Review

Folic Acid and Folinic Acid for Reducing Side Effects in Patients Receiving Methotrexate for Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To perform a systematic review of the benefits and harms of folic acid and folinic acid in reducing the mucosal, gastrointestinal, hepatic, and hematologic side effects of methotrexate (MTX); and to assess whether folic or folinic acid supplementation has any effect on MTX benefit.

Methods. We searched the Cochrane Library, MEDLINE, EMBASE, and US National Institutes of Health clinical trials registry from inception to March 2012. We selected all double-blind, randomized, placebo-controlled clinical trials in which adult patients with rheumatoid arthritis (RA) were treated with MTX (dose ≤ 25 mg/week) concurrently with folate supplementation. We included only trials using low-dose folic or folinic acid (a starting dose of ≤ 7 mg weekly) because the high dose is no longer recommended or used. Data were extracted from the trials, and the trials were independently assessed for risk of bias using a predetermined set of criteria.

Results. Six trials with 624 patients were eligible for inclusion. Most studies had low or unclear risk of bias for key domains. The quality of the evidence was rated as "moderate" for each outcome as assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group, with the exception of hematologic side effects, which were rated as "low." There was no significant heterogeneity between trials, including where folic acid and folinic acid studies were pooled. For patients supplemented with any form of exogenous folate (either folic or folinic acid) while receiving MTX therapy for RA, a 26% relative (9% absolute) risk reduction was seen for the incidence of gastrointestinal side effects such as nausea, vomiting, or abdominal pain (RR 0.74, 95% CI 0.59 to 0.92; p = 0.008). Folic and folinic acid also appear to be protective against abnormal serum transaminase elevation caused by MTX, with a 76.9% relative (16% absolute) risk reduction (RR 0.23, 95% CI 0.15 to 0.34; p < 0.00001), as well as reducing patient withdrawal from MTX for any reason [60.8% relative (15.2% absolute) risk reduction, RR 0.39, 95% CI 0.28 to 0.53; p < 0.00001].

Conclusion. The results support a protective effect of supplementation with either folic or folinic acid for patients with RA during treatment with MTX. There was a clinically important significant reduction shown in the incidence of GI side effects and hepatic dysfunction (as measured by elevated serum transaminase levels), as well as a clinically important significant reduction in discontinuation of MTX treatment for any reason. (First Release April 15 2014; J Rheumatol 2014;41:1049–60; doi:10.3899/jrheum.130738)

Key Indexing Terms:
RHEUMATOID ARTHRITIS COCHRANE REVIEW FOLIC ACID FOLINIC ACID

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This report is based on a Cochrane review published in The Cochrane Library 2013, Issue 5 (see www.thecochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

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Accepted for publication January 31, 2014.

Methotrexate (MTX) is an antimetabolite with an antagonistic effect on folic acid metabolism. Although its exact mechanism of action in rheumatoid arthritis (RA) is uncertain, it has become the first-line drug of choice[1].

Three metaanalyses[2,3,4] estimate that a third of the patients show major improvement. However, toxicity does prevent many patients from obtaining benefit from the drug. It has been reported that mild toxicity occurs in about 60% of patients, and roughly 7% to 30% of patients discontinue MTX therapy within the first year of treatment because of toxicity[1,5].

Folic acid (also known as vitamin B9) has demonstrated health benefits in a variety of areas. Folinic acid (5-formyl tetrahydrofolate) is one active form in the group of vitamins known as folates. In contrast to folic acid (which is a synthetic form of folate), folinic acid is found naturally in foods. In the body, folinic acid can be converted into any of the other active forms of folate.

Folate deficiency occurs frequently in patients with RA, and folate stores are further decreased in patients with RA who receive MTX[6]. Gastrointestinal (GI) and hematologic side effects have been related to folate deficiency. There has been concern that high doses of folate supplementation may reduce the efficacy of, and therefore benefit seen with, MTX if the antirheumatic effects are also mediated through folate antagonism[7,8,9]. The aim of this systematic review was to determine the effect of low doses of folic acid and folinic acid in reducing GI symptoms, hepatic (liver) toxicity, and hematologic side effects of low-dose MTX in patients with RA, and to determine whether folate supplementation with folic acid or folinic acid reduces the anti-arthritis benefit of MTX therapy.

MATERIALS AND METHODS

Types of studies, participants, and interventions. We included all double-blind, randomized, placebo-controlled clinical trials comparing low doses of MTX (≤ 25 mg/week) concurrently with low-dose folate supplementation (either folic or folinic acid), with a starting dose ≤ 7 mg/week in patients older than 18 years, fulfilling the American College of Rheumatology criteria for RA[10].

Outcome measures. Major outcomes included GI symptoms (such as nausea, vomiting, or abdominal pain), mouth ulcers (stomatitis), liver toxicity (as measured by raised serum transaminases), hematologic side effects (anemia or cytopenia), and discontinuation of MTX therapy. Minor outcomes included alteration of the beneficial effect of MTX (loss of efficacy) as measured by any of the following: swollen joint count (SJC), tender joint count (TJC), pain, disability score, grip strength, patient global assessment, and physician global assessment.

Search methods for identification of studies. We searched the following electronic databases, unrestricted by language: Cochrane Library Issue 2 of 12, February 2012 (by Wiley), MEDLINE (through OVID 1946–March 2, 2012), and EMBASE (through OVID 1947–February Week 4, 2012). Reports of ongoing trials were searched in the US National Institutes of Health trial registry, ClinicalTrials.Gov (www.clincaltrials.gov). Reference lists from related publications and abstracts of selected rheumatology meetings were scanned for possible inclusion.

The MEDLINE search strategy combined the subject search with the Cochrane highly sensitive search strategy for identifying reports of randomized controlled trials (RCT)[11], and was adapted for the other databases. Full search strategies are available on request.

Following an *a priori* protocol, at least 2 review authors (BS, ZO, WK, MS, TR) independently screened all titles or abstracts generated by the searches for potentially relevant studies. We assessed the full-length articles of the selected titles or abstracts for eligibility. We resolved disagreements by consensus or third-party adjudication.

