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PERSISTENCE WITH METHOTREXATE THERAPY IN RHEUMATOID ARTHRITIS AT TWO TERTIARY CARE CENTRES IN INDIA

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ABSTRACT **Background:** The goal of rheumatoid arthritis (RA) therapy is to obtain remission or low disease activity. Most guidelines recommend initiation of disease modifying anti-rheumatic drugs (DMARDs) at the time of diagnosis, with methotrexate (MTX) being the DMARD of first choice. Persistence with therapy is one of the key factors determining the outcome.
Aim: To investigate the persistence with MTX among RA patients.
Method: A prospective observational study was conducted at two tertiary centres of the Armed Forces of India over a period of one year in which 100 (female-71, male- 29) patients with RA satisfying the 1987 ACR classification criteria were enrolled. They were initiated on methotrexate, either as monotherapy (n= 58) or in combination with other DMARDs, i.e, methotrexate with hydroxychloroquine (n=24) and methotrexate with hydroxychloroquine and sulphasalazine (n=18) and followed up once every 4 weeks for a period of at least 6 months.
Results: The persistence rate to methotrexate in our study was 88% at 6 months. Reasons for discontinuation (n=12) included lack of tolerability (41.6% of discontinuers), lack of efficacy (8.3%), lost to follow up (25%), poor compliance (16.6%) and prior to conception (8.3%).
Conclusions: Lack of tolerability was the leading cause for discontinuation of therapy. A high persistence rate observed in our study could be attributed to the meticulous counseling of patients and the fact that majority of the patients were defence personnel or their relatives.

KEYWORDS : Methotrexate, Rheumatoid arthritis, Persistence

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease possessing articular and extra-articular features with a prevalence of approximately 1 % [1]. The goal of rheumatoid arthritis (RA) therapy is to obtain remission or low disease activity. According to the guidelines of all major rheumatological associations (European League Against Rheumatism [EULAR], American College of Rheumatology [ACR] and French Society for Rheumatology), treatment with a synthetic disease-modifying anti-rheumatic drug (DMARD) should be initiated as soon as possible after disease diagnosis [2-4].The DMARDs are known for their ability to change the course of RA (for the better) and to retard or halt radiographic progression.

Methotrexate (MTX) is the disease-modifying anti-rheumatic drug (DMARD) of first choice in the treatment of RA [2-4]. The recommendation was based on the evidence that MTX has the best drug retention rate (persistence), and equivocal or superior efficacy, in comparison with other synthetic disease modifying anti-rheumatic drugs (sDMARDs) [5].MTX has multiple mechanisms of action that contribute to improvement in clinical symptoms and disease control in patients with RA, including inhibition of inflammatory cell proliferation, interference with T-cell activity and cytokine secretion, and augmented release of adenosine, which in turn activates receptors on macrophages and neutrophils to decrease the release of pro-inflammatory cytokines (such as tumor necrosis factor [TNF]-α and interleukin [IL]-6) and elevate the secretion of anti-inflammatory molecules (such as IL-10) [6].However, response to MTX is not universal; only 28–45% of patients achieved disease activity score (DAS)-defined remission (DAS28 < 2.6) one year after starting methotrexate monotherapy [7,8].Although reasons for not achieving or for losing disease control are complex, one factor that may influence outcome is medication adherence (compliance), defined as the degree to which a patient takes medication in accordance with clinician's instructions [9]. Medication persistence is considered an aspect of adherence and refers to the act of continuing the treatment for the prescribed duration. It may be defined as the duration of time from initiation to discontinuation of therapy [10].Our study investigated the persistence with MTX among RA patients at two tertiary centres in India.

MATERIAL AND METHODS:

A prospective observational study was conducted at two tertiary centres of the Armed Forces of India located in Kolkata and Mumbai over a period of one year from 01.07.2015 to 30.06.2016. Both the principal investigators were trained rheumatologists with adequate clinical experience. After obtaining an informed consent, one hundred patients satisfying the 1987 American College of Rheumatology (ACR) criteria for the classification of RA were enrolled on this study.

