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Real-world experiences of folic acid supplementation (5 *versus* 30 mg/week) with methotrexate in rheumatoid arthritis patients: a comparison study

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SUMMARY

The objective of this study was to compare the tolerability of methotrexate in two different regimes of folic acid (FA) supplementation in rheumatoid arthritis (RA). We performed a multicenter, cross-sectional observational cohort study on 240 RA patients with 120 patients each in 5 mg of FA weekly and 30 mg of FA weekly supplementation.

There were no significant differences for side effects (14.2 versus 22.5%, P=0.523) and discontinuation of methotrexate (3.6 versus 13.3%, P=0.085). RA patients given 5 mg of FA weekly supplementation had a lower disease activity score 28 compared to 30 mg of FA weekly supplementation [3.44 (1.10) versus 3.85 (1.40), P=0.014].

FA supplementation of 5 mg per week and 30 mg per week was associated with similar tolerability of methotrexate in RA patients.

Key words: *Folic acid; methotrexate; rheumatoid arthritis; disease activity score 28; treatment regimes.*

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INTRODUCTION

Methotrexate (MTX) is the anchor treatment for rheumatoid arthritis (RA), whether as a monotherapy or as a combination therapy (1, 2). However, MTX is associated with significant number of side effects, which can lead to discontinuation of treatment. It has been reported that mild toxicity occurred in about 60% of patients, and roughly 7 to 30% of patients discontinued MTX therapy within the first year of treatment because of toxicity (3). MTX side effects range from gastrointestinal (nausea, vomiting, abdominal pain), stomatitis, transaminitis, bone marrow suppression and alopecia.

The current major guidelines suggest folic acid (FA) supplementation in MTX treated RA patients to reduce side effects of MTX and to improve drug survival. In patients with RA treated with MTX, administration of 5 mg of folic or folinic acid/week is recommended, separating the intake of it from MTX by 24 h (4). The recently published FOLVARI Study concluded that there was no additional benefit (or harm) of a higher dose of folic acid (30 mg/week) over a usual dose (10 mg/week) in a clinical trial setting (5). A recent review suggests that low dose FA (≤7 mg per week) can reduce gastrointestinal side effects, hepatic dysfunction and discontinuation of MTX treatment (3). On the other hand, another study has shown that the use of FA supplementation may reduce the efficacy of MTX and increases the dosage requirement of MTX (6). There is no consensus for the optimal dosing or administration of FA supplementation in MTX treated RA patients. Therefore, the search for the optimal dosing and administration of FA supplementation can potentially benefit RA patients receiving MTX therapy.

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The aim of our study is to compare the tolerability of MTX in RA patients assuming 5 mg versus 30 mg of FA weekly in a real world setting. Specifically, we compared the side effects of MTX (gastrointestinal side effects, hepatic dysfunction, pulmonary fibrosis, infection and others) and discontinuation of MTX between the 2 folic acid regimes in real-world settings.

MATERIALS AND METHODS

Study design

We conducted a cross-sectional observational cohort study of 240 patients with a diagnosis of RA who received treatment at Sarawak General Hospital, Miri Hospital and Tuanku Ja'afar Hospital. There were 120 patients each in 5 mg of folic acid weekly and 30 mg of folic acid weekly supplementation. In Sarawak General Hospital and Miri Hospital, the practice of folic acid supplementation was 5 mg weekly. Patients were given folic acid 5 mg one day after they took their MTX. In Tuanku Ja'afar Hospital, folic acid supplementation was 30 mg weekly. Patients were given folic acid 5 mg daily except on the day they took their MTX (total 30 mg/week). This study was approved by Malaysian Research Ethnics Committee.

Sample size

The study was designed to have statistical power of 0.8 and P-value of 0.05. Since there were no previous studies that directly compared these 2 doses of FA supplementation, we used the estimated incidence of gastrointestinal side effects for MTX with folic acid supplementation and placebo, which was 9 and 29.2% (7). Thus, to detect a 20% difference for our primary outcome, we needed 54 patients in each arm of our study.