Data extraction and management. Data were independently extracted by 4 authors (ZO, BS, WK, MS). Folate supplementation was considered as "the administration of folic or folinic acid at any time with respect to MTX." The GI effects were combined (where possible). The incidence of stomatitis, as well as the incidence of abnormal serum liver enzymes, was analyzed independently. The following hematologic side effects were included, if reported: cytopenia, macrocytosis, or pancytopenia.

To assess changes in disease activity, the following measurements were considered *a priori* and ultimately included in the efficacy analysis: SJC, TJC, pain, disability score, grip strength, patient global assessment, and physician global assessment. A starting dose of ≤ 7 mg/wk folic or folinic acid was used as a cutoff value for studies to be included in the analysis. Worldwide guidelines currently support co-administration of folic acid with MTX, and where a dose value is suggested, it usually falls in the range of 0.5 to 2 mg daily[12,13,14,15].

Assessment of risk of bias (ROB) in included studies. Assessment of ROB was undertaken for each included study using the Cochrane Collaboration's ROB tool[16]. The following 7 key domains were assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other issues" (comparability of treatment and control group at entry, and appropriateness of duration of surveillance). Pairs of review authors judged the key domains as either "high risk," "low risk," or "unclear" ROB. In cases of disagreement, the decision was made by consensus.

Statistical analysis. For each trial, risk ratio (RR) and the 95% CI were calculated for dichotomous outcomes. Mean differences and 95% CI were calculated for continuous outcomes. If the scale for each assessment varied among the studies, we calculated a standardized mean difference based on end-of-trial results. If the SD of the change scores were not available we used the SD of the baseline score for each group. If we noticed missing data during data extraction, we attempted to contact the original investigators of the study to request the required information.

Heterogeneity between comparable trials was tested using a standard chi-square test and considered statistically significant at $p < 0.10$; after due consideration of the value of the I^2 statistic, a value > 50% may indicate substantial heterogeneity. If there were sufficient studies (at least 10) it was intended to assess the possibility of publication bias with funnel plots.

Data synthesis. Where appropriate, results of comparable groups of trials were pooled using the fixed-effect model, and 95% CI were calculated. If heterogeneity existed between studies, a random-effects model was used. Since folic and folinic acid do not act at the same point on the folate pathway, they were analyzed separately as well as together. Metaanalysis was facilitated by RevMan 5 software.

Grading of evidence and summary of findings tables. Major outcomes (including benefits and adverse events) were presented in summary of findings tables, which provide information on the quality of evidence and the magnitude of the intervention effect, as well as a summary of the main outcome data[17]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group approach was used to assess the quality of evidence per outcome (high, moderate, low, and very low) as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[18].

RESULTS

We initially screened 421 references, from which 15 papers

in total were selected for full text appraisal. Six RCT[19,20,21,22,23,24] met the eligibility criteria (Figure 1). The other 9 (2 abstracts and 7 articles) were excluded. All RCT included in the analysis assessed hematologic side effects with a complete blood count including platelet count. Some trials also measured mean corpuscular volume. Three of 6 included trials did not report number of patients with hematologic side effects, mean values, or measures of variance and could not be included in the analysis. Overall, the included trials reported 624 participants, of whom 385 were treated with either folinic (211 participants) or folic acid (174 participants). The study flow diagram is given in Figure 2 and characteristics of included studies in Table 1.

Effects of interventions. There was no evidence of heterogeneity between included trials. The results from the random-effects model were not substantively different from the fixed-effect model.

Folic acid versus placebo. An 81% relative (16.8% absolute) reduction in risk was observed for the incidence of abnormal serum transaminase levels (RR 0.19, 95% CI 0.10 to 0.36; $p \leq 0.00001$), and there was a statistically significant decrease in the number of people who dropped out of the studies for any reason while taking folic acid (–14.2% absolute difference; RR 0.43, 95% CI 0.29 to 0.64; $p \leq 0.0001$). A 24% relative (8.1% absolute) reduction was seen for the risk of developing GI side effects such as nausea, vomiting, or abdominal pain, although this failed to reach statistical significance. A trend toward a reduction in the incidence of stomatitis (mouth sores) was seen; however, this also failed to reach statistical significance. Table 2 provides a detailed summary of findings, including the quality of evidence. Figures 3A and 3B show the pooled data based on liver toxicity and total withdrawals when taking folic acid as compared to placebo.

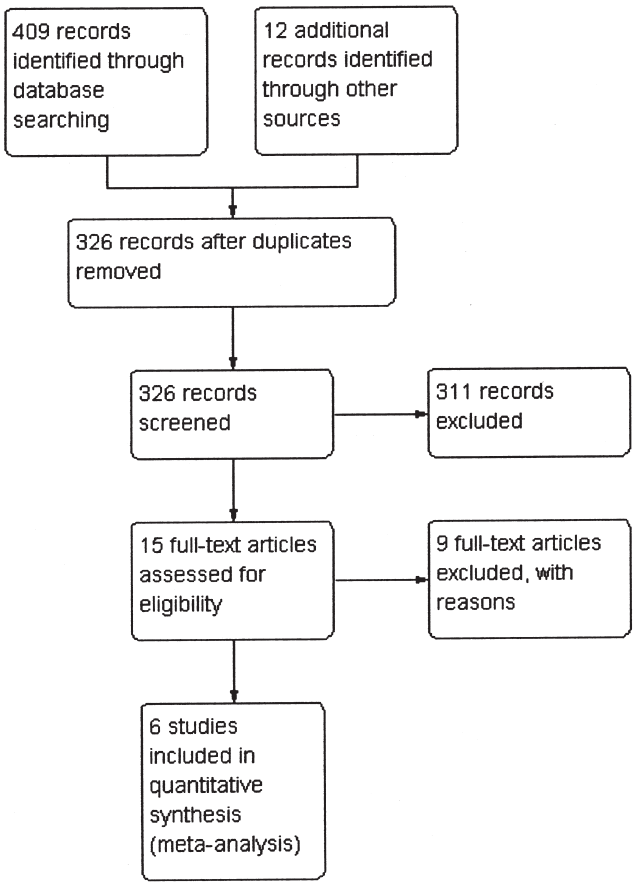

Figure 2. Study flow diagram.

