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The Effects of Low-Dose Weekly Folate Supplementation Versus High-Dose Daily Folate

Romatoid Artritli Hastalarda Metotreksat Toksisitesini Önlemede Yüksek Doz Günlük Folat Desteğine Karşın Düşük Doz Haftalık Folat Desteğinin Etkileri

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Abstract
Objectives: There is no consensus on the dosage of folic acid required for the prevention of methotrexate (MTX) toxicity in rheumatoid arthritis (RA). The aim of the study was to assess the effects of low-dose weekly folate versus high-dose daily folate on prevention of MTX toxicity in RA patients.
Materials and Methods: Randomized controlled study of rheumatoid arthritis patients who were treated at Department of Rheumatology in Gazi University between October 2009 and February 2010. Thirty-eight RA patients were received 10 mg/week MTX and 5-10 mg/day prednisolon were randomly allocated to receive 5 mg/week folate or 2.5 mg six days/week folate. All patients were evaluated for complete blood cell count, liver function tests, alopecia, stomatitis and gastrointestinal symptoms before and six months after the treatment.
Results: There were no significant differences in the development of stomatitis, alopecia, gastrointestinal symptoms, anemia, leukopenia, erythropenia, thrombocytopenia, elevated liver function tests between the groups at sixth month.
Conclusion: Our results support that 5 mg folate supplementation once a week is adequate in RA patients.
Key words: Methotrexate, rheumatoid arthritis, folate supplementation

Öz:
Amaç: Romatoid artritte metotreksat toksisitesinin önlenmesinde gerekli folik asit dozu ile ilgili ortak bir görüş yoktur. Bu çalışmanın amacı romatoid artritli hastalarda metotreksat toksisitesinin önlenmesinde yüksek doz günlük folat kullanımına karşın düşük doz haftalık folat kullanımının etkilerini değerlendirmekti.
Materyal ve Metot: Ekim 2009 ile Şubat 2010 tarihleri arasında Gazi Üniversitesi Romatoloji Bölümü'nde tedavi edilen romatoid artritli hastalarda yapılan randomize kontrollü bir çalışma. 10 mg/hafta ve 5-10 mg/gün prednisolon kullanan 34 romatoid artritli hastaya randomize şekilde 5mg/hafta folat veya 2.5 mg 6 gün/hafta folat verildi. Hastaların tam kan sayımları, karaciğer fonksiyon testleri, alopesi, stomatit ve gastrointestinal semptomları tedaviden önce ve tedaviden 6 ay sonra değerlendirildi.
Bulgular: Tedavinin 6. ayında stomatit, alopesi, gastrointestinal semptomlar, anemi, lökopeni, eritropeni, trombositopeni, eleve karaciğer fonksiyon testleri açısından gruplar arasında fark yoktu.
Sonuç: Sonuçlarımız haftalık 5 mg folat desteğinin romatoid artritli hastalarda yeterli olduğunu desteklemektedir.
Anahtar Kelimeler: Metotreksat, romatoid artrit, folat desteği

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Introduction

Methotrexate (MTX) is one of the most commonly used disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA).[1] MTX is a potent inhibitor of

dihydrofolate reductase enzyme. Dihydrofolate reductase catalyzes the reduction of dihydrofolate to tetrahydrofolate, which is the biologically active form of folate. Therefore, MTX is an anti-folate drug and inhibits a number of folate-dependent pathways.[2,3]

Side effects of MTX occur in about 60% of patients, nevertheless most of them are mild and reversible.[4,5] It has been reported that 7% to 30% of patients discontinue MTX therapy within one year due to drug toxicity.[1,4] Some of the side effects have been suggested to be result of folate antagonism of MTX. Folic acid supplementation has been shown to reduce the risk of some of these side effects, especially gastrointestinal intolerance, bone marrow toxicity, hair loss and elevated liver enzymes.[1,4,9] However, there is no consensus on the dosage of folic acid required for the prevention of MTX toxicity in RA.

The aim of the study was to assess the effects of folic acid supplementation 5 mg once a week versus 2.5 mg six days a week on prevention of MTX toxicity in patients with RA.

