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Assessment of Drug Adherence and Adverse Effects of Disease-Modifying Antirheumatic Drugs (DMARDS) in Patients of Rheumatoid Arthritis Attending a Tertiary Care Hospital in India

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Abstract

Adherence to drug treatment is one of the key factors in treating chronic diseases like rheumatoid arthritis (RA) to maintain remission and prevent functional disability. Poor medication adherence is directly associated with a worse prognosis and an increase in healthcare utilization, adding to a financial burden. Hence, the present study was proposed to assess drug adherence in diagnosed patients of RA attending a tertiary care hospital. The study was initiated after obtaining institutional ethics committee permission, and written informed consent was requested from all the eligible patients before their enrolment. This cross-sectional questionnaire-based study was conducted on RA patients attending the rheumatology outpatient department. The patient's adherence to the drugs prescribed was assessed using the 19-item Compliance Questionnaire Rheumatology (CQR), and the correlation between drug adherence with various demographic, disease, and medication-related variables was studied. After screening 103 patients, 75 patients fulfilling the selection criteria were enrolled, and their data was analyzed. The adherence measured using the CQR score was in the range of 54.39% to 68.42%, with a mean CQR score of 62.27 ± 2.76. A negative correlation was found between the CQR score and the number of ADRs ($r = -0.12$, $p>0.05$) and age ($r =-0.06$, $p>0.05$). A positive correlation was found between the CQR score and variables like sex, education, and number of medications, but none were statistically significant. Unsatisfactory compliance was evident in the present study. Therefore, integrating drug treatment with strategies to improve patient adherence may improve clinical outcomes and quality of life, reducing healthcare costs.

Keywords: adherence, compliance questionnaire, rheumatology, MMAS scale, antirheumatic drugs

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by symmetric peripheral polyarthritis.[1] If left untreated, it can progress from self-limiting arthritis to irreversible joint destruction, progressing to physical disability and death.[1,2] RA affects people worldwide, with 20 million prevalent cases and 1.2 million incident cases reported by the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017. An estimated 246 per 100,000 people suffer from RA worldwide, showing an increase of 7.4% between 1990 and 2017.[3] The burden of RA in India is also massive, with an estimated prevalence of 0.1 to 0.4%.[1]

Disease-related inefficiency in work and household activities is not just due to the physical limitations posed by RA but also emotional distress, which remarkably affects patients' health-related quality of life and productivity.[4] In the past decade, there has been a substantial change in the management of RA, with short-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to combat acute inflammatory response to the long-term use of disease-modifying antirheumatic drugs (DMARDs) so as to attain clinical remission, arrest the disease progression and to improve patient's quality of life.[5-7]

In addition, the biologics targeting various cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 receptor, and B-lymphocytes have considerable potential to change the long-term outcomes in patients of RA.[8] However, adequate adherence to physician's recommendations is necessary to reach the therapeutic goals. Compliance may be defined as 'The extent to which the patient's behavior matches the prescriber's recommendations', whereas the term 'adherence,' which is often used as a substitute for compliance, may be defined as 'the extent to which the patient's behavior matches agreed recommendations from the prescriber'.[9,10]

Adherence to treatment helps achieve the therapeutic goals and is one of the key factors in treating chronic diseases like RA. However, published literature states that adherence to drugs in RA patients ranges from 30% to 100% using different methods to measure adherence.[11-15] Failing to adhere to the physician's advice often results in disease progression, poor prognosis, functional disability, additional medical therapy, and surgical intervention, contributing to increased financial burden.[16,17]

Apart from the doctor-patient relationship, multiple factors are expected to influence the nonadherence behavior to medication, such as socioeconomic profile, literacy status, patient perception of the disease, patient faith in medication, several drug-related factors like duration of the treatment, complexity of the regimen, and also disease-related factors such as the duration of disease, severity of disease, presence of comorbidities and functional disabilities.[14,18] The management of RA is thus challenging and multifaceted as it is influenced not only by the level of non-adherence but also by adverse drug reactions related to medication, a requirement of laboratory investigations, frequent follow-up, monitoring, and often patients' dissatisfaction due to natural remissions and exacerbations experienced.[17,19]

Hence, the present study was proposed to assess the treatment adherence in diagnosed patients of RA and study the correlation between drug adherence with various demographic, disease, and medication-related variables in patients receiving antirheumatic drugs in a tertiary care hospital.

