REVIEW

Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference

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Background: Methotrexate remains a valuable option for the treatment of psoriasis. This report will summarize studies regarding the use of methotrexate since the last guidelines were published in 1998.

Objective: A task force of the National Psoriasis Foundation Medical Board was convened to evaluate treatment options. Our aim was to achieve a consensus on new updated guidelines for the use of methotrexate in the treatment of psoriasis.

Methods: Reports in the literature were reviewed regarding methotrexate therapy.

Results: A consensus was achieved on use of methotrexate in psoriasis including specific recommendations on dosing and monitoring. The consensus received unanimous approval from members of the Medical Board of the National Psoriasis Foundation.

Limitations: There are few evidence-based studies on the treatment of psoriasis with methotrexate. Many of the reviewed reports are for the treatment of rheumatoid arthritis.

Conclusions: Methotrexate is a safe and effective drug for the treatment of psoriasis. Appropriate patient selection and monitoring will significantly decrease the risks of side effects. In patients without risk factors for hepatic fibrosis, liver biopsies may not be indicated or the frequency of liver biopsies may be markedly reduced. (J Am Acad Dermatol 2009;60:824-37.)

INTRODUCTION

Methotrexate was first used for the treatment of psoriasis over 50 years ago. Its use predates the age of randomized clinical trials. High-quality data concerning its efficacy and side effects are sparse. Monotherapy and combination therapy with methotrexate continue to be widely used in dermatology primarily in psoriasis and psoriatic arthritis, and for diseases as varied as sarcoidosis, dermatomyositis, and pyoderma gangrenosum.[1-3]

The treatment of psoriasis has changed dramatically in the past decade. There has been an explosion of basic research and clinical research. Five biologic agents—alefacept, efalizumab, etanercept, infliximab, and adalimumab—have been approved by the Food and Drug Administration (FDA) for the treatment of psoriasis. A sixth biologic agent, ustekinumab, has been recommended for approval; more novel agents are forthcoming. Methotrexate is much less costly than biologics, even when the costs of blood monitoring and liver biopsies are considered. Many insurance companies therefore require an inadequate response or intolerance to methotrexate as a prerequisite. These targeted

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Abbreviations used:

ACR:	American College of Rheumatology
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
CDC:	Centers for Disease Control and Prevention
FDA:	Food and Drug Administration
NASH:	nonalcoholic steatohepatitis
NSAID:	nonsteroidal anti-inflammatory drug
PASI:	Psoriasis Area and Severity Index
PIIINP:	aminoterminal peptide of procollagen III
PPD:	purified protein derivative
PUVA:	psoralen plus ultraviolet A

biologic therapies are alternative treatment options to methotrexate in the long-term management of psoriasis, especially in patients with hematologic or hepatic side effects of methotrexate. Nevertheless, methotrexate remains a valuable therapeutic option for patients.

Methotrexate was approved by the FDA for psoriasis at the same time the initial guidelines were published in 1972. The listed indication was for the treatment of severe, recalcitrant, disabling psoriasis. Minimum body surface area was not specified in the approved indication, allowing treatment of patients with functional disability due to palmoplantar disease, recalcitrant scalp disease, or other limited but severe forms of psoriasis. The approved indication suggests lack of response to topical therapy and phototherapy, when available and practical. Methotrexate has been used to successfully treat plaque, guttate, pustular, and erythrodermic forms of psoriasis. It is interesting to note that the approval of methotrexate for psoriasis was not associated with double-blind, placebo-controlled trials that the FDA now requires for most drugs. The guidelines written by several dermatologists in 1972 have provided standards for the use of methotrexate for psoriasis. There have been updates on these guidelines; the most recent was published in 1998.[4] The format and content of the 1998 guidelines were used as a template for this review, and two of the authors (G. W. and M. L.) participated in the writing of the 1998 guidelines. The contributions of Henry Roenigk, Howard Maibach, and Robert Auerbach to previous guidelines will have a positive lasting impact on this and future guidelines.

Methotrexate was approved for treatment of rheumatoid arthritis in 1988 and guidelines published by the American College of Rheumatology (ACR) differed from those of earlier dermatology guidelines by not requiring liver biopsy before methotrexate treatment. The requirement for a routine pretreatment liver biopsy was eliminated in the 1998 dermatology guidelines. In contrast to those of dermatology, the rheumatologic guidelines differ in their recommendations in monitoring for possible liver toxicity associated with methotrexate.[5]

This article reviews available data to achieve a consensus on new updated guidelines for the use of methotrexate in the treatment of psoriasis; it was reviewed by members of the Medical Board of the National Psoriasis Foundation and approved by unanimous vote. To minimize the toxicity of any therapy, proper patient selection and appropriate monitoring are crucial. The decision to administer methotrexate should be individualized. Each patient should be evaluated with reference to disease severity, quality of life, and general medical and psychological status.

