Hepatic Toxicity in Patients with Rheumatoid Arthritis and Psoriasis Taking Methotrexate Therapy

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Abstract

Background: We had made a study to demonstrate the adverse hepatic effects of MTX in patients taking MTX for treatment of RA and psoriasis taking in consideration the following variables: BMI, gender, cumulative dose, age, weekly dose, duration of treatment, serum level of cholesterol and creatinine.

Patient and method: We had a prospective study of 85 patients with RA and 50 patients with psoriasis. All patients were analyzed by history, clinical examination and investigations in the form of liver enzymes, blood sugar, serum cholesterol, serum creatinine, HBS Ag and anti HCV antibody. Persistently elevated level of liver enzymes 2 to 3 times the upper limit of normal on two occasions 3 months apart indicate hepatic toxicity

Results: We found that 7 patients with psoriasis and 6 patients with RA have significant elevated liver enzymes which reflect MTX hepatotoxicity

Conclusion: Our study show that patients with psoriasis at significantly greater risk of elevated liver enzymes than patient with RA (14% and 7% respectively) were gender, BMI, cumulative dose, weekly dose and serum cholesterol level are risk factors for hepatic toxicity due to MTX therapy

Key words: *Hepatic Toxicity, MTX therapy, Arthritis*

Introduction

Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase. DNA synthesis is inhibited as the concentration of thymidine and purines falls after treatment with methotrexate.(1) The relevant targets of low dose methotrexate have not been defined with precision, but an attractive candidate is the enzyme 5- amino-imidazole -4- carboxamide ribonucleotide (AICAR) transformylase. Inhibition of AICAR transformlase leads to accumulation of AICAR, which in turn stimulate the extracellular release adenosine which has a number of anti-inflammatory and immunomodulatory effects that may contribute to the therapeutic effect of methotrexate.(2) Recently, in vitro studies showed that methotrexate was 10-100 times more effective at inhibiting the proliferation of lymphoid cell lines than cultured kerationocytes, suggesting that lymphoid cells may be a more important cellular target than epithelial cells in psoriasis and also inhibits polymorpho nuclear leukocyte chemotaxins.These actions may explain its clinical effect.(3)

Methotrexate is now the most widely used disease modifying antirheumatoid drug (DMARD) in the developed world. It was first used in the treatment of psoriasis and psoriatic arthritis in 1951, (4) and has been shown to be of clinical benefit in this condition. (5, 6)

Methotrexate has been used for the treatment of diseases characterized by inflammation or cellular proliferation. In 1985, the first randomized placebo-controlled trials were published that demonstrate the short term efficacy of low dose weekly methotrexate in Rheumatoid arthritis. (7-8)

Comparative studies of methotrexate with azathioprine (9), gold sodium thiomalate(10) and cicolosporine(11) in the treatment of Rheumatoid arthritis show that methotrexate is well tolerated, with retension rates between 93% and 95%.

Oral therapy is given once a week. Daily dose schedules are dangerous and have been abandoned. The oral triple-dose regimen is the most common method

used. A dose is taken at 12 hours intervals during a 36 hours period once each week. An initial test dose of 2.5 to 5mg is given and complete blood cell counts and liver function tests are obtained once week later. Maintenance doses should be achieved by gradual increases of 2.5-5mg per week up to 20mg/week [12].

The most common adverse effects are gastrointestinal, such as anorexia, nausea, vomiting, stomatitis and diarrhoea. Central nervous system toxicity including headache, dizziness, fatigue and mood disturbance may occur. Haematological toxicity is not common, and although all types of cytopenia has been documented. Pulmonary complications such as methotrexate pnemonitis may be linked to risk factors as increased age, diabetes mellitus and pre-existing pulmonary diseases [13]. It is now thought that the frequency of severe liver disease occurring in rheumatoid arthritis patients receiving long term methotrexate is not high; the incidence of mild fibrosis has been reported as being between 0% and 2% [14-15].

Base line monitoring include history, physical examination, complete blood count, platelet count, renal function test, liver chemistry including (AST, ALT, alkaline phosphate, albumin) and viral serology mainly for hepatitis B, C and HIV antibody and chest radiograpghy to exclude pulmonary fibrosis.Follow up monitoring include monthly complete blood count and differential, platelet count for the first and second dose then every two months, liver chemistries monthly or every two months, and renal function test including blood urea, serum creatinine at three to four months interval.

