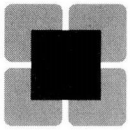
CME CREDIT



DONALD G. VIDT, MD, EDITOR

Methotrexate in rheumatoid arthritis: when NSAIDs fail

JOHN A. FLYNN, MD, AND DAVID B. HELLMANN, MD

SUMMARY Methotrexate has become the agent of choice for rheumatoid arthritis that does not respond to nonsteroidal anti-inflammatory drugs. In appropriately selected patients and with diligent monitoring, methotrexate in low weekly doses is effective and has a much better safety profile than was originally perceived.

KEY POINTS In theory, methotrexate can interact with many other medications, but with low, weekly doses (7.5 to 15 mg), very few of these interactions are of clinical importance. More than half of patients experience side effects, but only about 15% need to stop taking methotrexate within 5 years because of severe toxicity. Many side effects are manageable with dosage adjustment and exclusion of factors that may increase toxicity. The most common side effects are gastrointestinal (nausea, dyspepsia, diarrhea, anorexia, and oral ulcers). About one in five patients who take a cumulative dose of 3 grams of methotrexate progress at least one grade on liver biopsy, and about one in 35 develop advanced pathologic changes. The risk of advanced fibrosis is 2.5 to 5 times higher in patients who use alcohol heavily. Methotrexate is teratogenic and must be avoided by women unwilling to use effective birth control. Fewer than 5% of patients taking methotrexate develop bone marrow suppression. We advise our patients to take folic acid supplements (1 mg daily), to reduce methotrexate-related side effects.

INDEX TERMS: ARTHRITIS, RHEUMATOID; METHOTREXATE
CLEVE CLIN J MED 1995; 62:351–359

From the Department of Medicine, the Division of Molecular and Clinical Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address reprint requests to J.A.F., Suite 7150, 600 North Caroline Street, Baltimore, MD 21205.

IT IS UNUSUAL for the treatment of a chronic disease to change greatly over 10 years. Yet that is exactly what has happened in the management of rheumatoid arthritis, as methotrexate has supplanted gold salts as the most common treatment for cases that do not respond satisfactorily to nonsteroidal anti-inflammatory drugs (NSAIDs).[1] Three factors have brought about this change: methotrexate has been shown effective, its relative safety in long-term use (with proper monitoring) has been documented, and rheumatologists are tending to initiate aggressive therapy earlier.[2,3]

Because rheumatoid arthritis is so prevalent, affecting 1 in 100 adults, the expanded use of methotrexate means that family practitioners, general internists, orthopedists, and rheumatologists will see more patients who take it. This clinical review of methotrexate's pharmacology, efficacy, toxicity, indications, and monitoring guidelines is based on some of the many excellent studies reported.

TABLE 1
IMPORTANT METHOTREXATE DRUG INTERACTIONS

Medication	Potential effect	Mechanism
Trimethoprim-sulfamethoxazole Pyrimethamine	Pancytopenia	Synergistic interference with folic acid synthesis
Phenytoin Tetracycline Sulfonamides Sulfonylureas	Increased methotrexate toxicity	Displacement of protein-bound methotrexate
Probenecid	Increased methotrexate toxicity	Decreased renal elimination of methotrexate

HISTORY

Since first used for childhood leukemia in the 1940s, methotrexate has become the most widely used antimetabolite for cancer chemotherapy.[4] Its use in rheumatic diseases has developed more slowly. Aminopterin, an analog of methotrexate, was used in 1951 to treat a few patients with rheumatoid arthritis and psoriasis.[5] By the early 1970s, several reports had suggested that methotrexate was effective in refractory rheumatoid arthritis.[5] However, few patients with rheumatoid arthritis received methotrexate until the 1980s, when many reports convincingly established its efficacy in low oral doses given once weekly.[6–16]

PHARMACOLOGY

Methotrexate, a folic acid analog, is well absorbed from the gastrointestinal tract in doses of up to 20 mg.[17] Food does not affect the bioavailability of low oral doses.[18] The peak serum concentration is achieved in 1 to 2 hours,[17] and approximately half of a dose is bound to plasma albumin. Methotrexate's half-life in the circulation is 8 hours, and 80% to 90% is excreted unchanged in the urine within 24 hours.[17]

Mechanisms of action

Methotrexate has many effects on inflammatory cells and mediators, but its exact mechanism of action in rheumatoid arthritis is not yet fully known.[4,19,20] As a folate antagonist, it can competitively inhibit cellular dihydrofolate reductase, an enzyme that helps synthesize purines and thymidylic acid, the building blocks of DNA synthesis and cell division.[4] This ability of high-dose methotrexate to inhibit cell division explains its efficacy in cancer chemotherapy.[4] At low doses, methotrexate has been shown to reduce mononuclear cell proliferation in vitro.[21] Other studies have shown that low doses also inhibit the release or synthesis of inflammatory cytokines such as interleukin 1[22] and leukotrienes[23] and can induce endothelial cells and fibroblasts to release adenosine, which in turn has powerful anti-inflammatory effects.[24]

