

Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference

Robert E. Kalb, MD,^a Bruce Strober, MD, PhD,^b Gerald Weinstein, MD,^d and Mark Lebwohl, MD^c
Buffalo and New York, New York; and Irvine, California

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

From the Departments of Dermatology: State University of New York at Buffalo, School of Medicine and Biomedical Science, Buffalo^a; New York University School of Medicine^b; The Mount Sinai School of Medicine, New York^c; and University of California at Irvine.^d

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Reprint requests: Mark Lebwohl, MD, 5 E 98th St, 5th Floor, New York, NY 10029. E-mail: Lebwohl@aol.com. 0190-9622/\$36.00

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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 al⁶ 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 Svensson⁷ 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 al⁸ 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 Cockcroft and Gault formula¹⁰ can be used to estimate the creatinine clearance in adults:

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

$$\begin{aligned} \text{For women: Estimated creatinine clearance} \\ &= \text{Above formula} \times 0.85 \end{aligned}$$

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 child-bearing 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 Hepato-toxicity 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 child-bearing 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

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

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.

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 toxicity¹⁵ (Table D). 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 report¹⁸ 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

with a 3-fold increase in melanoma, 5-fold increase in non-Hodgkin lymphoma, and nearly 3-fold increase in lung cancer.²⁷ In short, clinicians need to have a high index of suspicion for any patient receiving immunosuppressive therapy.

In discussing the side effects of methotrexate, we should also point out new data regarding unanticipated benefits. A protective effect against cardiovascular disease has been demonstrated.²⁸ It should be emphasized that recent reports suggest that methotrexate is an anti-inflammatory medication that may have beneficial cardiovascular effects in a subset of patients.²⁹ From this perspective, the benefits of methotrexate therapy in many patients may outweigh the risks.

METHOTREXATE AND HEMATOLOGIC TOXICITY

The primary risk factors reported for hematologic toxicity are renal impairment, advanced age, lack of folate supplementation, drug interactions, and medication errors (see Table D). Much of the data regarding myelosuppression has been published in patients with rheumatoid arthritis. The relative risk of this side effect in patients with psoriasis compared to patients with rheumatoid arthritis is unknown. The published data suggest that clinically significant myelosuppression is rare in properly monitored psoriasis patients without risk factors for hematologic toxicity.

While pancytopenia is a rare side effect with the use of low-dose weekly methotrexate, it may occur at any time during treatment, particularly in those with hematologic risk factors.^{30,31} Rarely, significant cytopenia has been reported, even after single doses of low-dose methotrexate.³¹⁻³⁴ In all cases, however, there were significant risk factors, particularly impaired renal function or medication errors.

Since pancytopenia may occur at any time during methotrexate therapy, it is important to monitor complete blood cell counts regularly. Patients should regularly be reminded of the proper use of their therapy and possible medication interactions. In some of the reported cases, pancytopenia occurred 4 to 6 weeks after the methotrexate dosage was increased, so more frequent monitoring is suggested with such dose changes.

In the absence of hematologic risk factors, such as renal insufficiency, pancytopenia with low-dose weekly methotrexate is rare. After methotrexate treatment has been initiated, it is necessary to monitor regularly for hematologic toxicity. The first repeat laboratory check should be within a 2-week period for patients without risk factors. The glomerular filtration rate should be calculated for those patients who have normal blood urea nitrogen and

creatinine levels but are at risk for renal insufficiency, such as the elderly or those with a decreased muscle mass. This frequency of laboratory monitoring may be slowly decreased over time (1- to 3-month intervals), provided there are no problems or changes in the medical history. Some experts believe that complete blood cell counts should be performed at least every 4 weeks, though others reduce the frequency of monitoring in patients whose conditions are consistently stable. Patients with significant renal impairment are at a high risk even after single doses of methotrexate. These patients require careful monitoring. Initial laboratory checks should be obtained before the second dose. After any dose increases, laboratories should be checked before the next dose is administered.

