OPTIMAL DOSE AND ADVERSE EFFECTS OF METHOTREXATE USED IN RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL OF PAKISTAN

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ABSTRACT

Objective: To find out optimum dosage and frequency of side effects with methotrexate (MTX) used in rheumatoid arthritis (RA).

Design: Quasi experimental study.

***Place and duration of study*:** Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad from November 2011 to April 2012

Patients and Methods: Patients of rheumatoid arthritis were treated with methotrexate (MTX). Dosage of MTX ranged from 7.5 to 30 mg per week. In patients who were tolerating MTX and still had an active disease according to DAS 28 index, their dose was increased further. The dose was increased till the disease activity was controlled or they developed side effects. Each case was followed on monthly basis for a total of 6 months. In the end all the data was analyzed.

Results: Out of 103 patients, 78 successfully completed the study. Mean age of patients was 42.4 ± 12.7 years and disease duration was 4.9 ± 4.6 years. After 6 months of therapy, it was observed that an average dose of 13.9 ± 4.2 mg per week of methotrexate was well tolerated by the patients. Side effects included: gastrointestinal 38(48.7%), neuropsychiatric 22(28.2%), dermatological 10(12.8%), reproductive 3(3.8%) and respiratory 1(1.3%).

Conclusion: An average of 13.9 ± 4.2 mg per week of MTX was found to be the optimum dose which was used and tolerated by most of the patients. Most common adverse effects were gastrointestinal while respiratory were the least common in the study.

Keywords: Methotrexate (MTX), optimal dose, adverse effects, rheumatoid arthritis.

INTRODUCTION

Methotrexate (MTX) is the most commonly used disease-modifying anti-rheumatic drug (DMARD) for the treatment of Rheumatoid Arthritis(RA)[1]. It has been found superior to other synthetic DMARDs because of its favourable efficacy profile[2]. Combining MTX with other biologic therapies shows a more promising clinical and functional outcome than using it as a mono therapy. Except for radiographic improvement, MTX is as effective as the newer biological drugs in terms of clinical response [3] but at much less cost.

The present standard approach for the management of rheumatoid arthritis dictates that the patient should be treated as effectively and as quickly as possible to achieve remission. Methotrexate remains the backbone in its management. Despite being the cornerstone treatment of RA, discontinuation rate due to adverse effects is as high as 30% after 1 year[1]. The probability of a patient remaining on methotrexate treatment after 5 years is 58.5[4].

Methotrexate therapy in RA is started with a low dose in the range of 7.5 to 15 mg orally once weekly. If patients continue to have an active disease, the dose should be increased in 5-mg per week increments each month or two till a dose of 20 to 30 mg per week[5]. Although methotrexate has been extensively used for rheumatoid arthritis, there is no consensus among rheumatologists regarding the optimal dose and the preferred route of administration. More research is required regarding the optimum dose[6]. In routine practice, the choice of route and dose adjustments, are left on the individual views of the rheumatologists[7]. In most cases, the

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decision to stop the drug is the occurrence of adverse effects. These may be minor ones like, mouth ulcers and gastrointestinal intolerance, or major side-effects such as bone marrow toxicity and liver abnormalities[1].

A thorough literature review of 38 publications reveals that although high starting doses in the range of 25 mg/week or fast escalation were associated with good clinical response; such patients however experienced more adverse events[6]. In light of above, MTX therapy therefore requires close monitoring for a possible toxicity[4].

In this study, we tried to find the optimal dose of methotrexate tolerated and the frequently encountered side effects due to methotrexate in patients suffering from rheumatoid arthritis.

MATERIAL AND METHODS

It was a quasi experimental study conducted in the Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, over a period of 6 months (November 2011 to April, 2012). Patients above 16 years of age, of either sex, diagnosed to have rheumatoid arthritis according to ACR/EULAR criteria, 2010 were included in the study using non-probability convenient sampling.

Exclusion criteria included

- Renal function derangement i.e., serum creatinine above 1.2mg/dl or frank renal failure.
- Disturbed liver function i.e., ALT twice above the normal limit or having cirrhosis.
- Patients who want to conceive in the near future.
- Pregnant women or breast feeding mothers[1].
- Patients having active infections at time of study.
- Patients with cytopenia i.e. if hemoglobin <8mg/dl and if it was not contributed due to the chronic disease of RA, TLC <3,000/Ul, or platelet <80,000/Ul.
- Patients with other autoimmune diseases.
- Patients with interstitial lung disease.
- Patient taking other DMARDs that might cause similar adverse effect.

