The Use of Methotrexate in Rheumatoid Arthritis

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Objective: **To address the long-term efficacy and toxicity issues related to methotrexate (MTX) and compare it with other disease-modifying antirheumatic drugs (DMARDs).**

Methods: **Review of the international literature on the clinical use of MTX in rheumatoid arthritis (RA) disease.**

Results: **MTX has emerged as a relatively safe and effective treatment for RA that compares favorably with other therapies, particularly because of its considerably longer median drug survival. The toxicity profile of MTX is well established and includes serious and sometimes fatal liver disease, pneumonitis, and cytopenias. Hence, regular and careful monitoring of patients taking MTX is essential, particularly when MTX is combined with other DMARDs. Folate supplementation can reduce some of the most common side effects of MTX, but it has not yet been established whether this translates into a reduced risk of serious disease. Another potential approach to reducing the toxicity of MTX is therapeutic drug monitoring and dose individualization. However, correlations between pharmacokinetics and clinical response have been addressed in only a few studies and with conflicting results.**

Conclusions: **MTX is an effective DMARD with a relatively safe profile compared with other therapies. Folate supplementation can significantly reduce the risk of MTX toxicity. Finally, it is essential that patients be monitored carefully to reduce the potential serious toxicities of MTX.**

INDEX WORDS: Bone marrow suppression; liver toxicity; methotrexate; rheumatoid arthritis.

RHEUMATOID ARTHRITIS (RA) is a systemic autoimmune disease characterized by chronic inflammation of synovial joints resulting in destruction of cartilage and, ultimately, bone. There is no cure for RA, and treatment aims at limiting joint damage, preventing loss of function, and decreasing pain. The armamentarium of drugs used for these purposes includes nonsteroidal antiinflammatory drugs, disease modifying antirheumatic drugs (DMARDs), and corticosteroids. Unfortunately, joint destruction can often progress despite treatment, leading to deformity and disability in a substantial number of patients. In recent years, several studies have shown that a greater impact on slowing disease progression can be achieved if patients with recent-onset RA are treated with DMARDs earlier than had previously been recommended (1). Hence, the current American College of Rheumatology (ACR) guidelines recommend initiation of DMARD treatment within 3 months of diagnosis (2). According to these guidelines, methotrexate (MTX) is the standard by which new DMARDs are evaluated, and MTX as monotherapy, or in combination with other DMARDs, should be instituted if a satisfactory

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response has not been achieved with hydroxychloroquine (HCQ) or sulfasalazine (SSZ). In patients with very active disease or a poor prognosis, it may even be advisable to use MTX as the initial DMARD. This has been the practice among rheumatologists in the United States even before publication of the updated guidelines (3). For patients with severe RA, MTX is the DMARD of first choice for rheumatologists in the United States and in Europe (England and The Netherlands), and in both regions it is the anchor drug in therapy based on the combination of 2 DMARDs (4,5).

METHODS

A Medline search of published studies with key words "methotrexate," "rheumatoid arthritis," "DMARDs," and "amethopterin" from 1950 to 2003 was conducted. From these studies and their accompanying references, a total of 1114 studies dating from 1952 to the present were reviewed and 131 were determined to be pertinent to our discussion. These manuscripts included a variety of subjects, including pharmacology, therapy of connective-tissue diseases, and use of DMARDs. The manuscripts were reviewed with particular reference to the usage of MTX in RA, with emphasis on double-blinded studies and on mechanisms of action.

Pharmacology

MTX (amethopterin) is a methyl-derivative of aminopterin, a drug that was first used for the treatment of RA in 1951. Both aminopterin and MTX are folate analogues, but they are also folate antagonists in that they compete with folate for cellular uptake and intracellular polyglutamation and they reversibly inhibit dihydrofolate reductase (DHFR). DHFR participates in single carbon transfers necessary for methionine, purine, and thymidylate synthesis and, ultimately, DNA synthesis. The inhibition of other folate-dependent enzymes by polyglutamated MTX further contributes to this reduction of nucleotides available for cellular proliferation. Through partial substrate depletion and inhibition of thymidylate synthase, MTX polyglutamates block the de novo synthesis of thymidylate. In addition, they interfere with de novo purine synthesis by directly blocking the activity of 5-amino-imidazole-4-carboxamide ribonucleotide (AICAR) transformylase and by resulting in the accumulation of dihydrofolate polyglutamates, which are even more potent inhibitors of this enzyme (6).