Patients were started on methotrexate, either as monotherapy or in combination with other DMARDs (Methotrexate with Hydroxychloroquine/Methotrexate + Hydroxychloroquine + Sulfasalazine). Methotrexate (MTX) was administered in doses of 10-25 mg/ week. Doses upto 15 mg/ week were administered orally. If the weekly dose exceeded 15 mg, it was administered parenterally (subcutaneously or intramuscularly). Hydroxychloroquine (HCQ) was administered orally in a dose of 200 mg twice daily for the first 6 weeks, followed by 200 mg once a day. Sulfasalazine (SSZ) was initiated in a dose of 500 mg twice daily, gradually increased upto a maximum of 3 gm/ day. Concomitant folic acid supplementation in a dose of 5 mg twice weekly was given to all patients. In addition, parenteral (intramuscular) methyl prednisolone was administered in a dose of 80 mg weekly for 2-4 weeks as bridge therapy. Blood investigations (hemogram, liver and renal function tests, fasting and postprandial blood sugars, serology for Hepatitis B and Hepatitis C viruses), urine routine examination and a chest radiograph were done in all patients before commencement of therapy. Patients with deranged liver function tests, active tuberculosis and interstitial lung disease and those on biologics were excluded from the study. Patients were educated by the doctors (rheumatologist, medical officer or intern) about the drugs, including their delayed onset. The need for adherence and persistence to therapy was emphasized. Patients were followed up every 4 weekly for a minimum period of six months. Compliance with medications was documented at each visit based on self reporting by the patient and checking the medications brought by the patients at follow up visit. Hemogram, liver function tests (LFT), blood urea and serum creatinine were repeated after 4 weeks and thereafter every 8 weekly. No new cases were enrolled after 31.12.2015. If a patient made at least five 4 weekly visits out of 6 over a period of 6 months, he/she was included in the study. Any patient with fewer than 5 visits was labelled as irregular and excluded from the study.

RESULTS:

A total of 100 patients (female-71, male-29) with mean age of 38.8 ± 8.62 (SD) were included in the study. Of these, 58 patients were started on MTX monotherapy, 24 on a combination of MTX with HCQ and 18 on combination therapy of MTX with HCQ and SSZ (triple combination therapy). Eighty eight of the 100 patients had regular follow up and completed at least 6 months of treatment. Three patients were lost to follow up while 2 were irregular in reporting for follow-up (poor compliance). Of the other 7 patients in whom treatment was discontinued before completion of 6 months, lack of tolerability was the reason for withdrawal in 5 (elevated liver enzymes in 3 and nausea and vomiting in 2) and lack of efficacy after 3 months of methotrexate monotherapy in one patient, who was later switched to leflunomide. Methotrexate, being a teratogenic drug (FDA Category X) had to be discontinued in one patient receiving methotrexate monotherapy as she was planning to conceive (Figure 1). Of the 3 patients in whom deranged liver function tests necessitated withdrawal of therapy, two were receiving MTX monotherapy and another, triple combination therapy. One patient each from the MTX+HCQ group and triple combination therapy group had to discontinue therapy due to nausea and vomiting. There were another 8 patients who developed nausea and vomiting as side effects of the treatment, but their symptoms were relieved by the administration of ondansetron (8 mg) prior to MTX.