Methods

This cross-sectional study was conducted at the Department of Pharmacology in collaboration with the Department of Medicine at HBT Medical College and Dr RN Cooper Municipal General Hospital, Juhu, Mumbai, Maharashtra, India. It was performed by the Declaration of Helsinki and initiated after obtaining institutional ethics committee permission. Patients attending the rheumatology outpatient (OPD) department were randomly screened for inclusion and exclusion criteria before participating. After screening 104 patients for selection criteria, 75 diagnosed patients of RA were included in the study. The selected patients were explained the purpose of the study and requested to give written informed consent before their inclusion in the study. The study was conducted between March 2020 to November 2021.

Diagnosed patients of RA attending the rheumatology outpatient department having age more than or equal to 18, of either sex receiving DMARDs for at least three months or more were included in the study. Detailed demographic profile of each patient, such as age, sex, personal habits (smoking, chewing tobacco, and alcohol consumption), duration of the disease, any comorbidity, duration of concurrent medication, and any adverse drug reactions experienced while on the treatment was recorded with the help of a case record form.

The adherence was assessed with the help of the 19-item compliance questionnaire for rheumatology (CQR), specifically developed for measuring drug adherence in patients of RA. It has a sensitivity of 98% and a specificity of 67% in detecting adherence in patients with rheumatoid arthritis. CQR is specific for measuring drug adherence in RA and is one of the validated tools to assess adherence. It is easy to use, cost-efficient, and used in some studies to calculate adherence.[11,18,20-25] It includes items scored on a 4-point Likert response scale ranging from 1 (do not agree at all) to 4 (agree very much). The score for this measure ranges from 0 (complete noncompliance) to 100 (perfect compliance).[21]

Selection Criteria

Inclusion criteria:

1. Patients of either sex, more than or equal to 18 years of age
2. Patients diagnosed with RA receiving treatment for more than three months.
3. Patients on DMARDs treatment, such as methotrexate alone or methotrexate in combination with either hydroxychloroquine and/or sulfasalazine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids for more than 3 months.
4. Patients diagnosed with RA with co-morbidities such as hypertension, diabetes mellitus, bronchial asthma, thyroid disorders, or epilepsy are well controlled with medication, as per the physician's opinion.

Exclusion criteria:

1. Patients were not willing to give informed consent.
2. Patients with any mental disorders or linguistic problems that could affect adequate understanding and response to the questionnaire.

After screening the patients for selection criteria and obtaining the written informed consent, a detailed demographic profile of each patient was recorded, such as age, sex, personal habits (smoking, chewing tobacco, and alcohol consumption), duration of the disease, any other co-morbidity, duration of concurrent medication, baseline laboratory investigations (Hemoglobin, ESR, Liver enzymes, renal function tests, rheumatoid factor) with the help of a case record form.

The patients were requested to fill up the 19-item compliance questionnaire rheumatology (CQR) questionnaire, specifically developed for measuring drug adherence in patients of RA. It has a sensitivity of 98% and a specificity of 67% in detecting adherence in patients with RA.

CQR is specific for measuring drug adherence in RA and is one of the validated tools to assess adherence. It is an easy-to-use and cost-efficient tool used in similar studies.[11,17,19,20-24] It comprises items scored on a 4-point Likert response scale ranging from 1 (do not agree at all) to 4 (agree very much). The score for this measure ranges from 0 (complete noncompliance) to 100 (perfect compliance).[20] The investigator asked each patient to respond to the questionnaire in the language they understood and about the adverse drug effects they experienced while on the treatment.