The inhibition of DNA synthesis rapidly affects proliferating cells, such as malignant cells, and also lymphocytes. This is likely the major mechanism of action of high-dose MTX in leukemia and other malignancies. "High-dose" refers to MTX therapy consisting of between 200 mg/m^2 and 30 g/m^2 body surface administered intravenously over a period of 24 hours, first at weekly intervals and then at much longer intervals. However, patients with RA and psoriasis are treated with low-dose MTX (ie, doses ranging between 7.5 and 20 mg per week). However, we caution that "low-dose" refers to the comparative use of higher dosages in cancer and does not imply the doses used are nontoxic.

The mechanism(s) of action of low-dose MTX have still not been fully elucidated. It has recently been reported that low concentrations of MTX either inhibit proliferation or induce apoptosis in activated, but not resting, peripheral blood lymphocytes (7). These findings suggest that antiproliferative and immunosuppressive effects contribute to the effectiveness of low-dose MTX. However, somewhat conflicting results have been reported concerning the effect of MTX on proliferative responses, partly caused by the use of different methodologies for measuring proliferation (8).

MTX exerts a variety of antiinflammatory activities (6,9). These are at least partly mediated via the increased release of adenosine as a consequence of AICAR transformylase inhibition by MTX polyglutamates. Inhibition of this enzyme results in the accumulation of AICAR, which in turn inhibits adenosine deaminase, thereby increasing the intracellular adenosine concentration and the subsequent release of adenosine into the extracellular fluid. Adenosine exhibits a variety of antiinflammatory activities, including the inhibition of leukocyte accumulation and neutrophil-mediated endothelial injury at sites of inflammation; the reduction in tumor necrosis factor (TNF)-α synthesis; and inhibition of a variety of natural killer, monocyte/macrophage, and T-cell activities (6,9-11).

In addition to its effects on de novo purine synthesis, low-dose MTX therapy was recently reported to be associated with decreased activity of several enzymes participating in the salvage pathway of purine synthesis (12). This effect was seen

after 48 weeks, but not after 6 weeks, of MTX treatment, was independent of folate supplementation, and was not associated with measures of MTX efficacy or toxicity. An exception was 5′-nucleotidase, which exhibited decreased activity only in those patients who discontinued MTX because of hepatotoxicity.

A further mechanism of action may involve an MTX-induced reduction in the synthesis of polyamines via inhibiting the conversion of homocysteine to methionine, the precursor for the methyl-donor S-adenosyl-methionine that is required for polyamine synthesis. Polyamines may play a role in the pathogenesis of RA and other inflammatory diseases (9).

Efficacy in RA

MTX is among the most commonly used DMARDs in the treatment of patients with RA. It is taken once a week in doses commonly ranging between 7.5 and 20 mg. Whereas in some clinical trials the weekly dose was divided into 3 equal aliquots taken in 12-hour intervals (13,14), patients with RA generally take the entire dose at once. The most common route of administration is oral, but parenteral (intramuscular, subcutaneous, and occasionally intravenous) routes are preferred for some patients. Although bioavailability of oral MTX is similar to that of parenteral MTX (15-17), there are reports of patients who respond to intramuscular injections but not to oral MTX. A possible explanation for this observation is that the bioavailability of oral MTX relative to intramuscular MTX was 13.5% lower at the usual maintenance dose (mean, 17 mg) than at the 7.5-mg dose commonly used at the initiation of MTX therapy (18).

The efficacy of MTX in the treatment of RA has been shown in a number of randomized, controlled trials (RCTs) (19,20). A Cochrane systematic review concluded that, despite a fairly high (22%) withdrawal rate caused by adverse events, short-term MTX therapy provided substantial benefit to patients with RA and this benefit was both clinically and statistically significant (20). Compared with placebo, MTX therapy induces significant improvement in the number of tender and swollen joints, pain, physician and patient global assessment, and functional status. Approximately 60% to 70% of patients have a significant response to MTX, although the estimates depend to some extent on how “significant response” is defined (19). The onset of MTX-induced improvement is generally within 3 months in the majority of patients who will eventually respond. After an initial period of rapid improvement, a plateau in the response is often reached after 6 to 12 months (21,22).

