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Research Article

A COMPARISON BETWEEN ENTERAL AND PARENTERAL METHOTREXATE INTAKE IN IRAQI PATIENTS WITH RHEUMATOID ARTHRITIS REGARDING EFFICACY AND LIVER FUNCTION IMPAIRMENT

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ABSTRACT

Objectives: Methotrexate (MTX) is a disease-modifying ant-rheumatic drug that has been used commonly in patients with rheumatoid arthritis (RA) with a goal of reducing RA activity or RA remission. Response to MTX varied among patients and side effects including liver impairment are not uncommon. The study aimed to compare oral and parenteral MTX intake regarding the efficacy and risk of liver impairment in patients with RA.

Subject: Thirty patients who were newly diagnosed with RA according to EULAR/ASAR were included in the study. MTX was given for them for 6 months in a dose ranging between 2 and 25 mg either orally or parenterally intramuscular and subcutaneously once weekly. Patients were assessed depending on clinical disease activity index (CDAI) score and liver enzymes were measured before and after the start of the treatment.

Results: The study showed that parenteral MTX intake significantly improves the CDAI score more than oral intake, CDAI reduced from 13.15±3.25 to 5.57±2.34 following 6 months of treatment in comparison to its' insignificant reduction from 12.72±3.13 to 8.90±3.08 following oral treatment. Regarding liver enzymes, the impairment in alanine aminotransferase and aspartate aminotransferase is significantly less than that with oral ones with the same effect on alkaline phosphatase.

Conclusion: Parenteral MTX intake tends to be more efficacious in attaining low disease activity than oral intake with a lower rate of impaired liver function.

Keywords: Rheumatoid arthritis, Methotrexate, Parenteral, Enteral, Impaired liver enzymes, Clinical disease activity index score.

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INTRODUCTION

Rheumatoid arthritis (RA) is a disorder of systemic inflammation that mainly involves joints and connective tissues with an exact etiology that remains not well recognized [1]. Both genetic and environmental factors could predispose to the disease. It is estimated to be of a frequency ≤0.1–1.9% worldwide exhibiting an incidence of 1% more common (up to 4 times) and severe in women with a peak age of 35–35 years old [2]. Patients with RA usually presented with pain and/or swelling of the small joints of hands, wrists, and feet and morning stiffness often more than 1 h [3]. Fever, fatigue, and insomnia could be a possible associate. Extra-articular manifestation can occur in about 50% of cases [4]. The diagnosis is usually made depending on the typical clinical presentation aided by laboratory and radiological results. In 2010, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) put diagnostic criteria for RA (Table 1). A patient with a score ≥6 is classified as definite RA [5]. Rheumatoid factor (RF) is positive in the serum of 60–80% of cases with a specificity of up to 85% RA. A positive RF patient usually exhibits extra-articular manifestations [4]. Anti-citrullinated protein antibody is positive in 10–15% of cases with negative RF. Both of them are associated with more severe disease and joint erosions, a higher titer carries a higher specificity for RA [6]. The activity of the disease is calculated depending upon a certain score called clinical disease activity index (CDAI) Table 2, with a score ranging from 0 to 28 representing the number of swollen and tender joints during a patient's physical examination [7]. The aim of RA treatment is usually to get a low disease activity, disease remission, controlling the progression of the disease, and avoiding joint damage. This usually can be provided by the early start of disease-modifying ant-rheumatic drugs [8]. Methotrexate (MTX) is the most frequently used disease-modifying ant-rheumatic drugs (DMARDs) for RA either as a mono-therapy or a combined therapy (other DMARDs or biological drugs). When used as mono-therapy for RA treatment, it induces a low disease activity in 30% of cases [6]. Mechanism of action is not precisely known with some anti-inflammatory and immune-modulation actions [9]. Methotrexate can be given either orally or parenterally (intramuscular or subcutaneous [IM/SC]) with a fast absorption rate even at a low dose and distributed to the synovium of the joints together with the serum. Oral MTX is absorbed through the gastrointestinal system with a first-pass hepatic metabolism. While parenteral MTX has higher systemic levels [10]. IM/SC MTX are equivalent with a maximum serum concentration reached within 2 h following administration [11]. Certain side effects have been reported during MTX use such as oral ulcer, hepatic toxicity, respiratory problems, and hematological abnormalities. Fortunately, most of them are reversible and disappear following discontinuation [12].

METHODS

It is an interventional prospective. Thirty patients who visited the rheumatology outpatient clinic were included throughout the period from January 2022 to August 2022. They presented with pain and swelling of multiple joints and the diagnosis of RA was given depending upon EULAR/ACR diagnostic criteria. Patients' age between 30 and 50 years old, RA duration between 6 months and 2 years, and MTX was given for 6 months were included, whereas patients with an age <30 and more than 50 years old, RA duration <6 months and more than 2 years, MTX intake for <6 months, patients on combination therapy

