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METHOTREXATE INDUCED FOLATE DEFICIENCY IN PATIENTS WITH RHEUMATOID ARTHRITIS: A REVIEW

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Abstract:

Objectives: 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 it is frequently discontinued due to adverse effects. The negative effects are thought to be mediated by folate antagonism. In this paper, we summarise the current data on the use of folates as a supplement to MTX in RA for the prevention of adverse effects and as a potential modulator of cardiovascular risk, and we propose guidelines for standard practise. Methods:A Medline search was conducted using the terms'methotrexate,' 'folic acid,' 'folinic acid,' 'folate,' and 'homocysteine'. The literature on the use of folates as a supplement to MTX in the treatment of RA was reviewed, and other papers referred to as references were investigated. Results: Supplemental folates, such as folic and folinic acid, have been shown to improve MTX adherence by lowering the incidence of liver function test abnormalities and gastrointestinal intolerance. Folate supplements do not appear to reduce the effectiveness of MTX in the treatment of RA. Furthermore, supplemental folic acid reduces the increase in plasma homocysteine caused by MTX use. This may reduce the risk of cardiovascular disease, which is over-represented in RA patients and for which hyperhomocysteinaemia is now recognised as an independent risk factor. Conclusions: We propose that all patients receiving MTX for the treatment of RA be given folic acid supplements on a regular basis. We recommend a practical dosing schedule of 5 mg of oral folic acid given the morning after MTX administration.

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

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INTRODUCTION:

Methotrexate (MTX) has become the most widely used disease-modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA), and it is also widely used in other inflammatory conditions.[1] There has been a trend in recent years toward more aggressive use of MTX in the treatment of inflammatory arthropathies, in terms of both dose and early intervention. MTX is also involved in the use of some tumour necrosis factor-blocking monoclonal antibodies. 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 are summarized in this review. Aminopterin, a folic acid analogue, was first used to treat RA in 1951.[(1,3)] By 1972, it had been demonstrated that the related compound MTX (N-10-methylaminopterin) reduced disease activity [4], and it has since become the first-line DMARD in the treatment of RA due to its superior efficacy:toxicity profile.[5]

MECHANISM OF ACTION

Despite being in use for more than 30 years, the precise mechanism of action of MTX in the treatment of RA is unknown. MTX inhibits the enzyme dihydrofolate reductase, depleting the pool of reduced folates, which act as donors of 1-carbon moieties in the formation of metabolic intermediates such as purines, deoxythymidylate monophosphate, and methionine, and causing a state of effective folate deficiency.[1] In high doses, such as those used in 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 immune or inflammatory cell replication.[1]At the doses used to treat RA, MTX is likely to act through a variety of intracellular pathways. MTX is converted to polyglutamated forms in cells, which promote intracellular retention. These intracellular polyglutamates are strong inhibitors of dihydrofolate reductase as well as a number of folate-dependent enzymes, including 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase .[(1,6)]AICAR accumulation increases adenosine release into the extracellular space. Adenosine exerts an anti-inflammatory effect by interacting with neutrophil and mononuclear cell receptors.[(1,7)] MTX also influences cytokine responses at multiple levels and may promote apoptosis in activated lymphocytes.[6] These and other mechanisms could all play a role in MTX's clinical effects. Current evidence suggests that adenosine plays a critical role in a pathway that is not dependent on dihydrofolate reductase.[1]

ADVERSE EFFECTS AND FOLATE SUPPLEMENTATION:

Despite its efficacy as a disease-modifying agent in RA, the likelihood of discontinuing MTX one year after starting therapy is 30%.[8] The occurrence of adverse effects is the most important factor influencing the decision to discontinue the drug.[8] These are classified as minor side effects, such as mouth ulcers and gastrointestinal intolerance, and major side effects, which include bone marrow toxicity and abnormal liver function tests. Some of these side effects are likely due to folate antagonism, and several, such as gastrointestinal intolerance, cytopenias, and alopecia, are similar to those seen in folate deficiency states. Furthermore, MTX toxicity is associated with folate deficiency.[(3,9)] Cellular folate stores are reduced in RA patients taking MTX.[(9,10)].Elevated erythrocyte mean corpuscular volume (MCV) has been linked to MTX toxicity and has been proposed as a predictor of early toxicity.[(10,11)] However, this relationship has not been replicated in all studies, which may reflect MCV's insensitivity as a measure of intracellular folate stores.[(10,12,13)]