METHOTREXATE EFFICACY IN PSORIASIS

Three recent blinded studies have been published concerning the efficacy of methotrexate in psoriasis. Heydendael et al[6] compared methotrexate to cyclosporine without a placebo arm. There were approximately 45 patients in each group. The primary end point of PASI (Psoriasis Area and Severity Index) 75 response at 12 weeks was 60% for methotrexate and 71% for cyclosporine. Fourteen of 45 patients in the methotrexate arm dropped out because of abnormally elevated liver function tests, although no folic acid supplementation was given to the enrolled patients. The mean dose of methotrexate at the primary end point was not stated. Flytstrom, Stenberg, and Svensson[7] also compared methotrexate to cyclosporine without a placebo arm. Eighty-four patients were randomized and 68 were included in the analysis. The mean PASI change from baseline was 72% in the cyclosporine group and 58% in the methotrexate arm. Cyclosporine was statistically more effective, but more patients dropped out from this arm. The mean dose of methotrexate at the primary end point was not stated. Saurat et al[8] reported a double-blind, controlled study of methotrexate versus adalimumab in 250 patients. A placebo arm was also included; therefore this was the first placebo-controlled analysis of methotrexate for the treatment of psoriasis. The primary end point of PASI 75 achievement at 16 weeks was 19% for the placebo arm, 36% for the methotrexate group, and 80% for the adalimumab group. The methotrexate was dosed 7.5 mg for the first 2 weeks, 10 mg for the next 2, 15mg for the next 4, and could be slowly increased thereafter depending on the response and the presence or absence of laboratory abnormalities. Importantly, if, after week 8, a subject receiving methotrexate had achieved a PASI 50 response, no

further increase in that subject's methotrexate dose was allowed. After 16 weeks, the mean methotrexate dose was 19 mg. This group was then crossed over to receive adalimumab, although the response to methotrexate was still increasing and the maximum response may not have been reached. These two issues suggest that this study may have underestimated the true efficacy of methotrexate in psoriasis.

CONTRAINDICATIONS

The following are relative contraindications to the use of methotrexate for the treatment of psoriasis:

1. Any abnormalities in renal function may require another therapy or a marked reduction in the dose as 85% of methotrexate is excreted through the kidneys.
2. Significant abnormalities in liver function—liver function tests must be followed and any elevation warrants closer monitoring
3. Hepatitis, active or recurrent
4. Cirrhosis
5. Excessive current alcohol consumption—there are few data to support specific limits on alcohol consumption. Some physicians advise patients to refrain from alcohol altogether, whereas others allow as much as two drinks per day. A history of alcoholism is problematic if there is evidence of liver damage.
6. Concomitant use of hepatotoxic drugs (see drug interactions below)—more frequent monitoring of liver function tests may be necessary.
7. Active infectious disease, especially chronic infections likely to be exacerbated by methotrexate's immunosuppressive effects—for example, active untreated tuberculosis or advanced HIV infection. During acute infections, methotrexate can be temporarily withheld.
8. Immunosuppressed state; this does not apply to patients receiving treatment with other agents, such as biologic therapies.
9. Conception should be avoided during methotrexate therapy and afterward for at least 3 months in the male or one ovulatory cycle in the female.
10. Recent vaccination, especially with live vaccine
11. Obesity (body mass index greater than 30)
12. Diabetes mellitus
13. Unreliable patient

The following are absolute contraindications to the use of methotrexate for psoriasis:

1. Pregnancy or nursing
2. Significant anemia, leukopenia, or thrombocytopenia

Circumstances may arise in which the contraindications must be waived such as when benefits can be expected to outweigh the risks of methotrexate therapy in an individual patient. For example, if an obese, diabetic patient needed short-term methotrexate therapy, it might be reasonable to prescribe short-term methotrexate despite the relative contraindications.

PRE-METHOTREXATE EVALUATION

The pre-methotrexate evaluation starts with the history and physical examination. The history should focus on psoriasis, psoriatic arthritis, response to prior therapies, and presence of contraindications to methotrexate. Physical examination should likewise focus on psoriasis, psoriatic arthritis, and signs of renal, hepatic, or infectious diseases.

