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**Editorial**


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**METHOTREXATE IN RHEUMATOID ARTHRITIS**

Over the past few years 'low dose pulse' methotrexate has gained increasing popularity as an effective treatment for refractory rheumatoid arthritis (RA). The use of methotrexate and the development of practical guidelines have been addressed by a number of recent reviews.<sup>1-4</sup> Methotrexate has been shown to be better than placebo in controlled clinical trials.<sup>5-8</sup> These studies showed methotrexate to be relatively safe and efficacious with treatment up to six months duration. Methotrexate seems to maintain its antirheumatic activity for at least two years,<sup>9</sup> and is well tolerated over long periods of time.<sup>10</sup> However, patients controlled on methotrexate for up to 40 months of continuous therapy have been shown to flare within four weeks of ceasing methotrexate,<sup>11</sup> suggesting that the disease is suppressed rather than eliminated.

Using a meta-analysis on the four placebo controlled clinical trials,<sup>5-8</sup> Tugwell *et al.*, have shown that patients have a 26% greater improvement in inflamed joint count and a 39% greater improvement in pain than did controls receiving non-steroidal anti-inflammatory agents.<sup>3</sup> The meta-analysis also suggested that improvement began rapidly within one month reaching a maximum at six months. Although these initial results are encouraging, it is important to continue to follow these patients over a longer period of time to answer the questions of long term efficacy such as does methotrexate reduce erosion rate and deterioration of function in the long term (five years)?

The optimum dose of methotrexate has not yet been determined, but most published studies use a weekly dose of between 5 and 15 mg. The weekly dose of methotrexate seems to produce less hepatotoxicity than does more frequent dosing although some authors still recommend parenteral rather than oral therapy.<sup>5,12,13</sup> More recently, low dose methotrexate has been shown to be of similar efficacy to Azathioprine with beneficial effect maintained for up to two years,<sup>14</sup> and when given in a weekly intramuscular dose to be as effective and less toxic than sodium aurothiomalate during the first six months of therapy.<sup>15</sup> Although further studies are required comparing methotrexate with other specific antirheumatic drugs and for longer periods of time, methotrexate does seem to have established

itself a place in the management of rheumatoid arthritis.

The major problem with the use of methotrexate is the potential for long term side effects. The major adverse effects of methotrexate reported in patients with rheumatoid arthritis is shown in Table 1. Gastrointestinal side effects are usually relatively mild and include nausea and dyspepsia. These side effects are often dose related and can be reduced by giving the drug over a 24 hour period rather than in one single dose. A small number of patients develop stomatitis and this again is dose related. Skin rashes have been reported and occasionally a small vessel vasculitis. Hematological side effects include leucopenia, thrombocytopenia and pancytopenia. These adverse reactions are usually dose related. In a recent issue of the *Journal*, Kevat, *et al.*,<sup>23</sup> reported four cases of pancytopenia associated with low dose oral pulse methotrexate therapy for rheumatoid arthritis. These patients were all over the age of 60 years and had mild renal impairment. Pharmacokinetic studies carried out in two of these patients suggested a prolonged tissue drug exposure perhaps contributing to the adverse reactions. Pneumonitis, presenting as a non-productive cough, fever and dyspnea, is one of the more serious problems which needs careful monitoring in the long term.

The major long term concern of methotrexate therapy is that of hepatic fibrosis. Although liver enzyme elevations are seen frequently and do not correlate with fibrosis or cirrhosis, minor fibrosis

TABLE 1  
Major Adverse Effects of Methotrexate Reported in Patients with Rheumatoid Arthritis

		Reference
Gastrointestinal	Nausea, dyspepsia, vomiting	3,5-11,16
	Stomatitis	17,18
	Elevation of liver enzymes	14,18
Hepatic	Hepatic fibrosis	19
	Rash	9
Cutaneous	Vasculitis	20
Pulmonary	Pneumonitis	18,21
	Hematological	18
	Leucopenia	18
	Thrombocytopenia	
	Pancytopenia	22

is seen in a significant number of patients with rheumatoid arthritis who have received a total cumulative methotrexate dose of greater than 2 gms.<sup>4</sup> This question requires further research and careful monitoring but on the present evidence it would seem advisable to obtain a liver biopsy in rheumatoid arthritis patients whose total cumulative dose of methotrexate exceeds 1.5 gm.<sup>2,4</sup>

As our experience with methotrexate increases, it is likely that this drug will be used earlier in the disease, and in combination with other agents. It is important that physicians using this drug be aware of the potential for serious side effects, monitor patients carefully and include them in some type of ongoing clinical trial so that the much needed long term data on efficacy and side effects can be obtained.

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