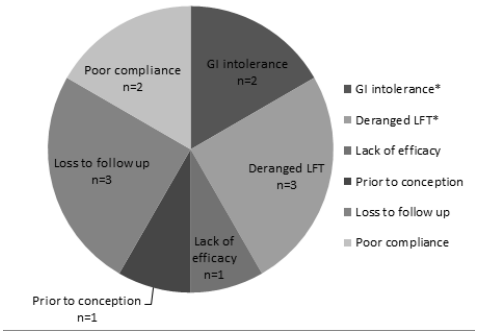

Figure 1- Reasons for discontinuation of Methotrexate therapy in RA (n=12)

DISCUSSION:

MTX is the DMARD of choice in the treatment of RA. Generally, RA patients experience improvement of symptoms 3–6 months after initiation of MTX treatment, and at the same time, many patients develop minor adverse events [11]. Medication adherence and persistence are among the key factors which influence response to treatment (outcome).

Factors associated with increased drug adherence and persistence include patient's stronger belief in necessity of RA medications [12-15], increased knowledge of available treatment or patient educational interventions [16,17,18], positive relationship or satisfaction with the clinician [16,18,19], more frequent visits to the rheumatologist [18], increased professional or family support [15]. Factors associated with decreased drug adherence and persistence include concern about side effects [15, 18, 20, 21], longer disease duration [22, 23], higher medication costs [24, 25] and multiple concomitant medications [26, 27].

Our study investigated the level of persistence with methotrexate (MTX), either as monotherapy or in combination with other DMARDs (HCQ and/or SSZ) in patients with rheumatoid arthritis. Cutis et al in their systematic review of published clinical studies evaluating MTX adherence and persistence in patients with RA treated with MTX alone or in combination with non-biologic or biologic DMARD found 29 studies which evaluated persistence with MTX [28]. Different definitions of MTX discontinuation were used across studies, including MTX withdrawal, adding another treatment to MTX, or MTX interruption. Persistence rates ranged from 50 to 94% at 1 year and 25 to 79% at 5 years. Lack of tolerability was the main reason for withdrawal (23%-79% of withdrawals). Inefficacy was the other primary reason for withdrawal (6%-72% of withdrawals). The persistence rate to methotrexate in our study was 88% at 6 months. Reasons for discontinuation (n=12) in our study included lack of tolerability (41.6% of discontinuers), lack of efficacy (8.3%), lost to follow up (25%), poor compliance (16.6%) and prior to conception (8.3%). The high persistence rate in our study could be related to the fact that majority of patients in our study were defence personnel (known for their inherent discipline and obedience) or their relatives, meticulous counseling of patients by doctors with emphasis on adherence and persistence to therapy and that all patients were administered folic acid supplementation, which may have improved tolerability to MTX.

Table-1: Comparison of various studies evaluating persistence with MTX in RA

Study	Receiving MTX, n	Measurement	No. discontinuers, reasons for discontinuation
Alarcon,et al [29]	152	Chart data/ patient self- report	n= 78, lack of tolerability 60%, inefficacy 8%, elective surgical procedure 8%, other 24%
Salaffi, et al[30]	51	Chart data	n= 15, lack of tolerability 53%, inefficacy 27%, elective surgical procedure 7%, poor compliance 13%
De La Mata, et al[31]	152	Chart data	n= 51, lack of tolerability 37%, inefficacy 43%, other 20%
Lie, et al[32]	927	Chart data	n= 446, lack of tolerability 32%, inefficacy 45%, other 23%
Gibofsky, et al[33]	1893	Chart data	n= 316, lack of tolerability 25%, inefficacy 6%, cost 2%, patient decision 41% other/ unknown 27%
Present study	100	Patient self-report	n=12, lack of tolerability(GI intolerance- 16.6%, deranged LFT-25%)- 41.6%, lost to follow up-25%, poor compliance-16.6%, lack of efficacy-8.3%, discontinuation prior to conception-8.3%

CONCLUSION:

Lack of tolerability (transaminitis, nausea and vomiting) was the leading cause for discontinuation of MTX (mono therapy or combination therapy) in our study. A higher persistence rate to methotrexate in patients with RA observed in our study could be related to the meticulous counseling of patients with emphasis on adherence to therapy, majority of the patients were defence personnel or their relatives and our study had a shorter duration (6 months) compared to most of the other similar studies.

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