A written consent was taken from all patients who fulfilled the inclusion criteria. Study was approved by the hospital ethics committee.

DAS28 is an internationally accepted disease activity score used to measure disease activity in patients with RA (Figure 1). It comprises of four components: swollen joints, tender joints, ESR, patient's self assessment of his/her general health (GH) on visual analogue scale ranging from 0-100 (0 means no effect and 100 means maximum affected life due to disease). In DAS28, we assess 28 joints.

DAS28 is calculated from the following formula:

$$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times GH$$

Specific DAS28 portable calculators are available as well as on the internet. Healthcare provider has to simply put the required values (www.4s-dawn.com/DAS28/DAS28.html) to calculate the activity score.

DAS28 measures RA disease activity as high (>5.1), moderate (>3.2 to 5.1), low (2.6 to 3.2) or disease in remission (<2.6). Aim of management in RA is to attain disease activity in low score i.e. between 2.6 to 3.2 or in remission i.e. <2.6.

The study variables included: age, sex, disease duration, DAS28 score, dose, drug tolerability and side effects.

MTX tablet is available in 2.5mg strength and was taken once a week followed by folic acid. Dose of methotrexate used in study was in a range of minimum 7.5 per week up to a maximum of 30mg per week. Cases induced at baseline were taking variable doses of same drug and was increased to 2.5-5mg/wk every month depending upon their disease activity and

tolerability. Patients either bought the medicines themselves or it was arranged through hospital social services for poor patients. Patients at each visit had to show the remaining tablets and were asked about number of tablets he/she had taken to check for compliance. "Optimum dose" was

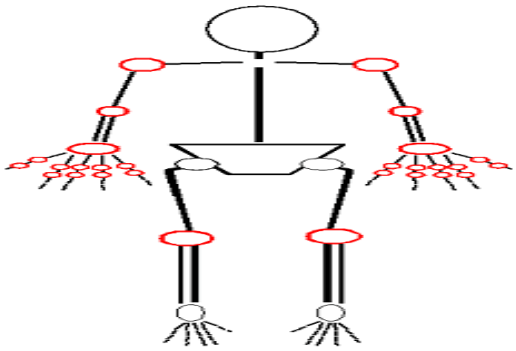

Figure-1: Joint involvement in DAS28.

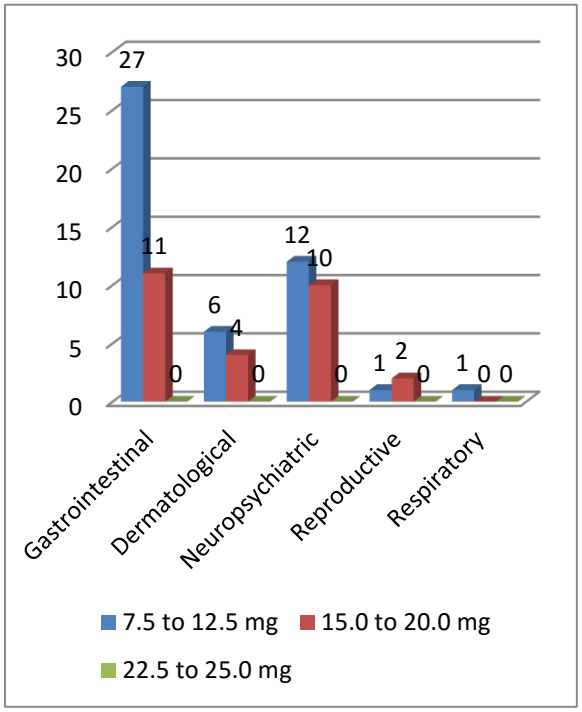

Figure-2: Distribution of side effects of Methotrexate according to body systems after 6 months.

the dose of drug which patient had been taking and it had effectively controlled the disease activity without causing any side effects. Blood complete picture, liver and renal function tests were done at the time of enrollment in all these patients. In subsequent visits, complete blood picture and liver function tests was checked. Other tests, if required, were individualized depending upon patient's complains or after investigator's assessment. DAS 28 was calculated at each visit. A decision regarding continuation, stopping, increasing or decreasing the dosage was made according to patient's clinical state and DAS28. Patient was labelled as "non-tolerable" to drug if he or she had any side effect which were severe enough to warrant discontinuation of the drug. A side effect ass considered as "minor" if continuation of the drug did not result in any life threatening complication or did not affect patient's compliance to the drug. A minor side effect was recorded and the drug was continued in either the same dose or reduced or discontinued after discussing with the patient. All study patients were followed on monthly basis for a six months period. Drug dosage range was categorized in four groups; 7.5-12.5, 15-20, 22.5-25 and >25mg for the purpose of statistical analysis. Data was entered and analyzed in SPSS version 11.0. Descriptive statistics were used to calculate means and standard deviations from continuous quantitative variables i.e. age and drug dose. Frequency and percentages were calculated from all qualitative variables i.e. sex, drug tolerability and side effects. Similarly the dose categories were compared among drug tolerability and non-tolerability using chi-square test. The level of significance was a *p*-value of less than 0.05.

