthritis: in the only randomized controlled study of 190 patients with psoriasis and psoriatic arthritis, 59% of patients treated with leflunomide vs 30% of patients treated with placebo were responders by the PsARC

CBC, Complete blood cell; *FDA*, Food and Drug Administration; *LFT*, liver function test; *PASI*, Psoriasis Area and Severity Index; *PsARC*, Psoriatic Arthritis Response Criteria.

The strength of recommendations for the treatment of psoriasis using sulfasalazine is shown in Table VIII.

TACROLIMUS

Tacrolimus is a macrolide antibiotic, a metabolite of the fungus *Streptomyces tsukubaensis*, that is indicated for prophylaxis of organ transplant rejection. It acts by inhibiting calcineurin, which in turn inhibits T-lymphocyte activation. There are major structural similarities between tacrolimus and CSA, but tacrolimus is up to 100 times more potent in vitro. Although tacrolimus is approved in a topical formulation for the treatment of atopic dermatitis and has been successfully used off label for the treatment of intertriginous psoriasis,[170,171] the use of oral tacrolimus for psoriasis is relatively uncommon.

The therapeutic value of tacrolimus was discovered by accident when 4 organ transplant recipients experienced significant improvement in their recalcitrant psoriasis when they were treated with tacrolimus to prevent graft rejection. In a 9-week, randomized, placebo-controlled trial of 50 patients with moderate to severe psoriasis, oral tacrolimus, dosed at 0.05 to 0.15 mg/kg/d, reduced PASI scores by 83% compared with 47% for patients treated with placebo.[172] The side effect profile of tacrolimus in patients with transplantation typically includes hypertension, diabetes mellitus, nephrotoxicity, neurotoxicity (tremors, paresthesias, and insomnia), and gastrointestinal irritation (diarrhea, nausea, constipation, vomiting, and abdominal pain). Recommendations for the use of tacrolimus are shown in Table XVIII. The strength of recommendations for the treatment of psoriasis using systemic tacrolimus is shown in Table VIII.

Table XVI. Recommendations for mycophenolate mofetil

- Indication
  - There is no FDA-approved use for psoriasis
- Dosing
  - 1.0-1.5 g orally two times/d
- Short-term results
  - 47% Mean reduction in PASI at 12 wk in 23 patients with psoriasis treated with 1.0-1.5 g twice daily
  - 47% Mean reduction in PASI at 6 wk in 11 patients with psoriasis treated with 1 g twice daily for 3 wk then 0.5 g twice daily for 3 more wk
- Long-term results: no data
- Contraindications
  - Hypersensitivity to MMF, mycophenolic acid
- Toxicity
  - GI side effects (diarrhea, nausea/vomiting, abdominal cramps); these occur early and decrease with continued use
  - Hematologic (leukopenia is most common; anemia, thrombocytopenia)
  - Genitourinary (urgency, frequency, dysuria, sterile pyuria)
  - Increased incidence of viral, bacterial and mycobacterial infections
  - Progressive multifocal leukoencephalopathy
  - Hypercholesterolemia, hypophosphatemia, hyperkalemia, hypokalemia
  - Fever and myalgias
  - Headache, insomnia
  - Peripheral edema
  - Hypertension
  - Patients taking MMF should not be given live attenuated virus vaccines
- Drug interactions
  - Antacids containing aluminum and magnesium
  - Calcium and iron
  - Cholestyramine
  - Antibiotics including cephalosporins, fluoroquinolones, macrolides, penems, penicillins, sulfonamides inhibit enterohepatic recirculation and decrease MMF levels
  - High-dose salicylates
  - Phenytoin
  - Xanthine bronchodilators
  - Probenecid
  - Acyclovir, ganciclovir, valganciclovir
- Baseline monitoring
  - History and physical examination
  - CBC and platelet counts
  - Chemistry screen, LFTs
  - Pregnancy test if indicated
- Ongoing monitoring
  - CBC and platelet counts weekly for 1 mo, then every 2 wk for 2 mo; then monthly thereafter
  - Monthly chemistry panel and LFTs
  - Biannual physical examination focusing on lymph node examination and skin cancer examination (SCCs in particular)
  - Pregnancy testing if indicated
- Pregnancy/nursing: pregnancy category D
  - Pregnancy and breast-feeding should be avoided during treatment and patients (including male) must use adequate contraceptive precautions
- Pediatric use: no data
- Psoriatic arthritis: case reports suggest improvement[183]

CBC, Complete blood cell; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *LFT*, liver function test; *MMF*, mycophenolate mofetil; *PASI*, Psoriasis Area and Severity Index; *SCC*, squamous cell carcinoma.

