Hepatic Toxicity in Patients with Rheumatoid Arthritis and Those with Psoriasis taking Methotrexate Therapy

Haider Hamza Umran

Abstract

Background: This Study is 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.

Patients and methods:This is 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:The study results found that 7 patients with psoriasis and 6 patients with RA have significant elevated liver enzymes which reflect MTX hepatotoxicity

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

مية الكبد عند المصابين بداء الرثوية وداء الصدفية المعالجين بعقار الميثوتركسيت

الخلاصة

هدف الدراسة: هدفت الدراسة لتحديد نسبة ظهور أضطرابات الأنزيمات الكبدية عند المصابين بداء الرثوية وداء الصدفية المعالجين بعقار الميثوتركسيت ودراستها تبعا لكتلة الجسم, الجنس, الجرعة التراكمية, العمر, الجرعة الأسبوعية, مدة العلاج, مستوى الكولسترول والكرياتينين .

طرائق البحث: أجريت الدراسة بشكل تزامني على 85 مصاب بداء الرثوية و 50 مصاب بداء الصدفية. جميع المصابين تم أخذ تاريخ الطبي وفحصهم سريريا ومختبريا والتي تشمل نمط أنزيمات الكبد, سكر الدم, كولسترول الدم والكرياتينين, فايروس الكبد نمط ب ونمط ج حيث ان أرتفاع أنزيمات الكبد أكثر من مرتين الى ثلاثة مرات عن المعدل الطبيعي خلال فترتين المدة بينهما 3 أشهر تعني سمية الكبد.

النتائج: وجدنا في الدراسة أن سبعة مصابين بداء الصدفية وستة مصابين بداء الرثوية عندهم أرتفاع نمط أنزيمات الكبد والتي تعكس سمية الكبد.

الأستنتاج: وجدنا في الدراسة أن هنالك نسبة ملحوظة أحصائيا في أرتفاع أنزيمات الكبد عند المصابين بداء الصدفية والمصابين بداء الرثة (14% و7% بالتتابع) حيث أن كتلة الجسم, الجرعة التراكمية, الجرعة الأسبوعية ومستوى الكولسترول هي عوامل مساعدة لزيادة السمية بسبب عقار الميثوتركسيت في حين أن الجنس, العمر, مدة العلاج, الكرياتينين لم يحقق نسبة ملحوظة.

Abbreviations

RA	Rheumatoid arthritis
BMI	Body mass index
MTX	Methotrexate
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
NSAID	Non steroidal anti-inflammatory drugs
HBS Ag	Hepatitis B surface antigen
HCV	Hepatitis C virus

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 ribonuc-leotide (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 antirheumatic drug (DMARD) in the developed world. It was first used in the treatment of psoriasis and psoriatic arthritis in 1951, 3 and has been shown to be of clinical benefit in this condition. [4, 5]

The Aim of the Study

To assess the prevalence of liver enzyme abnormality in patients with RA and psoriasis taking MTX therapy.

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 (ACR)[6] and 50 patients with psoriasis diagnosed by the presence of psoriasis with or without seronegative peripheral arthritis [7], underwent a prospective study

The study was conducted in Marjan Teaching Hospital in Babylon for outpatient clinic of rheumatological and dermatological disease from Jan. 2007 to oct. 2007

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) were recorded

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

Comprehensive physical examination concentrated mainly on jaundice, ascites, organomegaly was performed, BMI represent the height and weight recorded as Wt. in Kg / Height in m2 were 18 - 25 considered normal, 25 - 29.9 considered overweight, 30 – 39.9 considered obese and >40 considered extreme obesity.

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 indicating hepatic toxicity[8]

Statistical Analysis

Statistical significance levels of liver enzymes between patients with RA and those with 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/m2 and for psoriasis group was 27kg/m2.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 [Table3] which was significantly 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 [Table4], statistically not significant.

The age, the average age in RA was 46 and 52 years in psoriasis group [Table 5], statistically not significant.

The BMI, in RA group was 23 kg/m2 and in psoriasis group was 28 kg/m2 [Table 6], statistically significant.

The MTX dose, the average dose in RA group was 9.5 mg/week and 14.5 mg/week [Table 7] statistically significant.

The cumulative dose, in RA group was 1850 mg, and 2500 mg in psoriasis group [Table 8], statistically significant. Regarding duration of MTX treatment, the average duration in RA group was 4 years and in psoriasis group was 3. [Table 9],statistically not significant.

The serum cholesterol level, the average level in RA group was 3.5 mmol/L and 6 mmol/L in psoriasis group [Table 10], statistically significant.

