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Original Research Article

Adherence to methotrexate therapy among rheumatoid arthritis patients in Eastern India

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ABSTRACT

Background: This study aims to identify adherence rate of methotrexate (MTX) therapy in rheumatoid arthritis (RA) patients of Eastern India and recognize factors contributing to treatment adherence in those patients.
Methods: In this cross-sectional observational study, a total of 140 patients (17 males, 123 females; mean age 37.6±7.4 years) with pre-diagnosed RA attending the rheumatology outpatients clinic between February 2019 and January 2020 fulfilling the inclusion and exclusion criteria, were included. The patients were evaluated in terms of sociodemographic factors, clinical and medication details, disease activity score (DAS28-CRP) values and patient - doctor considerations that might contribute to treatment adherence. They filled out a series of standardised present questionnaires including the Morisky 8-item Medication Adherence Scale (MMAS-8). Data was analysed statistically and compounded.
Results: Of the patients, 29 (20.7%) were adherent and 111 (79.3%) were non-adherent to medication with MTX. 65% were on MTX monotherapy and 35% on polytherapy with csDMARDs. 45.7% of the non-adherent forgot taking medication, 50.7% skipped during travel, 79.3% intentionally did not comply with strict regimen. The DAS28-CRP scores were much higher amongst non-adherent group and fewer reached remission as compared to adherent participants. Commonest reason for non-adherence being adverse drug reaction and financial constraints. **Conclusions:** This study showed a significantly higher adherence to MTX treatment compared to most previous studies. Adverse drug reactions, financial constraints, complex treatment regimen, long treatment duration, and frequent travel history significantly affect medication adherence in this patient population. Higher the adherence better the treatment response.

Keywords: Adverse drug reactions, Conventional synthetic disease modifying anti-rheumatic drugs, Medication adherence, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, incapacitating disease that needs uninterrupted therapy with many medications.[1,2]

Functional disability is considerably reduced with efficient management of RA, hence in this respect drug efficacy and patient adherence with the treatment prescribed is equally important.[3-5] Adherence to a medication regimen is "the extent to which a person's medication-taking behaviour coincides with medical advice."[6]

The conventional synthetic disease modifying anti-rheumatic drug (csDMARD) methotrexate (MTX) is the appropriate first-line agent for most patients with RA.[7]

As treatment strategies for patients with RA require more aggressive dosage modifications and changing of drug regimens to achieve lower disease activity, the importance

of measuring adherence and understanding its impact remains critical.[8-10] Medication adherence has three components: initiation, implementation, and discontinuation.[11] Initiation is when the first dose is taken; implementation is the extent to which a patient's actual dosing matches the prescribed regimen from initiation until the last dose; and discontinuation is when the last dose is taken.[12]

The Morisky Medication Adherence Scale - 8 (MMAS-8) is a low cost, simple and self-reported tool for assessment of adherence to chronic medications specifically designed to facilitate identification of barriers to medication adherence in real-time, which is critical in clinical practice.[13,14] In this study, authors aim to assess in RA patients, adherence to methotrexate medication and explore factors associated with lower adherence in the community.

Adherence to medical treatment in patients with RA is not well understood as compared with other chronic diseases such as asthma and diabetes due to scanty data.[5] Adherence rates in RA ranged from 30% to 93% in different studies.[5,15] Adherence to therapy is an individual patient-behaviour that is difficult to objectively measure.[16] The MMAS-8 scale is supplemented with additional items addressing the circumstances surrounding adherence behaviour and is a commonly used self-reported adherence measure that has been shown to be predictive of adherence.[14] Lack of adherence elicited from various surveys are related either to patients or physicians.

The most common reasons cited by patients for not taking their medications included forgetfulness, other priorities, decision to omit doses, lack of information and emotional factors.[17] In addition, physician factors contributing to patients' poor adherence is inadequate interaction with the patients and lack of proper explanation of complex regimens and failure to explain the risk and benefits of the disease and drugs to the patients.[18,19] Adherence to MTX may fluctuate; that is, patients do not quit their medication fully but possibly taper the intake over time.[20]

According to authors knowledge, there are no studies on adherence to drug therapy among RA patients in Eastern India. The objective of this study was to quantify adherence rate of MTX therapy in patients with RA attending the rheumatology clinic at K.P.C. Medical College Hospital and to assess the factors contributing to it.

METHODS

This cross sectional observational study was conducted in the rheumatology clinic at K.P.C. Medical College and Hospital between February 2019 to January 2020, after approval from the Institute's Ethical Committee. The participation was entirely voluntary. The enrolment was done after a verbal and written consent. It was followed by detailed record keeping and analysis of factors affecting adherence to MTX treatment among RA patients attending the clinic.