For the second outcome of discontinuation of MTX, we used the MTX discontinuation rate due to toxicity, which ranges from 7-30% (3). In order to detect a 23% difference, we needed 44 patients in each arm of our study. There was no missing data in our population. Hence, a sample size of 240 was adequately powered for the study.

Patients

We recruited 240 consecutive RA patients who fulfilled inclusion and exclusion criteria during their clinic visit from April 1 to June 30, 2014. Data collection was stopped once 120 patients were recruited in each group. Patients were included into the study if they were diagnosed with RA based on the 1987 revised American College of Rheumatology (ACR) criteria (8), more than 18 years old and received MTX with FA supplementations in their treatment regimes. We excluded patients who had history of gastrointestinal disease (peptic ulcer disease, gastritis, gastroesophageal reflux syndrome), liver disease (viral hepatitis, autoimmune hepatitis and alcoholic liver disease), hematological disease causing cytopenias, mixed connective tissue disorder and overlap syndrome.

Data collection

We collected demography data and clinical data of RA based on face-to-face interviews and case notes review. Clinical data on RA included date of diagnosis, treatment regimes (current dose of prednisolone, other disease modifying anti rheumatic drugs (DMARDs) and biologic DMARDs, non-steroidal anti-inflammatory drugs, other analgesics, anti-emetics, H2-anatagonists and proton pump inhibitors) and IgM rheumatoid factor. Dosages of FA and MTX were identified from the patient's prescription. Adherence to FA and MTX were quoted as good or poor based on patient's self report of adherence. Adherence rate of 80% was used as a cut off point for good adherence. Data on MTX included the date of starting, date of discontinuation, reason for discontinuation, current dose, and side effects [including methotrexate intolerance severity score (MISS)].

MISS is a validated questionnaire to determine the severity of gastrointestinal side effects of MTX (9). It consists of 4 domains: abdominal pain, nausea, vomiting and behavioral symptoms. Symptoms are assessed by after MTX, anticipatory (before taking MTX) and associative (thinking of MTX). Symptoms were graded as 0 (no symptom), 1 (mild symptom), 2 (moderate

symptom) and 3 (severe symptom). It has a sensitivity of 88% and specificity of 80% in diagnosing MTX intolerance with a cut-off score of ≥6, including at least 1 anticipatory, associative or behavioral symptom. Assessment of disease activity of RA was scored using disease activity score 28 (DAS 28), a continuous measure consisting of the number of tender and swollen joints in a 28 joint count, erythrocyte sedimentation rate and patient global health as measured on a visual analogue scale of 100 mm (10). DAS 28 was applied by physicians and rheumatologists trained in performing DAS 28 assessment.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics version 20 (IBM Corp., Armonk, NJ, USA). Quantitative variables were examined for normal distribution prior to statistical analysis. Normal quantitative variables were compared using independent Student's t test and results were expressed as mean (standard deviation). Qualitative variables were compared using chi-square test and results were expressed as number (percentage). When the conditions of validity of the chi-square test were not met, it was replaced by the Fisher's exact test. The significance level was set at 5% for all tests used.

RESULTS

Baseline characteristics of patients

Baseline characteristics are summarized in Table I. There was no significant difference in the baseline characteristics between the 2 folic acid regimes except for higher percentage of prednisolone usage (65.8 versus 20.8%, P<0.001) and lower usage of biologic DMARDs (0 versus 7.5%, P=0.002) in 5 mg folic acid weekly group. There was no significant difference in the mean dose for methotrexate (mg/week) between the 2 groups [13.54 (4.03) versus 13.81 (4.24),

Table I - Baseline characteristics.