Statistical Analysis

The data collected was analyzed with the help of statistical software SPSS, version 22 for Windows. Categorical variables were represented as percentages and mean ± standard deviations. CQR score and adverse drug reactions were represented as counts and percentages. Spearman and Pearson's correlations were used to estimate the association between adherence and demographic, disease, and drug-related variables. A p-value of less than 0.05 was considered for statistical significance.

Results and Discussion

A total of 75 patients' data was considered for final analysis. The mean age was 47.9± 0.8 years. Among all patients, 70 were females, and 5 were males. A similar finding was reported by Sripreethy etal,[2] Moreland et al,[8] Nakagava et al,[10] Marras et al,[11] Bharthi etal,[12] Sharma et al,[18] van den Bemt et al.[23] Refer Table 1 for the detailed demographic characteristics of the patients.

Based on the duration of the disease, patients were divided into three groups: 50 patients with a duration of the disease more than or equal to 3 years, 24 patients with a duration between 2-3 years, and one with less than 1 year of duration. With regards to medication use, it was found that 5 or more than 5 antirheumatic drugs were prescribed to 10 patients. In contrast, most patients (N=60) received 2-4 antirheumatic drugs, and 5 patients were prescribed only one.

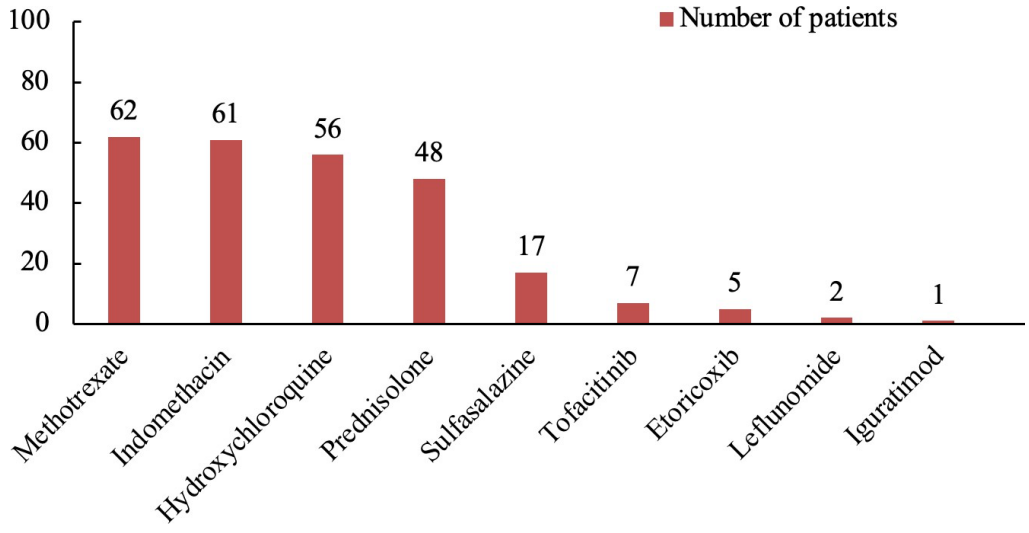

Figure 1. Distribution of Antirheumatic Drugs Prescribed to Patients

Table 1. Details of Patients' Demographic Characteristics

Demographic profile		Number of patients N (%)
Gender	Male	05 (6.7)
	Female	70 (93.3)
Age (years)	20-40	15 (20)
	41-60	43 (57.3)
	>60	17 (22.7)
Level of education	Primary	25 (33.3)
	Secondary	46 (61.3)
	Graduation & above	4 (84)
Employment status	Employed	11(14.7)
	Unemployed	01(1.3)
	Housewife	63 (84)
Personal history	Smoking	00
	Alcohol	01 (1.32)
	Tobacco	14 (18.7)
	None	60 (80)
Co morbidities	None	47 (60)
	Hypertension	16 (21.3)
	Hypertension & Diabetes mellitus	03 (4)
	Hypothyroidism	07 (9.3)
	Anemia	02(2.7)

*Others- One patient each of hyperlipidemia, Liver disease, Lung fibrosis, spondyloarthropathy