Materials and Methods

Forty patients (10 male and 30 female) who were diagnosed as RA according to the 1987 ACR criteria referred to our clinic between October 2009 and February 2010 were enrolled in the study. Exclusion criteria included being ≤ 18 years of age, use of MTX, folic acid supplementation, sulphasalazine, leflunamide, hydroxychloroquine, sulfonamides or trimethoprim within the past 3 months, elevated liver function tests (higher than twice the upper limit of normal), creatinine clearance ≤ 30 ml/minute, white blood cell count (WBC) ≤ $3.5x10^3$/μL, platelet count ≤ $100x10^3$/μL and pregnancy. Because of mildly elevated liver function tests, 2 patients were excluded from the study.

Thirty-eight patients were started 10 mg/week of MTX orally, and the dosage was increased by 2.5 mg every 4 weeks if there was no initial benefit. 5-10 mg/day prednisolon according to the activity of disease was also started. The use of non-steroidal antiinflammatory drugs was permitted only when the presence of high pain intensity. Thirty-eight patients were randomly allocated to receive 5 mg/week folic acid supplementation (n=19; 5 male and 14 female) or 2.5 mg 6 days/week (15 mg/week) folic acid supplementation (n=19; 7 male and 12 female). Because most trials have avoided administration of folic acid on the same day as MTX, we recommended not taking folic acid doses on the day of MTX dosing. The informed consent from patients was obtained as required. The study was approved by the local ethics committee.

All patients were evaluated for symptoms including hair loss, stomatitis, abdominal pain, nausea and vomiting before starting MTX treatment and then after six months. Hemoglobin (Hb) (g/dl), red blood cell count (RBC) (10^6/μL), mean corpuscular volume (MCV) (fL), WBC (10^3/μL), platelet count (10^3/μL), alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L), alkaline phosphatase (ALP) (U/L), gamma glutamyl transpeptidase (GGT) (U/L) and total protein (TP) (g/dl) levels were assessed before and six months after the treatment. Normal values were defined as 12-16 g/dl for Hb, 3.8-5.2 10^6/μL for RBC, 79-98 fL for MCV, 4.5-10.3 10^3/μL for WBC, 150-373 10^3/μL for platelet count, 10-50 U/L for ALT, 5-40 U/L for AST, 0-38 U/L for GGT and 5.7-8.2 g/dl for TP.

Statistical analysis

The sample size was determined based on the findings from a previous study. To achieve a 54% reduction in the risk of adverse reactions in the folic acid supplementation groups, we calculated 19 patients per group using the 5% significance level and 80% statistical power.[7] As the continuous variables under investigation were abnormally distributed, non-parametric tests were employed. The Mann-Whitney U and chi-square tests were used for the comparison of demographics characteristic, clinical characteristics and baseline laboratory results between

the groups. At the end of sixth month, percentages of patients with laboratory results above the upper limit of normal and less than the lower limit of normal in both groups were calculated and assessed with chi-square test. For all analyses, SPSS 11.5 for Windows was used. p-values less than 0.05 were considered to represent a significant difference for all statistical analyses.

Results

There were no significant differences in demographic characteristics, clinical characteristics and baseline laboratory results between the 5 mg once a week folate supplementation group and 2.5 mg 6 days a week folate supplementation group (p>0.05) (Table-1).

Table 1. Demographic characteristics, clinical characteristics and baseline laboratory results of the study groups (means with standart deviations)

	5 mg/week folate group (n=19)	15 mg/week folate group (n=19)	p value
Male / Female (n)	5/14	7/12	0.25
Age (years)	50.4±12.3	45.8±15.2	0.37
Disease duration (months)	28.4±25.4	18.3±23.9	0.29
Beginning dose of MTX (mg/week)	11.32±1.5	10.3±1.1	0.15
Hb (g/dl)	12.4±1.7	12.9±1.6	0.22
MCV (fL)	83.3±6.1	83.8±5.7	0.67
RBC (10^6/µL)	4.5±0.5	4.6±0.4	0.38
WBC (10^3/µL)	9.1±2.6	7.9±1.7	0.15
Platelet (10^3/µL)	341,8±96,4	297,6±71,9	0.17
ALT (U/L)	16.5±12.6	18.5±8.7	0.35
AST (U/L)	16.2±3.0	19.2±6.2	0.08
ALP (U/L)	103.8±48.2	82.2±24.7	0.17
GGT (U/L)	26.2±16.1	19.1±10.7	0.13
TP (g/dl)	7.4±0.5	7.4±0.5	0.92

MTX: Methotrexate; Hb: Hemoglobin; MCV: mean corpuscular volum; RBC: red blood cell count, WBC: white blood cell count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase; TP: total protein

At sixth month, two patients (10.5%) in 5 mg folate group and three patients (16.7%) in 15 mg folate group had erythtopenia. There was no significant difference between the groups (p=0.58). Leukopenia, elevated AST and elevated ALP levels were detected in only one patient (5.3%) of 5 mg folate group and not detected in 15 mg folate group (p=0.31). Two patients (10.5%) in 5 mg folate group and one patient (5.3%) in 15 mg folate group had elevated GGT levels (p=0.55). There was no thrombocytopenia, anemia, elevated ALT levels and decreased TP levels in both groups at sixth month.