	5 mg 1 day after MTX n=120	5 mg daily except on the day of MTX n=120	P-value
Age, mean (SD), years	52 (11.6)	53 (11.4)	0.282*
Female gender, n (%)	101 (84.2)	100 (83.3)	0.861°
Use of NSAIDs, n (%)	66 (55.0)	63 (52.5)	0.698°
Use of anti-emetics, n (%)	1 (0.8)	1 (0.8)	1.00#
Use of H2-Antagonists, n (%)	7 (5.8)	5 (4.2)	0.554°
Use of PPI, n (%)	16 (13.3)	12 (10)	0.421°
Use of analgesics, n (%)	26 (21.7)	23 (19.2)	0.631°
Adherence to FA, n (%)	117 (97.5)	111 (92.5)	0.076°
Adherence to MTX, n (%)	116 (96.7)	109 (90.8)	0.062°
MTX dose, mean (SD), mg/week	13.54 (4.03)	13.81 (4.24)	0.612*
Prednisolone, n (%)	79 (65.8)	25 (20.8)	<0.001°
Other DMARDs, n (%)			0.759°
None	43 (35.8)	37 (30.8)	
Hydroxychloroquine	26 (21.7)	32 (26.7)	
Sulfasalazine	15 (12.5)	15 (12.5)	
Leflunamide	11 (9.2)	9 (7.5)	
Sulfasalazine + HCQ	17 (14.2)	21 (17.5)	
Leflunamide + HCQ	8 (6.6)	5 (4.2)	
Sulfasalazine + Leflunamide	0 (0)	1 (0.8)	
Use of Biologic DMARDs, n (%)	0 (0)	9 (7.5)	0.002#

MTX, methotrexate; SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitors; FA, folic acid; DMARDs, disease modifying anti rheumatic drugs; HCQ, hydroxychloroquine. *Independent Student's t test; °Chi-square test for independence; #Fisher's exact test.

Table II - Tolerability of methotrexate.

	5 mg 1 day after MTX n=120	5 mg daily except on the day of MTX n=120	P-value
MISS score ≥6, n (%)	0 (0)	5 (4.2)	0.060*
Side effects of MTX, n (%)			0.523°
No	103 (85.8)	93 (77.5)	
Gastrointestinal	12 (10)	18 (15)	
Hepatitis	3 (2.5)	5 (4.2)	
Pulmonary	1 (0.8)	1 (0.8)	
Infection	1 (0.8)	3 (2.5)	
Discontinuation of MTX, n (%)	8 (6.7)	16 (13.3)	0.085°

MTX, methotrexate; MISS, methotrexate intolerance severity score. *Fisher's exact test; °Chi-square test for independence.

P=0.612, 95% confidence interval (CI) –1.323, 0.781].

Tolerability of methotrexate

The tolerability of MTX was summarized in Table II. There was no significant difference noted on the side effects (gastrointestinal, hepatitis, pulmonary and infection) of MTX (14.2 versus 22.5%, P=0.523). MTX intolerance measured by MISS score of ≥6 was not significantly different between the 2 groups (0 versus 4.2%, P=0.060). There was no significant difference on the discontinuation of MTX (6.7 versus 13.3%, P=0.085). Analysis of tolerability of MTX according to baseline char-

Table III - Logistic linear regression model for tolerability of methotrexate.

Variables	β (ΣE)	OR	95% CI	P-value
Gastrointestnal side effects of MTX				
Age	–0.049 (0.018)	0.952	0.919, 0.986	0.006
Female gender	0.278 (0.547)	1.321	0.452, 3.860	0.611
Dose of folic acid 30 mg per week	–0.716 (0.480)	0.489	0.191, 1.252	0.136
Dose of mehotrexate	–0.005 (0.050)	0.995	0.902, 1.098	0.927
Usage of prednisolone	–0.180 (0.483)	0.836	0.324, 2.153	0.710
Usage of biologic DMARDs	0.834 (1.131)	2.304	0.251, 21.151	0.461
Any side effects of MTX				
Age	–0.038 (0.016)	0.963	0.934, 0.993	0.015
Female gender	0.653 (0.434)	1.921	0.821, 4.496	0.132
Dose of folic acid 30 mg per week	–0.682 (0.409)	0.506	0.227, 1.127	0.095
Dose of mehotrexate	–0.030 (0.042)	0.970	0.893, 1.055	0.480
Usage of prednisolone	–0.110 (0.412)	0.896	0.400, 2.007	0.789
Usage of biologic DMARDs	–0.226 (0.786)	0.798	0.171, 3.724	0.774
Discontinuation of MTX				
Age	–0.025 (0.020)	0.975	0.938, 1.014	0.205
Female gender	0.990 (0.513)	2.691	0.984, 7.362	0.054
Dose of folic acid 30 mg per week	–0.877 (0.545)	0.416	0.143, 1.211	0.108
Dose of mehotrexate	0.029 (0.055)	1.030	0.924, 1.146	0.596
Usage of prednisolone	–0.175 (0.532)	0.840	0.296, 2.384	0.743
Usage of biologic DMARDs	–0.192 (0.906)	0.825	0.140, 4.873	0.832