	Allocation concealment (selection bias)	Adequate allocation generation?	Participants blinded?	Personnel involved in the trial blinded?	Outcome assessors blinded?	Incomplete data addressed?	Free of selective reporting?	Free of other bias?
Buckley 1990	?	?	?	+	?	?	-	-
Morgan 1990	+	-	+	+	+	?	-	-
Morgan 1994	+	+	+	+	+	?	?	+
Shiroky 1993	+	+	+	+	+	?	?	+
Van Ede 2001	-	+	+	?	?	-	+	+
Weinblatt 1993	?	?	+	?	?	+	?	-

Figure 1. Methodological quality summary of included studies. +: low risk of bias; –: high risk of bias; ?: unclear risk of bias.

Folinic acid versus placebo. A 73% relative (15.2% absolute) reduction in risk was observed for the incidence of abnormal serum transaminase levels (RR 0.27, 95% CI 0.16 to 0.44; $p \leq 0.00001$), and there was a statistically significant decrease in the number of people who dropped out of the studies for any reason while taking folinic acid (–16.2% absolute difference; RR 0.35, 95% CI 0.23 to 0.53; $p \leq 0.00001$). A 22% relative (7.6% absolute) reduction was seen for the risk of developing GI side effects such as nausea, vomiting, or abdominal pain. Similarly, a trend toward a reduction in the incidence of stomatitis (mouth sores) was seen. However, both failed to reach statistical significance. It was not possible to draw meaningful conclusions on the effect of folic or folinic acid on hematologic side effects of MTX because of the small numbers of events and poor reporting of this outcome in included trials. Table 3 provides a detailed summary of findings, including the quality of evidence. Figures 4A and 4B show the pooled

Table 1. Characteristics of included studies of patients with rheumatoid arthritis for more than 18 years.

Study	Methods/Duration	Participants	Interventions	Outcomes
Buckley 1990	Randomized, controlled, double-blind clinical trial. A crossover study design. 48 weeks	Twenty patients (11/9 placebo/folinic acid, respectively), treated with low dose of MTX (< 20 mg/week). 7 males, 13 females, mean age 57.5 yrs	Folinic acid or placebo weekly for 24 weeks, then crossed over to receive the alternate treatment. The dose of folinic acid was about equal to the dose of MTX, between 5 and 15 mg per week (mean dose: 9.9 mg/week)	Reduction of MTX toxicity (GI and hematologic side effects). Reduction of MTX efficacy (joint count, 50-foot walk time, grip strength, rheumatoid factor, ESR, patient and physician assessment)
Morgan 1990	Randomized, controlled, double-blind clinical trial. A parallel study design. 24 weeks	Thirty-two patients (16/16 placebo/folic acid, respectively) treated with low dose of MTX (< 20 mg/week). Six males, 26 females. Mean age 52.0 and 50.9 yrs for the folic acid and placebo group, respectively	Folic acid 1 mg/d or placebo. The median dose of MTX was 7.5 mg/week (2.5–15 mg/week).	Reduction of MTX toxicity (GI, hepatic, and hematologic side effects). Reduction of MTX efficacy (SJC, TJC, joint swelling index, joint tenderness index, joint pain (VAS), patient global assessment of disease activity, duration of morning stiffness, grip strength). The definition of elevated liver enzymes was AST or ALP ≥ 2 × baseline values
Morgan 1994	Randomized, controlled, double-blind clinical trial. A parallel study design. 48 weeks	Seventy-nine patients (28/25/26 placebo/low-dose folic acid/high-dose folic acid, respectively) treated with low-dose MTX (< 20 mg/week). Twenty males and 59 females. Mean age 54.4 years for the folic acid group and 52.2 for the placebo group	Folic acid or placebo weekly. The dose of folic acid was 5 mg/week or 27.5 mg/week. The mean dose of MTX was 9.16 mg/week. Only the patients receiving low-dose (5 mg/wk) folic acid or placebo were included in the study (25 and 28 patients)	Reduction of MTX toxicity. GI and hematological side effects
Shiroky 1993	Randomized, controlled, double-blind clinical trial. A parallel study design. 52 weeks	Ninety-two patients (48/44 placebo/folinic acid, respectively) treated with low-dose of MTX (< 20 mg/week). Thirty males, 62 females, with a mean age of 53.1 and 53.4 years for the folinic acid and placebo groups, respectively	Folinic acid 2.5–5 mg/wk or placebo. The mean dose of MTX was 13.6 mg/week (2.5–30 mg/week)	Reduction of MTX toxicity (GI, hepatic, and hematologic side effects). Reduction of MTX efficacy (SJC, TJC, patient global assessment, physician assessment of disease activity, duration of morning stiffness, grip strength, 50-foot walk time, morning stiffness, and HAQ). Side effects relating to toxicity were reported in the no. clinic visits at which the side effect occurred, not by no. patients. The no. patients suffering particular side effects were reported when severe enough to result in withdrawal from the study protocol. We used the latter data in the review. We extracted liver enzyme elevation data defined in the study as "moderate" or "severe" derangement, which was AST or ALT ≥ 2 × ULN

data based on liver toxicity and total withdrawals when taking folinic acid as compared to placebo.

Effect of folic or folinic acid on disease activity (efficacy of MTX). No statistically significant difference in disease activity (i.e., no statistically significant lowering of the effectiveness of the MTX to treat RA) was observed between placebo and folic or folinic acid at low dosages. There was a weak signal for an increased number of tender joints in patients treated with folic acid (+2.46 swollen joints per patient, 95% CI –6.08 to 11.00; p = 0.61), and both tender and swollen joints for folinic acid (+1.13 tender joints per patient, 95% CI –4.25 to 6.51; p = 0.68), and +1.72 swollen joints per patient (95% CI –3.47 to 6.92; p = 0.52); however, the wide CI suggest that this is likely due to

Table 1. Continued.