While there is a theoretical basis for using folate supplements to reduce adverse effects, there is currently no agreement on the use of folate supplements in patients taking lowdose MTX. Regional and national differences in practise persist. Since the early 1990s, folate supplementation has become standard practise in the United States, but practise in the United Kingdom and Europe has varied.According to the British Society of Rheumatology guidelines for second-line drug monitoring,'regular folic acid (FA) supplements are thought to reduce toxicity'[14], whereas guidelines in the United States recommend that folate supplementation be considered in all patients taking MTX.[15] There is no clear explanation for this difference in practise, but it has most likely caused some confusion and identified a need for evidence base clarification.

In the early 1990s, the first randomised controlled trials of folic acid supplementation in MTX-treated RA patients were conducted.[(3,10)] MTX toxicity was significantly reduced at 6 and 12 months in patients receiving supplemental folic acid at 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. Only these two trials were included in a meta-analysis of trials assessing the benefits of either folic acid or folinic acid

supplementation.[9] This study found that folic acid supplementation significantly reduced the risk of mucosal and gastrointestinal (GI) side effects (odds ratio 0.21, 95% confidence interval 0.10-0.44). There was insufficient evidence to show an effect on cytopenias or liver enzyme abnormalities. Similarly, a meta-analysis of five trials evaluating the use of folinic acid supplementation revealed a decrease in GI and mucosal side effects. When folinic acid doses greater than 5 mg per week were used, this benefit was lost.[9] Folic and folinic acid were recently directly compared in a large randomised trial of 434 MTX-treated patients conducted in the Netherlands over 48 weeks.[16] Folic acid, at 1 mg daily, and folinic acid, at 2.5 mg per week, both reduced the rate of MTX discontinuation in RA patients who started the drug. The two folate supplements provided the same benefit. In this trial, the difference in MTX continuation rates between the folate and placebo groups was almost entirely explained by increases in hepatic transaminases; however, unlike the meta-analysis of folate supplementation, treatment did not appear to reduce GI symptoms such as nausea, abdominal pain, and stomatitis. A randomised, double-blind study of 75 patients on MTX and folic acid for an average of 30 months found that substituting placebo for folic acid 5 mg daily was associated with a significantly increased risk of discontinuing MTX therapy due to adverse effects, as well as a significantly increased incidence of nausea.[12] A small study of 14 patients with a sustained elevation of serum ALT (alanine transaminase) while taking MTX found that folic acid administration caused ALT to decrease in all patients within 3 months.[17]A recent study of 236 patients taking MTX found an increased risk of discontinuing MTX treatment in patients with the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene.[18] This supports the theory that the hepatic toxicity associated with MTX may be mediated by impaired homocysteine metabolism. The mutated gene causes decreased conversion of 5,10-methyleneTHF to methylTHF, preventing homocysteine remethylation to methionine and resulting in homocysteine accumulation.

Because rapidly dividing cells in the bone marrow are vulnerable to folate deficiency, folate supplementation may reduce the risk of MTX-induced cytopenias. Only nine of 434 patients taking MTX for RA at doses ranging from 7.5 to 25 mg per week developed leucopenia. Two were given a placebo, four were given folic acid, and three were given folinic acid. In three patients (two placebo, one folic acid), adverse haematological effects necessitated MTX withdrawal.[16] A retrospective study linked MTX-related haematological toxicity to a lack of folate.[11] However, insufficient patient numbers have been included in prospective studies to detect a protective effect of folic acid supplementation

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Table 1: Folate use suggested in RA patients taking MTX

	Indication	Benefit	
Folic acid	All patients taking MTX	5-10mg Dose once weekly by month given morning after MTX dose	Reduction of side effects (LFT abnormalities, GI intolerance, ± cytopenia) [9,16]
Folinic acid	MTX overdose are acute hematological toxicity	15mg by mouth every 6h, for 2-8 doses (depending on the dose of MTX)	Reduction of plasma homocysteine [30-32] Reversel of hematological toxicity

LFT, liver function tests.