Drug interactions

In theory, methotrexate can interact with many other medications, but with low, weekly doses, very few of these interactions are of clinical importance (*Table 1*).[4] Patients taking methotrexate should avoid antifolate antibiotics such as trimethoprim-sulfamethoxazole, as the combination has been associated with rare incidents of pancytopenia.[25,26] Because methotrexate is partly bound to serum proteins, it can potentially displace (or be displaced by) other drugs that bind to these proteins, such as phenytoin, tetracycline, sulfonamides, and sulfonylureas.[27] Since renal clearance of methotrexate involves renal tubular secretion,[27,28] concomitant use of probenecid should be avoided. Aspirin decreases methotrexate's renal excretion, but to a small and clinically unimportant degree in patients taking methotrexate in low doses.[29] The impact of other NSAIDs on methotrexate's toxicity also appears negligible in patients with rheumatoid arthritis.[29]

EFFICACY

Multiple studies have found methotrexate more effective than placebo in treating rheumatoid arthritis.[7,13–15,30,31] Its beneficial effect varies from modest to substantial[7,15]; it rarely produces remissions, but 50% to 75% of patients taking it experience clinically important improvement,[7,32,33] as reflected by patient and physician assessment, decreased joint swelling and pain, and decreased 50-foot walking time.[7] Approximately half of patients who

TABLE 2
TOXICITIES OF LOW, WEEKLY DOSAGE OF METHOTREXATE

Toxicities	Frequency	Response
Gastrointestinal (nausea, diarrhea, anorexia, stomatitis)	10%	Spread dose out over 24 hours Assure compliance with folic acid supplementation Give methotrexate intramuscularly
Hematologic		Decrease dose or discontinue treatment
Thrombocytopenia	4%	Search for causes of bone marrow suppression (drugs, infection)
Anemia	1%	Assure compliance with folic acid supplementation
Pulmonary (pneumonitis)	< 2%	Stop methotrexate Evaluate for infectious cause Give steroids in high doses
Hepatic		
Liver function test values > 3 times normal	5%	Discontinue methotrexate Evaluate for other hepatotoxins
Liver function test values 2 to 3 times normal	10%	Decrease methotrexate dose by half Evaluate for other hepatotoxins
Persistently elevated aspartate aminotransferase (AST) concentration, depressed serum albumin concentration	1%	Perform liver biopsy (see *Figure*)

take methotrexate experience at least a 50% reduction in joint pain and swelling.[4] Rheumatoid nodules tend to shrink with methotrexate use,[14] but in some cases the nodules may become more prominent or extensive.[34]

The clinical response to methotrexate has been compared favorably with that induced by other second-line agents. Methotrexate is more effective than oral gold,[30,32,33] azathioprine,[33,35] or hydroxychloroquine.[30] It is at least as effective as parenteral gold and is less toxic.[30,36] Pooled data suggest that methotrexate, penicillamine, and sulfasalazine have similar effectiveness.[30] This type of analysis likely underestimates the efficacy of methotrexate, which, more often than the other drugs, has been tested in patients with severe and long-standing disease.[30]

One advantage of methotrexate over other second-line agents is its relatively rapid onset of action.[21] In contrast to parenteral gold or hydroxychloroquine, which can take up to 6 months to produce improvement, methotrexate usually begins to work within 3 to 6 weeks.[15,34] The maximal effect at a given dosage is usually evident by 8 weeks.

It is not certain whether methotrexate, or any agent for that matter, alters the long-term course of rheumatoid arthritis. Most studies suggest that erosions continue to develop during methotrexate use.[7,15,31,37–39] However, long-term methotrexate use does maintain symptomatic improvement and allows important reductions in prednisone dosage.[40–42] In one study, more than 80% of patients who had an initial response continued to enjoy symptomatic improvement 7 years later, and half of them were able to discontinue taking prednisone.[42] The efficacy of methotrexate in rheumatoid arthritis extends to the elderly population: Wolfe and Cathey[43] showed that patients older than 65 years had at least as much improvement with methotrexate as did younger patients.

TOXICITY

More than half of patients who take methotrexate in low doses for rheumatoid arthritis experience side effects[31,40–42,44]; however, clinical studies show that only about 15% of patients need to stop taking it within 5 years because of severe toxicity.[32,42,44] Many of the side effects described below can be managed by adjusting the dosage and by excluding factors that may increase toxicity (*Table 2*).

Gastrointestinal toxicity

The most common side effects are related to the gastrointestinal tract and include nausea, dyspepsia,

TABLE 3
HISTOPATHOLOGIC CLASSIFICATION OF METHOTREXATE-INDUCED LIVER TOXICITY*

Grade	Findings
I	Normal; mild fatty infiltration, mild nuclear variability, mild portal inflammation
II	Moderate to severe fatty infiltration, moderate to severe nuclear variability, portal tract expansion, moderate to severe portal tract inflammation and necrosis
IIIA	Mild fibrosis
IIIB	Moderate to severe fibrosis
IV	Cirrhosis

*Based on Roenigk et al, reference 49

diarrhea, anorexia, and oral ulcers.[41] These problems typically occur early in therapy and can be reduced either by dividing the dose into three equal doses taken 12 hours apart or by decreasing the dose for several weeks. If severe gastrointestinal symptoms persist, equal doses can be given by subcutaneous or intramuscular injection.

