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Adherence to Methotrexate therapy in patients with rheumatoid arthritis - a hospital based cross sectional study from Kochi, Kerala.

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ABSTRACT

INTRODUCTION: Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease that affects the joints, connective tissues, muscle, tendons, and fibrous tissues. The main symptoms of rheumatoid arthritis are joint pain, swelling, and stiffness. **METHODOLOGY:** A hospital-based cross-sectional survey was carried out among the RA patients attending rheumatology OPD at a tertiary care hospital in Kochi between January -April 2019. The minimum calculated sample size was 52 and data were collected using a semi-structured questionnaire containing questions from CQR 5 to assess adherence to treatment and DAS28 & VAS to assess disease severity. Ethical clearance was given by the Institution Ethical Committee and all participants were interviewed after taking written informed consent. Data were analyzed using SPSS version 22. **RESULT:** A total of 86 individuals were included in the study and the compliance to methotrexate therapy was found to be 73.3% among participants aged ≥ 18 years using the CQR 5 questionnaire. Homemakers and the elderly were more compliant. Side effects following methotrexate therapy, family history, the severity of the disease did not have an effect on compliance to methotrexate. **CONCLUSION:** Approximately one-fourth of our participants were found to have low compliance to methotrexate. A multi-centric cohort study might help us in better understanding the factors influencing adherence to methotrexate therapy in patients with rheumatoid arthritis.

Key word: compliance, adherence, methotrexate therapy, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is an auto immune and inflammatory disease that affects the joints, connective tissues, muscle, tendons, and fibrous tissues. In a joint with RA, the lining of the joint becomes inflamed, causing damage to joint tissue. This tissue damage can cause long-lasting or chronic pain, unsteadiness, and deformity and the age group commonly involved is 20 to 40years (1). In some people, the condition also can damage a wide variety

of body systems, including the skin, eyes, lungs, heart, and blood vessels (2).

Globally, in 2015, around 24.5 million were reported to have RA (3). Around 0.5 -1% of this are adults in the developed world and around 5-50 per 100,000 people are newly diagnosed each year (4). According to a study conducted in Delhi, India the prevalence of rheumatoid arthritis was 0.75 %;

projected to the whole population, this would give a total of about seven million patients in India (5).

The 2015 treatment guidelines for RA by the American College of Rheumatology addresses the use of DMARDs, biologics, tofacitinib and glucocorticoids in early and established RA (6). Among the Disease Modifying Anti Rheumatic Drugs (DMARDs), Methotrexate is the commonly used drug in the treatment of RA and is often given alone or in combination with conventional or biologic DMARDs (7,8). MTX is also extensively used for other auto immune conditions like psoriatic arthritis, juvenile idiopathic arthritis, uveitis, vasculitis, inflammatory bowel disease.

Although MTX is less toxic and the preferred first line therapy for RA compared to other treatment alternatives; the side effects of the drug decreases patient compliance. The common side effects of methotrexate include nausea and vomiting, stomatitis, mild alopecia, mild leukopenia, liver toxicity, oral ulcers, and loss of appetite. The adverse events following methotrexate therapy appear to be related to the antifolate activity of MTX and mimic the symptoms of folate deficiency (9).

This study was hence carried out to assess the compliance to and factors associated with methotrexate therapy among patients with RA along with understanding the side effect profile of methotrexate as perceived by the patients.

MATERIAL AND METHODS

A cross sectional survey was carried out among patients attending the out-patient department of Rheumatology of Amrita Institute of Medical Sciences in Kerala between January to April 2019. Patients (age ≥ 18) with confirmed diagnosis of Rheumatoid Arthritis according to the 1987 ACR Classification Criteria for Rheumatoid Arthritis (American College of Rheumatology) and who were undergoing treatment with methotrexate for >6 months were included in the study.

The sample size was calculated based on the compliance to methotrexate among patients with rheumatoid arthritis as reported by a study done in Kasturba Medical College, Manipal (10). Therefore with 20 % allowable error and 66% prevalence the minimum calculated sample size was 52. After considering 20 % drop out, the sample size was reworked to be 63. A written informed consent was taken prior to the administration of questionnaire. A semi structured questionnaire was used to collect data

and the questionnaire created in English was later translated to Malayalam

The questionnaire had four parts: socio-demographic profile and history related to RA, compliance to methotrexate using CQR-5 (Compliance Questionnaire form for Rheumatology modified for methotrexate), questions to assess the side effect profile to RA and disease severity assessment was done using DAS 28 (Disease activity score) and VAS (Visual Analogue Scale).