DOES FOLATE SUPPLEMENTATION REDUCE MTX EFFICACY?

Folic acid supplementation may reduce the efficacy of MTX in the treatment of RA. Ortiz et al. [9] conducted a meta-analysis and found no consistent differences in disease activity parameters when comparing placebo and folic acid; similarly, van Ede et al.[16] found no differences in disease activity between treatment groups in a prospective study of 434 patients. However, in the latter study, the final MTX dose was higher in folic acid patients compared to placebo patients (mean dose 18 and 14.5 mg/week, respectively), suggesting that higher doses of MTX are required to achieve the same response. Alternatively, it has been proposed that co-administration of folic acid may allow higher doses of MTX to be used before side effects occur.[19] Whatever the reason, supplementing with folate allowed 83% of patients to

continue using MTX at 48 weeks, compared to only 62% of those receiving MTX alone.[16]

The significance of findings from large phase III trials of leflunomide in RA compared to MTX has been debated. In the American study, 52% of MTX-treated patients achieved an American College of Rheumatology 20% improvement (ACR 20), while 98% of those receiving MTX were given folic acid supplementation, compared to 65% of MTX-treated patients in the international trial, where only 11% of patients received folic acid during MTX therapy.[20-22] It has been proposed that the difference in ACR 20 response can be explained by folic acid's negative effect on MTX efficacy.[21] Post-hoc analysis of these two demographically distinct treatment groups yields no firm conclusions, not least because the American trial was placebo-controlled, whereas the international study included all patients who received an active compound. Folic acid, on the other hand, has been shown to reduce the effectiveness of MTX treatment at a dose of 15 mg per week.[23] It is likely that the timing of the folinic acid in relation to the MTX, as well as the dose size, play a role in efficacy.[23] Folic acid does not have a similar effect, even at higher folate to MTX ratios.[9] This could be explained by competition between folinic acid and MTX for binding to cellular transport molecules after MTX dosing, which does not occur with folic acid .[24] Given the potential for disease-modifying activity improvement, the lack of benefit in preventing MTX side effects, and the significantly higher cost of folinic acid, there appears to be no reason to recommend folinic acid over folic acid for routine administration based on current evidence. Folnic acid, on the other hand, plays an important role in the treatment of MTX overdose or acute haematological toxicity because it is a fully reduced folate that can function in biosynthetic pathways independent of dihydrofolate reductase (Table 1).

There is no agreement on folic acid dose and frequency guidelines in RA patients taking MTX. The evidence base is currently insufficient to determine the optimum dose for folic acid supplementation, and randomised controlled trials have shown that weekly folic acid doses ranging from 5 to 27.5 mg per week are effective in reducing MTX side effects.[3,10,16] Prospective trials have not directly compared daily and once-weekly folic acid dosing schedules. A recent Scandinavian review and proposal for guidelines contends that routine supplementation is unnecessary and that the introduction of folic acid should be delayed until adverse effects or an increase in MCV occur.[24] This recommendation is solely based on side-effect data and ignores the potential significant benefit in terms of cardiovascular profile.