Study	Methods/Duration	Participants	Interventions	Outcomes
Van Ede 2001	Randomized, controlled, double-blind clinical trial. A parallel study. 48 weeks	Four hundred eleven patients (137/133/141 placebo/folic acid/folinic acid). One hundred twenty-one males, 291 females. Mean age 56.3, 54.5, and 57.1 yrs for the folic acid, folinic acid, and placebo groups, respectively	Folic acid 1 mg/d, folinic acid 2.5 mg/wk, or placebo. Mean dose of MTX 13.6 mg/week (2.5–20 mg/week)	Reduction of MTX toxicity (GI, hepatic, and hematologic side effects). Reduction of MTX efficacy (SJC, TJC, Ritchie index, pain score, patient global assessment, physician assessment of disease activity, and ESR). Liver toxicity data extracted was reported as "moderate" or "severe" and was defined as values ≥ 3 × ULN
Weinblatt 1993	Randomized, controlled, double-blind clinical trial. A parallel design. 8 weeks	Sixteen patients (8/8 placebo/folic acid, respectively), treated with low dose of MTX (< 20 mg/week). Six males, 10 females. Mean age 55.9 years for the folinic acid group and 62.3 for the placebo group	Folic acid 1 mg/wk or placebo. Mean dose of MTX 13.6 mg/week (2.5–20 mg/week)	Reduction of MTX toxicity (GI and hematologic side effects). Reduction of MTX efficacy (SJC, TJC, patient global assessment, physician assessment of disease activity, duration of morning stiffness, grip strength, 50-foot walk time, morning stiffness, and HAQ)

MTX: methotrexate; GI: gastrointestinal; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count; VAS: visual analog scale; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HAQ: Health Assessment Questionnaire; ULN: upper limit of normal.

chance. The mean differences in disease activity (SJC and TJC, patient global assessment) between placebo and folate supplementation were analyzed. There was no evidence of a reduction in the mean differences in disease activity (SJC and TJC, patient global assessment) in the folate supplementation groups compared to placebo.

Folic acid or folinic acid versus placebo. When studies using either folic acid or folinic acid were pooled, the results were similar to the analyses of the individual agents versus placebo. Table 4 provides a detailed summary of findings, including the quality of evidence. Figures 5A, 5B, and 5C show the pooled data for nausea, liver toxicity, and total withdrawals when taking either folic acid or folinic acid compared to placebo.

Publication bias. A funnel plot to assess publication bias was not provided because there were not enough included studies to conduct this type of analysis.

DISCUSSION

The results support the protective effect of folic or folinic supplementation in patients with RA during treatment with MTX. There was a clinically important and statistically significant reduction in the incidence of abnormal transaminase elevation as well as a clinically important and statistically significant reduction in discontinuation of MTX treatment for any reason in the population studied. A trend toward a reduction in GI side effects and stomatitis was demonstrated, and although this did not reach statistical significance the concurrent statistically significant reduction in discontinuation of MTX treatment for any reason may indicate that the decrease in these side effects was greatest where the side effects were severe enough to result in MTX withdrawal. Although the analysis of hematologic side effects was made difficult by small numbers of events and the outcome being poorly reported in included studies, pooled trials reported no statistically significant differences between patients with RA who received folate supplementation or placebo. The incidence of clinically important cytopenia in patients treated with low dose MTX is estimated to be < 1%[25], and therefore the size of a trial designed to detect any differences would be enormous.

Overall completeness and applicability of evidence. Sample size could potentially be a confounding variable because only 1 folinic acid study entered more than 40 patients per group. Interestingly, it appears that the benefit shown was greater for trials with higher numbers of patients and overall higher quality. Several authors[26,27] have reported that the inverse is usually true with lower-quality studies showing greater benefits, suggesting biases from poor design. The finding of a trend in the opposite direction in this metaanalysis is reassuring and indicates the likely validity of the reduction of side effects from folate co-administration.

A concern with metaanalysis is the potential existence of publication bias. It is possible that some trials have been completed that found no benefit of folic or folinic acid supplementation. It is difficult to be more definitive about publication bias in this review but we feel it is unlikely that we would be unaware of negative studies of sufficient size to eliminate the benefit seen in this metaanalysis.

Three studies (excluded from our analysis) have

Table 2. Summary of findings: folic acid compared to placebo for reducing side effects in patients receiving methotrexate (MTX) for rheumatoid arthritis.

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. Participants (No. studies)	Quality of Evidence (GRADE)	Comments
	Assumed Risk, Placebo	Corresponding Risk, Folic Acid				
GI side effects (i.e., incidence of nausea, vomiting, abdominal pain) Followup: 24 to 52 weeks	346 per 1000	263 per 1000 (197 to 349)	RR 0.76 (0.57–1.01)	355 (3)	Moderate[1,2]	Absolute risk difference –8.3% (–14.9% to 0.3%). Relative risk difference –24.0% (–43.1% to 0.8%). Not statistically significant
Stomatitis/mouth sores (incidence) Followup: 24 to 52 weeks	223 per 1000	201 per 1000 (118 to 343)	RR 0.90 (0.53–1.54)	302 (2)	Moderate[1,2]	Absolute risk difference –2.2% (–10.5% to 12.0%). Relative risk difference –9.9% (–47.1% to 53.8%). Not statistically significant
Liver toxicity (incidence of transaminase elevation) Followup: 24 to 52 weeks	208 per 1000	40 per 1000 (21 to 75)	RR 0.19 (0.10–0.36)	302 (2)	Moderate[1,2]	Absolute risk reduction –16.8% (–18.7% to –13.3%; p < 0.00001). Relative risk difference –80.8% (–89.9% to –63.9%). NNT = 6 (5 to 8)
Hematological disorders (neutropenia, etc.) Followup: 24 to 48 weeks	< 10 per 1000	See comment	RR 1.70 (0.42–6.96)	443 (2)	Low[1]	This is a rare event[3]. The studies included in this review were underpowered to detect a meaningful difference in rates of neutropenia
Total withdrawals Followup: 24 to 48 weeks	250 per 1000*	108 per 1000 (73 to 160)	RR 0.43 (0.29–0.64)	343 (3)	Moderate[1,2]	Absolute risk reduction –14.2% (–17.7% to –9.0%; p = 0.000039). Relative risk difference –56.8% (–70.8% to –36.0%). NNT = 7 (6 to 11)
No. swollen joints with folic acid (≤ 7 mg/wk) Change in no. swollen joints Followup: 48 weeks	Mean no. swollen joints per patient = 16.00	Mean no. swollen joints per patient = 14.35	See comment	42 (1)	Moderate[1,2]	Mean differences between groups in no. swollen joints Absolute difference –1.65 (–7.96 to 4.66)[4]. Relative risk difference 10.4% (–49.8% to 29.1%). Not statistically significant
No. tender joints with folic acid (≤ 7 mg/wk) Change in no. tender joints Followup: 48 weeks	Mean no. tender joints per patient = 17.63	Mean no. tender joints per patient = 20.09	See comment	42 (1)	Moderate[1,2]	Mean differences between groups in no. tender joints 2.46 (–6.08 to 11.00)[5]. Relative risk difference 14.0% (–34.5% to 62.4%). Not statistically significant