In direct comparisons of traditional DMARDs in RCTs, their efficacy is generally quite similar, although MTX has been found to be superior to azathioprine and auranofin (19,23). The duration of most clinical trials is between 6 months and 2 years, which is short compared with the natural history of RA in the majority of patients. In addition, only select patients are included in RCTs and a variety of aspects of patient treatment, including dose adjustments and drug termination, are handled differently in RCTs than in common clinical practice. Long-term observational studies, although frequently not randomized and therefore liable to some bias, can offer a different perspective on the efficacy and toxicity of a drug and on the reasons for its discontinuation.

With few exceptions (24), long-term observational studies indicate that toxicities–rather than lack of efficacy–are the most common cause of discontinuing MTX (22,25-32). As will be discussed later, folic acid supplementation can reduce some of the toxicities of MTX. Many of the available data stem from a time when patients treated with MTX did not routinely receive folate supplementation, and, in some of the more recent studies, information on the extent of supplementary folate intake was unavailable. This makes it difficult to assess whether the now-widespread use of folate has had an impact on the frequency of MTX discontinuations and the reasons for them.

Studies comparing different second-line drugs show that discontinuations are less frequent in patients taking MTX than in those taking other DMARDs (24,26,27). Thus, MTX therapy has the highest median drug survival among DMARDs and the greatest cumulative probability of being continued for 5 years or even longer. The median time on MTX of 4.25 years was more than twice as long as that of other DMARDs (1.6 to 2 years) (26). Others have reported similar, occasionally even longer, median survival times (24,25,27). The percentage of patients still taking MTX after 5 years ranges between 45% and 65% (25,27,31,33), but it has been reported to be as high as 73% in 1 study (22) and only 25% in another (29). Even after 10 years, 30% of patients with RA continued

to take MTX at a tertiary care center in Alabama (30). At last follow-up, 53% of patients with RA treated in 6 Australian community practices were still taking MTX after 12 years, but this percentage decreased to 38% if intermittent discontinuations of >3 months were considered as terminations (32). It should be emphasized that careful monitoring is required no matter how long a patient takes MTX.

Notwithstanding its long median survival times, MTX is associated with some serious toxicities, discussed in more detail later. Thus, despite its proven effectiveness, it is important to examine whether newer DMARDs offer similar or even greater effectiveness with fewer toxicities. In recent years, several new agents for the treatment of RA have been developed, including leflunomide (Arava; Aventis, Bridgewater, NJ) and anticytokine agents, such as etanercept, infliximab, and anakinra.

Leflunomide is a new DMARD approved for the treatment of RA by the Food and Drug Administration (FDA) in 1998. It is an isoxazolyl derivative that is converted by first-pass metabolism in the liver and gut to the active metabolite, A77 1726. This metabolite inhibits the rate-limiting enzyme in pyrimidine synthesis, dihydroorotate dehydrogenase, and thereby prevents cellular proliferation, particularly that of $CD4^+$ T cells, which are known to proliferate rapidly during the initiation of RA. Recent comparisons between MTX and leflunomide indicate that they are similarly effective in treating RA (34,35), equally slowing radiographic progression (36) and both showing sustained clinical benefit over at least a 2-year period (35,37) (Tables 1 and 2). In 1 study, the clinical response rates to leflunomide were equivalent to those seen with MTX during the first year (34) but significantly higher after the second year (37). Conversely, in another study, MTX resulted in greater improvements did than leflunomide in all outcome measures after 1 year, but the benefits from the 2 drugs were similar at the end of the second year in the subgroup of patients who chose to continue the double-blind treatment (35). The frequency of adverse events, including serious ones, was similar with the 2 drugs, although the proportion of withdrawals because of toxicity tended to be higher in the leflunomide group in 1 trial (35). However, in the MTX group, there were 2 treatment-related deaths, whereas no deaths occurred in the leflunomide group. Asymptomatic transaminase elevations resulting in withdrawal were more than twice as frequent in the leflunomide group than in the MTX group in 1 trial (7.1% vs 3.3%, respectively) (34), but half as frequent in another (1.6% vs 3.2 %) (35).