Inclusion criteria

- Diagnosed RA according to 2010 ACR/EULAR classification criteria,
- Duration of illness of at least 1 year.
- Duration of treatment of at least 6 months,
- Willing to participate in the study after giving a written consent
- Patients currently receiving oral or injectable MTX that had been initiated at least 6 months prior to study enrolment as per the prescription records.

Exclusion criteria

- Patients having associated psychiatric ailments
- Patients requiring hospitalisation in last 6 months
- Pregnancy
- Below 18 years of age

A total of first 200 patients registered in the rheumatology outpatient clinic at K.P.C. Medical College fulfilling the inclusion and exclusion criteria and willing to participate in the study were enrolled. Using Epi Info statistical package version 7 for cross-sectional study, the total number of patients with RA registered was 200. Expected frequency of adherence rate among patients with RA was taken to be 58%, as was revealed in an US study in 2015.[21] Calculation of sample size at 95% confidence interval and power of test 80%, revealed that at least 126 were required and after adjusting for expected 10% dropout, a sample size of 140 patients with RA was adapted. All patients were informed about their disease, treatment options, and possible adverse drug reactions (ADR) on a regular basis. The follow up visits at every 12 weeks interval was planned and recorded during the scheduled visit. Patients were evaluated in between the scheduled visits, in case of any adverse drug reaction or disease flare.

An interview questionnaire was used to collect the following data.

- Sociodemographic, clinical and medication information directly obtained from patients and from their medical records.
- Medication adherence test was done using the English version of the validated Morisky's Medication Adherence Scale - 8 (MMAS-8) and recorded, in addition to information on prescription and reasons of non-adherence as stated by patients. The MMAS-8 has 7 questions having to choose from 2 answers and 1 question answered on a 5-point Likert scale, a widely used method to measure self-reported medication-taking behaviour. The MMAS-8 is an ordinal scale. Total MMAS-8 scores can range from 0 to 8 and have been categorised into three levels of adherence: high adherence (score = 8), medium

adherence (score of 6 to <8), and low adherence (score <6).[22]

- Factors affecting adherence such as - Patient knowledge as an index measure was assessed using a 4-item questionnaire answered on a 3-point Likert scale, patient beliefs assessed using 4-item questionnaire answered on a 3-point Likert scale and patient satisfaction assessed using short form patient satisfaction questionnaire answered on 5-point Likert scale.[23]
- Objective method to measure adherence using Disease Activity Score (DAS-28-CRP) by DAS calculator, which measured disease activity by entering the number of tender joints, swollen joints, pain assessment by VAS score and C- reactive protein value. After assessing DAS-28-CRP score, the results were noted under the following categories:
  - DAS-28: >5.1 (high disease activity.)
  - DAS-28: >3.2 to 5.1 (moderate disease activity)
  - DAS-28: 2.6 to 3.2 (low disease activity).
  - DAS-28: <2.6 (remission).

The DAS-28-CRP used in this study was performed by the examining physician.

Data management and statistical analysis

Data collected through the structured interview using the preset questionnaires were analysed using Statistical Package for the Social Sciences (SPSS) predictive analytic software version 12. Data obtained from Likert item were analysed using chi-square chart. For each question, missing data (<1%) were excluded from analysis, and no imputation was performed. Descriptive statistics (e.g., mean, standard deviation, range) for continuous variables and frequencies with percentages for categorical variables were reported.

RESULTS

The majority (87.9%) of study participants were females, the mean age being (37.6±7.4) years. 13.6% participants were illiterate, 36.4% and 33.6% completed primary and secondary level education respectively, 73.6% were unemployed and 82.9% were married (Table 1). The mean duration of disease and medication use were (5.4±2.3) years and (4.6±3.1) years respectively. All study participants were on MTX either as monotherapy (65%) or as polytherapy (35%) with other csDMARDs. 26.4% and 37.9% were on NSAIDs and steroids respectively and none were on biological DMARDs. Nearly all (99.3%) were on Folic acid and 85.0% on supplementary Calcium (Table 2).

Table 1: Demography of study population.

		Frequency (n=140)	%
Age	Mean±SD (range)	37.6±7.4	
Gender	Male	17	12.1
	Female	123	87.9
Education	Illiterate	19	13.6
	Primary	51	36.4
	Secondary	47	33.6
	University	23	16.4
Marital Status	Married	116	82.9
	Single	13	9.3
	Divorced/ Widowed	11	7.8
Occupation	Unemployed	103	73.6
	Employed	37	26.4

Table 2: Duration and severity of disease, medication history and adherence to MTX in the study population.