Hepatotoxicity

When methotrexate's efficacy was "rediscovered" in the early 1980s, fear of hepatotoxicity constrained its widespread use. Early worries were fueled by reports in which more than 20% of psoriasis patients who took methotrexate for 5 years developed significant hepatic disease, as determined by liver biopsy.[45–47] Fortunately, these rates have not been seen in patients with rheumatoid arthritis.[44,48] The most widely used classification system for histologic changes on liver biopsy was developed by Roenigk and colleagues[49] for psoriasis patients treated with methotrexate (*Table 3*). There appear to be no clinical adverse effects at grade I, II, or IIIA. Grades IIIB and IV (moderate to severe fibrosis and cirrhosis, respectively) are much more strongly associated with clinical hepatic dysfunction.[49]

Longitudinal studies of rheumatoid arthritis patients in the United States report a consistently low rate of fibrosis. In one review, more than 700 patients underwent surveillance biopsies, and 8% had evidence of mild fibrosis (grade IIIA) after receiving a median cumulative dose of methotrexate of 1.5 grams (roughly 3 years of therapy).[50] A meta-analysis of 636 patients from 15 studies showed that about one in five patients who received 3 grams (a dose achieved after about 4 years at 15 mg/week or 8 years at 7.5 mg/week) progressed at least one grade on liver biopsy, and about one in 35 (2.7%) developed advanced pathologic changes (grade IIIB or IV).[51] The risk of advanced fibrosis was 2.5 to 5 times higher in patients who used alcohol heavily (more than 100 grams per week).[51] This underscores the importance of restricting alcohol use in patients taking methotrexate.

It should be emphasized that most patients who develop hepatic damage have mild changes, chiefly grade II or IIIA. Indeed, clinical liver failure has been so rare that it has been almost exclusively confined to case reports.[52,53] A recent survey of American rheumatologists placed the risk of clinically serious liver disease at one case per 1000 patients per 5 years of methotrexate therapy.[54]

Hematologic toxicity

Bone marrow depression develops in fewer than 5% of patients who take methotrexate.[55] This can occur in the form of megaloblastic anemia, leukopenia, thrombocytopenia, or pancytopenia.[56–59] The most common of these is leukopenia, which typically occurs in conjunction with other events that may suppress the bone marrow (ie, infection, folate deficiency, or concomitant use of other folate antagonists such as trimethoprim-sulfamethoxazole).[25] Mild cytopenia usually reverses rapidly after methotrexate is stopped. In the case of overdosage or severe cytopenia, high doses of folinic acid may accelerate recovery.[60]

Pulmonary toxicity

Acute pulmonary inflammation is an important but rare and poorly understood manifestation of methotrexate toxicity, occurring in fewer than 2% of patients.[61] This appears to be an idiosyncratic reaction that can occur at any cumulative dose. Pre-existing pulmonary disease and concurrent tobacco use may be risk factors.[62] Tests that monitor pulmonary function do not predict the development of this complication.

Patients with methotrexate-induced pulmonary toxicity present with flu-like symptoms, fever, non-

productive cough, and hypoxemia.[63] Although the chest radiograph may be normal initially, most patients soon develop diffuse bilateral interstitial infiltrates.[64] The pathologic findings are nonspecific, frequently demonstrating a hypersensitivity pneumonitis with lymphocytic infiltrates with or without an admixture of eosinophils.[63] Treatment requires prompt recognition, evaluation for possible infection, discontinuation of methotrexate, and administration of corticosteroids in high parenteral doses.[63–65] Most patients rapidly improve; however, fatal respiratory failure may occur

Secondary malignancies

There have been recent, isolated reports of lymphoproliferative malignancies in patients with rheumatoid arthritis who were taking methotrexate.[66] In two reported cases, lymphomas were associated with Epstein-Barr virus infection in patients taking methotrexate for rheumatoid arthritis and dermatomyositis.[67] These lymphomas resolved with discontinuation of methotrexate. A recent retrospective study showed that, although hematologic malignancies (lymphoma, leukemia, and myelodysplastic syndromes) do occur in rheumatoid arthritis patients taking methotrexate, they are rare and the risk is no higher than that in rheumatoid arthritis patients taking other disease-modifying drugs.[68] Although the risk of secondary malignancy with methotrexate appears very low, the oncogenic consequences of long-term methotrexate use have not yet been well studied.

Central nervous system toxicity

Various central nervous system side effects have been reported on rare occasions. These consist primarily of headache and dizziness, and less often, transient mood alterations and memory impairment.[69] These effects reverse when the drug is reduced in dosage or discontinued.

Immunosuppression

Various infections have been reported, typically in immunosuppressed patients receiving low doses of methotrexate.[66] Many of these patients were also taking corticosteroids. The most common infection appears to be herpes zoster[66]; there have also been cases of *Pneumocystis carinii* pneumonia, cryptococcosis, and nocardiosis.[70–73] These infections, though rare, underscore the importance of diligently seeking an infectious source in patients who present with acute pulmonary compromise.