A recent review offers useful guidelines in starting and continuing methotrexate.[9] Laboratory tests consist of the following studies:

1. Complete blood cell count and platelet count
2. Renal function tests (blood urea nitrogen and serum creatinine); calculated glomerular filtration rate or creatinine clearance when indicated; the Cockroft and Gault formula[10] can be used to estimate the creatinine clearance in adults:

$$\textit{For men}: \text{Estimated creatinine clearance} = (140 - \text{Age (yrs)}) \times \text{Body Weight (kg)} \text{ divided by } (72 \times \text{Serum Creatinine (mg/dl)})$$

$$\textit{For women}: \text{Estimated creatinine clearance} = \text{Above formula} \times 0.85$$

3. Liver chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, bilirubin, albumin); hepatitis B and C serology tests when indicated. While some experts advocate hepatitis serologies in all patients before methotrexate therapy, others do not obtain viral titers unless there is additional evidence of viral hepatitis, such as elevated liver function tests.
4. Pregnancy test, if indicated in a woman of childbearing potential
5. HIV antibody determination in patients at risk for HIV infection
6. Some experts recommend a baseline purified protein derivative (PPD) test or other screening

test for latent tuberculosis, particularly if the patient's history indicates risk. Some argue that this is not explicitly the standard of care, but the Centers of Disease Control and Prevention (CDC) Web site recommendations on tuberculosis suggest that any patient about to start immunosuppressive drugs should be considered for a pretreatment PPD.[11]

7. Consider baseline liver biopsy in patients with a history of significant liver disease (see Hepatotoxicity section below).

CONTINUING LABORATORY STUDIES

The following laboratory studies should be continued during the entire course of methotrexate therapy for psoriasis:

1. Complete blood cell count and platelet count (quantitative) 7 to 14 days after starting or increasing the dose, every 2 to 4 weeks for the first few months, then approximately every 1 to 3 months, depending on leukocyte count and stability of patient. Patients with risk factors for hematologic toxicity (Table I) need closer monitoring, particularly at the onset of therapy and after dosage increases.
2. Renal function studies: blood urea nitrogen and serum creatinine levels at 2- to 3-month intervals. For those patients with normal values, who may be at risk for decreased renal function, a glomerular filtration rate should be calculated. Most commercial laboratories now report this value for all patients.
3. Liver chemistries: ALT, AST, alkaline phosphatase, and serum albumin levels every 4 to 12 weeks (more frequent liver chemistry monitoring in lieu of an initial liver biopsy for patients with hepatic risk factors, see Table I).
4. Pregnancy test if indicated in women of childbearing potential.
5. More frequent monitoring may be required under certain circumstances, such as dosage changes or if there are concomitant medications.

A significant reduction in leukocyte or platelet counts necessitates reduction or temporary discontinuation of methotrexate therapy. The maximum depression of the leukocyte count and platelet count usually occurs 7 to 10 days after a dose of methotrexate. Immediate administration of folinic acid (20 mg) orally or intravenously should be considered in cases of clinically significant leukopenia or thrombocytopenia. Progressively increasing mean corpuscular volume is common in patients on a regimen of methotrexate and signals the onset of macrocytic anemia. Folic acid administered orally in dosages of 1 to 5 mg per day may prevent or reverse this side effect. Folinic acid given orally at 5 mg for 3 doses every 12 hours, once weekly, with the first dose 12 hours after the last dose of methotrexate is also acceptable. Both types of folic acid supplementation are available in a generic form and are relatively inexpensive.

Table I. Risk factors for hematologic toxicity from methotrexate

Renal insufficiency
Advanced age
Lack of folate supplementation
Medication errors
Drug interactions
Hypoalbuminemia
Excess alcohol intake
Multiple concurrent medications

When liver chemistry tests are obtained, there should be at least a 5-day interval between the last methotrexate dose and the blood tests because liver chemistry values may be elevated 1 to 2 days after a dose of methotrexate. If a significant persistent abnormality in liver chemistry develops, methotrexate therapy should be withheld for 1 to 2 weeks and then the battery of liver chemistry tests should be repeated. Liver chemistry values should 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.

DRUG DOSE SCHEDULES

Methotrexate is typically given as a single weekly oral dose or in 3 doses at 12-hour intervals weekly. Oral administration can be in the form of a tablet or a carefully measured parenteral solution given orally (0.1 mL of a 25 mg/mL multi-dose vial is equivalent to a 2.5-mg oral tablet). The parenteral solution of methotrexate is less costly than the tablets. A single weekly dose will likely increase compliance. Dividing the dose can decrease minor gastrointestinal side effects in some patients. Since medication errors can be a significant problem with methotrexate, it is of utmost important to ensure that patients understand the proper dose schedule.[12] Patients in the United Kingdom carry a "methotrexate card" for proper administration and to calculate the cumulative dose.[13]

The multi-dose vial can also be used for physician- or patient-administered subcutaneous or intramuscular injections. A recent blinded study in

patients with rheumatoid arthritis compared subcutaneous and oral methotrexate. This study revealed greater efficacy in the subcutaneous group with equal tolerability.[14] Some patients may have decreased gastrointestinal side effects when switched to subcutaneous administration from the oral route. With the advent of biologic therapy, more patients are familiar with self injection techniques.

