

Does folate supplementation make sense in patients with rheumatoid arthritis treated with methotrexate?

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The potential value of the antifolate methotrexate (N10-methylaminopterin) in the treatment of rheumatoid arthritis (RA) was first recognised in 1951.¹ The low dose drug administration in divided doses 12 hours apart was developed for the treatment of patients with psoriasis, based on properties of psoriatic epithelial cells and the biological action of methotrexate on these cells.² To date its mode of action has not been well established.³ It is generally believed that low dose weekly pulses of methotrexate are not markedly immunosuppressive. This is based on the inconsistency of in vitro and in vivo observed changes in immune variables.^{3, 4} During treatment with low dose methotrexate, however, complications suggestive of immunosuppression may occur, such as varicella zoster, *Pneumocystis carinii*, and fungal infections.⁵ Only with a high dose of methotrexate, comparable with that used in patients with malignancies, does a decrease in surface DR expression on peripheral T lymphocytes occur.⁶ As activated T lymphocytes—bearing Ia antigens—have a role in the pathogenesis of rheumatoid arthritis⁷ this is an interesting finding.

Biochemically the following mode of action of methotrexate is suggested: methotrexate competes with reduced folates for active transport into the cell and binds tightly (reversible) to dihydrofolate reductase, thus decreasing the intracellular formation of reduced folates with a consequent disturbance of thymidine, purine, and protein synthesis. Although the cellular basis for the action of methotrexate in RA remains unknown, it is presumed to be through its action on folate transport and metabolism. The hypothesis that a common folate dependent pathway is involved is reinforced by the fact that two antifolate drugs, methotrexate and sulphasalazine, are effective in the treatment of RA.

Depletion of folate and inhibition of folate dependent enzymes may contribute to efficacy by altering inflammation and proliferation in arthritis target tissues,⁸ but may also contribute to adverse drug effects of methotrexate in non-target tissues. This is illustrated by the fact that methotrexate toxicity mimics clinical manifestations of folate deficiency, such as gastrointestinal intolerance, diarrhoea, stomatitis, and cytopenia. Unfortunately, serum folate concentrations merely reflect dietary intake rather than intracellular folate levels. Measurement of intracellular folate stores is indirectly possible by a biological assay of the activity of an enzyme system which synthesises serine from glycine and formate, and requires reduced folate coenzymes, the so called C1 index.⁸

As bone marrow and gastrointestinal tract have a high cell turnover, depending on a high intracellular supply of reduced folates needed for DNA, RNA, and protein synthesis, these non-target tissues may be the most sensitive to the adverse effects of methotrexate. The mechanism of methotrexate liver toxicity is not completely understood. Hepatocytes retain methotrexate in the active polyglutamated form for a prolonged period of time, which may augment toxicity.⁹

Mild adverse experience with low dose methotrexate is common in patients with RA, but continued treatment without methotrexate dose reduction is usually possible; in several five year follow up studies 50–60% of the patients continued to receive methotrexate with sustained clinical benefit.^{10–12}

As methotrexate is an effective second line drug for RA it is worthwhile questioning whether oral folate supplementation in rheumatoid patients treated with low dose methotrexate will decrease methotrexate toxicity without affecting its efficacy.

Five studies^{13–17} and at least two case reports^{18, 19} have been published dealing with folate supplementation in patients with RA treated with methotrexate; three studies dealt with folinic acid and two with folic acid supplementation (table).

These prospective studies differ not only in study design (uncontrolled or double blind, placebo controlled), but also in study duration, relative dose of folic or folinic acid, and interval between supplementation and weekly pulse methotrexate. Except for Stewart's study the number of studied patients was low (seven to 32) and the duration of the study short (four to 48 weeks). Unfortunately, the C1 index was not measured in any of these studies.

Hanrahan and Buckley's double blind, cross-over study comparing folinic acid (leucovorin) with placebo did not show any decrease in toxic reactions in patients receiving folinic acid.^{13, 15} Tishler's unblinded case controlled study¹⁴ showed folinic acid to be effective in preventing nausea caused by low dose methotrexate treatment in RA. This benefit was overshadowed, however, by increased rheumatic disease activity in all patients. Delaying folinic acid treatment for four to six hours after methotrexate administration should reduce competition for methotrexate uptake for entry into the cell. The extent of elimination of the uptake of methotrexate by folinic acid will be dependent on the relative dose of both drugs. The higher folinic acid dose in relation to methotrexate used by Tishler compared with the doses used by Hanrahan and

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Review of published studies on folic/folinic acid supplementation in patients with rheumatoid arthritis treated with methotrexate (MTX)

Author (ref)	Study design (n)*	Mean dose of MTX (mg/wk)	Supplementation	Outcome	
				Adverse effects	Efficacy
Stewart (17)	A (198)	8.5	Folic acid 7 mg/wk	Diminished	Not known
Morgan (16)	B (32)	7.5	Folic acid 1 mg/day	Diminished	Unchanged
Buckley (15)	B (20)	Not known	Folinic acid, dose=dose of MTX, 4 h after MTX	Unchanged	Unchanged
Hanrahan (13)	B (13)	18.5	Folinic acid, 10 mg/day for 2 days, starting 4 days before MTX	Unchanged	Unchanged
Tishler (14)	A (7)	9.6	Folinic acid, 15 mg/day for 3 days, starting 4-6 h after MTX	Diminished	Diminished

*A=prospective, open study; B=randomised, placebo controlled, double blind, crossover study.

Buckley may explain the exacerbation of the rheumatic disease in the first study.

As folic acid is a stable reduced folate that bypasses dihydrofolate reductase, doses and intervals of administration may be more critical than with the fully oxidised form of the vitamin, folic acid.

Both studies dealing with concurrent use of folic acid and methotrexate reported a significant decrease in methotrexate adverse effects, whereas the clinical efficacy of methotrexate seemed to be unchanged. One study was double blind, placebo controlled crossover during 24 weeks¹⁶ and the other study was uncontrolled during 41.5 months.¹⁷ The latter study compared the incidence of adverse effects in 198 patients receiving a folic acid supplement with those in a previously reported group. A significant reduction in methotrexate adverse effects was found for the following gastrointestinal complications: nausea/vomiting, diarrhoea, and stomatitis. The decrease of liver function abnormalities in this study was remarkable, suggesting that some folate depletion occurs in methotrexate liver toxicity.⁹ Stewart's analysis also suggests that an increase in the mean cell volume—which correlates inversely with intracellular red blood cell folate concentrations—in rheumatoid patients treated simultaneously with methotrexate and folic acid did not predict methotrexate toxicity.

Until now, long term studies have shown that most patients with RA treated with methotrexate have radiographic deterioration despite clinical improvement.²⁰ Methotrexate might be more effective in chondroprotection and preventing bone erosions and deformities if introduced at an earlier stage of the disease.

According to Morgan *et al*,¹⁶ low dose folic supplementation—that is, 1 mg once a day, may enable methotrexate to be used at an earlier stage of RA as it decreases methotrexate toxicity without influencing its beneficial effects in RA. Future prospective controlled studies are needed to investigate the relative doses of methotrexate and folic acid as well as the long term effects of supplementation.

We conclude that as long as the mechanism of action—folate antagonism or otherwise—of methotrexate in RA is not known the beneficial

effect of folate supplementation may still be considered to be a result of the relative reduction of the dose of methotrexate. As only minor side effects are reduced (there are no data about major complications, such as cytopenia and opportunistic infections) a reduction in the dose of methotrexate makes more sense than oral folate supplementation.

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