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

Alan Menter, MD, Chair,[a] Neil J. Korman, MD, PhD,[b] Craig A. Elmets, MD,[c] Steven R. Feldman, MD, PhD,[d] Joel M. Gelfand, MD, MSCE,[e] Kenneth B. Gordon, MD,[f] Alice B. Gottlieb, MD, PhD,[g] John Y. M. Koo, MD,[h] Mark Lebwohl, MD,[i] Henry W. Lim, MD,[j] Abby S. Van Voorhees, MD,[k] Karl R. Beutner, MD, PhD,[l] and Reva Bhushan, PhD[m]

Dallas, Texas; Cleveland, Ohio; Birmingham, Alabama; Winston-Salem, North Carolina; Philadelphia, Pennsylvania; Chicago and Schaumburg, Illinois; Boston, Massachusetts; San Francisco and Palo Alto, California; New York, New York; and Detroit, Michigan

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

From the Baylor University Medical Center, Dallas[a]; Murdough Family Center For Psoriasis, Department of Dermatology, University Hospitals Case Medical Center, Cleveland[b]; Department of Dermatology, University of Alabama at Birmingham[c]; Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem[d]; Department of Dermatology and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania[e]; Division of Dermatology, Evanston Northwestern Healthcare and Department of Dermatology, Northwestern University, Fienberg School of Medicine, Chicago[f]; Tufts Medical Center, Tufts University School of Medicine, Boston[g]; Department of Dermatology, University of California—San Francisco[h]; Department of Dermatology, Mount Sinai School of Medicine, New York[i]; Department of Dermatology, Henry Ford Hospital, Detroit[j]; Department of Dermatology, University of Pennsylvania[k]; Anacor Pharmaceuticals Inc, Palo Alto, CA, Department of Dermatology, University of California, San Francisco[l]; and American Academy of Dermatology, Schaumburg.[m]

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Reprint requests: Reva Bhushan, PhD, 930 E Woodfield Rd, Schaumburg, IL 60173. E-mail: rbhushan@aad.org.

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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

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