Q&A 84.3

**What is the Dose of Folic Acid to use with Methotrexate therapy for Rheumatoid Arthritis?**

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals.

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**Background**

Methotrexate is a first line disease-modifying-anti-rheumatic-drug (DMARD) for rheumatoid arthritis (1, 2). It is an antifolate agent with a chemical structure similar to that of folic acid and folinic acid (3), but its exact mechanism of action in treating this condition is unclear (3- 5). Administered in low doses, methotrexate inhibits a number of folate dependent metabolic steps, including a very potent inhibition of dihydrofolate reductase which reduces folic acid to dihydrofolic acid and to tetrahydrofolate (3). This causes a depleted pool of reduced folates and produces a state of effective folate deficiency (6). The half-life of methotrexate in the serum is in the range of 6 to 8 hours after administration of the drug and is undetectable in the serum by 24 hours (4).

It is likely that some of the side-effects of methotrexate are due to folate antagonism, (6) and the main factor influencing the decision to discontinue methotrexate is the occurrence of adverse effects, rather than lack of response (7). Between 7 and 30% of patients discontinue methotrexate in the first year due to toxicity (8). The common adverse effects associated with methotrexate can be divided into:

* minor effects e.g. mouth ulcers and gastrointestinal disturbance (2, 6, 9).
* major effects e.g. bone marrow toxicity and liver function test abnormalities (2, 6, 9)

The British Society for Rheumatology recommends that patients on methotrexate are co-prescribed a minimum dose of 5mg folic acid once weekly (10). 70 However there has been much discussion regarding the dose of supplementation and whether it has benefits in reducing toxicity without being detrimental to methotrexate efficacy.

**Answer**

Effects of Folate Supplementation on Toxicity of Methotrexate

Overall toxicity of methotrexate appears to be lower in folate supplemented patients (11-14). The risk of side-effects with methotrexate is slightly higher in the first 6 months, but the risk of any adverse effect remains throughout treatment and long-term monitoring is therefore required (15).

A systematic review of 6 double blind, randomised, placebo-controlled trials in which adult rheumatoid arthritis patients were treated with a low dose of methotrexate (<25mg/week) concurrently with folate supplementation (< 7mg per week) revealed that folate supplementation achieved (8):

* a reduced incidence of gastrointestinal side effects such as nausea, vomiting, or abdominal pain (absolute risk reduction [ARR] 9%; relative risk reduction [RRR] 26%; relative risk [RR] 0.74, 95% CI 0.59 to 0.92; p = 0.008)
* a protective effect against abnormal serum transaminase elevation caused by methotrexate, (ARR 16%, RRR 76.9%; RR 0.23, 95% CI 0.15 to 0.34; p < 0.00001)
* a reduction in patient withdrawal from methotrexate for any reason (ARR 15.2%, RRR 60.8%, RR 0.39, 95% CI 0.28 to 0.53; p < 0.00001)

A 48 week, multi-centre, randomised, double-blind, placebo-controlled study has demonstrated that folate supplementation increases the rate of continuation of methotrexate by decreasing the incidence of elevated alanine transaminase (ALT) values (12, 16). Lack of folate and untreated hyperlipidaemia are considered independent risk factors for abnormal aspartate transaminase (AST) levels according to a retrospective cohort study of 481 patients (17).

A systematic review of 6 randomised controlled trials found that folic acid supplementation significantly reduced the incidence of hepatic side-effects of methotrexate (ARR -0.358; 95% CI -0.467 to -0.248) (18).

A study investigating folate levels in methotrexate patients with rheumatoid arthritis concluded that there is a close relationship between folate status and side-effects during methotrexate therapy and that only a minority of side-effects are reported when concomitantly measured red cell folate levels are above 600 – 800 nanomol/l (13).

Raised levels of homocysteine are associated with coronary heart disease and stroke (19). Homocysteine levels are frequently elevated in rheumatoid arthritis patients and low dose methotrexate treatment may increase them further (20, 21). Folic acid supplementation lowers the prevalence of chronic hyperhomocysteinemia (19, 20, 22). Two trials (HOPE 2 and NORVIT) investigated the effect on homocysteine and cardiovascular disease in patients taking folic acid supplements and neither found a reduction in cardiovascular risk (6, 19, 22).