The effect of the addition of leflunomide to a stable, but clinically unsatisfactory, dose of MTX was assessed in an open-label trial (38) and an RCT (39). In the open-label trial, 20% of subjects met the ACR20 response criteria after 1 month of leflunomide treatment; this percentage increased to 57% after 9 months, with a similar response rate maintained at 12 months. Similar results were reported in the RCT (39). Although generally well tolerated, the combination of leflunomide and MTX was associated with elevated liver enzymes in 63% of patients (38). Elevations of alanine aminotransferase (ALT) >2 times the upper limit of normal were observed in 34% of the patients and elevations of aspartate aminotransferase (AST) were observed in 24%. For comparison, in a randomized study comparing MTX and leflunomide, serum transaminase elevations 2 times the upper limit of normal occurred in 9.3% of patients treated with MTX and 11% of patients treated with leflunomide (34).

The first report of serious liver disease (early cirrhosis) associated with the use of a combination of leflunomide and MTX was published in 2000 (40). Since then, a number of serious hepatic abnormalities have been described in postmarketing reports, resulting in considerable controversy over the safety of leflunomide (41). This issue was recently addressed by an FDA-appointed advisory panel. Based on the currently available evidence, this panel deemed the safety of leflunomide adequate and acceptable and its benefits greater than its potential safety risks.

Anticytokine Agents

Based on the recognition that TNF-α and interleukin (IL)-1 play important roles in the pathogenesis of RA (42), several biologic agents that block the activity of these two proinflammatory cytokines have been developed. These include etanercept, a soluble TNF receptor (p75):Fc fusion protein; infliximab, a chimeric human-murine monoclonal anti–TNF-α antibody; and anakinra, a recombinant human IL-1 receptor antagonist (IL-1ra).

Etanercept (Enbrel; Immunex, Seattle, WA) has

Table 1: MTX Versus Leflunomide or Etanercept in 12-month RCTs

	MTX (34)	Leflunomide	MTX (35)	Leflunomide	MTX* (48)	Etanercept
Dose	7.5 mg/wk, increased to 15 mg/wk if active disease persisted	Loading dose of 100 mg/d for 3 d; 20 mg/d thereafter	7.5 mg/wk in wks 1-4, 10 mg/wk in wks 2-12, then 10-15 mg/wk	Loading dose of 100 mg/d for 3 d: 20 mg/d thereafter	7.5 mg/wk, increased to 15 mg/wk at wk 4, and to 20 mg/wk at wk 8	25 mg subcutaneously twice weekly
ACR20 (%)	46	52	64.8†	50.5	65	72
ACR50 (%)	23	34	—	—	MTX < Etanercept†	
Time to reach ACR20	9.5 (6.5) wk	8.6 (7.4) wk	101 ± 92.5 d†	74 ± 80 d	MTX > Etanercept†	
Joint count						
Tender	−6.6 ± 7.6	−7.7 ± 7.8	−9.7 ± 7.9†	−8.3 ± 7.9	—	—
Swollen	−5.4 ± 5.5	−5.7 ± 6.5	−9.0 ± 7.3†	−6.8 ± 7.3	—	—
Change in Sharp score (units)	0.88 (3.3)†	0.53 (4.5)	—	—	1.59	1.00
Change in Larson score (units)	—	—	0.03	0.03	—	—
Change in erosion score (units)	0.48 (1.8)	0.23 (2.2)	—	—	1.03†	0.47
Discontinuation						
Because of toxicity	10‡	22	15‡	19	11†	5
Because of lack of efficacy	24‡	17	3‡	7	4	5

*Some data were presented as figures (ie, actual numbers were not provided).
†Statistically significantly different from treatment comparison.
‡No statistical evaluation was presented.

been approved by the FDA for RA as monotherapy or in combination with MTX. The approval was based on the significant clinical benefit, as assessed by ACR criteria, that this agent exhibited either alone or in addition to MTX in multi-center, double-blind, placebo-controlled trials (43-45). Clinical trials of longer duration have further confirmed the efficacy of etanercept and have added the findings that the benefit is sustained over at least a 2-year period and that etanercept can slow, or even halt, radiographic progression (46,47).

A recent RCT directly compared MTX and etanercept (48). The weekly MTX dose was increased from the initial 7.5-mg dose to 20 mg in all patients, but the dose had to be reduced in 15% of them because of adverse events or serum transaminase elevations. Etanercept was administered subcutaneously twice a week at a dose of either 10 mg or 25 mg. Compared with MTX, the higher dose of etanercept was found to induce an ACR20 response faster and in a greater proportion of patients during the first 6 months of the 12-month trial. Thereafter, the percentages were similar in the 2 groups. Several factors are likely to account for the

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