RESULTS

Total 103 patients were enrolled, 78 patients were successfully completed the study period of 6 months. Remaining patients were dropped out of the study because of various reasons for their poor compliance.

The mean age of patients was 42.4 + 12.7 years with female predominance of 91%. The overall mean disease duration at the time of enrollment was 4.9 + 4.6 years.

All the patients were analyzed for the variables at intervals of 1, 3 and 6 months.

At 1 month, out of the 78 patients, 65 (83.3%) patients were tolerating drug methotrexate while 13(16.7%) patients were withdrawn due to non tolerance. Only those patients who were tolerating methotrexate i.e. 65 were further followed. Detailed drug tolerance at different drug dosages breakup mentioned in table 2.

At months 3, out of 65 tolerable patients. 61(93.8%) patients tolerated the drug and 4(6.2%) were withdrawn due to non tolerance.

At 6 month, 61 cases were successfully followed up. Fifty five (90.2%) patients tolerated MTX while 6(9.8%) were in non tolerant group.

At the end of study 70.5% tolerated while 29.5% were in non tolerant group.(Table 1)

Further analysis was done to quantitatively assess the drug tolerance according to average dosage of methotrexate at different visits. At 1, 3 and 6 month the mean tolerable dose was 11.8 ± 4.1 mg, 14.1 ± 4.1 mg, 16.3 ± 4.6 mg respectively. After 6 months average tolerable dose was 13.9 ± 4.2 mg.

At the end of the study, all the side effects according to systemic involvement were noticed. After 6 months, 38 (48.7%) cases had gastrointestinal, 22 (28.2%) had neuropsychiatric, 10 (12.8%) had dermatological, 3 (3.8%) had reproductive and 1 (1.3%) had respiratory side effects (Figure 2).

Further, elaborated side effects which resulted in drug discontinuation were shown in Figure 3.

The DAS28 score was compared among patients who tolerated the drug and those who did not tolerate it at 6 months. Both in tolerable and non-tolerable group, it statistically improved from baseline when analyzed after 6 months (Table 2).

DISCUSSION

RA is a chronic disease which causes disability if remains uncontrolled. Joint damage occurs early in this disease process. Radiological damage is 30% at the time of diagnosis and

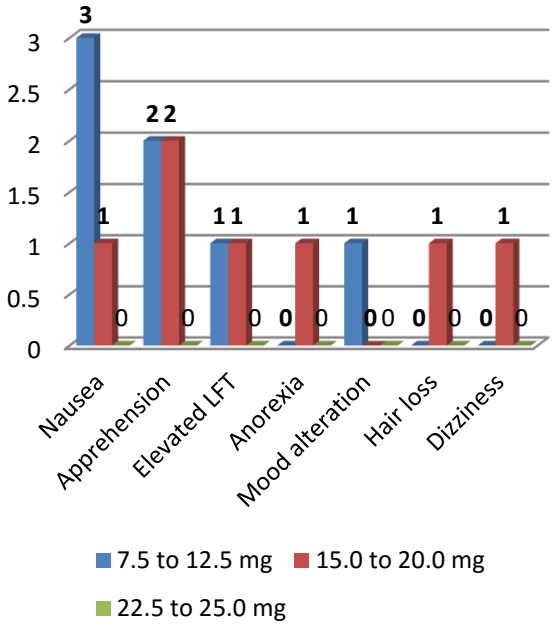

Figure-3: Side effects of methotrexate according to dose at 6 months.

Table-1: Breakdown of drug tolerance in the study.

