SHORT-TERM EFFECTIVENESS OF METHOTREXATE IN THE TREATMENT OF ACTIVE RHEUMATOID ARTHRITIS

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ABSTRACT

Objective: *To determine the effectiveness of 6-month treatment with methotrexate in a dose range of 5-15mg once weekly in 103 patients with active rheumatoid arthritis.*

Methodology: *This descriptive study was conducted in outpatient department of Medical B unit Lady Reading Hospital from October 2008 to August 2009 and included 103 active rheumatoid arthritis patients who received methotrexate in a dose range of 5-15mg once weekly for 6 months. The primary efficacy endpoint was a $\geq$20% response according to the American College of Rheumatology response criteria 20 and disease activity score 28 after 6 months.*

Results: *Female patients made up 51.5% of the study population while males were 48.5%. The mean age was 46.1 years and the mean disease duration was 10.90 ± 3.42 years. According to the disease activity score 28, 30.1% of patients had good while 38.8% had a moderate response. 31.1% were non-responders. Mean improvement in tender joint count were –8.3 ± 4.59(from baseline of 15.54 ± 5.85) and in swollen joint count were -7.37 ± 3.98 (from baseline of 10.59 ± 4.96). ESR improved to 15.24 ±10.42 from baseline of 58.7 ± 11.16 and physical global assessment improves to 34.42 ± 20.43 from baseline of 66.21 ± 10.58. At 6 months, the rate of American college of rheumatology response criteria 20 was 68.2%. Treatment related adverse events were reported in 27.2% of patients.*

Conclusions: *The study showed a favorable effectiveness for methotrexate in a dose range of 7.5-15mg once weekly.*

Key words: *Rheumatoid Arthritis (RA), Methotrexate (MTX), Disease Modifying Anti Rheumatic Drugs (DMARDs), American College of Rheumatology response criteria 20 (ACR20), Disease Activity Score 28 (DAS28).*

INTRODUCTION

Rheumatoid arthritis (RA) is a major disabling disease. It is slowly progressive disease. There should be an effective treatment to halt the progress of disease .A treatment paradigm for Rheumatoid arthritis has been established after a long history of trial and error. The use of non steroidal anti inflammatory drugs (NSA1Ds) in RA are the corner stone of modern pharmacological treatment of RA[1]. NSA1Ds are used to control acute pain[2]. Disease Modifying Anti Rheumatic Drugs (DMARDs) slow the chronic destruction and biological process that are responsible for persistent inflammation[3].

As the introduction of biologics has provided new treatment option for RA but mostly methotrxate (MTX) is considered as standard. Upto the introduction of biologics, MTX was considered as anchor in the treatment of RA. The major limitation of DMARDs is limited drug survival span because of toxicity and inflammation during course of disease[4].

MTX is an important DMARD used in RA. It was first used for treatment of RA and

psoriasis in 1951[5]. It emerged at the same time as glucocorticoids were developed. It came in the limelight when retrospective studies appeared in early 1980[6, 7].

MTX is a structural analogue of folic acid that can competitively inhibit the binding of dihydrofolic acid (FH2) to the enzyme dihydro folate reductase (DHFR). It reduces FH2 to folinic acid (FH3), which is active intracellular metabolite, so decreases intracellular FH4 affect metabolic pathway which are FH4 dependent[8].

The mechanism by which it improves signs and symptoms of RA is not certain .One mechanism is that it increases the extracellular concentration of adenosine, due to extracellular dephosphorylation of adenosine nucleotides via ecto-5-nuecleotidase[9,10]. Other proposed mechanisms include the inhibition of methylation reduction vital for cellular activation and replication, clonal deletion via apoptosis of activated peripheral T cells, decreased production of proinflammatory cytokines by activated T cells, suppression of IL-1 beta production by mononuclear cells, repression of clonal growth of peripheral and synovial T and B cells, increased production of IL-10 and suppression of intracellular adhesion by activated T cells[11-15]. MTX can be given via oral, intramuscular and subcutaneous routes. Oral MTX is variably absorbed in the dosage range used to treat RA e.g. a 7.5 weekly dose is absorbed better that 15-20mg dose[16].