*The basis for the assumed risk (e.g., the median control group risk across studies) is below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1] No. events < 300. [2] < 400 participants. [3] Incidence of clinically important cytopenia in patients treated with low-dose MTX is estimated to be < 1%. [4] Posttreatment no. swollen joints not reported. Change scores presented here. [5] Posttreatment no. tender joints not reported. Change scores presented here. RR: risk ratio; NNT: number needed to treat.

suggested that high-dose folinic acid supplementation may reduce the beneficial effects of MTX on RA[7,8,9]. In a previous version of this review (where these trials were included) there was a difference observed for high-dose folinic acid, which may have suggested a decrease in benefit of the MTX on the arthritis (an isolated increase in the number of tender joints but not in other clinical variables such as patient global assessment). These results were mostly driven by the study by Joyce, *et al*[8] and in our view are still inconclusive. We analyzed the effect of adding these studies back into our metaanalysis, and even when these studies were included the overall results did not show a statistically significant decrease in MTX efficacy. There are no studies that suggest folic acid may alter the efficacy of

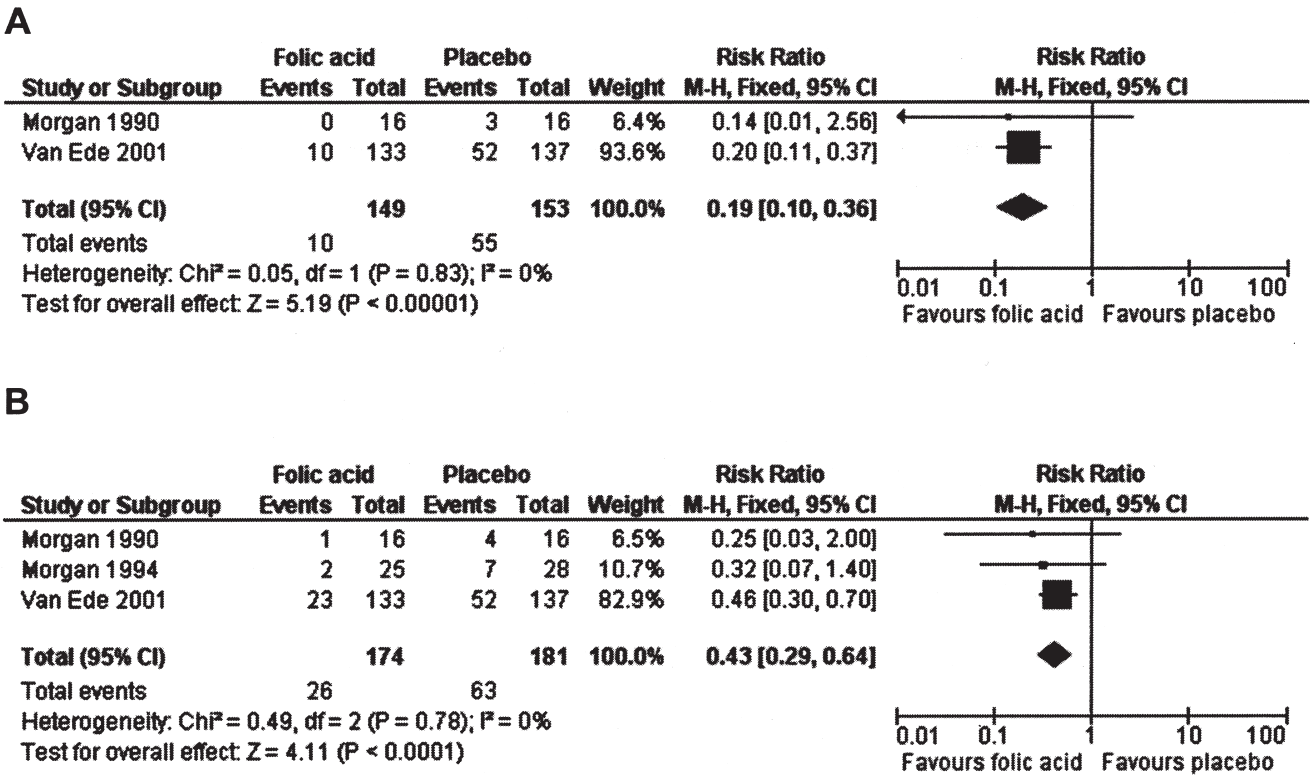

Figure 3. A. Liver toxicity (folic acid vs placebo). B. Total withdrawals (folic acid vs placebo).

MTX, despite a folic acid to MTX ratio in some trials higher than the folinic acid to MTX ratio used in the study by Joyce, *et al*[8], a finding that suggested a decrease in MTX efficacy. We did not find any major differences in disease activity between placebo and folic acid at low dosages. It is possible that the timing of administration of folinic acid and MTX, as well as the folinic acid to MTX ratio, may alter the efficacy of MTX, and it should be noted that this question was not possible to include in the design of this review.