TABLE 4
CONTRAINDICATIONS TO METHOTREXATE IN LOW DOSES

Absolute contraindications
Alcoholism
Cirrhosis
Active hepatitis
Renal failure
Leukopenia
Severe thrombocytopenia
Severe anemia
Pregnancy
Noncompliance
Relative contraindications
Renal insufficiency
Pulmonary disease
Depressed serum albumin

Reducing toxicity with folate supplementation

Several studies have suggested that folate (1 mg daily) or folinic acid (2.5 to 5 mg once per week, 24 hours after the methotrexate dose) both reduce methotrexate-related side effects without affecting efficacy.[74–76] This was confirmed in a recent trial comparing folic acid supplementation (5 or 27.5 mg/week) with placebo during methotrexate therapy for rheumatoid arthritis. Both dosages of folic acid equally prevented toxicity.[77] To date, no controlled trial comparing folic acid and folinic acid has been published. We currently advise our patients to take folic acid supplements (1 mg daily), which are cheaper than weekly doses of folinic acid.

USING METHOTREXATE

Indications

Methotrexate is indicated for rheumatoid arthritis that does not respond well to NSAIDs. Many rheumatologists have concluded that methotrexate's favorable balance of efficacy over toxicity makes it the most attractive second-line agent for most patients with rheumatoid arthritis.[1] Although this review is confined to its role in rheumatoid arthritis, methotrexate has also been increasingly used in treating vasculitis (especially Wegener's granulomatosis[78] and Takayasu's arteritis[79]) systemic lupus erythematosus,[80] psoriatic arthritis,[81] Reiter's syndrome,[82] and other conditions.[17]

Contraindications and patient education

The baseline evaluation should include the history, a physical examination, a complete blood

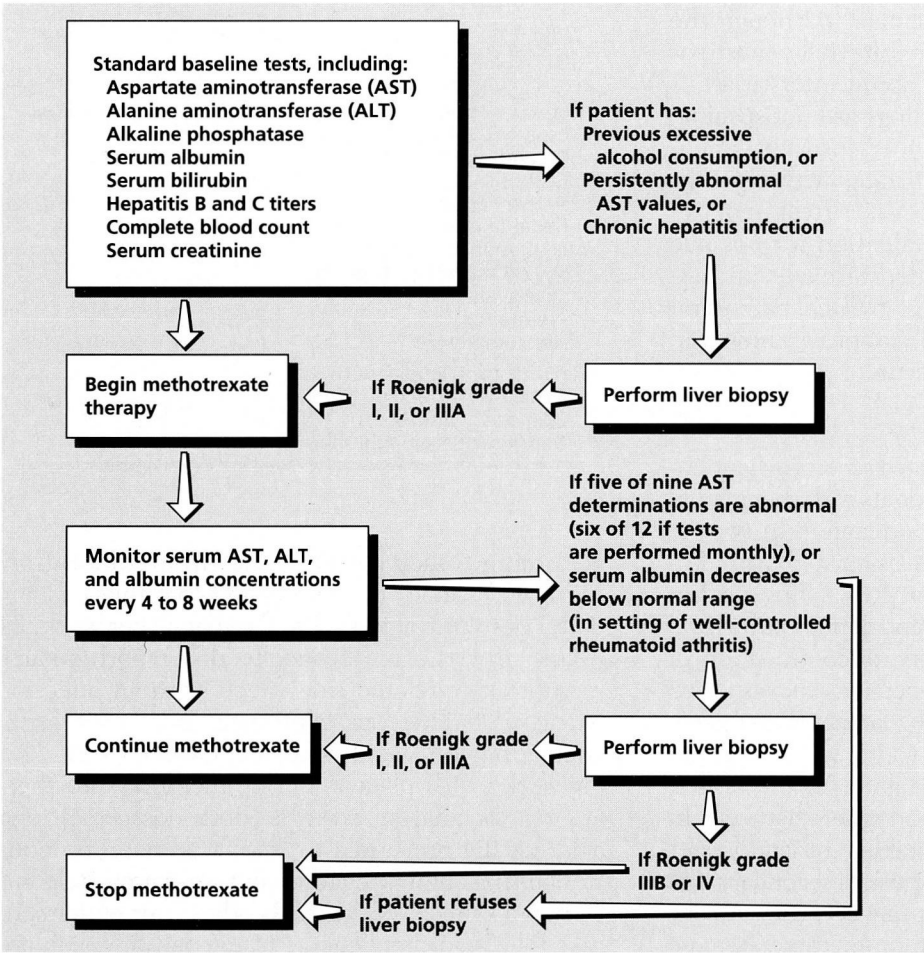


FIGURE. American College of Rheumatology recommendations for monitoring for hepatic safety in rheumatoid arthritis patients receiving methotrexate. Adapted from Kremer et al, reference 83.

count, renal and liver function studies, and serologic studies for active hepatitis B and C infection. Routine chest radiography and pulmonary function studies are not of proven value in predicting pulmonary toxicity. Absolute contraindications include pregnancy or the chance of pregnancy, active hepatitis or cirrhosis, renal failure, leukopenia (fewer than 2000 white blood cells per mm^3), severe anemia, thrombocytopenia, excessive alcohol consumption, and patient noncompliance.[15] Relative contraindications are renal insufficiency, a low serum albumin level, and significant pulmonary disease (*Table 4*). Renal insufficiency, as manifested by a serum creatinine concentration greater than 1.5 mg/dL, increases the risk of toxicity.[15] The safety of methotrexate in patients with serum creatinine concentrations greater than 2.0 mg/dL is not established. Although obesity and diabetes have been suggested as risk factors for methotrexate toxicity, this has not been a consistent finding in many studies. A pretreatment liver biopsy, once routine, is now considered reasonable only if there is a history of persistently elevated liver function test results, chronic hepatitis B or C infection, or heavy alcohol consumption.[83]