In Japan, a cross sectional analysis included 12 rheumatologists who prescribed MTX to more than 60 patients, show a significant positive relationship between average MTX dose and the percentage of patients with disease activity score 28 below 3.2[4]. In one study a total 148 patients with RA were included some of them were given MTX (15mg/wk) plus cyclosporine (2.5 to 5mg/kg) daily in two daily divided doses, while others were given MTX and placebos[17]. As compared to MTX and placebo group, the other group had net improvement in tender joint count (25%), swollen joint count (25%), overall disease activity (19%) and degree of disability (26%).

The present study was conducted to assess the effectiveness in our setup with methotrexate in RA in a dose range of 7.5mg-15mg per week for 6 months. The American College of Rheumatology response criteria 20 (ACR20) response rate and Disease Activity Score 28 (DAS28) were assessed as primary endpoints.

METHODOLOGY

This descriptive was conducted in outpatient department in MED B unit Lady Reading Hospital Peshawar from October 2008 to August 2009. A total 103 patients were included in the study. All the patients were diagnosed as a case of RA on the basis of ACR criteria 1987. All the patients must met the three of the four following criteria for active disease, swollen joint count (SJC) >28(based on a 28 joint count), tender joint count (TJC)> 10(based on a 28 joint count), erythrocyte sedimentation rate (ESR) > 28 and morning stiffness >45 minutes. A written informed consent was obtained from the patients.

The exclusion criteria of the study are intraarticular or parenteral corticosteroid injection in the past 4 weeks prior to inclusion, treatment with other DMARDs in the last 2 weeks or use of oral steroids in dosage higher than 10mg/day. Those who have contraindications for the methotrxate therapy like hypersensitivity, immunodeficiency, anemia, leucopenia or thrombocytopenia were excluded. Patients having renal failure, hepatic insufficiency and pregnant ladies were also excluded from the study.

The study included five visits: screening, baseline (1–4 weeks after the screening visit), and follow-up visits after 1, 3 and 6 months (end of study) respectively. Laboratory tests (red and white cell count, platelet count, blood pregnancy test, ALT, AST, serum albumin and renal function tests) were performed at the baseline visit and at visits 3, 4 and 5. Before treatment with the methotrexate was initiated, a washout period of 2 weeks was required in the case of prior treatment with DMARDs. If a patient was treated with intra-articular or parenteral corticosteroids, a washout period of 4 weeks was required.

After oral administration of an initial dose of methotrexate 7.5mg weekly,further dose was adjusted between 7.5mg-15mg according to activity and response of patient. If an increase in ALT levels twice the upper limit of normal occurred and persisted, the dosage was reduced. In any case, if ALT levels persisted between two and three times the upper limit of normal (ULN) for more than 2 weeks, methotrexate treatment was stopped.

NSAIDs and oral corticosteroids as concomitant medication were allowed during the study period. Other DMARDs and any other investigational drug and live vaccines were not allowed.

At each study visit the ACR 20 response rate (the primary efficacy criteria) was assessed with the following, tender joint count (TJC; 28 joints evaluated)[18], swollen joint count (SJC), investigator's and patient's global evaluation of health (on a visual analogue scale [VAS]), patient evaluation of pain (on a VAS), functional index

(Health Assessment Questionnaire [HAQ])[19], erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

The DAS28[20] was calculated based on the SJC, TJC, ESR and general health scale (GH). The disease activity was considered to be low if the DAS28 score was $\leq$3.2, as moderate if the score was >3.2 and $\leq$5.1, high in the case if DAS28 score >5.1 and in remission when it is <2.6. The duration of morning stiffness was assessed by asking the patient to estimate the time required after waking up to be able to perform usual everyday activities, and recorded in minutes. For the assessment of pain by the patient, a VAS using a 100mm horizontal scale (0 = no pain; 100mm = maximum, non-bearable pain) was used to record overall pain, pain at rest and pain on movement. The DAS 28 is more practical to implement as it eliminated grading of joints and reduced the number of joints to 28[21, 22]. The calculator for DAS 28 is also available.

Safety and tolerability were assessed on the basis of adverse events, physical examination, weight and blood pressure, laboratory tests (red and white cell counts and platelet count, serum ALT, serum pregnancy tests).

The adverse events evaluated during the study by examination or reported by the patient that developed or worsened during the period of treatment. Severity (mild, moderate or severe) was rated according to the assessment. An adverse event was classified as serious if it met any of the following criteria: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was otherwise an important medical event.