When methotrexate therapy is initiated, many experts recommend a "test dose" be administered and repeat laboratory tests for hematologic effects checked in approximately 7 days. Some experts recommend a small dose, such as 5 mg, whereas others start at the anticipated dose, such as 15 mg. This test dose practice is mandatory in any patient with a decreased calculated glomerular filtration rate or other significant risk factors for hematologic toxicity[15] (Table I). Using a test dose also provides an additional safeguard against rare, idiosyncratic reactions to methotrexate.

Doses are usually started with lower initial levels to minimize side effects and adjusted to achieve clinical effectiveness. Recent studies with other systemic therapies for psoriasis suggest that a weight-based dosing schedule may be more effective,[16] but there are no published weight-based studies for the treatment of psoriasis with methotrexate.

While there is not an established maximum or minimum dose, the weekly single or triple oral dosages are ordinarily 7.5 to 25 mg/wk. Reported schedules have been to start at lower doses (eg, 7.5 mg/wk) and gradually increased, whereas others recommend starting at the anticipated target dose (eg, 15 mg/wk).

All schedules should be adjusted to the individual patient. Patients on any schedule should have the dosage raised or reduced to obtain or maintain adequate disease control. It can take 4 to 8 weeks to see a response to changes in methotrexate dose. Some patients can be gradually weaned off therapy and restarted if the disease flares. The goal is to both decrease the total cumulative dose and improve tolerability.

FOLATE SUPPLEMENTATION

Some experts recommend all patients receiving methotrexate should receive folate supplementation. Some physicians will add folate only if patient issues occur such as gastrointestinal side effects or early bone marrow toxicity as manifested by an increased mean corpuscular volume. In patients already receiving folate, increasing the dose may also help in these situations. Options for folate supplementation include folic acid 1 mg daily or folinic acid given orally at 5 mg for 3 doses every 12 hours, once weekly, with the first dose 12 hours after the last dose of methotrexate. Folate supplementation reduces hematologic, gastrointestinal, and hepatotoxic side effects without decreasing the efficacy.[17] A recent report[18] using folic acid 5 mg daily suggests there is a slight decrease in efficacy, but the study's methodology has been questioned.[19] We believe that the benefits of folate supplementation greatly outweigh a slight decrease in efficacy, if it exists.

METHOTREXATE TOXICITY

The use of methotrexate is restricted by the risk of organ toxicity. The 3 primary concerns are myelosuppression, hepatotoxicity, and pulmonary fibrosis. Of the 164 possible methotrexate-associated fatalities reported to the United Kingdom Committee on the Safety of Medicines between 1969 and 2004, 67 were related to myelosuppression, 30 were due to pulmonary fibrosis, and 8 were due to liver toxicity.[20] A more recent survey of UK dermatologists again emphasized myelosuppression as the most serious side effect.[13] Pulmonary fibrosis is much less common in psoriasis patients treated with methotrexate compared to patients with rheumatoid arthritis, which is the reason a chest x-ray is not part of the routine baseline studies. Fibrosis should be considered, however, if pulmonary symptoms develop.[21,22] The hematologic and hepatotoxicity issues are discussed below.

Common minor adverse events include nausea, anorexia, stomatitis, fatigue, and malaise often at the time the medication is taken. Clinical experience suggests these side effects may be diminished by folate supplementation, administering the methotrexate by intramuscular or subcutaneous injection, splitting the dose, or by administering the dose at bedtime.

The advent of biologic therapy has prompted a more thorough study of patients with psoriasis. Side effects, such as reactivation of tuberculosis and hepatitis, and the development of lymphoma have been reported in trials of biologic agents and in postmarketing observations. Since methotrexate has never been subjected to the same scrutiny, such potential toxicities or adverse effects have not been considered. More recent reports suggest that methotrexate therapy may be associated with risks similar to those of other immunosuppressive treatments, although these reports almost exclusively involve patients with rheumatoid arthritis. Lymphoma, particularly Epstein-Barr virus associated, and the reactivation of tuberculosis and hepatitis have all been reported.[23-26] A recent study showed a 50% increased risk of malignancy relative to the general population

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