All patients should understand fully the potential adverse reactions. Because heavy alcohol use increases the risk of methotrexate-induced hepatotoxicity, patients should be counseled not to drink more than one alcoholic beverage per week.[51] Since trimethoprim-sulfamethoxazole is widely used, patients should be warned about receiving it from physicians who are unaware of this interaction. Because methotrexate is teratogenic, it must be avoided by women unwilling to use effective birth control.[84] Women who wish to become pregnant should discontinue this medication at least 1 month and one menstrual cycle before attempting to conceive.[85] Because methotrexate can cause reversible oligospermia, men should stop taking it several months before attempting conception.[86]

Dosage and monitoring

Starting treatment. Most patients start with 7.5 mg (three 2.5-mg tablets) once per week. Smaller initial doses may be appropriate for patients over age 65.[41] Folic acid supplements (1 mg/day) are also started, as discussed above. After starting therapy, the patient should be monitored clinically for symptoms of gastrointestinal intolerance and pulmonary toxicity. Gastrointestinal upset may improve if the pills are taken with food or if the dose is divided to provide 2.5 mg every 12 hours. For the

few patients with intolerable gastrointestinal effects, giving the same dose by subcutaneous or intramuscular injection is usually well tolerated and effective.[87] Any pulmonary symptoms should be evaluated quickly and thoroughly. The complete blood count, serum creatinine concentration, and liver function tests (including aspartate aminotransferase, alanine aminotransferase, and serum albumin concentrations) should be monitored every 4 to 8 weeks. If neutropenia or thrombocytopenia develop, therapy should be discontinued until they resolve.

Monitoring liver function. If the results of liver function tests increase to more than three times the upper limit of normal, methotrexate should be stopped and not restarted until the abnormalities resolve.[15] Other possible reasons for the liver function abnormalities, such as alcohol use or other hepatotoxic drugs, should be considered and eliminated. The physician should verify that the patient is taking folate supplements. If liver function test results are two to three times the upper limit of normal, the methotrexate dose should be halved every monitoring period until the abnormalities remit. For lesser elevations, dose reductions should be considered if the abnormalities persist.

When to perform a biopsy. The most recent guidelines from the American College of Rheumatology (*Figure*) suggest that a liver biopsy be obtained if continued treatment is planned and if aspartate aminotransferase levels are abnormal in six of 12 (or five of nine) blood determinations in a year or if the serum albumin concentration decreases below the normal range without a known cause. If the liver biopsy shows Roenigk grade I, II or IIIA, then methotrexate may be continued with cautious monitoring. If the biopsy shows grade IIIB or IV changes, methotrexate should be stopped.[83] In the absence of any liver function test abnormalities, the risks of liver biopsy probably exceed the benefit of detecting the rare case of significant liver fibrosis.[83]

Adjusting for nonresponse. If tolerated, the initial dosage should be continued for 4 to 6 weeks. If the patient does not show any response by then, the dose can be increased.[88] Most patients will tolerate an immediate doubling of the dose to 15 mg taken once per week. Elderly or frail patients may require a more gradual dose escalation. Oral doses of more than 20 mg per week are poorly absorbed.[17] Methotrexate may be given parenterally in cases in which higher dosages are deemed necessary to assure adequate bioavailability.[89–91] However, only physicians familiar with parenteral methotrexate administration should attempt it.

Managing favorable responses. If the disease responds favorably, the methotrexate dosage is kept constant for at least 6 months. Although most patients treated with methotrexate experience improvement, few have complete remission. The observation that most patients experience a "flare" when methotrexate is stopped provides further testimony to methotrexate's efficacy.[92] Some patients whose symptoms have been stable for 6 months, will, however, tolerate a slow and modest reduction in dosage.

SUMMARY

Although methotrexate has been available for nearly 50 years, its use in rheumatoid arthritis has become common only in the last decade. It is now the treatment of choice for most patients with rheumatoid arthritis that fails to respond to NSAIDs. Many careful studies and analyses conducted over the last 20 years have heightened enthusiasm for methotrexate. These have shown that, in appropriately selected patients and with diligent monitoring, methotrexate in low doses is effective and has a much better safety profile than was originally perceived.