Effects of Folate Supplementation on Efficacy of Methotrexate

A post hoc analysis from two randomised controlled studies suggested that folate supplementation may reduce the efficacy of methotrexate (23). Another study investigating the effect of folic acid on the pharmacokinetics of methotrexate found the mean Area Under the Curve (AUC) value for methotrexate decreased by 20% after co-administration with folic acid (24). In the US a small study of 36 RA patients found methotrexate doses were increased following mandatory supplementation of enriched flour, rice, pasta, cornmeal, and other grain products with folic acid. The mean dose increased from 12.4mg to 16.6mg after food supplementation (p <0.001) (25).

Other studies have not found any significant difference in efficacy of methotrexate whether given with or without folate supplements (11, 14, 15) or regarded any negative effect on efficacy as small and easily overcome by slightly higher methotrexate dosages (16).

The potential of folic acid interfering with the gastro-intestinal absorption of methotrexate is a matter of controversy, but this possibility may be overcome by administration of folic acid 24 hours prior to the weekly methotrexate dose and 24 hours following that dose (26).

Dosing schedule

The optimal dosing schedule of folic acid supplementation in relation to methotrexate is not known. Various dosing regimen have been used in clinical studies:

* A 48 week, randomised placebo controlled multi-centre trial of 434 patients used folic acid 1mg per day(16)
* A randomised, double-blind, placebo-controlled trial of 79 patients used 5mg or 27.5mg folic acid per week, divided into 5 daily doses given on the days when methotrexate was not ingested. Both these regimens decreased methotrexate toxicity without compromising efficacy (27).
* A prospective, randomised, double-blind, placebo-controlled study of 75 patients used folic acid 5mg daily (15)
* A double-blind randomised controlled trial of 100 methotrexate patients receiving either 10mg or 30mg folic acid weekly for 24 weeks found there was no additional benefit (or harm) of using the higher dose. (28)
* A multicentre, cross-sectional comparison study of 246 methotrexate patients; 123 received 5mg and 123 receiving 30mg folic acid. DAS28 scores were statistically significantly lower for the 5mg group but tolerability and side-effects were no different between groups. (29)
* A non-inferiority comparison study of methotrexate patients on weekly vs daily folic acid supplementation found no statistical difference in effects on liver enzymes but reduced protection against GI adverse effects. (30)

A group of 75 expert rheumatologists reviewed the evidence from a systematic literature search and recommended that folate supplementation can be given routinely to patients treated with methotrexate for RA. In practice, a minimal dosage of 5 mg of folic acid once a week, at a distance from the methotrexate dose, is appropriate (31). The time interval between methotrexate and folic acid dosing was not specified.

The British Society for Rheumatology guidelines for non-biologic disease-modifying anti-rheumatic drug therapy have taken their recommendations for folic acid dosing from some of the studies mentioned above. They recommend a minimum folic acid dose of 5mg once weekly but do not specify which day in relation to methotrexate (10).

**Summary**

There is no definitive answer regarding the optimal dose of folic acid for patients with rheumatoid arthritis who are being treated with methotrexate. It is generally agreed that folic acid supplementation reduces the toxicity of methotrexate without significantly affecting efficacy; and there seems to be a consensus of opinion that folic acid supplementation should be avoided on the day of methotrexate in case it adversely affects absorption. Folic acid supplementation should be continued for the duration of methotrexate therapy because adverse effects can occur at any time.

The most commonly recommended dose regimens:

* 5mg folic acid taken the day after the methotrexate dose
* 1mg folic acid daily except on the day of methotrexate

It is considered that the folic acid dose should be high enough to prevent folate deficiency. Many reviewers have extrapolated the data from the studies and recommend using 5mg folic acid weekly. Some administer this dose the day after the methotrexate dose and others suggest that a dose taken 48 hours prior to the methotrexate dose may give added protection against the gastrointestinal adverse effects. The dose can be increased to 10mg if the patient experiences any adverse effects to the methotrexate however the evidence does not support any further benefit from increasing the dose beyond 10mg. (28, 29)

The British Society for Rheumatology guidelines for non-biologic disease modifying anti-rheumatic drug therapy recommends that methotrexate patients are co-prescribed a minimum dose of 5mg folic acid once weekly.