Table 2. Level of Adherence in Patients based on CQR Score

CQR score (N=75)	
Range	54.39% to 68.42%
Mean ± SD	62.27% ± 2.76
Median	63.16%
CQR adherence categories	N=75
≥60%	57(76%)
50-60%	18(24%)

Table 3. Distribution of Different Types of ADR Experienced by the Patients

Types of ADR	N (%)	Types of ADR	N (%)
Dryness of mouth	23 (30.7)	Urticaria	8 (10.7)
Loss of hair	20 (26.7)	Rashes	6 (8)
Weakness	14 (18.7)	Fatigability	5 (6.7)
Epigastric pain	12 (16)	Vomiting	4 (5.3)
Loss of appetite	11 (14.7)	Diarrhoea	4 (5.3)
Nausea	10 (13.3)	Blurring of vision	4 (5.3)
Weight gain	9 (12)	Breathlessness	3 (4)
Oral ulcers	8 (10.7)	Stomatitis	2 (2.7)

Fig. 1 depicts the distribution of frequency of antirheumatic drugs prescribed. The adherence was measured using CQR score which revealed the adherence to prescribed medication in RA patients in the range of 54.39% to 68.42%, with the mean CQR score of 62.27 ± 2.76% and having the median of value of 63.16% (Table 2). On assessing adverse drug reactions (ADR) it was observed that 31 (41.3%) patients reported one ADR, 2-4 ADRs were reported by 36 patients (N=36, 48%) and 5 or more than 5 ADRs were reported by 8 patients (N=8, 10.7%). Distribution of different types of ADR experienced by the patients is shown in Table 3.

Out of 75, 60 patients were on two or more 2 drugs, which included methotrexate, hydroxychloroquine, indomethacin, prednisolone, and sulfasalazine, being prescribed in different combinations to different patients based on the disease presentation and clinical response. These medications shared some common ADRs hence causality assessment was not possible. Further, the focus of this study was to find out the correlation between drug adherence behavior and ADR experience.

The correlation between drug adherence and ADRs experienced was not found to be statistically significant implying that the adherence behavior was independent of the ADRs experienced. Other studies also have reported similar findings.[17,23,24] This could possibly be because patients are forced to take the drug despite experiencing the adverse effects due to the functional disability and health-related quality of life affecting their day-to-day activities. On the other hand, some of them take drugs during acute exacerbations, whereas some avoid taking medication, particularly during remission, due to perceived ADRs affecting their adherence behavior.

On assessing the correlation of various demographic variables such as age, sex, level of education, and disease variables such as number of RA medications, number of drugs prescribed, and duration of disease with the adherence level as calculated using CQR score, was not found to be statistically significant. Negative correlations were found between CQR score with age ($r = -0.06$, $p>0.05$) and number of ADRs ($r= -0.12$, $p>0.05$). A positive correlation was found between CQR score and variables like sex, education and number of medications but were not statistically significant. (Table 4)

This could be attributed to various factors such as, beliefs of patient on the doctor, treatment provided, their experience on the benefit obtained following drug treatment or ADRs experienced. This study was conducted at a public hospital in India where the patients seeking medical treatment come from low socioeconomic status, having lack of information about the disease, its complications and limited understanding of efficacy of drugs. As the patient load is very high even doctors have limited time to communicate information with regards to the disease and drugs. These factors may be perceived as a potential barrier to drug adherence as it was found to be less than satisfactory. This finding was in accordance in the systematic review published by Annalieke et al.[14]

Other studies carried out with a similar objective also reported similar findings.[23,24] In contrast to this, study conducted by Bharthi et al[12] and Wabe et al[17] showed improvement in adherence with increasing age. The level of education also did not correlate with the adherence to drugs, indicating that even highly educated individuals may have less than satisfactory drug compliance. This may be due to a lack of information about medication fear of adverse effects, or a hectic lifestyle, which leads to missed doses and poor adherence, all of which warrant further investigation.