REFERENCES

1. **Weinblatt ME.** Methotrexate in rheumatoid arthritis. Bull Rheum Dis 1993; **42:**4–7.
2. **Wilske KR, Healy LA.** Remodeling the pyramid—a concept whose time has come. J Rheumatol 1989; **16:**565–567.
3. **McCarty DJ.** Suppress rheumatoid arthritis and leave the pyramid to the Egyptians. J Rheumatol 1990; **17:**1115–1118.
4. **Jolivet J, Cowan KH, Curt GA, et al.** The pharmacology and clinical use of methotrexate. N Engl J Med 1983; **309:**1094–1102.
5. **Ward JR.** Historical perspective on the use of methotrexate for the treatment of rheumatoid arthritis. J Rheumatol 1985; **12:**3–6.
6. **Willkens RF.** Reappraisal of the use of methotrexate in rheumatic disease. Am J Med 1983; **75:**19–25.
7. **Weinblatt ME, Coblyn JS, Fox DA, et al.** Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985; **312:**818–822.
8. **Weinstein A, Marlowe S, Korn J, et al.** Low-dose methotrexate treatment of rheumatoid arthritis. Long-term observations. Am J Med 1985; **79:**331–337.
9. **Willkens RF, Watson MA, Paxson CS.** Low dose pulse methotrexate therapy in rheumatoid arthritis. J Rheumatol 1980; **7:**501–505.
10. **Steinsson K, Weinstein A, Korn J, et al.** Low dose methotrexate in rheumatoid arthritis. J Rheumatol 1982; **9:**860–866.
11. **Nordstrom DM, West SG, Andersen PA, et al.** Pulse methotrexate therapy in rheumatoid arthritis. A controlled prospective roentgenographic study. Ann Intern Med 1987; **107:**797–801.

