

Original Article

## Does chloroquine decrease liver enzyme abnormalities induced by methotrexate in patients with rheumatoid arthritis?

P. Mottaghi MD\*, H. Karimzade MD\*

### ABSTRACT

**Background:** Methotrexate has been the most frequently used antirheumatic drug in rheumatoid arthritis. Nevertheless, the possibility of hepatotoxicity continues to represent a major problem in tolerance. This study evaluated beneficial effect of chloroquine on incidence of liver enzyme abnormalities in patients with Rheumatoid Arthritis (RA) treated with Methotrexate.

**Methods:** Eighty patients with RA who had elapsed from onset of disease less than two years, randomly divided into two groups (MTX alone vs MTX with Chloroquine). Liver enzymes and some indicators of disease activity were evaluated in two months intervals and for maximum of 10 months follow-up.

**Results:** Five patients (12.5%) in MTX group and four patients (10%) in combination regimen developed abnormal liver enzymes. Response rate was more in combination therapy (87.5%) than MTX alone (80%) without significant difference.

**Conclusion:** The incidence of liver enzyme abnormalities were not different in patients received MTX alone and MTX with Chloroquine.

**Key words:** Rheumatoid Arthritis, Methotrexate, Chloroquine, Liver enzyme

JRMS 2005; 10(3): 135-138

Conventional drug therapy for patients with rheumatoid arthritis consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and will proceed to disease modifying antirheumatic drugs (DMARDs) such as chloroquine or methotrexate (MTX), if disease activity persist or become progressive<sup>1</sup>.

Methotrexate has been the most frequently used DMARDs in treatment of Rheumatoid Arthritis (RA), based upon its well-documented efficacy. Nevertheless, the possibility of hepatotoxicity continues to represent a major problem with tolerance and prolonged use of this drug<sup>1-5</sup>. Hepatotoxicity manifests at first by elevation in serum transaminases (AST and ALT)<sup>4-6</sup>. Meta-analyses of published clinical trials showed antimalarial drugs among DMARDs have minimum effect on liver enzymes and possible protective effect of antimalarials in combination with MTX over liver enzyme abnormalities<sup>7,8</sup>. It is showed that some drug combinations are less hepatotoxic which might result from differences in gastrointestinal absorption or serum binding or other

mechanisms. Based on this theory, the combination would be less effective as well as less toxic<sup>9</sup>. Because of this controversy on the benefit of chloroquine over development of liver enzyme abnormalities<sup>10-14</sup>, we evaluated the incidence of hepatotoxicity in two regimens: MTX alone and MTX with chloroquine. We also investigated the efficacy of combination therapy versus methotrexate regimen for treatment of RA.

### Subjects and Methods

Eighty RA patients aged 20-50 years were enrolled. The diagnosis of RA was based on American collage of rheumatology criteria The inclusion criteria were: disease onset less than two years, persistent disease activity, the patients who were not diabetic, alcoholic, markedly obese, previous MTX user and had no renal or hepatic disease. We maintained all the medications used by the patients, such as NSAIDs and prednisolon at least four weeks before entry and in the period of the study. The patients were systematically allocated

\* Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran  
Correspondence to: Dr Peyman Mottaghi, E-mail: motaghi@med.mui.ac.ir

into two groups (the patients every other on placed in each of groups). The first group received MTX (7.5-12.5 mg/wk) and the second group received MTX with the same dose range in combination with chloroquine (150 mg/day). Both groups were followed for a maximum of 10 months with serial clinical evaluation including; joint count, degree of tenderness, swelling, subjective improvement scale, morning stiffness (in hours and degree of limitation of movement) , laboratory tests indicating disease activity and drug side effects (CBC, ESR, CRP, ALT, AST, BUN)in two months intervals.

Elevation in liver enzymes (values > 1.2 times the upper limit of normal) for more than one occasion in consecutive measurements of liver function tests was considered abnormal<sup>5</sup> and for more than two times and in two consecutive occasions with mentioned definition was considered as severe abnormality.

Response to treatment was defined as 50% or more decrease in clinical measurements and laboratory tests (ESR, CRP), showing disease activity, according to American College of Rheumatology response rate criteria (ACR 50%) at any time during follow-up period.

The results in each group analyzed with cross tab statistics(Chi-square tests).

## Results

Most of patients in both groups were female (80%), aged 30-50 years old. As shown in Table 1, both groups were similar in sex and age distribution. Cumulative dose of methotrexate was 308 ± 22 mg in group 1 and 320 ± 28 mg in group 2, without significant difference between groups ( $p > 0.05$ ).

Incidence of liver enzyme abnormalities during follow-up period was 12.5% (5 cases) in patients who received MTX alone, and in three cases it was significant and caused discontinuation of MTX. Among other patients who received MTX with chloroquine, the incidence of liver enzyme elevation was 10 % (4 cases) , but in only one case it was significant and resulted in discontinuation of the drug (Table 2). These differences between groups were not statistically significant ( $p > 0.05$ ).

Evaluation of liver enzyme changes in relation to duration of treatment with MTX, showed that at six months of treatment, liver enzyme abnor-

malities were more prevalent in patients received MTX alone in comparison with patients received MTX and Chloroquine (8.3% vs. 4.2 %).