6-THIOGUANINE

6-Thioguanine is the natural metabolite of azathioprine but it appears to be more effective than its parent compound. It has been used extensively in the treatment of acute myelogenous leukemia and for inflammatory bowel disease. The mechanism of action of thioguanine is the inhibition of purine synthesis. Although there are no randomized trials of 6-

Table XVII. Recommendations for sulfasalazine

- Indication
  - There is no FDA-approved use for psoriasis
- Dosing for psoriasis
  - In psoriasis, initial dose of 500 mg PO twice daily increased to up to 3-4 g/d as tolerated
- Duration of dosing
  - As long as needed; there are no known cumulative toxicities
- Short-term results
  - Efficacy rates not well characterized; in the only randomized controlled trial, 8 wks of 3-4 g/d sulfasalazine led to moderate improvement (global improvement of 30%-59%) in 7/17 assessable patients given sulfasalazine compared with 1/27 assessable patients given placebo
- Long-term results
  - Not reported
- Contraindicatins
  - Patients with intestinal or urinary obstruction; patients with porphyria; patients hypersensitive to sulfasalazine, its metabolites, sulfonamides, or salicylates
- Toxicity
  - Anorexia, headache, GI symptoms (including nausea, vomiting, and gastric distress) and oligospermia can occur in up to one third of patients
  - Less frequent reactions include rash, pruritus, urticaria, fever, hemolytic anemia, and cyanosis, which may occur in $\leq$1/30 patients
- Drug interactions
  - Reduced absorption of folic acid and digoxin
- Baseline monitoring
  - History and physical examination
  - CBC count/diff and LFTs
  - Pregnancy test if indicated
- Ongoing monitoring
  - CBC count/diff and LFTs every other week for the first 3 mo; during the second 3 mo, CBC count/diff and LFTs monthly and thereafter once every 3 mo; urinalysis and renal function tests should be done periodically
  - Pregnancy test if indicated
- Pregnancy: category B
- Nursing: sulfonamides are excreted in the milk; in the newborn, they compete with bilirubin for binding sites on the plasma proteins and may thus cause kernicterus
- Pediatric use: no data
- Psoriatic arthritis: in the largest trial of sulfasalazine for psoriatic arthritis, after 36 wk of treatment with 2 g/d, 58% of patients given sulfasalazine compared with 45% of patients given placebo achieved PsARC[184]

CBC, Complete blood cell; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *LFT*, liver function test; *PsARC*, Psoriatic Arthritis Response Criteria.

thioguanine in psoriasis, there are several reports addressing the role of 6-thioguanine in the treatment of psoriasis.

The efficacy of 6-thioguanine was evaluated in a retrospective, open-label study of 40 subjects who received 6-thioguanine with varying treatment courses and dosages.[173] In this population, 78% achieved complete or almost complete clearing, 11% showed moderate improvement, and 11% showed little or no improvement. Reversible bone-marrow suppression was seen in approximately two thirds of subjects. A subsequent open-label analysis evaluated 81 subjects who were treated with a varying dose of 6-thioguanine according to initial disease severity and response during therapy.[174] Duration of therapy ranged from 1 to 220 months (median 16 months). A total of 49% of subjects were controlled, whereas 51% discontinued therapy because of initial failure of therapy (5%), side effects (36%), or relapse of psoriasis (10%). Myelosuppression was the most frequent side effect, occurring in 47% of subjects, and requiring discontinuation in 21% of subjects. Serum transaminase levels were elevated in 25% of evaluated subjects. In a novel dosing regimen of 6-thioguanine given as pulse dosing, either twice or 3 times per week, 10 of 14 patients showed marked improvement in previously recalcitrant psoriasis.[175] The advantage of this dosing regimen, where patients were given between 120 mg twice per week up to 160 mg 3 times per week, was a marked decrease in bone-marrow toxicity compared with