12. **Fehlauer CS, Carson CW, Cannon GW, et al.** Methotrexate therapy in rheumatoid arthritis: 2-year retrospective follow-up study. J Rheumatol 1989; **16:**307–312.
13. **Andersen PA, West SG, O'Dell JR, et al.** Weekly pulse methotrexate in rheumatoid arthritis. Ann Intern Med 1985; **103:**489–496.
14. **Williams HJ, Willkens RF, Samuelson CO Jr, et al.** Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. Arthritis Rheum 1985; **28:**721–730.
15. **Tugwell P, Bennett K, Gent M.** Methotrexate in rheumatoid arthritis. Indications, contraindications, efficacy, and safety. Ann Intern Med 1987; **107:**358–366.
16. **Health and Public Policy Committee, American College of Physicians.** Methotrexate in rheumatoid arthritis. Ann Intern Med 1987; **107:**418–419.
17. **Wilke WS, Biro JA, Segal AM.** Methotrexate in the treatment of arthritis and connective tissue disease. Cleve Clin J Med 1987; **54:**327–338.
18. **Kozloski GD, De Vito JM, Kisicki JC, et al.** The effect of food on the absorption of methotrexate sodium tablets in healthy volunteers. Arthritis Rheum 1992; **35:**761–764.
19. **Kremer JM.** The mechanism of action of methotrexate in rheumatoid arthritis: the search continues. J Rheumatol 1994; **21:**1–5.
20. **Hawkes JS, Cleland LG, Proudman SM, et al.** The effect of methotrexate on ex vivo lipoxygenase metabolism in neutrophils from patients with rheumatoid arthritis. J Rheumatol 1994; **21:**55–58.
21. **Olsen NJ, Murray LM.** Antiproliferative effects of methotrexate on peripheral blood mononuclear cells. Arthritis Rheum 1994; **32:**378–385.
22. **Chang D, Weinblatt ME, Shur PH.** The effects of methotrexate on interleukin 1 in patients with rheumatoid arthritis. J Rheumatol 1992; **19:**1678–1682.
23. **Sperling RI, Coblyn JS, Larkin JK, et al.** Inhibition of leukotriene B4 synthesis in neutrophils from patients with rheumatoid arthritis by a single oral dose of methotrexate. Arthritis Rheum 1990; **33:**1149–1155.
24. **Cronstein BN, Naime D, Ostad E.** The antiinflammatory mechanism of low-dose methotrexate (MTX): Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. J Clin Invest 1993; **92:**2675–2682.
25. **Maricic M, Davis M, Gall EP.** Megaloblastic pancytopenia in a patient receiving concurrent methotrexate and trimethoprim-sulfamethoxazole treatment. Arthritis Rheum 1986; **29:**133–135.
26. **Thomas MH, Gutterman LA.** Methotrexate toxicity in a patient receiving trimethoprim-sulfamethoxazole. J Rheumatol 1986; **13:**440–441.
27. **Furst DE.** Clinical pharmacology of very low dose methotrexate for use in rheumatoid arthritis. J Rheumatol 1985; **12:**11–14.
28. **Evans WE, Christensen ML.** Drug interactions with methotrexate. J Rheumatol 1985; **12:**15–20.
29. **Stewart CF, Fleming RA, Germain BF, et al.** Aspirin alters methotrexate disposition in rheumatoid arthritis. Arthritis Rheum 1991; **34:**1514–1520.
30. **Felson DT, Anderson JJ, Meenan RF.** Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A meta-analysis of published clinical trials. Arthritis Rheum 1992; **35:**1117–1125.
31. **Kremer JM, Lee JK.** The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum 1986; **29:**822–831.
32. **Felson DT, Anderson JJ, Meenan RF.** The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two meta-analyses. Arthritis Rheum 1990; **33:**1449–1461.
33. **Willkens RF, Urowitz MB, Stablein DM, et al.** Comparison of azathioprine, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. Arthritis Rheum 1992; **35:**849–856.
34. **Williams HJ, Ward JR, Reading JC, et al.** Comparison of auranofin, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. Arthritis Rheum 1992; **35:**259–269.
35. **Jeurissen MEC, Boerbooms AM Th, Van de Putte LBA, et al.** Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial. Arthritis Rheum 1991; **34:**961–972.
36. **Suarez-Almazor ME, Fitzgerald A, Grace M, et al.** A randomized controlled trial of parenteral methotrexate compared with sodium aurothiomalate (Myochrysine) in the treatment of rheumatoid arthritis. J Rheumatol 1988; **15:**753–756.
37. **Rau R, Herborn G, Karger T, et al.** Retardation of radiologic progression in rheumatoid arthritis with methotrexate therapy. Arthritis Rheum 1991; **34:**1236–1244.
38. **Alarcon GS, Lopez-Mendez A, Walter J, et al.** Radiographic evidence of disease progression in methotrexate treated and non-methotrexate disease modifying antirheumatic drug treated rheumatoid arthritis patients: a meta-analysis. J Rheumatol 1992; **19:**1868–1873.
39. **Hamdy H, McKendry RJR, Mierins E, et al.** Low-dose methotrexate compared with azathioprine in the treatment of rheumatoid arthritis. A twenty-four-week controlled clinical trial. Arthritis Rheum 1987; **30:**361–368.
40. **Weinblatt ME, Trentham DE, Fraser PA, et al.** Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. Arthritis Rheum 1988; **31:**167–175.
41. **Kremer JM, Lee JK.** A long-term prospective study of the use of methotrexate in rheumatoid arthritis. Update after a mean of fifty-three months. Arthritis Rheum 1988; **31:**577–584.
42. **Weinblatt ME, Weissman BN, Holdsworth DE, et al.** Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. Arthritis Rheum 1992; **35:**129–145.
43. **Wolfe F, Cathey MA.** The effect of age on methotrexate efficacy and toxicity. J Rheumatol 1991; **18:**973–977.
44. **Shergy WJ, Polisson RP, Caldwell DS, et al.** Methotrexate-associated hepatoxicity: retrospective analysis of 210 patients with rheumatoid arthritis. Am J Med 1988; **85:**771–74.
45. **Dahl MG, Gregory MM, Scheuer PJ.** Methotrexate hepatotoxicity in psoriasis—comparison of different dose regimens. Br Med J 1972; **1:**654–656.
46. **Weinstein G, Roenigk H, Mailback, et al.** Psoriasis-liver-methotrexate interactions. Arch Dermatol 1973; **108:**36–42.
47. **Podurgiel B, McGill D, Ludwig J, et al.** Liver injury associated with methotrexate therapy for psoriasis. Mayo Clin Proc 1973; **48:**787–792.
48. **Kremer JM, Lee RG, Tolman KG.** Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy. A prospective study with baseline and sequential biopsy samples. Arthritis Rheum 1989; **32:**121–127.
49. **Roenigk HH, Auerbach R, Mailbach H, et al.** Methotrexate in psoriasis: revised guidelines. J Am Acad Derm 1988; **19:**145–156.
50. **Weinblatt ME, Kremer JM.** Methotrexate in rheumatoid arthritis. J Am Acad Dermatol 1988; **19:**126–135.
51. **Whiting-O'Keefe QE, Fye KH, Sack KD.** Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med 1991; **90:**711–716.
52. **Clegg DO, Furst DE, Tolman KG, et al.** Acute, reversible hepatic failure associated with methotrexate treatment of rheumatoid arthritis. J Rheumatol 1989; **16:**1123–1126.
53. **Gilbert SC, Klintmalm G, Menter A, et al.** Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis. A word of caution in light of the expanding use of this 'steroid-sparing' agent. Arch Intern Med 1990; **150:**889–891.
54. **Walker AM, Funch D, Dreyer NA, et al.** Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rheum 1993; **36:**329–335.
55. **Weinblatt ME.** Toxicity of low dose methotrexate in rheumatoid arthritis. J Rheumatol 1985; **12 (Suppl 12):**35–39.
56. **Weinblatt ME, Fraiser P.** Elevated mean corpuscular volume as a predictor of hematological toxicity due to methotrexate therapy. Arthritis Rheum 1989; **32:**1592–1596.