**Limitations**

There are some small dose comparison studies published but no large clinical studies that have specifically investigated the optimal dose of folic acid for patients with rheumatoid arthritis who are treated with methotrexate. There is wide variation in the dosing schedules chosen by rheumatologists, with decisions being made on experience and anecdotal evidence. This review has not looked at the impact of taking methotrexate as a single dose or as a divided dose. It does not investigate any comparisons between folic acid and folinic acid.

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**Quality Assurance**

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**Search strategy**

**Search Strategy for Update 2020**

1. Embase (Methotrexate + Folic Acid + Rheumatoid-Arthritis) from 2012 to 2020
2. Medline (Methotrexate + Folic Acid + Rheumatoid-Arthritis) from 2012 to 2020
3. MiDatabank Database (Methotrexate / Folic Acid / Rheumatoid-Arthritis )
4. Summary of Product Characteristics. Methotrexate 2.5mg Maxtrex by Pfizer. Date of Revision of Text Dec 2019. https://www.medicines.org.uk/emc/product/1376/smpc
5. Summary of Product Characteristics. Methotrexate 2.5mg tablets by Hospira. Date of Revision of Text Dec 2019. https://www.medicines.org.uk/emc/product/6789/smpc
6. Internet Search (Google: Methotrexate + Folic Acid + Rheumatoid-Arthritis)
7. British Society for Rheumatology
8. American College of Rheumatology
9. NICE
10. Cochrane library

**Search Strategy for Update 2012**

1. Embase (Methotrexate + Folic Acid + Rheumatoid-Arthritis) from 2005 to 2012
2. Medline (Methotrexate + Folic Acid + Rheumatoid-Arthritis) from 2005 to 2012
3. In-house Database (Methotrexate / Folic Acid / Rheumatoid-Arthritis )
4. Manufacturer (Summary of Product Characteristics Methotrexate 2.5mg Maxtrex by Pharmacia. Date of Revision of Text June 2012)
5. (Summary of Product Characteristics Methotrexate 2.5mg tablets by Hospira. Date of Revision of Text April 2012)
6. Internet Search (Google Methotrexate + Folic Acid + Rheumatoid-Arthritis)
7. NHS Evidence (Methotrexate + Folate / Folic acid) 2005 to 2012
8. British Society for Rheumatology
9. American College of Rheumatology
10. NICE

**Search Strategy for Update March 2009**

1. Embase (Methotrexate + Folic Acid + Rheumatoid-Arthritis)
2. Medline (Methotrexate + Folic Acid + Rheumatoid-Arthritis)
3. In-house Database (Methotrexate / Folic Acid / Rheumatoid-Arthritis )
4. Manufacturer (Summary of Product Characteristics Methotrexate 2.5mg Maxtrex Pharmaceuticals Date of Revision of Text April 2008)
5. (Summary of Product Characteristics Methotrexate 2.5mg tablets by Hospira Date of Revision of Text January 2008)
6. Internet Search (Google Methotrexate + Folic Acid + Rheumatoid-Arthritis)
7. Pharmline (Methotrexate + Folate)
8. British Society for Rheumatology

**Search Strategy 2006**

1. Embase (Methotrexate + Folic Acid + Rheumatoid-Arthritis)
2. Medline (Methotrexate + Folic Acid + Rheumatoid-Arthritis)
3. In-house Database (Methotrexate / Folic Acid / Rheumatoid-Arthritis )
4. Manufacturer (Summary of Product Characteristics Methotrexate 2.5mg Wyeth Pharmaceuticals Date of Revision of Text 19th January 2006)
5. (Summary of Product Characteristics Methotrexate 2.5mg tablets by Mayne Pharma Date of Revision of Text January 2005)
6. Internet Search (Google Methotrexate + Folic Acid + Rheumatoid-Arthritis)
7. Pharmline (Methotrexate + Folate)
8. Idis IOWA (Methotrexate + Folic Acid)
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