Compliance of study patients was assessed by tablet counts and patients were questioned about medication intake. It was rated as good if the intake was $\geq$80%.

All information was recorded on standard Proforma. Statistical Package for Social Sciences (SPSS) version 15 was utilized for data storage, processing and analysis.

RESULTS

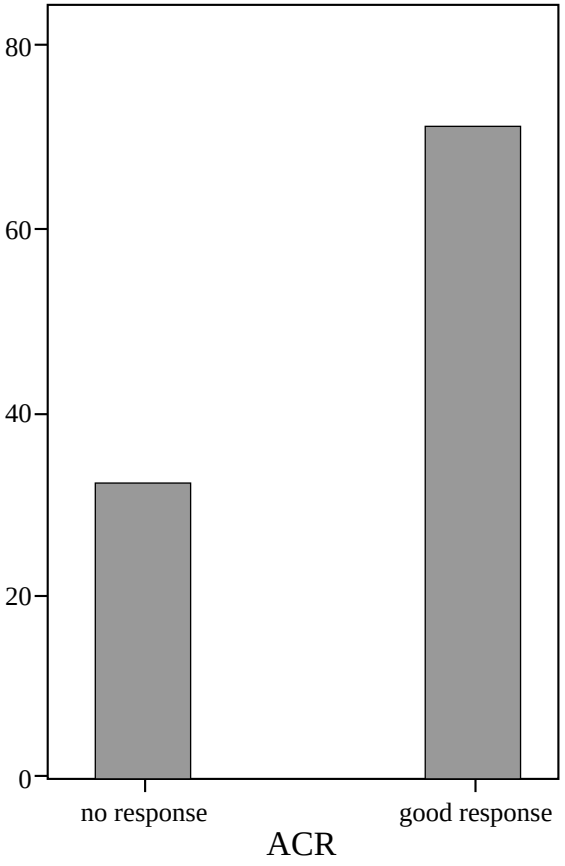
A total of 103 patients were screened for eligibility. All the 103 patients were treated with methotrexate in a dose range of 7.5mg-15mg once weekly. During the study period, 57 patients received concomitant corticosteroid therapy.

All the 103 patients were treated with methotrxate in a dose range of 7.5mg-15mg once weekly. At baseline, the mean disease duration of disease was 10.90± 3.42 years, and 32% had already been treated with a DMARD. The most frequently reported previous DMARD treatments were sulphasalazine (17%), Leflunomide (9%) and hydroxychloroquine (6%). The mean duration of morning stiffness at baseline was 2.44 ± 1.2 hours.

Effectiveness

Of 103 patients 68.2% responded to MTX treatment according to the ACR 20 criteria, and 31.8% patients were non-responders (Figure 1).

Figure 1: Response on ACR 20 criteria.



Disease activity according to the DAS28 was assessed from the data of 103 patients. 68.9% patients were responders out of which 30.1% patients showed good response while 38.8% patients had a moderate response. 31.1% patients were non-responders (Figure 2).

Mean improvement in tender joint count were –8.3 ± 4.59(from baseline of 15.54 ± 5.85) and in swollen joint count were -7.37 ± 3.98 (from baseline of 10.59 ± 4.96). ESR improved to 15.24 ±10.42 from baseline of 58.7 ± 11.16 and physical global assessment improves to 34.42 ± 20.43 from baseline of 66.21 ± 10.58 (Table 1).

The analyses of the RA disease assessment criteria revealed a progressive improvement in all

Figure 2: Response on ACR 20 criteria

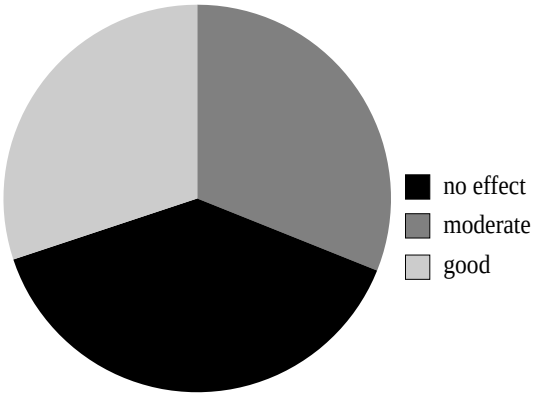


Table 1: Baseline and improvement after 6 months

Tender Joint Count	
Baseline	15.54±5.85
Δ (6Months)	8.3±4.59
Swollen Joint Count	
Baseline	10.59±4.96
Δ (6Months)	7.37±3.98
ESR	
Baseline	58.7±11.16
Δ (6Months)	15.24±20.4
Physical Global Assessment	
Baseline	66.21±10.5
Δ (6Months)	34.4±20.43

criteria between visit 1 and visit 5 (end-point). Biological signs (CRP and ESR) were reduced with MTX treatment. The TJC and SJC decreased accordingly to both patients and investigators judgment.