The socio demographic details included age, gender, marital status, education, occupation, and place of residence. History relating to RA included family history, whether they were on a single drug or multi drug therapy and side effects experienced by patients were noted.

Compliance to methotrexate was calculated using CQR-5 which consists of 5 questions, with options “completely agree, agree, disagree, or completely disagree the statement”. This CQR-5 questionnaire is a modified version of the original CQR-19 questionnaire. Scoring was done using a CQR-5 adherence calculator. D0 and D1 were calculated using two equations resulting from Fisher’s classification function coefficients, where D is compliance. If D1 is greater than D0, the respondent is highly compliant. Conversely, if D0 is greater than D1, then the respondent has low compliance.

Severity of disease was calculated by DAS28 score. DAS 28 is a very to make reproducible and comparable assessment of the rheumatoid arthritis activity. The score considers the number of tender joints (0-28), the number of swollen joints (0-28), the ESR values and the patient global health condition. These were recorded for each patient and then entered into an online software to get the DAS score for each patient. A remission score <2.6 suggests disease remission, 2.6-3.2 suggests low disease activity, >3.2 -5.1 suggests moderate disease activity and >5.1 suggests high disease activity.

Visual Analogue Scale (VAS) is an assessment of pain based on patient’s perspective. It is a 10 cm line with anchor statements on the left (no pain) and on the right (extreme pain). The patient is asked to mark their current pain level from 0-10. 0-4 indicates mild pain, 5-6 moderate and 7-10 severe pain.

The institutional ethical committee provided ethical clearance to conduct the study. Data were entered and analysed using SPSS version 21. The percentages, mean $\pm$ SD were calculated, and Chi

square test and multivariate logistic regression analysis were done to test for statistical significance of association and independent predictors for methotrexate compliance in treatment of RA.

RESULTS

A total of 86 patients, with confirmed diagnosis of RA, were interviewed to understand their compliance to methotrexate therapy. The mean age of the study participants were 55 ± 13.5 years. Around 63% of the study participants were more than 50 years of age, majority of them were females and less than 2% of the participants were unmarried. One third of the study participants had high school education and 60.7% of them were housewives and 19.6% were employed in clerical jobs or as shop owners and farmers. Approximately, 45% of the population were residing in rural areas.

The distribution of study participants based on history relating to rheumatoid arthritis and side effect profile have been described in Table 1 and 2 respectively.

Table 1: Distribution of the study population based on history relating to Rheumatoid Arthritis (n = 86)

Variable		Frequency (N=86)	Percentage
Family History	Yes	21	24.4
	No	65	75.6
Single/ Multi Drug Therapy	Single Drug	31	36
	Multi Drug	55	64
Visual Analogue Scale (VAS)	0-4	63	73.3
	05-06	13	15.1
	07-10	10	11.6
	<2.6	42	48.8
Disease Activity Score 28	2.6-3.2	17	19.8
	>3.2-5.1	23	26.7
	>5.1	4	4.7

The compliance to methotrexate in our study was 73.3%. The various factors influencing high compliance were: participants aged between 41-60 years ($X^2 = 0.185$, OR= 1.33 (0.36-4.93)), among females ($X^2 = 1.714$; OR= 0.48 (0.161-1.454)), participants with high school education ($X^2 = 1.406$) and among participants living in urban areas ($X^2 =$

0.079; 0.867(0.320-2.350)). However, none of these factors were found to be significantly associated.