Adherence to prescribed medication is one of the key factors that influence the disease outcome in many chronic diseases.Asystematic review of factors associated with adherence to pharmacological treatment for RA patients reported that adherence rates varied between 49.5% and 98.5%, depending on the definition and method used.[14] In this study, based on CQR score, the adherence score was less than satisfactory, consistent with similar studies that used CQR as a measure of medication adherence in RA patients.[11,14,15,17,20,23,24]

The questions in the CQR are directed towards gathering patients' information on general attitudes or habits towards taking antirheumatic drugs and perhaps ignorance about the disease drugs, which may be the reason for poor adherence in our setting.

In RA patients, adherence to the treatment recommended often retards the disease progression, thereby improving the quality of life of patients with a considerable reduction in healthcare expenditures. Given the benefits of adherence in managing chronic diseases, physicians must emphasize drug adherence right from the first consultation. Regarding the questions used in the CQR, for item number 16, which stated, 'I use dose organizer for my medication,' we found all patients answered that they did not use dose organizer, which could have influenced the final CQR score. This response was expected in our country, as dose organizer is neither popular nor advertised in our setting, and people rely on their close-knit social contacts and family members besides themselves to remind them to take the medication.

Other factors which may reduce patient adherence to drug treatment may include the cost of the drugs, which could be studied by correlating the monthly income of patients with the CQR scores. On analysis of ADRs experienced, we could not attribute causality of a specific adverse effect to a particular drug as patients were prescribed more than one drug.

Conclusion

The mean CQR score was 62.27 ± 2.76%, reflecting less than satisfactory adherence in the present study. No statistically significant correlation was identified between the CQR score and various demographic, disease, and drug-related variables. Improvement in adherence behavior needs integrating

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Table 4. Correlation of CQR Score with Various Demographic and Disease Variables

