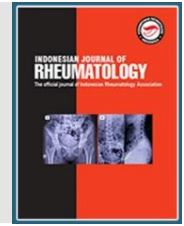




Indonesian Journal of Rheumatology

Journal Homepage: <https://journalrheumatology.or.id/index.php/IJR>



Effect of Folic Acid Supplementation for Reducing Methotrexate Side Effects in Patients with Rheumatoid Arthritis: an Evidence-based Case Report

Athira Presialia^{1*}, Bambang Setyohadi²

¹ Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

² Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ARTICLE INFO

Keywords:

Folic Acid Supplementation
Methotrexate
Rheumatoid Arthritis

Corresponding author:

Athira Presialia

E-mail address:

athira_presialia@yahoo.com

All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/IJR.v12i2.113>

ABSTRACT

Background: Rheumatoid arthritis is a chronic inflammatory joint disease, indicated by a symmetrical erosive synovitis. Disease-modifying anti-rheumatic drugs (DMARDs) are known to interfere with signs and symptoms of RA, improve physical function and therefore increase patient productivity. Methotrexate is an anchor drug for rheumatoid arthritis patients, however, its related mechanism of action with folate deficiency resulting in some side effects, including gastrointestinal and liver toxicity. Folic acid supplementation may reduce these side effects. **Method:** A search was conducted on *Pubmed*, *Cochrane*, *EBSCOhost*, and *ProQuest*. After the selection of title and abstract was done using inclusion and exclusion criteria, which led to one relevant article. The selected study was critically appraised for its validity, importance, and applicability. **Result:** In rheumatoid arthritis patient receiving methotrexate, there was a statistically significant reduction in the incidence of abnormal transaminase elevation (RR: 0.19, 95% CI: 0.10-0.36), but the reduction in gastrointestinal side effects did not reach statistical significance (RR: 0.76, 95% CI: 0.57-1.01). **Conclusion:** Folic acid supplementation has an effect in reducing gastrointestinal and liver toxicity as side effects of methotrexate in rheumatoid arthritis patients.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, indicated by a symmetrical erosive synovitis. The disease affects women 2 to 3 times more often than men, with a worldwide prevalence of about 5 per 1000 adults. RA caused disability, reduced physical function, and increased mortality.^{1,2}

In the last 15 years, there are improvements in RA treatment. Disease-modifying anti-rheumatic drugs (DMARDs) are known to interfere with signs and symptoms of RA, improves physical function and therefore increases patient productivity.^{1,2} Among conventional DMARDs, methotrexate is an anchor drug for rheumatoid arthritis. Aside of its superiority, its related mechanism of action with folate deficiency

resulting in some side effects, including gastrointestinal and liver toxicity. Guideline from European League Against Rheumatism (EULAR) recommended folate supplementation, including folic acid, to limit the toxicity of methotrexate.³ However, there is still controversy regarding the effect of the supplementation. This report was made to identify whether folic acid supplementation is effective in reducing methotrexate side effects, such as gastrointestinal and liver toxicity.

Case Illustration

A 40-year-old woman was diagnosed with rheumatoid arthritis. According to physical examination, the patient was in a good condition, boutonniere deformities were found in both hands,

and there was also an ulnar deviation of the right hand. The laboratory findings were all within normal range, including ALT and AST, except elevated rheumatoid factor (56.5 IU/mL) and erythrocyte sedimentation rate (83 mm/hour). Beside the regular prescription of methotrexate, the doctor considered to administer folic acid 5mg/week.

Clinical Question

Does the folic acid supplementation lead to reduction of methotrexate side effects (gastrointestinal side effects and liver toxicity) among rheumatoid arthritis patients?

2. Method

The search was conducted on Pubmed, Cochrane, EBSCOhost and ProQuest on November 1st-4th 2018, using the keywords “folate supplementation”, “methotrexate side effect”, and “rheumatoid arthritis” along with its synonyms and related terms (Table 1). Search strategy, results, the inclusion and exclusion criteria are shown in a flowchart (Figure 1). After the selection, critical appraisal was done using several aspects based on Center of Evidence-based Medicine, University of Oxford for systematic review.⁴