Table 2: Distribution of the study population based on symptoms (n = 86)

Variable		Frequency (N=86)	Percentage
Nausea	Absent	78	90.7
	Present	8	9.3
Vomiting	Absent	82	95.3
	Present	4	4.7
Hair Loss	Absent	64	74.4
	Present	22	25.6
Oral Ulcer	Absent	78	90.7
	Present	8	9.3
Loss Of Appetite	Absent	77	89.5
	Present	9	10.5

When assessing for compliance against side effect profile as depicted in Table 3; it was observed that treatment compliance were more among patients who did not have nausea ($X^2 = 0.521$; OR= 1.740 (0.381-7.947)), vomiting ($X^2 = 1.158$; OR= 2.905 (0.385-21.935)), oral ulcer ($X^2 = 0.521$; OR = 1.740 (0.381-7.947)) and loss of appetite ($X^2 = 1.607$; OR= 2.442 (0.594-10.035)). Most patients with high compliance did not have family history of RA ($X^2 = 0.047$; OR=0.885 (0.296-2.651)) and were on multi drug therapy ($X^2 = 0.130$; OR = 0.835 (0.312-2.234)).

DISCUSSION

Our study, done among 86 patients with RA to assess the treatment compliance to methotrexate, showed a high compliance among 73.3 % of the study participants. Majority of our study participants belonged to female gender (79.1%), had education of high school (41.9%), and were housewives (60.5%). Table 4 shows a comparison of various studies done to assess adherence to methotrexate therapy.

The findings of high compliance in our study is comparable to the findings from Denmark and Lahore and higher than the findings reported from Finland (63%)⁽¹⁴⁾. The findings of better compliance among people aged more than 40 years and among females, in this study are like findings from a study done by Nasim Arshad et al among RA patients in Lahore and Henning Bliddal in Denmark^(11,15). However, the findings from Denmark, showed a higher non-compliance among females⁽¹³⁾.

Table 3: Univariate analysis for association of CQR-5 with side effects

Sl. No	VARIABLE	CQR – 5		CHI SQUARE	ODDS RATIO	
		High Compliance	Low Compliance	(P Value)	(95% CI)	
1	NAUSEA	ABSENT	58	20	0.521	1.74
		PRESENT	5	3	-0.47	(0.381-7.947)
2	VOMITING	ABSENT	61	21	1.158	2.905
		PRESENT	2	2	-0.282	(0.385-21.935)
3	HAIR LOSS	ABSENT	46	18	0.243	0.752
		PRESENT	17	5	-0.622	(0.241-2.342)
4	ORAL ULCER	ABSENT	58	20	0.521	1.74
		PRESENT	5	3	-0.47	(0.381-7.947)
5	LOSS OF APPETITE	ABSENT	58	19	1.607	2.442
		PRESENT	5	4	-0.205	(0.594-10.035)

Table 4: Adherence to Methotrexate therapy in RA, results from different parts of the globe.

Study done by	Sample size	Population	Place	Compliance to methotrexate therapy	Tool used
Kanav Kher et al ⁽¹⁰⁾	110	Adult population with age greater than or equal to 18 years	Kasturba Medical College, Manipal	66.36%	CQR-19 questionnaire
Nasim Arshad et al ⁽¹¹⁾	100	Adults with mean age of 41.55±11.24	Lahore, Pakistan	77%	-
Pelajo C F et al ⁽¹²⁾	76	1-17 years	Rio de Janeiro and Boston	62%	-
De Thurah et al ⁽¹³⁾	941	Adults aged >18 years	Denmark	82%	Pharmaco-Epidemiological Prescription Database (PEPD)

In our study, participants with better educational qualification had more compliance to therapy compared to a study done by Jayanti P Acharya et al in Hyderabad, were better compliance was reported among illiterate and just literate participants (74.2%)⁽¹⁶⁾. An increasing DAS 28 score showed decreasing compliance to Methotrexate therapy in our study. These findings are similar to several studies done in Pakistan (NASIM), USA⁽¹⁷⁾, Mexico⁽¹⁸⁾, and Sweden⁽¹⁹⁾.

CONCLUSION: The non-adherence to methotrexate therapy in our research was found to be 26.7%. One of the major determinants for adherence were found to be the absence of side effects from treatment in rheumatoid arthritis. Hence addressing the side effects from treatment with the help of apt medicines and by considering other strategies to address the same, might help us increase the adherence to methotrexate therapy.

LIMITATION: The current research being a hospital-based study, the results cannot be extrapolated to patients with rheumatoid arthritis in the community. To understand the interplay of several factors which might influence the compliance to methotrexate therapy in all patients with Rheumatoid Arthritis and the reasons for non-compliance to treatment, a mixed methodology cohort study needs to be deliberated.

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