Table XVIII. Recommendations for tacrolimus

- Indication
  - There is no FDA-approved use for psoriasis
- Dosing for psoriasis
  - 0.05-0.15 mg/kg
- Duration of dosing
  - Unknown
- Short-term results
  - Efficacy rates are poorly characterized; patients dosed at 0.05 mg/kg showed no difference from placebo at 3 wk; when dosed at 0.10-0.15 mg/kg, by 9 wks there was a statistically significant improvement in PASI compared with placebo
- Long-term results
  - Not reported
- Contraindications
  - Patients with hypersensitivity to tacrolimus or its metabolites
- Side effect profile similar to cyclosporine
  - Most common side effects include tremor, headache, nausea, diarrhea, hypertension, and abnormal renal function test results
  - Less common side effects include: hyperglycemia, hyperkalemia, elevated LFT results, anemia, leukocytosis, dyspnea, fever, arthralgias, edema, diabetes, insomnia, paresthesias,
- Drug interactions
  - Numerous drug interactions as tacrolimus is metabolized by cytochrome P450 system
  - Do not give tacrolimus and cyclosporine together
- Baseline monitoring
  - History and physical examination
  - CBC count/diff, renal and LFTs
  - Pregnancy test if indicated
- Ongoing monitoring—proper frequency is not established
  - Blood pressure
  - Serum chemistry
  - Renal function
  - Liver function
  - Pregnancy test if indicated
  - Pregnancy: category C
  - Nursing: tacrolimus should not be used by nursing mothers
  - Pediatric use: no data
  - Psoriatic arthritis: case reports suggest improvement[185]

CBC, Complete blood cell; *FDA*, Food and Drug Administration, *LFT*, liver function test; *PASI*, Psoriasis Area and Severity Index.

daily dosing.[175] Recommendations for the use of 6-thioguanine are shown in Table XIX. The strength of recommendations for the treatment of psoriasis using 6-thioguanine is shown in Table XVIII.

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Table XIX. Recommendations for 6-thioguanine

- Indication
  - There is no FDA-approved use for psoriasis
- Dosing
  - Start at 80 mg two times/wk; increase by 20 mg every 2-4 wk; maximum dose is 160 mg 3 times/wk
- Short-term results
  - Open-label trial of 14 patients treated with pulse dosing followed by maintenance dosage (120 mg twice/wk to 160 mg 3 times/wk); of 11 patients who became longer-term responders, 6/11 showed a response after 2-4 wk
- Long-term results
  - 76 Patients followed up for >1 mo; at 24 mo, 58% were effectively maintained; safely used up to 145 mo
  - Another study showed 14/18 patients had 90% improvement
- Contraindications
  - Pre-existing liver disease
  - Immunosuppression
  - Anemia, leukopenia, and/or thrombocytopenia
- Toxicity
  - Myelosuppression
  - Liver toxicity from hepatic veno-occlusive disease
  - Increased ALT and AST
  - Hyperuricemia
  - Photodermatitis
  - Taste changes
  - Gastroesophageal reflux, gastric ulcers
  - Headache
  - Nausea/vomiting
  - Aphthous ulcers
  - Fatigue
  - Nonmelanoma skin cancer
  - Multiple warts, herpes zoster
- Drug interactions
  - Aminosalicylate derivatives (olsalazine, mesalazine, or sulfasalazine) may inhibit TPMT
- Baseline monitoring
  - History and physical examination
  - CBC and platelet counts, chemistry screen, LFTs, hepatitis B and C, PPD
  - Pregnancy test if indicated
- Ongoing monitoring
  - CBC and platelet counts every 2-4 wk; serum chemistry every 3 mo
  - Biannual physical examination focusing on lymph node examination and skin cancer examination (SCCs in particular)
  - Pregnancy test if indicated
- Pregnancy/nursing: pregnancy category D
  - Pregnancy and breast-feeding should be avoided during treatment, and patients (including male) must use adequate contraception
- Pediatric use: no data
- Psoriatic arthritis: no data

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *CBC*, complete blood cell; *FDA*, Food and Drug Administration; *LFT*, liver function test; *PPD*, purified protein derivative; *SCC*, squamous cell carcinoma; *TPMT*, thiopurine methyltransferase.

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Henry W. Lim, MD: Dr Lim is an investigator for Orfagen, receiving grants; a consultant with LaRoche-Posay, receiving honoraria; and consultant and investigator with Johnson & Johnson, receiving grants and honoraria. As chairman, Dr Lim's department's clinical research office participates in many clinical trials, none of which benefit him directly.

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