Table 1. Searching strategy

Database	Search terms	Results	1st Selection	Selected
PubMed	(folate supplementation OR folic acid supplementation) AND (methotrexate side effect) AND (rheumatoid arthritis)	488	4	0
Cochrane	((folate) OR folic acid) OR folic acid) AND methotrexate) AND rheumatoid arthritis	48	1	1
EBSCOhost	(AB folate supplementation OR AB folate OR AB folic acid supplementation OR AB folic acid) AND (AB methotrexate OR AB methotrexate toxicity) AND (AB rheumatoid arthritis OR AB arthritis rheumatoid)	1145	3	0
ProQuest	(ab(methotrexate) OR ab(methotrexate side effect) OR ab(methotrexate toxicity)) AND (rheumatoid arthritis OR arthritis rheumatoid) AND (ab(folate) OR ab(folate supplementation) OR ab(folic acid) OR ab(folic acid supplementation))	343	0	0

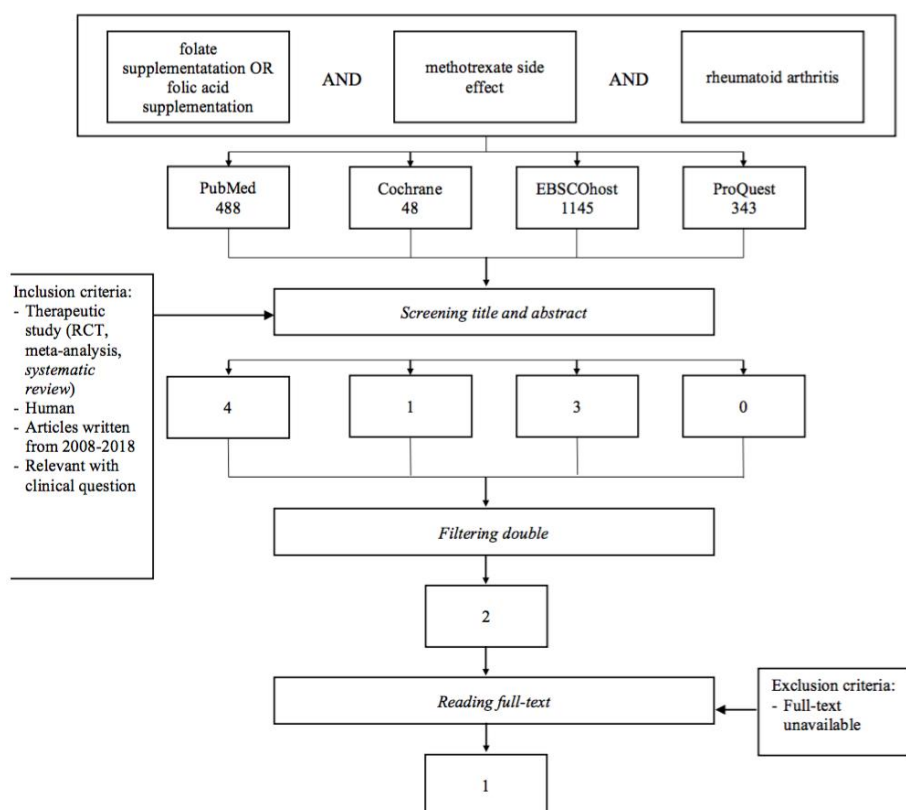


Figure 1. Flow chart of search strategy

3. Result

From the selection and filtration, one meta-analysis study was obtained. Meta-analysis from double-blind, randomized, placebo-controlled clinical trials done by Shea et al. The critical appraisal result of the meta-analysis was shown on Table 2. From the table, it was concluded that the meta-analysis study is valid, important, and relevant to our patient with level of evidence 1a. This meta-analysis

aimed to determine the effect of folic acid and folinic acid in reducing gastrointestinal, hepatic (liver toxicity), and hematologic side effects of low dose MTX in patients with rheumatoid arthritis, and to determine if folate supplementation reduces the arthritis benefit of MTX therapy. This meta-analysis searched studies from Cochrane, MEDLINE, and EMBASE, and NIH clinical trials registry from 1999 to 2012.