57. **Hoffmeister RT.** Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med 1983; **75:**69–73.
58. **Steinsson K, Weinstein A.** Low dose methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1981; **24:**S71. Abstract.
59. **MacKinnon SK, Starkebaum G, Willkens RF.** Pancytopenia associated with low dose pulse methotrexate in the treatment of rheumatoid arthritis. Semin Arthritis Rheum 1985; **15:**119–126.
60. **Kremer JM, Galivan J, Streckfus A, et al.** Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum 1986; **29:**832–838.
61. **Carson CW, Cannon GW, Egger MJ, et al.** Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. Semin Arthritis Rheum 1987; **16:**186–195.
62. **Searles G, McKendry RJR.** Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. J Rheumatol 1987; **14:**1164–1171.
63. **Stostman HD, Matthay RA, Putman CE, et al.** Methotrexate-induced pneumonitis. Medicine 1976; **55:**371–388.
64. **Engelbrecht JA, Calhoon SL, Scherrer JJ.** Methotrexate pneumonitis after low-dose therapy for rheumatoid arthritis. Arthritis Rheum 1983; **26:**1275–1278.
65. **Green L, Schattner A, Berkenstadt H.** Severe reversible interstitial pneumonitis induced by low dose methotrexate: report of a case and review of the literature. J Rheumatol 1988; **15:**110–112.
66. **Shiroky JB, Frost A, Skelton JD, et al.** Complications of immunosuppression associated with weekly low dose methotrexate. J Rheumatol 1991; **18:**1172–1175.
67. **Kamel OW, van de Rijn M, Weiss LM, et al.** Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 1993; **328:**1317–1321.
68. **Moder KG, Tefferi A, Luthra HS.** Hematologic malignancies and the use of methotrexate in rheumatoid arthritis. Arthritis Rheum 1993; **36:**S78. Abstract.
69. **Wernick R, Smith DL.** Central nervous system toxicity associated with weekly low-dose methotrexate treatment. Arthritis Rheum 1989; **32:**770–775.
70. **Flood DA, Chan CK, Pruzanski W.** *Pneumocystis carinii* pneumonia associated with methotrexate therapy in rheumatoid arthritis. J Rheumatol 1991; **18:**1254–1256.
71. **Lang B, Riegel W, Peters T, et al.** Low dose methotrexate therapy for rheumatoid arthritis complicated by pancytopenia and pneumocystis carinii pneumonia. J Rheumatol 1991; **18:**1257–1259.
72. **Altz-Smith M, Kendal LG, Stamm AM.** Cryptococcosis associated with low-dose methotrexate for arthritis. Am J Med 1987; **83:**179–181.
73. **Keegan JM, Byrd JW.** Nocardiosis associated with low-dose methotrexate for rheumatoid arthritis. J Rheumatol 1988; **15:**1585–1586.
74. **Weinblatt ME, Maier AL, Coblyn JS.** Low dose leucovorin does not interfere with the efficacy of methotrexate in rheumatoid arthritis: an 8 week randomized placebo controlled trial. J Rheumatol 1993; **20:**950–952.
75. **Shiroky JB, Neville C, Esdaile JM, et al.** Low-dose methotrexate with leucovorin (folinic acid) in the management of rheumatoid arthritis. Arthritis Rheum 1993; **36:**795–803.
76. **Morgan SL, Baggott JE, Vaughn WH, et al.** The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 1990; **33:**9–18.
77. **Morgan SL, Baggott JE, Vaughn WH, et al.** Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. Ann Intern Med 1994; **121:**833–841.
78. **Hoffman GS, Kerr GS, Leavitt RY, et al.** Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; **116:**488–498.
79. **Hoffman GS, Leavitt RY, Kerr GS, et al.** Treatment of Takayasu's arteritis with methotrexate. Arthritis Rheum 1991; **34(Suppl):**S74. Abstract.
80. **Rothenberg RJ, Graziano FM, Grandone JT, et al.** The use of methotrexate in steroid-resistant systemic lupus erythematosus. Arthritis Rheum 1988; **31:**612–615.
81. **Willkens RF, Williams HJ, Ward JR, et al.** Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984; **27:**376–381.
82. **Lally EV, Ho G Jr.** A review of methotrexate therapy in Reiter syndrome. Semin Arthritis Rheum 1985; **15:**139–145.
83. **Kremer JM, Alarcon GS, Lightfoot RW, et al.** Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. Arthritis Rheum 1994; **37:**316–328.
84. **Milunsky MB, Graef JW, Gaynor MF.** Methotrexate-induced congenital malformations. J Pediatr 1968; **72:**790–795.
85. **Shamberger RC, Rosenberg SA, Seipp CA, et al.** Effects of high-dose methotrexate and vincristine on ovarian and testicular functions in patients undergoing postoperative adjuvant treatment of osteosarcoma. Cancer Treat Rep 1981; **65:**739–746.
86. **Sussman A, Leonard JM.** Psoriasis, methotrexate and oligospermia. Arch Dermatol 1980; **116:**215–217.
87. **Brooks PJ, Spruill WJ, Parish RC, et al.** Pharmacokinetics of methotrexate administered by intramuscular subcutaneous injections in patients with rheumatoid arthritis. Arthritis Rheum 1990; **33:**91–94.
88. **Furst DE, Koehnke R, Burmeister LF, et al.** Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. J Rheumatol 1989; **16:**313–320.
89. **Thompson RN, Watts C, Edelman J, et al.** A controlled two-center trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. J Rheumatol 1984; **11:**760–763.
90. **Gabriel S, Creagan E, O'Fallon WM, et al.** Treatment of rheumatoid arthritis with higher dose intravenous methotrexate. J Rheumatol 1990; **17:**460–465.
91. **Shiroky J, Allegra C, Inghirami G, et al.** High dose intravenous methotrexate with leukovorin rescue in rheumatoid arthritis. J Rheumatol 1988; **15:**251–255.
92. **Kremer JM, Rynes RI, Bartholomew LE.** Severe flare of rheumatoid arthritis after discontinuation of long-term methotrexate therapy. Double-blind study. Am J Med 1987; **82:**781–786.