(MTX and biological therapy), patients with mixed connective tissue disease, seronegative RA and those with chronic diseases (chronic liver diseases) or chronic drug intake (drugs that induce or inhibit with cytochrome p 45 liver enzyme). Following informed consent for inclusion in the study, demographic data were taken in the form of age, sex, address, and occupation. Duration of symptoms (RA), drug history, and rheumatological examination (CDAI score) were done for them to assess the activity of RA. MTX was prescribed for them in a dose ranged between 20 and 25 mg either orally or by injection once weekly for 6 months together with a folic acid tablet of 5 mg once daily. A 5 mL venous blood was collected before the start of MTX and 6 months later for assessing liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) and evaluate its effects on these enzymes. These were measured using biochemistry full auto analyze, (AST/ALT test kit/IFCC method, reference range for male <41 U/L and female <31 U/L), whereas ALP KIT linear chemicals S.L/Barcalona/Spain with a reference limit up to 180 U/L for adult. Six months later, the CDAI score was calculated again to assess disease activity. The patients were divided into two groups according to the mode of intake: Group 1: Orally given MTX (n=15) and Group 2: Parenterally given MTX (n=15) and a comparison between the two groups was done regarding MTX efficacy in reducing RA activity and liver enzymes impairments. All included patients were on prednisolone tablets as a maintenance therapy of doses ranged between 5 and 7.5 mg daily. The study was approved by the Ethical Approval Committee of the College of Medicine/University of Kerbala/no.5, January 26, 2022. Data were presented and analyzed in a SPSS V.24 spreadsheet. Independent Student t-test for continuous data that are represented in mean±SD, whereas Chi-square test for categorical data that are represented in number and percentage. The difference between the studied variables is considered significant when p-value≤ 0.05.

Table 1: American College of Rheumatology/European League against Rheumatism had put diagnostic criteria for rheumatoid arthritis [5]

2010 ACR/EULAR Criteria for RA Diagnosis		
A.	**Joint involvement**	
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (≥1 small joint)	5
B.	**Serology (≥1 test result needed)**	
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
C.	**Acute-phase reactants (≥1 test result needed)**	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D.	**Duration of symptoms**	
	<6 wk	0
	≥6 wk	1
Definite diagnosis requires total score ≥6/10.		

Table 2: Clinical disease activity index score and interpretation [7]

Variable	Range	Interpretation
Total number of tender joints	(0–28)	(0–2.8) disease remission
Total number of swollen joints	(0–28)	(2.9–10) low disease activity
Patient global assessment	(0–10)	(10–22) moderate disease activity
Doctor global assessment	(0–10)	(22–76) highly active disease

RESULTS AND DISCUSSION

Table 3 illustrates the demographic characteristics of the included patients' age, sex, and duration of RA. Among the 30 patients, 24 were females and six were males with a mean age and duration of RA are 37.33±4.99 and 1.4±0.56 years, respectively.

Table 4 shows RA activity in the patients represented by CDAI score before MTX intake and 6 months after in both groups (mean±SD). CDAI score decreased after MTX start in both oral and parenteral with a significant reduction in the parenteral one at p=0.002.

Liver enzymes (ALT, AST, and ALP) comparison represented by (mean±SD) illustrated in Table 5. There was a significant impairment in ALT in the group in whom MTX was given orally than in the group who was given parenterally at p=0.001. Regarding AST and ALP, both of them exhibited mild impairment in both groups with an insignificant variation.

The current study showed that parenteral MTX is more efficacious in getting a low disease activity (as shown in Table 4, the CDAI score significantly decreased from 13.15±3.25 to 5.57±2.34), whereas oral MTX causes an insignificant reduction in CDAI score from 12.72±3.13 to 8.90±3.08. This result is similar to studies by Bakry *et al*., and Choonhakarn *et al*. [13,14]. While a study by Heuvelmans *et al*. had some arguments about the efficacy of oral MTX and concluded that tends to be not inferior to the parenteral one, especially when the dose approaches 25 mg weekly [15]. Wang *et al*. totally disagreed and suggested that oral MTX is not of lower efficacy than parenteral MTX [16]. Regarding MTX

Table 3: Demographic data of the patients enrolled in the study

Parameter	Mean±SD/total number, %
Age (years)	37.33±4.99
Gender	
Male	6 (20)
Female	24 (80)
Duration of RA (years)	1.4±0.56

RA: Rheumatoid arthritis

Table 4: CDAI score before and 6 months after MTX intake

Parameter	Group 1 (enteral MTX) n=15	Group 2 (parenteral MTX) n=15	p-value
CDAI before MTX	12.72±3.13	13.15±3.25	0.002
CDAI after MTX	8.90±3.08	5.57±2.34	

CDAI: Clinical disease activity index, MTX: Methotrexate

Table 5: Liver enzymes before and 6 months after MTX intake

Liver enzymes	Group 1 (enteral MTX) n=15	Group 2 (parenteral MTX) n=15	p-value
ALT (mean±SD), U/L			
Before	19.37±7.17	18.84±6.69	0.001
After	33.96±8.59	21.47±6.83	
AST (mean±SD), U/L			
Before	20.48±7.32	20.11±7.14	0.13
After	35.79±9.66	26.07±19.41	
ALP (mean±SD), U/L			
Before	95.53±11.41	104.06±13.11	0.29
After	100.20±12.79	105.44±12.92	

MTX: Methotrexate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase

effects on liver enzymes, the study showed that oral and parenteral MTX cause liver enzyme impairment commonly in the ALT and AST, but oral MTX caused more significant impairment in ALT than AST, with mild non-significant impairment in ALP. As we know, MTX can induce liver injury or even hepatotoxicity due to its 1st pass hepatic metabolism and this side effect could be overcome by shifting from oral to injectable [17]. A study by Lambert *et al.* concluded that sifting MTX treatment from oral to injectable is more efficacious in controlling RA with a lower rate of liver function impairment [18]. A study by Otón *et al.* believed that parenteral MTX can be considered an alternative to oral use in terms of disease control and safety [19].

CONCLUSION

Parenteral MTX intake tends to be more efficacious in attaining low disease activity than oral intake with a lower rate of impaired liver function.

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