Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review

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Objective. The folate antagonist methotrexate (MTX) has become established as the most commonly used disease-modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA) but is commonly discontinued due to adverse effects. Adverse effects are thought to be mediated via folate antagonism. In this paper we summarize the current data on the use of folates as a supplement to MTX use in RA for the prevention of adverse effects and as a potential modulator of cardiovascular risk, and propose guidelines for standard practice.

Methods. A Medline search was performed using the search terms ‘methotrexate’, ‘folic acid’, ‘folinic acid’, ‘folate’ and ‘homocysteine’. Literature relevant to the use of folates as a supplement to MTX in the treatment of RA was reviewed and other papers referred to as references were explored.

Results. The use of supplemental folates, including folic and folinic acid, in RA patients treated with MTX has been shown to improve continuation rates by reducing the incidence of liver function test abnormalities and gastrointestinal intolerance. Folate supplements do not appear to significantly reduce the effectiveness of MTX in the treatment of RA. Furthermore, supplemental folic acid offsets the elevation in plasma homocysteine associated with the use of MTX. This may in turn reduce the risk of cardiovascular disease, which is over-represented amongst patients with RA, and for which hyperhomocysteinaemia is now recognized as an independent risk factor.

Conclusions. We propose that folic acid supplements be prescribed routinely to all patients receiving MTX for the treatment of RA. We recommend a pragmatic dosing schedule of 5 mg of oral folic acid given on the morning following the day of MTX administration.

Key words: Methotrexate, Folic acid, Folinic acid, Homocysteine.

Methotrexate (MTX) has become established as the most commonly used disease-modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA) and is widely used in other inflammatory conditions [1]. In recent years there has been a trend towards more aggressive use of MTX in the treatment of inflammatory arthropathies, with regard to both dose and early intervention. MTX also plays an important role in the use of some tumour necrosis factor α-blocking monoclonal antibodies. This review summarizes the current data on the use of folic acid as a supplement to MTX use in RA for the prevention of adverse effects and as a potential modulator of cardiovascular risk.

The folic acid analogue aminopterin was first used in the treatment of RA in 1951 [1–3]. By 1972 the related compound MTX (N-10-methylaminopterin) had been shown to reduce disease activity [4], and it has subsequently become established as the DMARD of first choice in the management of RA due to its superior efficacy:toxicity profile [5].

Mechanism of action

Despite MTX having been in use for over 30yr, its precise mechanism of action in the treatment of RA remains unknown. MTX inhibits the enzyme dihydrofolate reductase, thereby depleting the pool of reduced folates, which act as donors of 1-carbon moieties in the formation of metabolic intermediates, including purines, deoxythymidylate monophosphate and methionine, and producing a state of effective folate deficiency [1]. In high doses, such as those used for cancer chemotherapy, MTX acts as a cytotoxic drug by interfering with purine and pyrimidine synthesis in tissues with a high rate of cellular turnover. However, there is no evidence that the beneficial effect of MTX in a low, once-weekly dose is mediated by inhibition of the replication of immune or inflammatory cells [1].

At doses used in the treatment of RA, MTX is likely to act via a number of intracellular pathways. Upon transport into cells, MTX is converted to polyglutamated forms which promote intracellular retention. These intracellular polyglutamates are potent inhibitors not only of dihydrofolate reductase but also of a number of folate-dependent enzymes, including 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase [1, 6]. The resulting accumulation of AICAR enhances adenosine release into the extracellular space. Adenosine exhibits an anti-inflammatory effect via interaction with receptors on neutrophils and mononuclear cells [1, 7]. An alternative hypothesis suggests that interference with the transmethylation of homocysteine to methionine leads to inhibition of polyamine synthesis by S-adenosyl-methionine, which may in turn reduce...
inflammation mediated by toxic oxygen species produced by the metabolism of polyamines such as spermine and spermidine [1]. MTX also modulates cytokine responses at a number of levels, and may promote apoptosis of activated lymphocytes [6]. These and other mechanisms may all play a role in the clinical effects of MTX. Current evidence suggests a central role for adenosine, a pathway which is independent of dihydrofolate reductase [1].