METHOTREXATE AND HEPATOTOXICITY

New data prompt a re-evaluation of the most recent dermatology guidelines for performing liver biopsies in patients receiving methotrexate. Several studies have shown that methotrexate-associated hepatic fibrosis and cirrhosis are considerably less aggressive than initially reported.^{35,36} Many rheumatologists deem the liver biopsy as unnecessary, particularly in healthy patients. The more stringent dermatology guidelines rest on the assertion that hepatic toxicity is greater in patients with psoriasis than in patients with rheumatoid arthritis. The reduced hepatotoxicity among patients with rheumatoid arthritis is in part related to the higher incidence of rheumatoid arthritis in women who consume less alcohol than men. Patients with psoriasis have a higher incidence of obesity, diabetes, and alcoholism.³⁷

The histopathologic features of methotrexate-induced liver toxicity resemble nonalcoholic steatohepatitis (NASH), the pattern of liver histology observed in people who are obese, hyperlipidemic, or diabetic. In fact, psoriasis patients with risk factors for NASH may develop liver fibrosis at a lower cumulative methotrexate dose than those without risk factors. Methotrexate likely aggravates preexisting NASH, implying that patients with psoriasis at greatest risk while receiving methotrexate are those with diabetes, obesity, and those who drink alcohol.^{38,39} The presence of these risk factors may represent inherent phenotypes of psoriatic patients that increase the risk of hepatotoxicity. If these studies were controlled for such confounding variables, then the methotrexate-related liver injury rate in patients with psoriasis would most likely resemble that of patients with rheumatoid arthritis.^{38,40,41} Recently published updates suggest that when evaluating a patient for methotrexate treatment, risk factors such as alcohol consumption, obesity,

Table II. Risk factors for hepatic toxicity from methotrexate

History of or current alcohol consumption*
Persistent abnormal liver chemistry studies
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
Lack of folate supplementation
Hyperlipidemia

*Methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy. The exact amount of alcohol that confers risk is unknown and differs among persons.

hyperlipidemia, diabetes, previous exposure to liver toxins, and hepatitis should be considered.^{39,42} In short, the clinical scenario of each patient must dictate the necessity of the liver biopsy.

The updated guidelines suggest that patients being considered for methotrexate therapy be divided into two groups based on their risk factors for liver injury (Table II). Patients with no risk factors for liver injury likely have a low risk of fibrosis that is similar to that of RA patients; therefore the ACR criteria for monitoring methotrexate are applied to these patients by some experts. Specifically, every 1- to 3-month evaluation of liver chemistries with liver biopsy performed if 5 of 9 serum AST levels are elevated over a 12-month period or if there is a decline in the serum albumin (in the context of normal nutritional status) below the normal range in the setting of well-controlled disease (Table III). This approach was validated and displayed a safe reduction in the number of biopsies performed.^{5,43} Other recent data suggest that 3.5 to 4.0 g instead of 1.0 to 1.5 g of cumulative methotrexate should prompt the first liver biopsy in patients without preexisting risk factors for hepatotoxicity.^{38,44,45} In the presence of normal findings on liver chemistry tests, history, and physical examination, the decision to perform or omit liver biopsies for low-risk patients receiving methotrexate should be made on a case-by-case basis after consideration of the relative risk. Options for such patients who reach a cumulative dose of 3.5 to 4.0 g include following the ACR guidelines and continuing to monitor without a biopsy, performing the first biopsy at this 3.5- to 4.0-g level, or stopping or switching methotrexate to another therapy if possible. If this first liver biopsy shows no significant abnormalities in these low-risk patients, repeat liver biopsies would be dictated by following the ACR guidelines shown in Table III.

Table III. Monitoring for hepatotoxicity in low-risk patients

No baseline liver biopsy
Monitor liver function tests monthly for the first 6 months and then every 1 to 2 months thereafter.
→ For minor elevations (<2-fold upper limit of normal), repeat in 2 to 4 weeks.
→ For moderate elevations (>2-fold but <3-fold upper limit of normal), closely monitor, repeat in 2 to 4 weeks, and dose reductions as necessary.
→ For persistent elevations in 5 of 9 AST levels over a 12-month period or if there is a decline in serum albumin with normal nutritional status below the normal range in the setting of well-controlled disease, liver biopsy should be performed.
Consider continuing to follow according to above ACR guidelines without biopsy
Or
Consider liver biopsy after 3.5 to 4.0 g total cumulative dosage
Or
Consider switching to another agent or discontinuing therapy after 3.5 to 4.0 g total cumulative dosage.

ACR, American College of Rheumatology; AST, serum aspartate aminotransferase.