Our results support the protective effects of low-dose folate supplementation in reducing GI and hepatic side effects of MTX in patients with RA. This is consistent with the recommendations by some authors[22,24,28,29], as well as current prescribing guidelines. Deciding which of the 2 forms of folate supplementation should be recommended is more difficult. Experts have differing recommendations, often acknowledging that there is insufficient evidence for advising the use of one compound over the other[5,24,26,27,30].

There is no evidence to date of a significant difference between folic or folinic acid. The results in this metaanalysis were less impressive for folinic acid, but 4 of the 5 studies had small sample sizes, and the larger study by Shiroky, *et al*[22] did show a benefit. Given both the efficacy of folic acid in reducing MTX side effects and its low cost compared with folinic acid, the use of folic acid is likely to be the more cost-effective therapy. For folinic acid to be considered cost-effective it must be proven more effective than folic acid at reducing MTX side effects.

One study[31] examined in detail the economics of folate supplementation in patients with RA and concluded that, aside from the differences in cost between folic and folinic acid, potentially the largest influence on overall treatment costs relates to the increased drug survival seen with either agent. If folate supplements can help patients tolerate MTX longer, it may delay or prevent a change in treatment to a far more expensive biologic agent. It is unclear whether all patients taking MTX, or only those with side effects, should receive folate supplementation. Our systematic review cannot address this issue. Most guidelines and texts recommend folate be given to all patients receiving MTX. Yet the effects of folic or folinic acid on the development of liver disease are unknown. It has been suggested that supplementation may have a protective effect on the development of liver disease, in which case universal administration could perhaps be considered.

Supplementation with folic or folinic acid in patients with RA who are taking MTX provides a reduction in the incidence of abnormal liver function tests and a reduction in overall withdrawal from treatment. There is also a trend toward a reduction in the incidence of GI side effects and stomatitis. The results of our review do not suggest any clear clinical advantage of one form of folate over the other.

Table 3. Folinic acid compared to placebo for reducing side effects in patients receiving methotrexate (MTX) for rheumatoid arthritis.

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. Participants (No. studies)	Quality of Evidence (GRADE)	Comments
	Assumed Risk, Placebo	Corresponding Risk, Folinic Acid				
GI side effects (i.e., nausea, vomiting, abdominal pain) Followup: 24 to 52 weeks	346 per 1000	270 per 1000 (204 to 353)	RR 0.78 (0.59–1.02)	426 (4)	Moderate[1,2]	Absolute risk difference –7.6% (–14.2% to 0.7%). Relative risk difference –22.0% (–41.0 to 2.0%). Not statistically significant
Stomatitis/mouth sores (incidence) Followup: 24 to 52 weeks	223 per 1000	156 per 1000 (103 to 239)	RR 0.70 (0.46–1.07)	410 (3)	Moderate[1,2]	Absolute risk difference –6.7% (–12.0% to 0.16%). Relative risk difference –30.0% (–53.8% to 7.2%). Not statistically significant
Liver toxicity (incidence of transaminase elevation) Followup: 8 to 52 weeks	208 per 1000	56 per 1000 (33 to 92)	RR 0.27 (0.16–0.44)	358 (3)	Moderate[1,2]	Absolute risk reduction –15.2% (–17.5% to –11.6%; p < 0.00001). Relative risk reduction –73.1% (–84.1% to –55.8%). NNT = 7 (6 to 9)
Hematological disorders (neutropenia, etc.) Followup: 52 weeks	< 10 per 1000[3]	See comment	RR 1.46 (0.25–8.59)	278 (1)	Low[1]	This is a rare event[3]. The studies included in this review were underpowered to detect a meaningful difference in rates of neutropenia
Total withdrawals Followup: 8 to 52 weeks	250 per 1000	88 per 1000 (58 to 133)	RR 0.35 (0.23–0.53)	386 (3)	Moderate[1,2]	Absolute risk reduction –16.2% (–19.2% to –11.7%; p < 0.00001). Relative risk reduction –64.8% (–76.8% to –46.8%). NNT = 6 (5 to 9)
No. swollen joints with folinic acid (≤ 7 mg/wk). Change in no. swollen joints Followup: 8 to 52 weeks	Mean no. swollen joints per patient = 19.13	Mean no. swollen joints per patient = 20.29	See comment	100 (3)	Moderate[1,2]	Mean differences between groups in no. swollen joints (absolute difference) –1.72 (–3.47 to 6.92)[4]. Relative risk difference 8.1% (–16.3% to 32.6%). Not statistically significant
No. tender joints with folinic acid (≤ 7 mg/wk) Change in no. tender joints Followup: 8 to 52 weeks	Mean no. tender joints per patient = 14	Mean no. tender joints per patient = 13.88	See comment	80 (2)	Moderate[1,2]	Mean difference between groups in no. tender joints 1.13 (–4.25 to 6.51)[5]. Relative risk difference: 6.3% (–23.9% to 36.6%). Not statistically significant

* The basis for the assumed risk (e.g., the median control group risk across studies) is below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1] No. events < 300. [2] Less than 400 participants. [3] The incidence of clinically important cytopenia in patients treated with low-dose MTX is estimated to be < 1%. [4] Posttreatment no. swollen joints not reported. Change scores presented here. [5] Posttreatment no. tender joints not reported. Change scores presented here. RR: risk ratio; NNT; number needed to treat; GI: gastrointestinal.

Quality of the evidence. A major problem in synthesizing evidence is the lack of uniformity in outcome measures. All studies described themselves as randomized but some did not give details of how the randomization sequence was generated and what precautions were taken in relation to concealment of allocation. We encourage investigators to describe fully the numbers and flow of patients by treatment group throughout the trial and to clearly report the reasons for dropouts for each group. The studies were small, with few events. This metaanalysis was hampered by lack of uniformity in the way these items were reported.

Potential biases in the review process. The review was restricted to RCT; we excluded clinical controlled trials, thus limiting the potential for bias.