**Adverse effects and folate supplementation**

Despite its effectiveness as a disease-modifying agent in RA, the probability of MTX discontinuation 1 yr after therapy is initiated is 30% [8]. The main factor influencing the decision to discontinue the drug is the occurrence of adverse effects [8]. These may be divided into minor side-effects, such as mouth ulcers and gastrointestinal intolerance, and major side-effects, primarily bone marrow toxicity and liver function test abnormalities. It is likely that at least some of these side-effects are due to folate antagonism, and several, including gastrointestinal intolerance, cytopenias and alopecia, are similar to those seen in folate deficiency states. Furthermore, folate deficiency is recognized as a risk factor for MTX toxicity [3, 9]. Cellular folate stores are decreased in MTX-treated patients with RA [9, 10]. Elevation of erythrocyte mean corpuscular volume (MCV) is associated with MTX toxicity and has been suggested as a predictor of incipient toxicity [10, 11]. This relationship has not been reproduced in all studies, however, which may reflect the insensitivity of MCV as a measure of intracellular folate stores [10, 12, 13].

Whilst there is a theoretical basis for using folate supplementation to reduce adverse effects, there is as yet no consensus regarding the use of folate supplements in patients taking low-dose MTX. Regional and national differences in practice remain pronounced. In particular, folate supplementation has become standard practice in the USA since the early 1990s but practice in the UK and Europe has differed. The British Society for Rheumatology guidelines for monitoring of second-line drugs state that ‘regular folic acid (FA) supplements are thought to reduce toxicity’ [14], whereas guidelines in the USA recommend that folate supplementation should be considered in all patients taking MTX [15]. There is no clear explanation for this difference in practice, but it has probably led to some confusion and has identified a need for clarification of the evidence base.

The first randomized placebo-controlled trials of folic acid supplementation in MTX-treated patients with RA were performed in the early 1990s [3, 10]. In each of two trials, MTX toxicity, as measured by a composite toxicity scale designed by the authors, was significantly reduced at 6 and 12 months respectively in patients receiving supplemental folic acid at a dose of 1 mg per day in the first trial, and either 5 or 27.5 mg per week in the second; there was no difference in benefit between the two folic acid doses. A meta-analysis of trials assessing the benefits of supplementation with either folic acid or folinic acid was able to include only these two trials in the folic acid analysis [9]. This demonstrated a significant reduction in the odds of mucosal and gastrointestinal (GI) side-effects (odds ratio 0.21, 95% confidence interval 0.10–0.44) in patients supplemented with folinic acid. There were insufficient data to demonstrate an effect on cytopenias or liver enzyme abnormalities.

Similarly, meta-analysis of five trials assessing the use of folinic acid supplementation demonstrated a reduction in GI and mucosal side-effects. This benefit was lost when folinic acid doses of greater than 5 mg per week were used [9].

More recently, folic and folinic acid were directly compared in a large randomized trial of 434 MTX-treated patients over 48 weeks in the Netherlands [16]. Both folic acid, at a dose of 1 mg daily, and folinic acid, at 2.5 mg per week, significantly reduced the rate of discontinuation of MTX in RA patients commencing the drug. There was no difference in benefit between the two folate supplements. In this trial, the difference in MTX continuation rates between the folate and placebo groups was almost entirely accounted for by elevations of hepatic transaminases; in contrast to the meta-analysis of folate supplementation, treatment did not appear to reduce GI symptoms such as nausea, abdominal pain and stomatitis. A randomized, double-blind study of 75 patients established on MTX and folic acid for an average of 30 months demonstrated that substitution of placebo for folic acid 5 mg daily was associated with a significantly increased risk of withdrawal from MTX therapy due to adverse effects and a significantly increased incidence of nausea [12]. A reduction in liver function test abnormalities was also suggested by a small study of 14 patients with a sustained elevation of serum ALT (alanine transaminase) while taking MTX, in whom the administration of folic acid caused ALT to decrease in all patients within 3 months [17]. It has been postulated that the hepatic toxicity associated with MTX may be mediated via impeded homocysteine metabolism; this is supported by a recent study of 236 patients taking MTX in whom an increased risk of discontinuing MTX treatment was demonstrated in patients with the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene [18]. The mutated gene leads to reduced conversion of 5,10-methyleneTHF to methylTHF, thus impeding remethylation of homocysteine to methionine and leading to accumulation of homocysteine.

The rapidly dividing cells of the bone marrow are sensitive to folate deficiency and folate supplementation might be expected to reduce the risk of MTX-induced cytopenias. Leucopenia was only encountered in nine of 434 patients taking MTX for RA at doses of between 7.5 and 25 mg per week. Of these, two were taking placebo, four folic acid and three folinic acid. Adverse haematological effects necessitated withdrawal of MTX in three patients (two placebo, one folic acid) [16]. A retrospective series has associated MTX-related haematological toxicity with folate deficiency [11]. However, prospective studies have included insufficient patient numbers to detect a protective effect of folic acid supplementation.