There is consensus that those patients with one or more risk factors for hepatic fibrosis should be followed with the previously published more stringent guidelines (Table IV). If a patient has significant risk factors, then the first consideration should be the feasibility of using a different systemic agent. If the risk/benefit consideration for an individual patient with such risk factors favors the use of methotrexate, then it is advisable that a liver biopsy be done, when feasible, at or near the beginning of methotrexate therapy. A small percentage of patients will not continue to take methotrexate after 2 to 6 months because of adverse effects, lack of clinical effectiveness, or other reasons. Therefore the early-treatment liver biopsy might be postponed until after this initial period. If long-term therapy is anticipated, the initial biopsy should be performed in patients with risk factors. No information is available to suggest that a short or several-month period of methotrexate treatment will cause clinically significant liver disease. In patients with risk factors for liver disease, a repeat biopsy should be planned at a cumulative dose of 1.0 to 1.5 g. In patients having persistent significant abnormalities in liver chemistry values, a liver biopsy is also indicated. The liver biopsy in these higher risk patients should be repeated with every additional 1.0 to 1.5 g. A liver biopsy might not be indicated or could be postponed if the risks of the biopsy exceed the benefits for an individual patient.

Unfortunately, we lack a safe and effective screening tool for liver fibrosis that eliminates or, at the very least, decreases the need for liver biopsies. A variety of tests including ultrasonographic and radiographic imaging techniques have been tried without success. In recent years the measurement of the amino-terminal peptide of procollagen III (PIIINP) has been utilized as such a potential marker. A recent study compared the use of the 1998 American Academy of Dermatology guidelines to Manchester PIIINP guidelines and showed 7-fold fewer biopsies in the latter group.⁴⁶ Another study revealed that liver biopsies could be entirely avoided if the PIIINP remained stable.⁴⁷ The majority of consultant dermatologists in the United Kingdom use this test to monitor for hepatic fibrosis.^{13,48} A radioimmunoassay for the PIIINP test is available from the distributor Immunodiagnostic Systems Inc.,* but it is not FDA approved or commercially available in the United States. In addition, there are no current plans to pursue formal testing in the United States. Moreover, the British study of PIIINP points out that not all commercially available kits for PIIINP have the same characteristics.

The liver biopsy is not an innocuous procedure. The risk of advanced fibrosis should be balanced with the risk of liver biopsy complications. Fortunately, in patients with psoriasis, the risks have tended to be lower than in patients with other diseases. These risks include subcapsular hemorrhage, gallbladder perforation, pneumothorax, and hemoperitoneum.⁴⁹ Most adverse events occur in patients with internal abnormalities related to other diseases. The risks of liver biopsy summarized by Kremer et al⁵⁰ showed an estimated frequency of complications to be 1.5 per 1000 procedures.

CLINICAL INTERPRETATION OF LIVER BIOPSY RESULTS

In patients selected for a liver biopsy based on the conditions discussed above, the decision regarding continuation or discontinuation of methotrexate therapy is made after consideration of the biopsy results. The following recommendations are based on liver abnormalities using the Roenigk scale⁵¹ (Table V):

- Patients with grade I or II changes may continue to receive methotrexate therapy.
- Patients with grade IIIA change(s) may continue to receive methotrexate therapy, but should have a repeat liver biopsy after approximately 6

Table IV. Monitoring for hepatotoxicity in high-risk patients

Consider the use of a different systemic agent.
Consider delayed baseline liver biopsy (after 2 to 6 months of therapy to establish medication efficacy and tolerability).
Repeat liver biopsies after approximately 1.0 to 1.5 g of therapy.

months of methotrexate therapy. Alternative systemic therapy should be considered.

- Patients with grades IIIB and IV changes should not be given further methotrexate therapy. Exceptional circumstances, however, may require continued methotrexate therapy, with thorough follow-up liver biopsies.

COMBINATION THERAPIES

The goal in combination therapy is to improve efficacy and decrease toxicity of each individual agent. In patients receiving a stable methotrexate dosage, the addition of a second agent may accomplish both. Since hepatotoxicity may be related to total cumulative dose, a decreased weekly dose would lead to a lower cumulative dose over time. The addition of methotrexate to a stable regimen of another systemic agent can also increase efficacy often at lower than normal weekly methotrexate doses.