		Frequency (n=140)	Percentage (%)
Duration of disease (Yrs)	Mean±SD (range)	5.4±2.3	
Duration of medication (Yrs)	Mean±SD (range)	4.6±3.1	
Disease activity	Remission	9	6.4
	Low	23	16.4
	Moderate	29	20.7
	High	79	56.5
MMAS	Moderate adherence	97	69.3
	Low adherence	14	10.0
	High adherence	29	20.7
Medication history	MTX as single csDMARD	91	65.0
	MTX as combination csDMARD	49	35.0
	NSAIDs	37	26.4
	Steroids	53	37.9
	Folic acid	139	99.3
	Calcium	119	85.0

According to MMAS-8, 10.0% of study participants had low adherence and 69.3% had moderate adherence (both low and moderate adherence are considered non-adherent), and 20.7% patients had high adherence (Figure 2).

Nearly half (45.7%) of participants at times forgot to take their medications, 33.3% intentionally missed dosage, 50.7% skipped medications while traveling, 62.9% took their medications the day preceding the survey and 79.3% found it inconvenient sticking to strict treatment regimen. 27.1% skipped dosage when felt that RA was under control. 45.7% rarely had difficulty in remembering to take the medicine (Table 3).

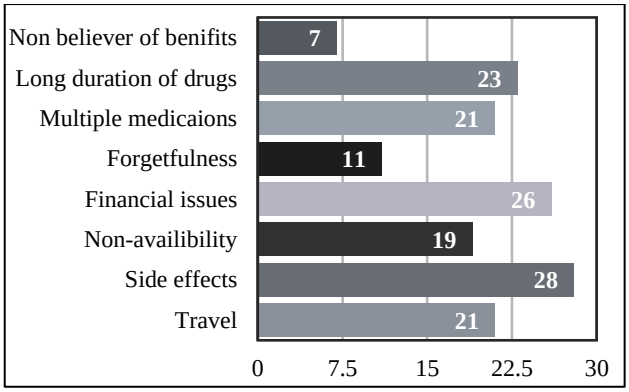

Figure 1: Reasons for non-adherence to MTX (in %).

Table 3: MMAS-8* questioner and responses among RA patients on MTX.

Adherence assessment questioners	Frequency (n=140)	Percentage (%)
Sometimes he or she forgets to take RA medication(s)	64	45.7
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 wk, any days he or she did not take RA medication(s)	47	33.6
Ever cut back or stopped taking medication(s) without telling the doctor, because felt worse when he or she took it	44	31.4
When traveling or leaving home, sometimes he or she forgets to bring along RA medication(s)	71	50.7
He or she has taken his RA medication (s) yesterday	88	62.9
When he or she feels like RA is under control, sometimes stops taking his medication(s)	38	27.1
Taking medication(s) every day is a real inconvenience for some people. Ever felt hassled about sticking to his/her high RA treatment plan	111	79.3
How often do you have difficulty remembering to take all your medication(s)?		
All the time	5	3.6
Sometimes	9	6.4
Usually	41	29.3
Once in a while	21	15
Rarely	64	45.7

Table 4: Beliefs of patients with RA concerning medications.

Do you think that RA medications		Frequency (n=140)	Percentage (%)
Will make you feel better	Disagree	4	2.9
	Uncertain	23	16.4
	Agree	113	80.7
Will make you live longer	Disagree	92	65.7
	Uncertain	46	32.9
	Agree	2	1.4
Will improve the quality of life	Disagree	2	1.4
	Uncertain	55	39.3
	Agree	83	59.3
Will prevent future RA-related complications	Disagree	29	20.7
	Uncertain	88	62.9
	Agree	23	16.4

Commonest reason for non-adherence as per the study is side effects of medications (28%) followed by financial constraints (26%), long term medicine intake (23%), multiple medication and discontinuation during travel (21% each), non-availability of drugs (19%) and forgetfulness 11%. This was followed by non-believer in benefits of medication (7.0%) (Figure 1)

The majority (80.7%) of study participants believed that RA treatment made them feel better and 59.3% believed that treatment improved quality of life, whereas 65.7% did not believe that treatment could improve their life expectancy and 62.9% of them were unsure that treatment could prevent future complications of RA (Table 4).

DAS 28 - CRP evaluation showed considerable improvement in the adherent group compared to the non-adherent group. Disease remission in adherent group was 27.6% as compared to only 0.9% in the non-adherent group. High disease activity was observed in 67.6% of non-adherent population and only 13.8% of the adherent population (Figure 2).

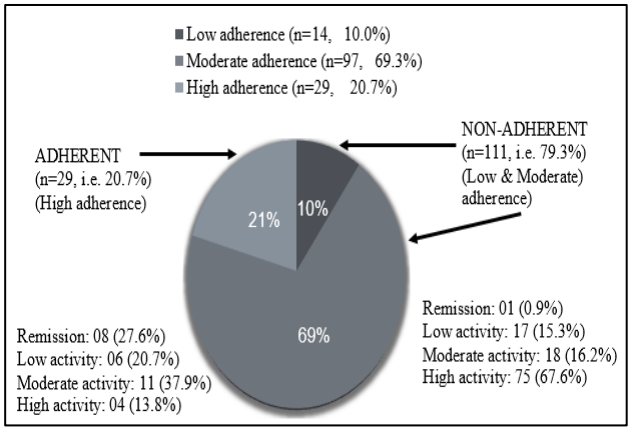

Figure 2: Adherence and its effect on disease activity.