Table 2. Critical appraisal of meta-analysis

	Guide	Result
Validity	Did the meta-analysis address a focused question?	Yes
	Were the criteria used to select articles for inclusion appropriate?	Yes
	Is it likely that important relevant studies were missed?	No
	Was the validity of the included studies appraised?	Yes
	Were the assessments of studies reproducible?	Yes
	Were the results similar from study to study?	Yes
Importancy	What are the overall results of the meta-analysis?	There was a statistically significant reduction in the incidence of abnormal transaminase elevation (RR: 0.19, 95% CI: 0.10-0.36), but the reduction in gastrointestinal side effects

		did not reach statistical significance (RR: 0.76, 95% CI: 0.57-1.01)
Applicability	Can the results be applied to my patient care?	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harm and costs?	Yes

4. Discussion

This study showed that there was a statistically significant reduction in the incidence of abnormal transaminase of methotrexate (RR: 0.19, 95% CI: 0.10-0.36) but the reduction in the gastrointestinal side effects did not reach a significant result (RR: 0.76, 95% CI: 0.57-1.01). However, there was a clinically important significant reduction in discontinuation of methotrexate treatment, as it was recommended by Japan College of Rheumatology 2016 guideline in Japan.^{6,7}

The precise mechanism of action of methotrexate has not been known yet. Methotrexate inhibits the enzyme dihydrofolate reductase which acts as donors of 1-carbon moieties in the formation of metabolic intermediates, resulting an effective folate deficiency. As a rheumatoid arthritis treatment, methotrexate acts via a number of intracellular pathways. Methotrexate is converted to polyglutamated forms, which are potent inhibitors to a number of folate-dependent enzymes. This folate deficiency states may influence the occurrence of adverse effects, including gastrointestinal problems, liver toxicity, and bone marrow toxicity. It is then concluded that folic acid supplementation should be recommended in all patients taking methotrexate.⁸ This recommendation also supported by a meta-analysis study conducted by Ortiz et al in 1998.⁹ Japan College of Rheumatology 2016 guideline in Japan stated that folic acid supplementation is especially recommended for patients receiving more than 8 mg of MTX per week, elderly patients at higher risk of adverse events, or those with renal insufficiency.⁷

Using a starting dose of < 7 mg per week, this study confirmed that low-dose folate supplementation has such protective effects. FOLVARI study conducted by Dhir et al.¹⁰ revealed

that the use of a higher dose of folic acid (30 mg per week) vs. the usual dose (10 mg per week) had not reduced the toxicity any further. This may reinforce the previous theory that folic acid solely corrects the intracellular folate deficiency from MTX consumption.^{10,11} Studies and guidelines recommended a single dose of 5 mg per week be taken on the morning following the MTX dosing and this can be increased to 10 mg per week should there be adverse effects. This approach was necessary to improve patient adherence to treatment.^{7,8}

Notwithstanding with the above, this study still has some limitations as it did not validate if folate supplementation is more beneficial to be given on daily or weekly basis. In addition, there is no current evidence on co-administration of folic acid on the same day as MTX. There was no confirmation either if the folate should be given to all patients receiving methotrexate or only those showing side effects.

5. Discussion

Low-dose of folic acid supplementation has an effect in reducing gastrointestinal and liver toxicity side effects of methotrexate in rheumatoid arthritis patients. The availability and cost offered from the supplementation also add a positive value, and therefore can be recommended in clinical practice. We suggest other further research to study the frequency and timing of folic acid administration, and also whether the folate should be given to all patients receiving methotrexate or only those with side effects.

6. References

1. Indonesian Rheumatology Association. Indonesian rheumatology association recommendation in diagnosis and management of rheumatoid arthritis. Indonesian Rheumatology Association. 2014.

2. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. *JAMA*. 2018;320(13):1360-1372
3. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76:960-977
4. Centre for Evidence Based Medicine. Oxford centre for evidence-based medicine-level of evidence. CEBM [cited 2018 Nov 4]. Available from:
<https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
5. Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, Bombardier C, Wells GA, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art No: CD000951
6. Berglin E, Dahlqvist SR. Comparison of the 1987 ACR and 2010 ACR/EULAR classification criteria for rheumatoid arthritis in clinical practice: a prospective cohort study. *Scand J Rheumatol*. 2013;42(5):362-8
7. Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. *Modern Rheumatology*, DOI: 10.1080/14397595.2018.1472358
8. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology*. 2004;4(3):267-271
9. Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis: A metaanalysis of randomized controlled trials. *J Rheumatol*. 1998;25:36-43
10. Dhir, V., Sandhu, A., Kaur, J. et al. Comparison of two different folic acid doses with methotrexate – a randomized controlled trial (FOLVARI Study). *Arthritis Res Ther* 2015;17:156.
<https://doi.org/10.1186/s13075-015-0668-4>
11. Morgan SL, Baggott JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. *Ann Intern Med*. 1994;121:833-41.