**Table 1. Suggested folate use in RA patients taking MTX**

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<tr>
<th>Indication</th>
<th>Dose</th>
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<tr>
<td>Folic acid</td>
<td>All patients taking MTX</td>
<td>5–10 mg once weekly by mouth given morning after MTX dose</td>
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<tr>
<td>Folinic acid</td>
<td>MTX overdose or acute haematological toxicity</td>
<td>15 mg by mouth every 6 h, for 2–8 doses (depending on the dose of MTX)</td>
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LFT, liver function tests.
Folate and methotrexate in rheumatoid arthritis

Does folate supplementation reduce MTX efficacy?

There is a theoretical risk that folic acid supplementation may reduce the efficacy of MTX in treating RA. The meta-analysis by Ortiz et al. [9] did not demonstrate consistent differences in disease activity parameters when comparing placebo and folic acid; similarly, in the prospective study of 434 patients by van Ede et al. [16] there were no differences in disease activity between treatment groups. In the latter study, however, the final MTX dose was higher in the patients taking folic acid compared with those receiving placebo (mean dose 18 and 14.5 mg/week respectively), which may suggest that higher doses of MTX are required to achieve the same response. Alternatively, it has been postulated that co-administration of folic acid may allow the use of higher doses of MTX before side-effects are encountered [19]. Regardless of the explanation, supplementation with folate allowed 83% of patients to continue using MTX at 48 weeks, compared with only 62% of those receiving MTX alone [16].

There has been debate regarding the significance of findings relative to MTX emerging from large phase III trials of leflunomide in RA. Fifty-two per cent of MTX-treated patients achieved an American College of Rheumatology 20% improvement (ACR 20) in the American study, in which 98% of those receiving MTX were given folic acid supplementation, compared with an ACR 20 response in 65% of MTX-treated patients in the international trial, in which only 11% of patients received folic acid during MTX therapy [20–22]. It has been suggested that the difference in ACR 20 response can be explained by a negative effect of folic acid on MTX efficacy [21]. No firm conclusion can be drawn from post hoc analysis of these two demographically distinct treatment groups, not least because the American trial was placebo-controlled whereas all patients in the international study received an active compound.

In contrast, folic acid, in a dose of 15 mg per week, has been shown to reduce the effectiveness of MTX treatment [23]. It is likely that the timing of the folic acid in relation to the MTX, as well as the size of the dose, is important in influencing efficacy [23]. A similar effect has not been demonstrated for folic acid, even at higher folate to MTX ratios [9]. This may be explained by competition between folic acid and MTX for binding to cellular transport molecules during the distribution phase following MTX dosing, which does not occur with folic acid [24]. Given the potential for amelioration of disease-modifying activity, the lack of advantage in prevention of MTX side-effects and the substantially higher cost of folic acid, there seems no reason on current evidence to recommend the use of folic acid in preference to folic acid for routine administration. However, as a fully reduced folate which is able to function in biosynthetic pathways independent of dihydrofolate reductase, folic acid retains an important role in the treatment of MTX overdose or acute haematological toxicity (Table 1).

No consensus exists regarding guidelines for dose and frequency of folic acid in RA patients receiving MTX. At present, the evidence base is insufficient to determine the optimum dose for folic acid supplementation and weekly folic acid doses ranging from 5 to 27.5 mg per week have been demonstrated to be effective in reducing MTX side-effects in randomized controlled trials [3, 10, 16]. Daily and once-weekly folic acid dosing schedules have not been directly compared in prospective trials.

A recent Scandinavian review and proposal for guidelines argues that routine supplementation is not required and that the introduction of folic acid should be deferred until the occurrence of adverse effects or an elevation in MCV [24]. This recommendation is based only on side-effects data and does not take into account the potential important benefit with regard to cardiovascular profile.

Folate supplementation and cardiovascular risk in RA

The importance of atherosclerotic vascular disease in patients with RA is becoming increasingly recognized. RA is associated with an increase in mortality comparable to triple-vessel coronary artery disease, and cardiovascular disease is the major cause of excess deaths [25–28]. Hyperhomocysteinaemia is recognized as an independent cardiovascular risk factor and homocysteine levels are often elevated in patients with RA [29]. It is therefore of some concern that folate antagonism by MTX has been shown to result in an increase in plasma homocysteine levels by interference with the remethylation of homocysteine to methionine via methyl-tetrahydrofolate [30–32]. Combination therapy with MTX and sulphasalazine, which may also alter folate absorption or metabolism, might lead to a greater increase in plasma homocysteine than treatment with MTX alone [33].