Adverse Events

Adverse events were reported in 27.2% patients. The most frequently reported adverse events were hepatotoxity in 14.6% patients while GI intolerance in 12.6% of total patients.

DISCUSSION

Rheumatoid arthritis is a common disease we come across in our community. It is mostly ill managed and should be treated in the initial phases of illnness to prevent complication of illness. The need to administer DMARDs in the initial phase of disease has been emphasized both locally and internationally. MTX is an important DMARD used in the treatment of RA for the last 20 years. The use of this agent has a beneficial effect not only on survival like healing of erosive disease but also halting the disease progression[23].

This study was conducted for the first time in a typical office based physician setup in our outpatient department. In our study MTX was administerd in a dose range of 5-15mg weekly. The present study was conducted to assess its clinical efficacy on basis of ACR 20 and DAS 28. The study showed effectiveness of 68.2% according to ACR crieteria and of 68.9% according to DAS 28 crieteria. The result was comparable to the studies done by Weinblatt et al[24] and Rich et al.[25]In one of above mentioned study the effectiveness of MTX over a five year period in 123 patients with RA,[24] it was observed that MTX improves the clinical variables (Joint tenderness and joint swelling index), measures of functional status and that of erythrocyte sedimentation rate. In another study a series of 24 patients with RA were treated with MTX and in about 50 percent of patient disease was halted[25]. In a study of about 27 RA patients in whom a DMARD agent was ineffective they were treated MTX for 108 months[26] the improvement in joint swelling and ESR was observed but disease remained progressives despite therapy. So further long term study is suggested if we want to assess the exact effectiveness of MTX.

MTX was initially started in RA who failed to NSAIDS[27-30]. So MTX can be used in patients who fail to respond to NSA1Ds .It is to mention that MTX can be started at the sometime as the NSAIDs are started.

The efficacy and side effects of the therapy should be monitored at 4-8 weeks interval. Efficacy should be monitored by joint count, improvement in functional status and periodic radiographic assessment every one to two years.MTX toxicities is monitored with complete blood count, chemistry profile and questions about different systemic problems. Patient with RA are generally treated indefinitely. This approval is both effective and safe[31, 32].

Patient who does not respond to MTX alone can improve with combination of MTX and other drugs like adding a sulphasalazine or cyclosporin or hydroxychlroquine or infiliximibe and Leflunomide.

In one study a total 148 patients with RA were included some of them were given MTX (15mg/wk) plus cyclosporine (2.5 to 5mg/kg) daily in two daily divided doses, while others were given MTX and placebos[17]. As compared to MTX and placebo group, the other group had net improvement in tender joint count (25percent), swollen joint count (25 percent), overall disease

activity (19 Percent) and degree of disability (26 percent).Side effect were not increased.

In another double blind trial, 102 patients were included, who had a previous poor response to at least one disease modifying drug. These patients were treated with MTX (7.5mg to 17.5mg/wk) alone or with combination of sulfasalazine (500mg) twice daily and hydroxychloroquine (200mg) twice daily[33]. There was 50 percent improvement is symptoms of arthritis and no evidence of drug toxicity.

As mentioned in the studies performed earlier the major side effects of MTX are hepatotoxicity[34, 35], pulmonary toxicity[36], kidney disease and myelosuppression[37, 38]. The other common toxicities of MTX are nausea, stomach upset, loose stools, stomatits and soreness of mouth. CNS system problems include headache, fatigue and impairment to concentrate. Alopecia, fever, lymph proliferative malignancies develop after long term therapy[39]. The present study confirms the safety profile of MTX .The overall frequency of the adverse events is 27.2%.The most commonly reported side effects in our study were hepatotoxity which was14.6% and GI intolerence of 12.6%.

CONCLUSION

This study showed feasible response to methotrexate in dose range of 7.5-15mg. The reported adverse events were manageable in the routine clinical practice.

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