The combination of cyclosporine with methotrexate has proven to be very effective. In fact, lower doses of both drugs can be used when they are combined, resulting in lower cumulative doses over time and therefore presumably less hepatotoxicity from methotrexate and less nephrotoxicity from cyclosporine.^{52,53}

Phototherapy, including broadband ultraviolet B, narrowband UVB, and PUVA, has been used very effectively in combination with methotrexate.⁵⁴⁻⁵⁶ Photosensitivity has been reported rarely, as has the even more uncommon radiation recall in which a patient's resolved sunburn can re-flare in the same locations after taking methotrexate. Methotrexate has also been combined with all of the biologic therapies that are now approved for the treatment of psoriasis or psoriatic arthritis.⁵⁷⁻⁶⁰ A recent report suggests that low-dose acitretin can also be combined with methotrexate.⁶¹

There is extensive literature regarding the combination of methotrexate and anti-tumor necrosis factor therapy in the treatment of rheumatoid arthritis and psoriatic arthritis both from a safety and efficacy standpoint. Other recent reports have detailed how patients have been able to decrease methotrexate dosages or discontinue the use of methotrexate

*Tel: +1 480 836 7435. E-mail: info@idsinc.us.com. Web site: www.idsinc.us.com.

Table V. Roenigk scale for histopathologic evaluation of liver biopsy findings

Grade	Findings
I	Normal; fatty infiltration, mild; nuclear variability, mild; portal inflammation, mild
II	Fatty infiltration, moderate to severe; nuclear variability, moderate to severe; portal tract expansion, portal tract inflammation, and necrosis, moderate to severe
IIIA	Fibrosis, mild (portal fibrosis here denotes formation of fibrotic septa extending into the lobules; slight enlargement of portal tracts without disruption of limiting plates or septum formation does not classify the biopsy specimen as grade III).
IIIB	Fibrosis, moderate to severe
IV	Cirrhosis (regenerating nodules as well as bridging of portal tracts must be demonstrated).

completely when biologic therapy has been initiated.^{59,60} In patients treated with infliximab, concomitant therapy with methotrexate reduces the likelihood of development of human anti-chimeric antibodies.⁶²

ROTATIONAL THERAPIES

Rotating different treatments for moderate to severe psoriasis is based on the concept that the duration of therapy may continue for many years, during which time significant risks of toxicity may accumulate. Examples include skin cancers after 200 PUVA treatments, hepatic fibrosis secondary to methotrexate, and renal disease from cyclosporine. Whether the long-term use of biologic agents in the treatment of psoriasis will lead to cumulative toxicity is unknown. Experience has proven that psoriasis is generally a disease of indefinite duration and toxicities appear often without predictability. Rotating therapies, if and when feasible, can potentially decrease cumulative toxicities and thus minimize long-term risks.

OVERDOSAGE

The leading causes of acute methotrexate toxicity are impaired renal function (which prevents excretion of normal doses of methotrexate), medication errors, and the concomitant administration of trimethoprim or trimethoprim-sulfamethoxazole. Leucovorin calcium (citrovorum factor or folinic acid) is the only antidote for the hematologic toxic effects of methotrexate. When an overdose of methotrexate is suspected for any reason, including minimal renal compromise, the patient should be given leucovorin

immediately. An immediate leucovorin dose of 20 mg (10 mg/m²) should be given parenterally or orally, and subsequent doses should be given every 6 hours, parenterally or orally, as tolerated by the patient. As the time interval between methotrexate administration and the initiation of leucovorin treatment increases, the effectiveness of leucovorin in counteracting the hematologic toxicity of methotrexate decreases. Rapid consultation with a hematologist is advisable, if possible.

EFFECT OF LOW-DOSE METHOTREXATE ON MALE FERTILITY AND SPERMATOGENESIS

Methotrexate is not mutagenic. It is toxic to cells undergoing division (ie, spermatogenesis).⁶³ Methotrexate is often used in combination with other drugs in chemotherapeutic regimens; thus its effect on male fertility is uncertain.⁶⁴ Its effects are usually reversible once the drug is withdrawn.