Persistently elevated liver enzymes more than two times would preclude further therapy. Although combined sensitivity of liver enzymes for detecting a significantly abnormal liver biopsy is 86%, whereas the predictive value of negative test result 93% [16], liver biopsy remain more reliable predicator of liver damage. Current study aimed to Assess the prevalence of liver enzyme abnormality in patients with RA and psoriasis taking MTX therapy and to identify the possible risk factors for MTX induce hepatotoxicity in these patients.

Patients and Method

Eighty five patients with rheumatoid arthritis diagnosed according to American college of rheumatology criteria [17] and 50 patients with psoriasis diagnosed by the presence of psoriasis with or without seronegative peripheral arthritis [18], underwent a prospective study

The study was performed in Marjan Teaching Hospital in Babylon for outpatient clinic of rheumatological and dermatological disease.

After taking the verbal consents of the patients, full history regarding age, gender, MTX dose per week, MTX duration, and cumulative dose defined as dose per week multiplied by duration of treatment, MTX adverse effects mainly the gastrointestinal problems (nausea, vomiting, abdominal pain and anorexia). Oral MTX therapy and folic acid supplement prescribed for all patients (5mg once daily). drug history concentrated on (NSAIDs, statins, cordaron, oral hypoglycemic drugs, psoraline+UVA treatment, gold, oral contraceptive pills, long term steroid and extreme obesity), any patient on these drugs for the last month were excluded, history of alcoholism so any patient drunk alcohol in the last 5 years were excluded from the study

History of other comorbid disease like congestive heart failure, chronic viral hepatitis, autoimmune hepatitis, Wilson's disease, chronic renal failure and diabetes mellitus were excluded from the study. Clinical examination include jaundice, ascites, organomegaly was performed, BMI represent the height and weight recorded as Wt. in Kg / Height in m^2 were 18 - 25 considered normal, 25 - 29.9 considered overweight, 30 – 39.9 considered obese and >40 considered extreme obesity[19] . Investigations in the form of liver enzymes (normal reference values for ALT, AST <20 U/100 ml, normal reference for ALP, 85 U/100 ml) done by colorimetric method, random blood sugar normal reference value <11.1 mmol/L by glucose oxidase method, cholesterol level normal reference value <5.2 mmol/L by cholesterol oxidase method, serum creatinine normal reference value <124µmol/L by alkaline picrate with Deprot method and viral serology for HBS Ag, anti HCV Ab. By bioelisa color method (direct immune enzymatic method).Persistently elevated level of liver enzymes 2 – 3 times the upper limit of normal on two occasions 3 months apart was indicate hepatic toxicity[20]

Statistical Analysis

Statistical significance of liver enzymes between patients with RA and psoriasis, and each risk factors were assessed by t-test and of the proportion, were p-value < 0.05 indicate Statistical significance the results were expressed as tables

Results

The average age of patients with RA was 48 years and for patients with psoriasis was 50 years, female outnumbered male in RA group were 56 to 29 and for psoriasis group, the female outnumbered male 23 to 27.body mass index in RA group was 24kg/m^2 and for psoriasis group was 27kg/m^2.The average duration of MTX therapy was 4 years in RA group and 3 years in psoriasis group. The average dose of methotrexate therapy in RA group was 10 mg/week and for psoriasis group was 15 mg/week [Table 1].

Regarding gastrointestinal symptom as nausea and vomiting were found in 20 patients (23.5%) with RA and in 10 patients (20%) with psoriasis [Table 2], statistically not significant.

Sustained rise in liver enzyme were seen in 6 patients (7%) in RA group while in 7 patients (14%) in psoriasis group [Table 3] which was significantly significant. The gender ,liver enzyme abnormalities were found in 2 males (33.3%) and in 4 females (66.6%) in RA group while 4 males (57.1%) and in 3 females (42.8%) in psoriasis group [Table 4],statistically not significant. The age, the average age in RA was 46 and 52 years in psoriasis group [Table 5], statistically not significant. BMI, in RA group was 23 kg/m^2 and in psoriasis group was 28 kg/m^2 [Table 6], statistically significant.