DISCUSSION

The findings from the cross-sectional observational study conducted in the outpatients clinic of this tertiary hospital in Kolkata, provides an insight into the adherence of methotrexate treatment in RA patients of Eastern India and highlights the various factors contributing to the same. Majority of the patients were middle aged females. RA is one of the many chronic inflammatory diseases that predominate in females.[24] The prevalence is about 2.5 times higher in females than males.[24] This study also confirms a considerably female predominance of RA (87.9%). Another Indian study by Mittal et al, in 2012 reported more than 80% of the RA patients to be females, as is in this study.[25] The majority of the participants in this study completed primary and secondary level education (36.4 and 33.6% respectively) and only 13.6% were illiterate, contrary to 30% illiterate participants in the study group of a similar MTX adherence Pakistani study by Arsad N et al, in 2016.[26] Amongst the participants, 82.9% were married and 73.6% unemployed, most of whom were housewives, which is in accordance to a similar study by Mohsen AG et al, where 93.6% were married and 79.2% unemployed.[27]

In this study, adherence rate calculated using the 8-item Morisky's scale (MMAS-8) shows that 10.0% of study participants had low adherence, 69.3% had moderate adherence and 20.7% had high adherence to MTX treatment. A Jordanian study conducted at King Hussein Medical Centre in 2007 using a specially designed questionnaire showed that 38 patients (35.0%) of 110 patients with RA did not adhere to their medications.[28] In 2015, an Egyptian study in Ain Shams University showed that 90.7% of study participants had low adherence and 9.3% had moderate adherence and none was highly adherent.[27] The discrepancy between this observation and that of various other studies may be due to the fact that the adherence calculation tools were different in different studies. Another cross-sectional study done by Bart et al, 2009, in the Netherlands, investigated 629 patients with RA using 2 tools, compliance questionnaire Rheumatology and Medication Adherence Scale (RMAS) revealed that 68% and 60% of patients were adherent respectively.[29] There is no gold standard method to evaluate patients' adherence to medication. Every method has its pros and cons.[2] Observations from various self-reported studies revealed variable adherence rates ranging from 30% to 93%.[5]

Adherence can be described as a balance between patients' beliefs about the necessity of the treatment and their concerns about its side effects.[30] Horne et al, suggested that patient beliefs about medications are an important factor in adherence.[31] According to this study, ADR to MTX was the commonest concern for non-adherence (28%), followed by financial constrains (26%), long term medicine intake (23%), multiple medication regimen (21%).

A Polish review report by Bogdan Batko pointed out that a joint consideration of the dosing regimen, convenient methods of administration and dispelling any doubts over adverse events are milestones that will translate into better adherence.[32] In an US study, Dana B DiBenedetti et al, concluded that nearly half the sample reported poor MTX adherence because they forgot to take it, thought it was not needed when they felt well, or had long-term safety concerns. Reducing treatment burden without sacrificing efficacy may be a strategy worth evaluating.[23]

This study recruits showed that disease remission was significantly higher (27.6%) in adherent participants than in non-adherent respondents (0.9%) with a p-value of <0.001. High disease activity was observed in 67.6% of non-adherence participants in contrast to 13.6% among the adherent ones, with a significant p value of <0.001. Nasim A et al, also opined in their study that non-adherent patients had significantly higher disease activity compared to adherent group, as measured by DAS 28 (p<0.001).[26]

CONCLUSION

This study, the first of its kind in Eastern India, was done to assess the adherence of MTX therapy in RA patients, and evaluate the probable factors for non-adherence, so that the rheumatologists can help patients achieve the maximum benefits from the treatment and attain remission or low disease activity as per the treat-to-target protocol. A validated standardised adherence questionnaire as in MMAS-8, has several advantages over other tools. It is easier to perform, inexpensive and provides relatively accurate measure. In addition, the disease activity score (DAS-28-CRP) was used to accurately measure the disease activity of RA. This study showed that higher adherence was significantly associated with more positive beliefs of medication, greater satisfaction to treatment, lesser disease activity and better outcome.

Further research towards understanding treatment adherence will be helpful to identify and address barriers to optimal compliance. Thus, further work, possibly with longer follow-up, is needed to gain a better understanding of MTX initiation, proper implementation and optimal adherence to csDMARDs and biological DMARDs in patients with RA.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of K.P.C. Medical College

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