	Tolerated	Not tolerated
Dose at 1 month (n = 78)	65(83.3%)	13(16.7%)
7.5 to 12.5 mg	46 (70.8%)	10 (76.9%)
15.0 to 20.0 mg	19 (29.2%)	3 (23.1%)
Dose at 3 months (n = 65)	61(93.2%)	4(6.2%)
7.5 to 12.5 mg	34 (55.7%)	4 (100.0%)
15.0 to 20.0 mg	25 (41.0%)	0 (0.0%)
22.5 to 25.0 mg	2 (3.3%)	0 (0.0%)
Dose at 6 months (n = 61)	55(90.8%)	6 (9.8%)
7.5 to 12.5 mg	21 (38.2%)	4 (66.7%)
15.0 to 20.0 mg	25 (45.5%)	2 (33.3%)
22.5 to 25.0 mg	9 (16.4%)	0 (0.0%)
Overall drug tolerance	55 (70.5%)	23 (29.5%)

increase to 60% at 2 yrs[5]. Disease modifying therapy should be started as soon as a diagnosis of RA is made[8].

MTX is considered the anchor drug and even in this era of biologics, it remains the standard DMARD to initiate the drug treatment[9]. EULAR's latest recommendations in 2010 emphasizes upon the use of MTX to be as the first treatment strategy. They also suggested MTX should be combined with biologics since this combination has superior efficacy than monotherapy[8]. In developing countries like Pakistan, where cost is a major issue, MTX remain the gold standard treatment for RA[10].

With these above facts in mind and a huge burden of RA in our outpatient department, we tried to find out the optimum tolerable dose for our patients. Patients were followed on intensified strategy i.e. more frequent visits to increase the drug dosage, if required. A recent literature review found that MTX is more effective when started in a high dosage (more than 10mg/week orally) and the dose is subsequently increased by increments of 5mg/month up to a total of 25-30mg/week. This strategy should however be tailored according to the disease activity and patient's requirement[11]. More recent insights suggest that MTX at higher weekly doses (20–30 mg) is more effective than MTX at lower weekly doses (7.5–15 mg)[6,12]. This study found 13.9±4.2 mg as the optimum dose for our patients. We think that genetic factor have an important contributory role on MTX responsiveness. This rational is supported by many genetic studies[13,14]. Differences in genotype may be a reason since despite the use of MTX for over a few decades, no consensus on the optimum dose has been reached worldwide. CAMERA trail found an average dose of 16.1±1.3 mg/wk as the optimum dose in their intensified strategy group in a Dutch population[7].

Another interesting outcome of our study is that the all patients who were able to take MTX above 20mg/wk dosage developed no side effects. So a conclusion can be drawn out of this fact is that side effects with MTX are not dose dependent. But, unfortunately none of our patients was able to reach the target of 30mg/wk. Our patients either got controlled or they became intolerant to MTX before that dose. DAS 28 was significantly decreased in patients who tolerated the drug well. This finding is also supported by another study, which showed a significantly lower DAS 28 in patients with RA when MTX was used above 8mg/wk[15].

Table-2: Comparison of DAS score with overall drug tolerance.

	Tolerated (n=49)	Not toleratd (n=12)
DAS 1 month	4.3 + 1.2	4.0 + 1.5
DAS 6 months	3.6 + 1.1	3.3 + 1.1
p-Value	0.001	0.003

The most common side effects seen in our study pertain to the gastrointestinal system (48.7%), which were also a major cause of drug intolerance. Many other studies also supplement these findings[16-18]. The frequency of these GI side effects in our study were however much higher compared to these other studies i.e. 31% in Saudi Arabia, 38% in France and 21% in India[16-18]. Probable explanation of this difference would also be explained on the basis of different genes that determine MTX toxicity[19,20]. Incidence of *Helicobacter pylori* infections, concomitant use of NSAIDs in greater amounts and use of more steroids may be the other reasons involved. Other side effects noticed in our study involve the neuropsychiatric, dermatological, reproductive and respiratory in descending order. Haematological side effects were not noticed in our study patients, probably because of the reason that they were so closely and frequently monitored. A reasonable conclusion that can be deducted from this is that some of these serious drug side effects are eliminated by keeping close monitoring and properly educating the patients.

The importance of our study lies in the fact that this is first time where an effort has been

made to find out the optimum dose of MTX needed to control RA disease activity, and its side effect.

Main disadvantage of the study is its short duration, relatively high dropout rate and failure to reach the target of 30mg/week of dose.

CONCLUSION

An average of 13.9±4.2 mg per week of MTX was found to be the optimal dose which was used and tolerated by most of the patients. Most common adverse effects were gastrointestinal while respiratory were the least common in the study.

A long term followup study with greater number of study subjects is therefore recommended.

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