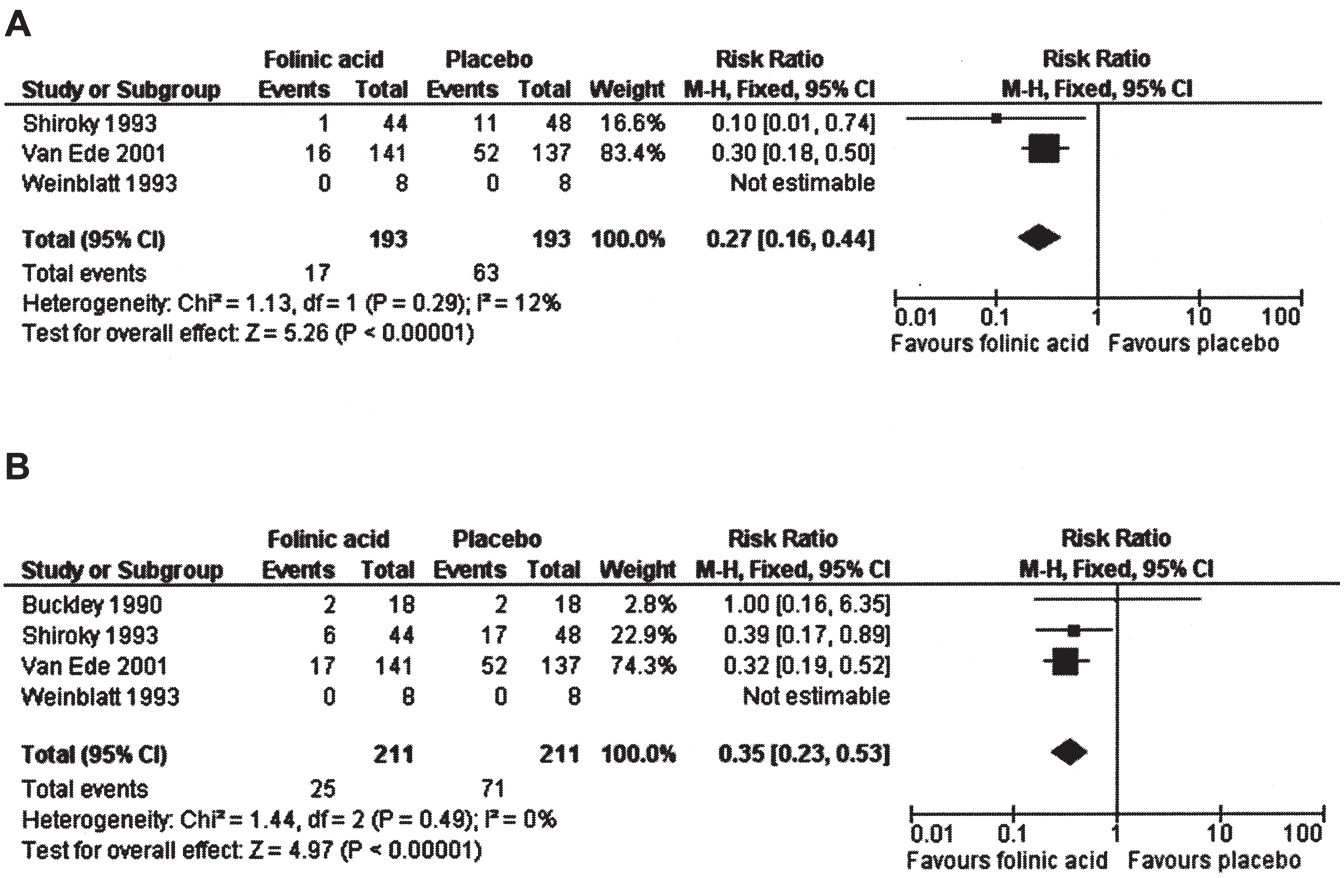

Figure 4. A. Liver toxicity (folinic acid vs placebo). B. Total withdrawals (folinic acid vs placebo).

Our results support the protective effect of low doses of folic or folinic acid supplementation in reducing GI and liver side effects of MTX in patients with RA as well as in reducing patient discontinuation of MTX therapy. A multicenter RCT comparing both folate compounds and including an economic analysis may be necessary to adequately assess potential differences between the drugs.

ACKNOWLEDGMENT

We acknowledge Maria E. Suarez-Almazor and David Moher for their contribution to the original systematic review. The authors also acknowledge Alicia White for preparing the retrospective risk-of-bias tables and the original summary of findings tables, and Jessie McGowan and Margaret Sampson for preparing and executing the original search strategy. We also acknowledge Micere Thuku, Jordi Pardo, Lara Maxwell, and the Cochrane Musculoskeletal Group for their ongoing support and their help with the preparation of this manuscript.

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Table 4. Summary of findings: folic or folinic acid (any) compared to placebo for reducing side effects in patients receiving methotrexate (MTX) for rheumatoid arthritis.