Hair loss, abdominal pain, nausea or vomiting was not observed in both groups before and six months after the treatment. Stomatitis was noted in only one patient (5.3%) who was taking 5

mg/week folic acid supplementation at sixth month, but not observed in 15 mg/week folic acid supplementation group. This difference was not statistically significant (p=0.31).

Discussion

MTX is an anti-folate drug and some of the side effects such as bone marrow suppression, gastrointestinal intolerance, alopecia, impaired liver function and stomatitis are due to folate antagonism.[1,3-10] Folic acid supplementation is commonly recommended for preventing these MTX-related side effects in RA patients.[3,5] There are many different administration ways of folic acid due to lack of sufficient data and there is no consensus about the use of low dose folic acid to reduce MTX toxicity in RA patients. To our knowledge, this is the first prospective study to investigate the effects of daily and once-weekly folic acid dosages on MTX associated side effects in patients with RA. According to our results, folic acid 5 mg once a week is enough to reduce MTX toxicity on liver functions, bone marrow, gastrointestinal system and oral mucosa.

In the present study, we observed no significant differences in WBC, RBC, platelet counts, Hb, Hct, ALT, AST, ALP and GGT levels between 5 mg/week folic acid supplementation group and 15 mg/week folic acid supplementation group at the end of the sixth month. In other words, 5 mg/week folic acid seemed to be adequate for preventing bone marrow and liver toxicity of MTX in patients with RA. Our findings are consistent with the previous studies.[6,7,11] Morgan et al. studied the effects of 5 mg/week folic acid (five days a week) or 27.5 mg/week folic acid (five days a week) versus placebo on the toxicity of MTX therapy for RA. They assessed 25 patients in low-dose folate group, 26 patients in high-dose folate group and 28 patients in placebo group. They recommended that low doses of folic acid is adequate for preventing side effects of MTX such as anemia, liver disfunctioning, citopenia, gastrointestinal intolerance, alopecia, stomatitis in RA patients.[7] In the study of Khanna et al., it is indicated that RA patients receiving 1 mg folic acid once or twice daily had significantly lower levels of ALT, AST and ALP than those who did not receive folic acid.[11] Similarly, van Ede et al. reported that 1-2 mg/day folic acid reduce MTX associated liver toxicity.[6] In the literature, elevation of MCV levels has been found to be related to folate deficiency in RA patients taking MTX therapy.[1,12] According to the literature, MCV levels did not statistically increase in patients who received low dose folic acid in the current study.

Our patients in both groups did not indicate alopecia or gastrointestinal symptoms such as abdominal pain, nausea and vomiting at the end of six months. However, one patient receiving 5 mg once weekly folic acid supplementation indicated stomatitis at the end of six months. This is consistent with a previous study which reported less nausea, vomiting and oral ulcers in RA patients receiving 5 mg/day folic acid at sixth month.[10] Similarly, low doses of folic acid supplementation showed an 80% reduction in mucosal and gastrointestinal side effects of MTX in a meta-analysis.[9]

Our study has several limitations. First, our study lacks the placebo arm. The inclusion of placebo may show whether the test and control treatments are truly effective. Second, we did not assess plasma levels of homocysteine. In the previous studies, it has been reported that folate deficiency due to MTX can cause an increase in homocysteine levels and thus the risk for cardiovascular disease.[8,13-15] Third, the use of NSAIDs was permitted in our study and NSAIDs may also increase levels of liver function tests.

In conclusion, both 5mg once a week and 2.5 mg six days a week folic acid supplementations in RA patients were found to be effective in preventing MTX side effects related to the hematological system, gastrointestinal system, oral mucosa and hair loss. Our results support that 5 mg once a week folic acid supplementation is adequate for preventing MTX side effects and could be prescribed to all RA patients receiving MTX therapy. Further prospective,

randomized-controlled studies with long term follow-up are needed for the assessment the effects of low dose folic acid supplemetation on MTX toxicity.

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