SE, standard error; OR, odd ratio; CI, confidence interval; MTX, methotrexate; DMARDs, disease modifying anti-rheumatic drugs.

Table IV - Efficacy of methotrexate.

	5 mg 1 day after MTX n=120	5 mg daily except on the day of MTX n=120	P-value	95% CI
DAS-28 score, mean (SD)	3.44 (1.10)	3.85 (1.40)	0.014*	-0.741, -0.084
TJC, mean (SD)	1.71 (3.86)	3.41 (4.82)	0.003*	-2.811, -0.589
SJC, mean (SD)	1.52 (2.40)	1.49 (2.05)	0.919*	-0.540, 0.599
VAS, mean (SD)	26 (18)	37 (23)	<0.001*	-1.598, -0.535

MTX, methotrexate; CI, confidence interval; DAS-28, disease activity score 28; SD, standard deviation; TJC, tender joint count; SJC, swollen joint count; VAS, visual analogue scale. *Independent Student's t test.

acteristics showed younger patients were more likely to have gastrointestinal side effects of MTX [odds ratio (OR)=1.05, P=0.006] and any other side effects of MTX (OR=1.04, P=0.015). Other baseline characteristics did not influence the tolerability nor discontinuation rate of MTX as shown in Table III.

Disease activity

Disease activity of our RA patients was measured by the parameters of DAS28 score, tender joint count (TJC), swollen joint count (SJC) and visual analogue scale (VAS), as presented in Table IV. RA patients given 5 mg of folic acid weekly supplementation had a lower DAS28 score compared to those given 30 mg of folic acid weekly supplementation [3.44 (1.10) versus 3.85 (1.40), P=0.014, 95% CI –0.741, –0.084]. There was also a lower TJC (1.71 versus 3.41, P=0.003, 95% CI –2.811, –0.589) and lower VAS (26 versus 37, P<0.001, 95% CI –1.598, –0.535) in folic acid 5 mg weekly group. SJC was not significantly different between the 2 groups (1.52 versus 1.49, P=0.919).

In view of the presence of multiple confounding factors that can potentially affect DAS28 score, multiple linear regression was calculated to predict DAS28 score based on dose of folic acid, dose of prednisolone, dose of methotrexate and usage of biologics (Table V). A significant regression model was found with dose of folic acid, dose of prednisolone and dose of methotrexate, F (3, 236) =19.600, P<0.001, adjusted R2=0.189. There was no significant association for the usage of biologics (P=0.557). Usage of 30 mg of folic acid weekly was associated with 0.693 increment of DAS28 score (P<0.001, 95% CI 0.360, 1.025).

DISCUSSION

Our study showed that both 5 and 30 mg FA weekly supplementation was well tolerated and efficacious in MTX-treated RA patients in clinical settings. There was no significant difference for side effects and discontinuation of MTX in both arms. Our findings were consistent with findings from other studies that showed FA supplementation reduced side effects and toxicities of MTX and increased MTX drug survivals (3, 6). The finding was also consistent with another study that showed no differences in the tolerability and discontinuation of MTX in both high and low dose of folinic acid

Table V - Multiple linear regression model for disease activity score 28.