Outcomes	Illustrative Comparative Risks* (95% CI) Assumed Risk, Placebo	Corresponding Risk, Either Folic or Folinic Acid	Relative Effect (95% CI)	No. Participants (No. studies)	Quality of Evidence (GRADE)	Comments
GI side effects (nausea, vomiting, abdominal pain) Followup: 24 to 52 weeks	346 per 1000	256 per 1000 (204 to 318)	RR 0.74 (0.59–0.92)	644 (6)	Moderate[1]	Absolute risk reduction –9.0% (–14.2% to –2.8%; p = 0.008). Relative risk reduction –26.0% (–1.0% to –8.1%). NNT = 11 (7 to 35).
Stomatitis/mouth sores (incidence) Followup: 24 to 52 weeks	223 per 1000	161 per 1000 (109 to 236)	RR 0.72 (0.49–1.06)	575 (4)	Moderate[1]	Absolute risk difference –6.2% (–11.4% to 1.3%). Relative risk difference –27.8% (–51.1% to 5.8%). Not statistically significant.
Liver toxicity (incidence of transaminase elevation) Followup: 8 to 52 weeks	208 per 1000	48 per 1000 (31 to 71)	RR 0.23 (0.15–0.34)	551 (4)	Moderate[1]	Absolute risk reduction –16.0% (–17.7% to –13.7%; p < 0.00001). Relative risk reduction –76.9% (–85.1% to –65.9%). NNT = 6 (6 to 7).
Hematological disorders (neutropenia, etc.) Followup: 24 to 52 weeks	< 10 per 1000	See comment	RR 1.55 (0.40–5.91)	443 (2)	Low[1]	This is a rare event[2]. The studies included in this review were underpowered to detect a meaningful difference in rates of neutropenia.
Total withdrawals Followup: 8 to 52 weeks	250 per 1000	98 per 1000 (70 to 133)	RR 0.39 (0.28–0.53)	640 (6)	Moderate[1]	Absolute risk reduction –15.2% (–18.0% to –11.7%) (p < 0.00001) Relative risk reduction –60.8% (–72.0% to –46.8%). NNT = 7 (6 to 9).
No. swollen joints Change in no. swollen joints Followup: 8 to 52 weeks	Mean no. swollen joints per patient in the control group is 18.24	Mean no. swollen joints per patient = 18.47	See comment	142 (4)	Moderate[1]	SMD between groups in no. swollen joints 0.05 (–0.28 to 0.38). Absolute risk difference 4.82% (–27.01% to 36.6%). Relative risk difference 26.42% (–148.08% to 201.04%). Not statistically significant
No. tender joints Change in no. tender joints Followup: 8 to 52 weeks	Mean no. tender joints per patient in control group is 15.23	Mean no. tender joints per patient = 16.05	See comment	122 (3)	Moderate[1]	SMD between groups in no. tender joints 0.09 (–0.27 to 0.45). Absolute risk difference 4.55% (–13.65% to 22.75%). Relative risk difference 29.88% (–89.63% to 149.38%). Not statistically significant

* The basis for the assumed risk (e.g., the median control group risk across studies) is below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1] No. events is < 300. [2] The incidence of clinically important cytopenia in patients treated with low-dose MTX is estimated to be < 1%. RR: risk ratio; NNT: number needed to treat; SMD: standardized mean difference.

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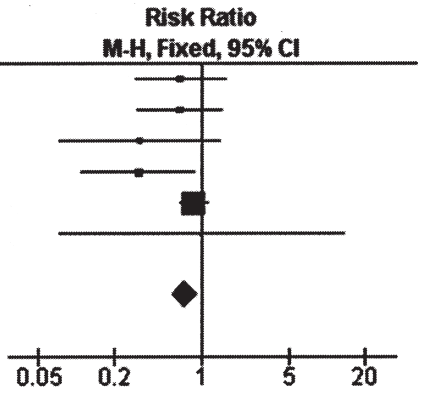
A

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buckley 1990	6	20	9	20	8.0%	0.67 [0.29, 1.52]
Morgan 1990	6	16	9	16	8.0%	0.67 [0.31, 1.43]
Morgan 1994	2	25	7	28	5.9%	0.32 [0.07, 1.40]
Shiroky 1993	4	44	14	48	11.9%	0.31 [0.11, 0.88]
Van Ede 2001	95	274	55	137	65.3%	0.86 [0.67, 1.12]
Weinblatt 1993	1	8	1	8	0.9%	1.00 [0.07, 13.37]
Total (95% CI)		**387**		**257**	**100.0%**	**0.74 [0.59, 0.92]**
Total events	114		95			

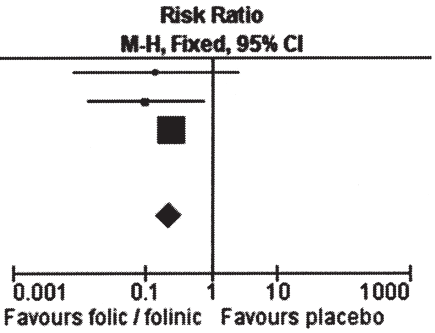
Heterogeneity: Chi² = 5.50, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 2.64 (P = 0.008)



B

Study or Subgroup	Folic / Folinic Acid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morgan 1990	0	16	3	16	4.2%	0.14 [0.01, 2.56]
Shiroky 1993	1	44	11	48	12.6%	0.10 [0.01, 0.74]
Van Ede 2001	26	274	52	137	83.2%	0.25 [0.16, 0.38]
Weinblatt 1993	0	8	0	8		Not estimable
Total (95% CI)		**342**		**209**	**100.0%**	**0.23 [0.15, 0.34]**
Total events	27		66			

Heterogeneity: Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 6.97 (P < 0.00001)



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Study or Subgroup	Folic / Folinic Acid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buckley 1990	2	18	2	18	2.0%	1.00 [0.16, 6.35]
Morgan 1990	1	16	4	16	4.1%	0.25 [0.03, 2.00]
Morgan 1994	2	25	7	28	6.7%	0.32 [0.07, 1.40]
Shiroky 1993	6	44	17	48	16.6%	0.39 [0.17, 0.89]
Van Ede 2001	40	274	52	137	70.6%	0.38 [0.27, 0.55]
Weinblatt 1993	0	8	0	8		Not estimable
Total (95% CI)		**385**		**255**	**100.0%**	**0.39 [0.28, 0.53]**
Total events	51		82			

Heterogeneity: Chi² = 1.25, df = 4 (P = 0.87); I² = 0%
Test for overall effect: Z = 5.91 (P < 0.00001)

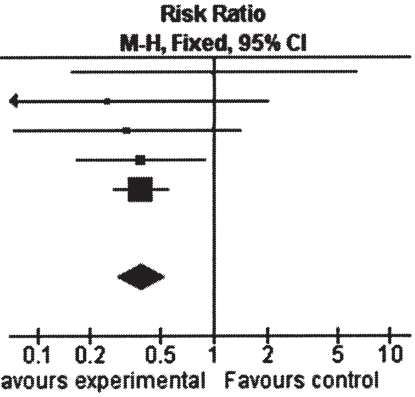

Figure 5. A. Nausea/gastrointestinal upset (folic or folinic acid vs placebo). B. Liver toxicity (folic or folinic acid vs placebo). C. Total withdrawals (folic or folinic acid vs placebo).

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