After six months MTX use till 10 months of follow-up, 12.5% of patients in MTX alone group and 10% of patients in combination therapy group developed liver enzyme abnormalities. Statistical analysis of these data showed no significant differences between two groups in follow-up intervals.

In the patients who received MTX alone, 80% respond to drug and achieved ACR 50 response in 10 months, but the response rate was as less as 47.5% in the first 6 months of therapy. In the patients who received MTX with Chloroquine, the response rate was 87% and most of them achieved ACR 50 in the first 6 months of therapy. Analysis of data on response rates also showed no significant difference.

## Discussion

Several studies have been reported incidence of liver enzyme abnormalities 9.2 -11% for MTX alone<sup>4, 5</sup> and 5.5-7%<sup>6, 8, 10</sup> for combined therapy with chloroquine and MTX during 12months follow up, but our results showed more prevalent liver enzyme abnormalities in patients.

The prevalence of abnormal liver enzymes that favors discontinuation of methotrexate was much less in combination therapy(7.5% vs. 2.5%) as others reported (5.8-7.5% vs. 1.9-2.7%)<sup>3,6,7,11</sup>.

We also observed a delay in appearance of liver enzyme abnormality and induction of a more rapid response in patients taken MTX combined with chloroquine, although this observation was not statistically significant.

A study on pharmacokinetics of MTX in combination therapy with hydroxychloroquine reported the reduction of maximum MTX concentration, when it co administered with hydroxychloroquine, compared to MTX administration alone<sup>12</sup>. A recent study in pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis showed that clearance was not affected by the presence of MTX and hence, steady state drug concentration and maintenance dosage requirements were similar<sup>13</sup>. Some studies showed that combination of these drugs is effective and well tolerated for 24 weeks, and other studies with more prolonged periods of follow-up re-

ported increased prevalence of liver enzyme elevation with time (up to 18-24% for MTX after 60 weeks of regular use) 7-9, 14.

In conclusion, although our study statistically didn't show the superiority of combined regimen

over MTX alone, a study with larger sample size and more follow-up period may confirm clinical value of the combined regimen observed in our study.

**Table 1:** Demographic data of patients and prevalence of liver enzyme abnormality in both groups

	No	Age Year $\pm$ SD	Sex		Prevalence of liver enzyme abnormality	Prevalence of discon- tinuation of MTX due to sever enzyme ab- normality
			Male	Female		
MTX	40	34 $\pm$ 8	6	34	8 (12.5%)	3
MTX and Chloroquine	40	30 $\pm$ 9	8	32	5 (10%)	1

**Table 2:** Characteristics of patients with sever liver enzyme abnormalities

MTX group	Age(year)	Sex	Cumulative MTX dose (mg)
Case1	35	Female Fe- male Female	350
Case2	23		325
Case3	33		245
MTX and Chloroquine			
Case1	29	Female	340

## References

- Harris ED. Treatment of rheumatoid arthritis. In: Ruddy S, Sledge CB, editors. *Kelley's Textbook of rheumatology*. 6th ed. Philadelphia: W.B. Saunders 2001:1001-19
- Weinblatt M. Methotrexate. In: Ruddy S, Sledge CB, editors. *Kelley's Textbook of rheumatology*. 6th ed. Philadelphia: W.B. Saunders 2001:1015-6
- Tugwell P, Bennett K, Weinblatt M. Methotrexate in rheumatoid arthritis. *Ann Int Med* 1987; 107:418-9
- Bellamy N, Mayer A. Current practice in antimalarial drug prescribing in rheumatoid arthritis. *J Rheumatol* 1986; 13: 551-6
- Fries JF, Singh G, Edward D. Aspirin, Hydroxychloroquine and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1990; 33(11):1611-9
- Felson DT, Anderson J, Armour WJ. Use of short term efficacy/ toxicity trade offs to select second-line drugs in rheumatoid arthritis, a Meta analysis of published trials. *Arthritis Rheum* 1992; 35(10): 1117-23
- Drosos AA, Psychos D, Andonopoulos AP. Methotrexate therapy in rheumatoid arthritis (a two years prospective follow up). *Clin Rheumatol* 1990; 9(3):333-41
- Weinblott ME, Maier AL, Pina I, Krevsky B. Long term experience with low dose weekly methotrexate in rheumatoid arthritis. *J Rheumatol* 1990; 22:33-7
- Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986; 29:822-7

10. Elkayam O, Yaron M, Zhukovsky G, Segal R, Capsi D. Toxicity profile of dual methotrexate combinations with gold, hydroxychloroquine, sulphasalazine and minocycline in rheumatoid arthritis patients. *Rheumatology international* 1997;17(2):49-53
11. Hurst S, Kallan MJ, Wolfe FJ, Fries JF, Albert DA. Methotrexate, hydroxychloroquine, and intramuscular gold in rheumatoid arthritis. *J Rheumatol* 2003; 30(8): 1981-2
12. Carmichael SJ, Beal J, Day RO, Tett SE. Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increase exposure to methotrexate. *J Rheumatol* 2002; 29(10):2031-3
13. Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. *Ther Drug Monit* 2003;25(6):671-81
14. Van jaarsveld CH, Jahngier ZN, Jacobs JW, Blaauw AA, Van Albada-kuijpers GA. Toxicity of antirheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39(12):1374-82

Archive of SID