There is controversy regarding its effect on male spermatogenesis and fertility.⁶⁵ Some studies support that methotrexate treatment may result in severe oligospermia in the face of normal hormone levels and these effects on spermatogenesis are reversible.⁶⁶ No increases in abnormal births have been documented with fathers on methotrexate.⁶⁷⁻⁶⁹ Several possible explanations have been put forth. The oligospermia may be severe enough to inhibit fertilization. Alternatively, the sperm have sufficient functional abnormalities to impair their ability to fertilize an egg.⁷⁰ Other studies revealed no changes in spermatogenesis and sperm counts.^{68,71}

Since one cycle of spermatogenesis requires 74 days, the conservative recommendation is to wait 3 months prior to conception to allow for the effects of methotrexate to completely pass. Based on the current evidence, it may be less likely for a man to conceive a child while exposed to low-dose methotrexate. However, if conception occurs, it is unlikely there will be any fetal abnormalities. Consultation with a medical geneticist may be appropriate in this situation.

EFFECT OF LOW-DOSE METHOTREXATE ON PREGNANCY

Methotrexate is a known abortifacient and teratogen; it is FDA pregnancy category X. There are characteristic methotrexate-induced fetal abnormalities, including skeletal, cardiac, and central nervous system.⁷² Women of childbearing potential exposed to methotrexate should use an adequate form of contraception. Methotrexate is contraindicated in women attempting to conceive.

There is a significant amount of literature documenting fetal exposure to methotrexate. The critical period of exposure is believed to be between 6 and 8 weeks after conception at a dose of 10 mg per week or higher. Abnormalities have been reported with all dosage levels and timing of exposure, however. On the other hand, there have been numerous first-trimester pregnancies exposed to large doses of methotrexate (primarily for leukemia) with no congenital or developmental problems reported.⁷³

In patients treated with low-dose weekly methotrexate, the majority of the published information involves patients with rheumatoid arthritis. One must take into account that women with rheumatic diseases have significantly higher rates of not only preterm labor, but also birth defects compared with their healthy counterparts. This risk has not been correlated with medication usage.⁷⁴ Despite this, there have been multiple cases of healthy births and multiple cases of congenital abnormalities in fetal exposures to low-dose weekly methotrexate.⁷⁵⁻⁸⁴ If a woman exposed to methotrexate inadvertently becomes pregnant, consultation with a genetic specialist is recommended. If exposure is stopped before the critical 6- to 8-week gestation period, it may be possible to continue the pregnancy with close medical follow-up.

METHOTREXATE USE IN CHILDREN

Methotrexate is FDA approved for the treatment of psoriasis in adults and for juvenile rheumatoid arthritis. The use of methotrexate in children for both dermatologic and rheumatologic indications was recently reviewed.⁸⁵ In general, low-dose weekly methotrexate is well tolerated in this age group. The primary side effects were increased liver function tests, stomatitis, nausea, and vomiting, which usually reversed with temporary discontinuation of methotrexate. When interpreting this report, the authors cautioned that the published studies in rheumatology usually included concomitant oral corticosteroid therapy. Additionally, the authors suggested monitoring for hepatotoxicity according to the above rheumatologic guidelines recommended for adults without risk factors. The addition of etanercept may allow for decreased methotrexate dosages in children.⁸⁶

DRUG INTERACTIONS

Many treatments interact with methotrexate by a variety of mechanisms that can result in elevated drug levels, thus creating the potential for methotrexate toxicity, including pancytopenia and death. There are numerous reports of fatal interactions with methotrexate. In one report, 70 cases of

pancytopenia were reported, including 12 deaths, and drug interactions were a common underlying cause.²⁷

Perhaps the most common offending drug is trimethoprim-sulfamethoxazole. The mechanism by which trimethoprim-sulfamethoxazole interferes with methotrexate is related to both components of this combination drug. Trimethoprim is a folic acid antagonist, while sulfamethoxazole competitively inhibits renal secretion of methotrexate. Interestingly, the combination of methotrexate and sulfasalazine, a drug which has occasionally been used for psoriasis, has been administered to patients with rheumatoid arthritis with limited benefit, but very little toxicity.⁸⁷ In a cellular assay, sulfasalazine reduced the efficacy of methotrexate, an observation that led one group of authors to suggest that the administration of two drugs be spaced.⁸⁸

Considering the hepatotoxicity of methotrexate, caution should be used when prescribing this drug to patients receiving other potentially hepatotoxic treatments, which would include commonly prescribed drugs such as statins. Additive hepatotoxicity, however, is not commonly reported. When methotrexate and retinoids are used together, concerns about additive hepatotoxicity have led to the inclusion of retinoids on lists of drugs that interact with methotrexate. These lists are not evidence based, and in clinical practice, this combination is often used safely in the appropriate patient.⁶¹ The combination of acitretin and methotrexate is often necessary for severe psoriasis and for conditions like pityriasis rubra pilaris.