The serum creatinine level, the average level in RA group was 128 µmol/L and 130 µmol/L in psoriasis group [Table 11], statistically not 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/m2	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%)	

Table 3 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 with elevated liver enzymes

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%)	

Table 5 Predictive value of age in RA and psoriasis with elevated liver enzymes

	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 with elevated liver enzymes

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

Table7 Predictive value of MTX dose in RA and psoriasis with elevated liver enzymes

MTX DOSE mg/week	Group	No.	Average dose	P-value
	RA	6	9.5(5-10) ± 2	<0.05 (Sign.)
	Psoriasis	7	14.5(10-20) ±3	

Table 8 Predictive value of cumulative dose in RA and psoriasis with elevated liver enzymes

Cumulative Dose Of MTX Therapy (mg)	Group	No.	Average of cumulative dose	p-value
	RA	6	1850(1080-2800) ±680	<0.05 (Sign.)
	Psoriasis	7	2500(1440-4800) ±1080	

Table 9 Predictive value of duration of MTX therapy in RA and psoriasis with elevated liver enzymes

Duration of MTX therapy (year)	Group	No.	Average duration	P-value
	R.A	6	4(3-7) ±3	Not sign.
	Psoriasis	7	3(3-6) ±2	

Table 10 Predictive value of total cholesterol level in RA and psoriasis with elevated liver enzymes

Total Cholesterol Level mmol/L	Group	No.	Average level	P-value
	RA	6	3.5(3-5) ±0.26	<0.05 (Sign.)
	Psoriasis	7	6(4.3-6.2) ±0.24	

Table 11 Predictive value of serum creatinine level in RA and psoriasis with elevated liver enzymes

Serum Creatinine Level µmol/L	Group	No.	Average level	p-value
	RA	6	128(95-130) ±6	Not sign.
	Psoriasis	7	130(100-145) ±7	

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, similar to study by Lindsey Tilliny et al in 2006, where nausea and vomiting in psoriasis group (9.8) and in RA group was 13% which also statistically not significant[8]

A significant rise in liver enzymes were seen in 6 patients (7%) with RA group and in 7 patients (14%) with psoriasis group, similar to study by Lindsey Tilliny et al in 2006 showed that significant rise in liver enzymes in psoriasis group (14.5%) and 7.5% in RA group.[8]

The study showed that the gender in RA group and psoriasis group not significantly correlated with hepatic toxicity in contrast to other study, similar to study by Lindsey Tilliny et al in 2006[8] other by Vera M.R.et al in 2004[3,4], both showed male in

psoriasis group significantly more affected than male in RA group, this may be due to small sample of psoriasis group in our study.

The study showed no significant correlation of both the age, duration of MTX treatment with the level of liver enzymes abnormality similar to study by Lindsey Tilliny et al in 2006[9] and other study by Lindsey K et al in 2004[10]

The study showed that both BMI, cumulative dose, were significantly correlated with hepatic toxicity in psoriasis versus RA group similar to study by Aithal GP et al in 2004[11], because patients with psoriasis have cosmetic conflict made them more isolated, depression and less daily activity which result in increase BMI, also large cumulative dose result in repeated injury to hepatocyte.

The study showed a significant association between weekly dose of MTX with hepatic toxicity in psoriasis group versus RA group in contrast to study by Lindsay K et al in 2004[10] because in psoriasis group the weekly dose of MTX prescribed more than patients with RA group.

The study showed a significant association between serum cholesterol level and hepatic toxicity in psoriasis group versus RA group similar to study by Mallbris L et al in 2006[12] but in contrast to previously reported studies by Mallbris et al in 2004 and Cimist G et al 1988 [13,14] were total cholesterol level did not correlate with hepatic toxicity, those patients with psoriasis may have high level of cholesterol prior to MTX therapy and this high level of cholesterol aggravate MTX toxicity. Early atherosclerosis is now considered in the management of rheumatoid arthritis, studies shows early DMARD therapy have beneficial effect in reducing serum lipids,MTX therapy not only improve diseases specific out come but may also improve collateral damage such as atherosclerosis.

The study showed no significant association between serum creatinine level and hepatic toxicity in psoriasis group versus RA group, a study by Lindsay K et al in 2004 [10]show that renal impairment, diabetes and obesity were significantly correlated with hepatic toxicity ,probably related to using serum creatinine level rather than creatinine clearance which is more sensitive to renal impairment.The study showed that MTX therapy result in both hepatocellular damage and cholestatic damage in RA group and those with psoriasis in comparison to study by M.G.C. Dahi et al which showed that the increase level of ALP more correlated with hepatotoxicity [15]

Limitation of the study

Smaller sample of patients with psoriasis than patients with RA which may limit our ability to compare between two groups.

Most patients in our community are overweight were increase BMI may affect hepatocyte integrity.

Although liver biopsy provide most reliable information regarding hepatic damage but it is invasive procedure and need patient cooperation.

Unavailability of serum aminoterminal propeptide of type III procollagen, were normal level might allow lengthening liver biopsy intervals.

Conclusion and Recommendations

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

Encourage life style modification for patients who are overweight or obese with psychological support especially for patients with psoriasis.

Consider 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.

Baseline lipid profile as hyperlipidaemia is an independent risk factor for MTX hepatotoxicity.

Need further study in the future including liver biopsy or serum aminoterminal propeptide of type III procollagen for detection of MTX hepatotoxicity.

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