FOLATE SUPPLEMENTATION AND CARDIOVASCULAR RISK IN RA

The importance of atherosclerotic vascular disease in RA patients is becoming better understood. RA is linked to a higher risk of death than triple-vessel coronary artery disease, and cardiovascular disease is the leading cause of death .[25-28] Hyperhomocysteinaemia is now recognized as a distinct cardiovascular risk factor, and homocysteine levels in RA patients are frequently elevated.[29] As a result, MTX folate antagonism has been shown to cause an increase in plasma homocysteine levels by interfering with homocysteine demethylation to methionine via methyl tetrahydrofolate.[30-32] Combination therapy with MTX and sulphasalazine, both of which may affect folate absorption or metabolism, may result in a higher increase in plasma homocysteine than MTX alone.[33]

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

An uncontrolled retrospective study found an apparent increase in mortality in MTX-treated RA patients with documented atherosclerotic vascular disease or hypertension compared to patients with RA starting other DMARDs.[36] This finding contradicts findings from a recent large cohort study in Wichita.[37] Between 1981 and 1999, 1,240 patients with RA were followed for an average of 6 years, with 588 receiving MTX by the end of the study. After controlling for confounding factors, MTX use was linked to a 60% reduction in the risk of all-cause mortality. Other DMARDs did not show a reduction in mortality. For cardiovascular mortality, which accounted for 44% of deaths in the cohort, the mortality benefit was even greater (hazard ratio 0.3).The suppression of inflammatory mechanisms that are central to the development of atherosclerosis may explain, at least in part, a reduction in cardiovascular risk in MTX-treated patients.[26] Although folic acid was administered to less than 20% of the MTX-treated patients in the Wichita cohort, the combination resulted in a mortality hazard

ratio of 0.2, compared to 0.5 for MTX alone.[38] This adds to the evidence that folic acid supplementation may reduce cardiovascular risk in MTX-treated RA patients. There is no clear explanation for the disparities in mortality data between these two cohort studies, but both emphasise the importance of vascular morbidity in RA patients. To better understand the impact of disease-modifying drugs on mortality and cardiovascular disease, more prospective data are needed.

SUMMARY AND GUIDELINES

In conclusion, folic acid supplementation in people with RA who are taking MTX is likely to lower the incidence of liver function test abnormalities and may lower the incidence of GI intolerance and stomatitis. The incidence of significant leucopenia during MTX treatment is low, and some evidence suggests that folic acid supplementation may help. Folic acid supplementation reduces cardiovascular risk by offsetting the increase in plasma homocysteine levels associated with MTX therapy; more research is needed in this area. Folic acid supplementation has not been shown to reduce MTX efficacy in the treatment of RA, and it is likely that efficacy and common toxicity are mediated through different metabolic pathways.

Folinic acid is no more effective than folic acid in preventing MTX-related side effects, but it may reduce MTX effectiveness in some cases and is more expensive. Folnic acid, as a fully reduced folate that bypasses dihydrofolate reductase, can be used to treat acute haematological toxicity and MTX overdose. Folic acid, according to current evidence, improves MTX continuation rates without compromising efficacy. It has almost no side effects and is inexpensive (about 2 p per week in the UK).[39] The emerging data on cardiovascular risk in patients with inflammatory disease, as well as the potential for reducing this risk with supplemental folic acid, adds to the case for considering folic acid in MTX-treated patients.

We propose that all patients receiving MTX for the treatment of RA be given folic acid supplements on a regular basis. Although there is no data comparing the relative benefits of weekly versus daily folic acid administration, a dose of 5 mg taken orally once per week is likely to be sufficient. More research is needed to provide evidence for dose, frequency, and timing selection. The timing of folic acid administration in relation to MTX is unlikely to affect the reduction of side effects. The majority of trials have avoided administering folic acid on the same day as MTX. To reduce patient confusion and improve adherence to treatment, we proposed a consistent and pragmatic approach to folic acid supplementation.

We recommend taking 5 mg of folic acid once a week in the morning after your MTX dose.If side effects persist, a single weekly dose of 10 mg may be considered. The results of large prospective trials examining the effect of folic acid supplementation on cardiovascular risk are awaiting publication. The increasing importance of MTX in the treatment of RA, both alone and in combination with other therapies, highlights the significance of any strategy that may improve tolerability.

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