Other therapies commonly prescribed with methotrexate for patients with psoriatic arthritis include non-steroidal anti-inflammatory drugs (NSAIDs). Many traditional NSAIDs result in elevation of methotrexate levels, including ibuprofen, salicylates, and naproxen.⁸⁹ Of interest, when naproxen 500 mg twice daily is administered to patients taking low-dose methotrexate along with lansoprazole, there does not appear to be an impact on methotrexate level.⁹⁰ Reduced uptake of methotrexate by human kidney has been demonstrated in the presence of salicylates, indomethacin, phenylbutazone, and probenacid.⁹¹ Ketoprofen, flurbiprofen, piroxicam, and meloxicam have all been studied with methotrexate and do not elevate serum levels.^{92,93} Many cyclooxygenase-2 selective inhibitors such as lumiracoxib, rofecoxib, and celecoxib do not impact methotrexate pharmacokinetics.⁹⁴⁻⁹⁶ Two additional drugs used for rheumatoid arthritis—leflunomide, a pyrimidine synthesis inhibitor, and anakinra, an interleukin 1 receptor antagonist—have been administered safely to patients taking methotrexate.^{97,98}

Table VI. An abbreviated list of medications that may increase methotrexate toxicity

Nonsteroidal anti-inflammatory drugs	Antibiotics	Other drugs
Salicylates	Trimethoprim-sulfamethoxazole	Barbiturates
Naproxen		Colchicine
Ibuprofen	Sulfonamides	Dipyridole
Indomethacin	Penicillins	Ethanol
Phenylbutazone	Tetracyclines	Phenytoin
	Ciprofloxacin	Probenecid
		Sulfonylurea
		Thiazide diuretics
		Furosemide

Other commonly prescribed drugs that have been given with methotrexate include a number of antibiotics. Reduced renal clearance of methotrexate has been demonstrated in an animal model with infusion of penicillin.⁹⁹ Similarly, piperacillin has been associated with reduced clearance of methotrexate in an animal model.¹⁰⁰ In clinical practice, methotrexate toxicity has been demonstrated in a patient treated with penicillin and furosemide.¹⁰¹ In contrast, cephalosporins increase renal clearance of methotrexate.¹⁰² Among other classes of antibiotics, ciprofloxacin has resulted in delayed elimination of methotrexate in patients, resulting in severe toxicity.¹⁰³ Because isoniazid can be hepatotoxic, concerns might be raised about its concomitant use with methotrexate. However, in a series of 44 patients treated with both drugs, only transient elevations of liver function tests were noted.¹⁰⁴

Numerous additional drug interactions can occur with methotrexate. Some of the clinically relevant interactions are summarized in Table VI.

CONCLUSION

Decades after its introduction, methotrexate remains an effective treatment in the therapeutic armamentarium of dermatologists. Despite the introduction of biologics, methotrexate is regularly used alone or in combination with biologics for the treatment of psoriasis, and it remains a valuable treatment option in many other dermatologic diseases.

Safe and effective use of methotrexate requires rational patient selection and, subsequently, fastidious and appropriate monitoring. Importantly, the clinician must recognize that patients differ in their inherent risks while taking methotrexate, with issues such as comorbidities and concomitant drug use always in need of consideration. Awareness of the risk factors for hematologic toxicity, primarily decreased renal function, will significantly reduce this

side effect. Awareness of the risks for hepatic toxicity is also crucial. Patients without hepatic risk factors may not require routine liver biopsies. Folic acid supplementation is recommended to increase the safety and decrease the potential side effects.

This consensus statement generated by members of the Medical Advisory Board of the National Psoriasis Foundation cannot address the nuances required in the care of every patient, but rather is intended to serve as a rough guide to the management of patients with psoriasis treated with methotrexate. As time goes on, further refinements in our management of these patients will undoubtedly occur and additional modifications in our approach will evolve.

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Appendix. Members of the Medical Advisory Board of the National Psoriasis

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