	Adjusted b* (95% CI)	Standard error	β	t-stat	P-value
Constant	1.788 (1.245, 2.331)	0.276		6.486	<0.001
Methotrexate dose	0.091 (0.054, 0.128)	0.019	0.288	4.840	<0.001
Prednisolone dose	0.112 (0.059. 0.165)	0.027	0.276	4.195	<0.001
Usage of folic acid	0.693 (0.360, 1.025)	0.169	0.266	4.106	<0.001

The dependent variable was DAS-28 score. Adjusted R2=0.189; the model reasonably fits well; model assumptions are met; there is no interaction between independent variables, and no multicollinearity problem). *Adjusted regression coefficient.

supplementation (11). The FOLVARI study showed that both 10 and 30 mg weekly FA supplementation had the same tolerability and MTX drug survival rates. Previous study by Morgan and colleagues showed that low dose FA (5 mg/week) and high dose FA (27.5 mg/week) had the same MTX toxicity (11). Compared to that study, our study population had a higher dose of MTX (median 15 versus 7.5 mg/week). Higher dose of FA supplementation (30 or 27.5 mg/week) probably has no additional benefit on the tolerability and discontinuation of MTX.

A prospective study of 434 patients conducted by van Ede and colleagues showed that there was a higher MTX dose in RA patients receiving FA than placebo (18 and 14.5 mg/week) (12). However, our study did not show significant difference in the average MTX dose. The authors concluded that FA decreased the efficacy of MTX and higher dosages of MTX were needed for the same clinical response. Alternatively, it was postulated that co-administration of FA may allow the use of higher dose of MTX to achieve a better disease control before side effects were encountered (13, 14).

The efficacy of MTX was not reduced in RA patients receiving low dose FA supplementation (≤7 mg per week) compared to placebo (3). However, post hoc analysis study done by Khanna and colleagues showed a significant reduction of MTX efficacy in RA patients receiving folic acid compared to placebo (6). There is no consensus regarding guidelines for dose and frequency of FA supplementation in RA patients receiving MTX (14). Our study showed that FA supplementation at 5 mg per week had a lower DAS28 score compared to FA supplementation at 30 mg per week. Patients receiving 30 mg of FA weekly supplementation had a lower efficacy of MTX than 5 mg FA weekly supplementation in clinical setting. This is in contrast to the finding of the FOLVARI study that showed that both 10 and 30 mg weekly FA supplementation had similar efficacy data.

The dosage of MTX in our study was higher than previous studies that showed no difference in the efficacy of MTX-treated patients receiving folic acid. The median MTX dose in the previous studies was 7.5 mg/week (11, 15).

These studies were done during the time that higher dosage of MTX was not commonly used. Post hoc analysis study by Khanna and colleagues using average MTX dose of 12 mg/week showed a reduction of MTX efficacy in patients receiving folic acid supplement than in those assuming placebo (6). The study by van Ede and colleagues showed a higher final MTX dose was required in patients receiving folate supplement than placebo (12). All recent studies of FA supplementation in RA did not include high dose FA supplementation as this regime has fall out of favor and no longer practiced in most Western countries (3).

Interestingly, we found that younger patients were more likely to have side effects of MTX compared to older patients. Further study on the relationship of age with side effects of MTX would be able to clarify this finding.

The results from our current study should be interpreted with caution, as it was a cross-sectional observational study with selection bias, recall bias and poor recovery of old data. The baseline characteristics for both arms of our study were similar except for usage of prednisolone and biologic DMARDs.

The higher usage of prednisolone in 5 mg of FA weekly can potentially lower the DAS28 score. However, multiple regression analysis after adjusting confounding factors for dose of prednisolone, dose of MTX, and usage of biologics showed significant association between dose of folic acid and DAS28 score, with increment of 0.693 in DAS28 score for patients using 30 mg of folic acid per week. The second limitation in our study is the validity of the measurement of disease activity. Our study only collected data at one time point; hence we were unable to compare the current DAS28 score to baseline DAS28 score. A randomized-controlled trial comparing the different doses of folic acid supplementation will be able to provide more substantial clinical evidence.

CONCLUSIONS

FA supplementation of 5 and 30 mg per week was associated with similar tolerability of methotrexate in RA patients. However, folic acid supplementation of 30 mg per week was associated with lower efficacy of methotrexate compared to folic acid supplementation of 5 mg per week in real world settings.

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