(Table 1) Demographics of study population

Variable	RA	Psoriasis
Total number of patients	85	50
Average age (year)	48(15-65) ± 12	50(18-65) ±13
Female	56(65%)	23(46%)
Male	29(35%)	27(44%)
Average of BMI Kg/m^2	24(17-30) ±2	27(20-35) ±4
Average dose of MTX Mg/week	10(5-10) ±3	15(10-20) ±4
Average duration of treatment (year)	4(1-6) ±2	3(1-5) ±2

(Table 2) Predictive value of gastrointestinal symptoms in RA and psoriasis

Variable	RA	Psoriasis	P-value
Total no. of patients	85	50	Not sign.
Nausea and vomiting	20(23.5%)	10(20%)	

(Table3) Predictive value of elevated liver enzymes in RA and psoriasis

Variable	R.A	Psoriasis	p-value
Total no. of patients	85	50	<0.05 (Sign.)
Elevated liver enzymes	6(7%)	7(14%)	

(Table 4) Predictive value of gender in RA and psoriasis

Variable	RA	Psoriasis	P-value
No. of patients with elevated liver enzymes	6	7	Not sign.
Female	4(66.6%)	3(42.8)	
Male	2(33.3)	4(57.1%)	

(Table5) Predictive value of age in RA and psoriasis

	Group	No. of patients with elevated liver enzymes	Average of age(year)	p- value
A G E	R.A	6	46(24-60)±13	Not sign.
	Psoriasis	7	52(35-65)±12	

(Table 6): Predictive value of BMI in RA and psoriasis

	Group	Number of patients with elevated liver enzymes	Average BMI	P-value
B M I Kg/m2	R.A	6	23(21-25)±2	<0.05 (Sign.)
	Psoriasis	7	28(21-38) ±3	

Discussion

The study showed that gastrointestinal problems like nausea, vomiting in RA group was 23.5% and in psoriasis group was 20% which was statistically not significant, in agree to study in 2006, where nausea and vomiting in psoriasis group (9.8) and in RA group was 13% which also statistically not significant[20]. A significant rise in liver enzymes were seen in 6 patients (7%) with RA group and in 7 patients (14%) with psoriasis group, our study agrees with study in 2006 showed that significant rise in liver enzymes in psoriasis group (14.5%) and 7.5% in RA group.[20] The study showed that the gender in RA group and psoriasis group not significantly correlated with hepatic toxicity in contrast to other study, one in 2006[20] other in 2004[34], both showed male in psoriasis group significantly more affected than male in RA group. The study showed no significant correlation of both the age, duration of MTX treatment with the level of liver enzymes abnormality in agree to a study in 2006[21] and other in 2004[22] The study showed that both BMI, cumulative dose, were significantly correlated with hepatic toxicity in psoriasis versus RA group in agree with study in 2004[23] The study showed a significant association between weekly dose of MTX with hepatic toxicity in psoriasis group versus RA group in contrast to study in 2004[22] The study showed a significant association between serum cholesterol level and hepatic toxicity in psoriasis group versus RA group in agree to study in 2006[24] but in contrast to previously reported studies [25--26] were total cholesterol level did not correlate with hepatic toxicity. This study showed no significant association between serum creatinine level and hepatic toxicity in psoriasis group versus RA group, a study in 2004[22] show that renal impairment, diabetes and obesity were significantly correlated with hepatic toxicity Current study show that liver enzymes (transaminases and ALP) both increased

in both groups (RA and psoriasis), although increase level of ALP more correlated with hepatotoxicity[27] .The study recommended encouragement of life style modification for patients who are overweight or obese with psychological support especially for patients with psoriasis,Viral serology for HBS Ag and HCV as baseline because MTX therapy in patient with positive serology may enhance viral replication and result in fulminant hepatitis and Baseline lipid profile as hyperlipidaemia is an independent risk factor for MTX hepatotoxicity

Conclusion

MTX related hepatic toxicity was more significant in patient with psoriasis than patient with RA. BMI, cumulative dose, weekly dose and serum cholesterol level are risk factor for hepatotoxicity in psoriasis group than in RA group.

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