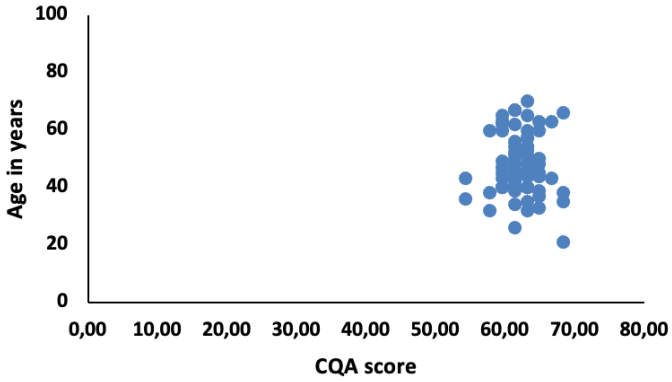
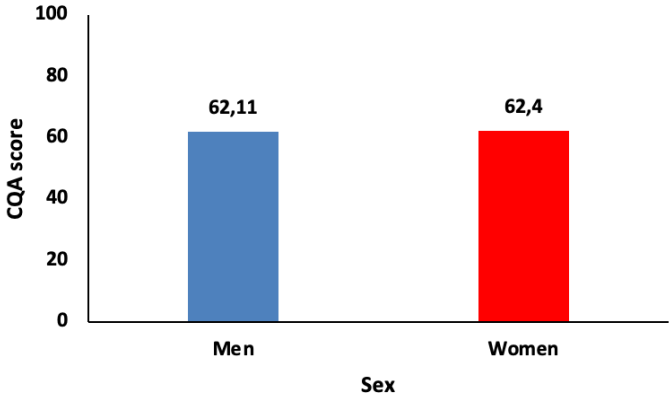
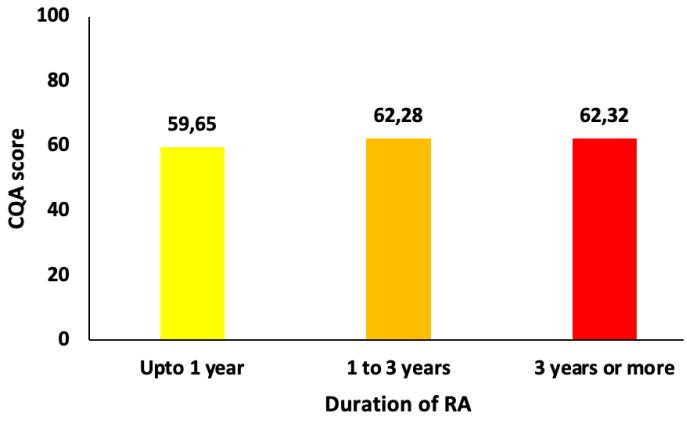
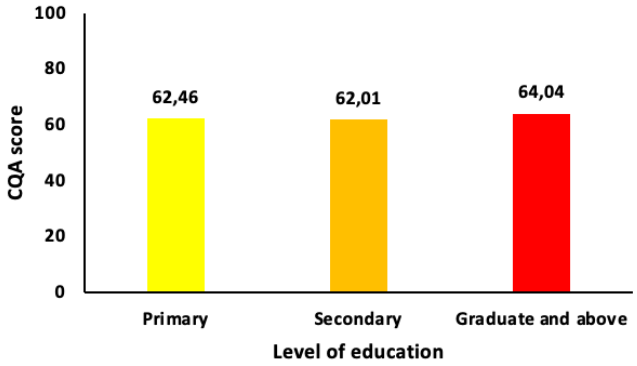
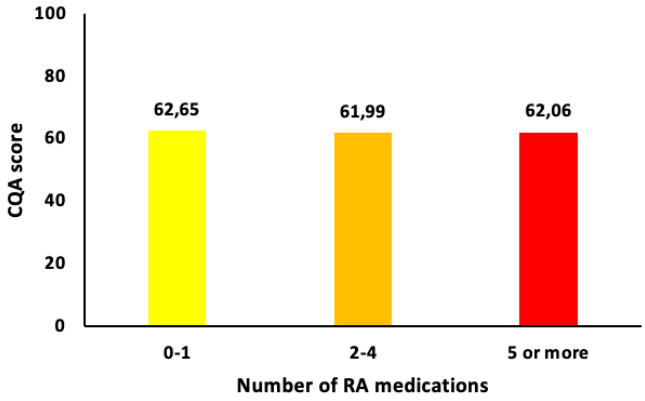
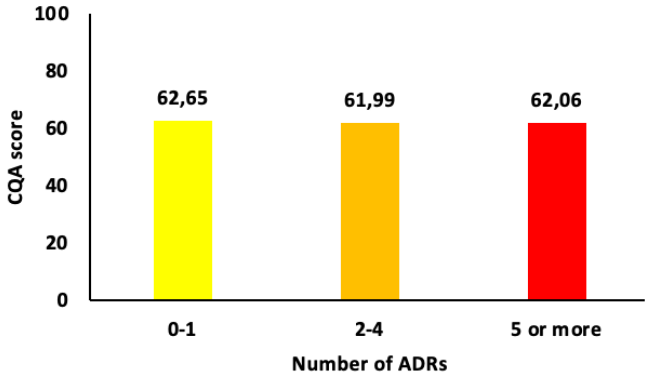
Variable	R	p-value	Graph
Age	-0.06	0.6332	
Sex	0.02	0.84612	
Duration of disease	0.00	0.9661	

Table 4. Correlation of CQR Score with Various Demographic and Disease Variables (cont...)

Variable	R	p-value	Graph
Education status	0.03	0.81862	
Number of RA medications	0.10	0.3898	
Number of ADRs	-0.12	0.309	

drug therapy with innovative technologies, spreading awareness of the disease, effectiveness of drug therapy, and addressing patient's apprehensions and concerns. It may change their attitude towards adherence behavior and thereby improve the quality of life of RA patients.

Therefore, physicians need to integrate drug therapy with an individualistic approach addressing patients' apprehensions and beliefs to improve drug adherence, thereby improving the quality of life in RA patients

Limitations

The larger sample size could have given a better insight into the correlation of CQR score with the patient, disease, and drug-related variables.

Conflict of Interest

None declared

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