The addition of folic acid, in doses ranging from 5 to 27.5 mg per week, in patients treated with MTX has been demonstrated to completely abolish the MTX-induced elevation in plasma homocysteine [30–32, 34]. It has yet to be demonstrated that reduction of plasma homocysteine with folic acid can decrease cardiovascular risk in MTX-treated patients with RA. However homocysteine-lowering with folic acid and vitamin B6 has been shown to reduce the risk of developing an abnormal exercise ECG in healthy siblings of patients with premature atherothrombotic disease [35].

A retrospective uncontrolled study has demonstrated an apparent increase in mortality in MTX-treated RA patients with documented atherosclerotic vascular disease or hypertension, compared with patients with RA commencing other DMARDs [36]. This result contrasts with data from a recent large cohort study in Wichita [37]. One thousand two hundred and forty patients with RA were followed for a mean of 6 yr between 1981 and 1999, of whom 588 had received MTX by the end of follow-up. After adjustment for confounding, MTX use was associated with a 60% reduction in risk of all-cause mortality. No reduction in mortality was demonstrated for other DMARDs. The mortality benefit was even greater (hazard ratio 0.3) for cardiovascular mortality, which accounted for 44% of deaths in the cohort. A reduction in cardiovascular risk in MTX-treated patients may be explained, at least in part, by suppression of inflammatory mechanisms which are central to the development of atherosclerosis [26]. Although fewer than 20% of the MTX-treated patients in the Wichita cohort received concomitant folic acid, the combination resulted in a mortality hazard ratio of 0.2, compared with 0.5 for MTX use alone [38]. This lends further weight to the hypothesis that folic acid supplementation may reduce cardiovascular risk in RA patients treated with MTX. There is no clear explanation for the conflicting mortality data in these two cohort studies, but both highlight the importance of vascular morbidity in individuals with RA. Further prospective data are required to better define the impact of disease-modifying drugs on mortality and cardiovascular disease.

Summary and guidelines

In summary, folic acid supplementation in individuals with RA treated with MTX is likely to reduce the incidence of liver function test abnormalities and may reduce the incidence of GI intolerance and stomatitis. The incidence of significant leucopenia during MTX treatment is low and some data suggest this may be reduced by supplementation with folic acid.

Folic acid supplementation offsets the increase in plasma homocysteine level associated with MTX therapy and may in turn reduce cardiovascular risk; further work is needed in this area. Folic acid supplementation has not been shown to reduce the efficacy of MTX in the treatment of RA and it is likely that efficacy and
common toxicities are mediated via different metabolic pathways. Folic acid is no more effective than folic acid in the prevention of MTX-related side-effects, may reduce the effectiveness of MTX in certain circumstances, and is more expensive. As a fully reduced folate which bypasses dihydrofolate reductase, folinic acid retains a role in the management of acute haematological toxicity and MTX overdose.

On current evidence, folic acid improves MTX continuation rates without compromising efficacy. It has essentially no side-effects and is inexpensive (approximately 2 p per week in the UK) [39]. The emerging data regarding cardiovascular risk in patients with inflammatory disease and the potential for the reduction of this risk with supplemental folic acid provide further impetus for the consideration of folic acid in all MTX-treated patients.

We propose that folic acid supplements be prescribed routinely to all patients receiving MTX for the treatment of RA. A dose of 5 mg given once per week orally is likely to be sufficient, although there are no data comparing the relative benefits of weekly versus daily folic acid administration. Further studies are required to provide evidence for choice of dose, frequency and timing. The timing of folic acid dosing in relation to MTX is unlikely to influence the reduction of adverse effects. Most trials have avoided administration of folic acid on the same day as MTX. In order to minimize patient confusion and enhance adherence to treatment, we have suggested a uniform and pragmatic approach to the provision of folic acid supplements.

We recommend a single dose of 5 mg of folic acid once per week, taken on the morning following the day of MTX dosing. If adverse effects still occur, an increase to a single dose of 10 mg per week may be considered.

The results of large prospective trials assessing the influence of folic acid supplementation on cardiovascular risk are awaited. The increasingly prominent role of MTX in the management of RA, both alone and in combination with other therapies, underscores the importance of any strategy that may improve tolerability.

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<th>Rheumatology</th>
<th>Key messages</th>
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<td>Supplementation of MTX with folic acid improves tolerability. Five milligrams of folic acid should be given on the morning after MTX. Folic acid supplementation has not been shown to reduce the efficacy of MTX in RA. Folic acid offsets the increase in plasma homocysteine associated with MTX treatment and may reduce cardiovascular risk in RA.</td>
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The authors have declared no conflicts of interest.

References
5. Felton DT, Anderson JI, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis.