

Adherence to treatment and associated factors in rheumatoid arthritis patients: a cross-sectional study from Iran

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SUMMARY

The aim of this study is to evaluate adherence to treatment and its related risk factors among a sample of rheumatoid arthritis patients (RA) attending the rheumatology outpatient clinic of Kermanshah university of medical sciences. In this cross-sectional study, RA patients were asked to complete the Morisky questionnaire and 19-item compliance questionnaire for rheumatology (CQR). Patients were divided into two groups: adherent and non-adherent to treatment, based on the CQR questionnaire results. Demographic and clinical characteristics (age, sex, marital status, education level, economical condition, occupational status, place of residence, underlying diseases, type, and number of drugs) were compared between the two groups to investigate possible risk associations for poor adherence. 257 patients completed the questionnaires (mean age: 43.22, 80.2% female). 78.6% were married, 54.9% were housekeepers, 37.7% had tertiary education, 61.9% had moderate economic status, and 73.2% were residents of an urban area with a large population. Prednisolone was the most commonly used drug followed by non-steroidal anti-inflammatory drugs, sulfasalazine, hydroxychloroquine, and methotrexate. The mean score of the Morisky questionnaire was 5.528 (standard deviation=1.79). 105 patients (40.9%) were adherent to treatment based on the CQR questionnaire. High education level (college or university) was correlated with non-adherence to treatment [27 (25.71%) vs 70 (46.05%), $p=0.004$]. We concluded that the prevalence of non-adherence to treatment is 59.1% in rheumatoid arthritis patients in Kermanshah, Iran. Having a higher education level is a risk factor for poor treatment adherence. Other variables could not predict treatment adherence.

Key words: Adherence to treatment, rheumatoid arthritis, Iran, CQR questionnaire, Morisky questionnaire.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by inflammatory synovitis, typically involving small joints, leading to cartilage and bone erosions. Destruction of the joints caused by RA leads to disability and influences the quality of life. Treatment by conventional and biological/targeted disease-modifying anti-rheumatic drugs (cDMARDs and bDMARDs) controls RA symptoms, reduces the risk of joint destruction, and influences long-term morbidity and mortality (1, 2).

Adherence to treatment is defined as the ability of the patient to follow the advice and to utilize medications as prescribed by the healthcare provider. Adherence to treat-

ment is a key component in the management of chronic diseases like RA, while lack of adherence is associated with disease relapses and failure to achieve remission, leading to joint destruction (3, 4).

Therefore, this study aimed to determine the prevalence of adherence to treatment among RA patients in Kermanshah city and investigate risk factors associated to poor adherence.

METHODS AND PATIENTS

This cross-sectional study was conducted in 2021. Convenience sampling was used to choose 257 RA patients from those attending the rheumatology outpatient clinics of Kermanshah, Iran. We included patients satisfying the American College of Rheu-

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matology/European League against Rheumatism (ACR/EULAR) 2010 diagnostic criteria for RA (5). These patients completed our questionnaire which consists of the Morisky questionnaire (MMAS), compliance questionnaire for rheumatology (CQR), and 13 questions about the demographical and clinical characteristics of the patients. Adherence to treatment was defined as adherence to anti-rheumatic therapy and patients were asked to answer questions about the anti-rheumatic drugs.

The following demographical and clinical characteristics were collected: age, sex, marital status, education level, economical condition, occupational status, place of residence, associated diseases including diabetes mellitus, systemic hypertension, hyperlipidemia, chronic heart disease (congestive heart failure and ischemic heart disease), chronic lung disease (asthma, chronic obstructive lung disease, interstitial lung disease) and chronic kidney disease, disease duration, type of medications used to treat RA, the total number of anti-rheumatic drugs used in one day, number of hospitalizations in the previous year due to disease flares, number of outpatient visits in the previous year due to disease flares. In this survey, anti-rheumatic drugs included corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), cDMARDs, and bDMARDs.

Patients were divided into two groups, adherent and non-adherent to treatment according to the results of the CQR questionnaire. Demographical and clinical variables were compared between the two groups to find out possible risk factors for poor adherence. The results of the MMAS questionnaire were reported in a separate table, but it was not used to divide patients and compare them.

Local Clinical Research Ethics Committee approved the study protocol. This study was performed according to the principles of the Declaration of Helsinki and patient consent was obtained.

Measuring adherence to treatment in rheumatoid arthritis patients

The eight-item Morisky questionnaire (MMAS-8) and 19-item CQR were used to

evaluate adherence to treatment in RA patients. Both questionnaires are self-administered.

MMAS-8 total score ranges from 0 to 8. Lower scores show higher adherence to treatment. The questionnaire consists of eight questions. The first seven questions are yes or no questions. The yes answer gets a zero score and the no answer gets a one score (inversely for the fifth question, the yes answer gets one score and the no gets a zero score). The eighth question has five possible answers and its score ranges from zero to one (never=1, hardly ever=0.75, sometimes=0.5, usually=0.25, always=0).

The 19-item CQR questionnaire total score ranges from 0 to 100. Higher scores indicate higher adherence to treatment. The four-point Likert answering scale is applied for scoring (definitely disagree gets one point, somewhat disagree two points, somewhat agree three points, and definitely agree four points). Six questions (4, 8, 9, 11, 12, and 19) are scored reversely. A total score ≥ 80 was considered as adherence to treatment.

Statistical analysis

Collected data were evaluated by SPSS software version 25. Quantitative variables (age, disease duration, and total score of the questionnaires) were reported as means and standard deviations (SD) and were compared by the independent T-test. Qualitative variables (sex, marital status, education level, economic condition, occupational status, place of residence, underlying disease, disease duration, type of drugs, number of drugs used in one day, number of hospitalizations, number of outpatient meetings) were expressed as number and percentage, and compared by Chi-square test or Exact Fisher test between the two groups.

A $p < 0.05$ was considered statistically significant.

■ RESULTS

The questionnaires were completed by 257 patients. Of these, 206 patients (80.2%) were female. The mean age was 43.22 ± 12.21 years. The mean disease duration reported

by the patients was 10.23 years (SD=7.61). Table I includes the demographical and clinical characteristics of the whole study population. The majority of the patients were married (n=202, 78.6%) and residents of the urban area with a population >100.000 (n=188, 73.2%). More than half of the patients (n=159, 61.9%) defined their economic status as moderate. Only 22.6% of the patients were employed and nearly half of them (n=141, 54.9%) were housekeepers. About one-third of the patients (n=97, 37.7%) had tertiary education and one-third (n=85, 33.1%) had secondary education. 56.4% of the participants claimed that they had at least another un-

derlying disease in addition to rheumatoid arthritis.

We asked the patients about the number of pills taken in one day, and most of them (86.8%) took ≤10 pills in one day (46.7% ≤5 pills and 40.1% 5 to 10 pills). A great majority of the patients (n=235, 91.4%) experienced no disease flare leading to hospitalization, while 60.8% reported unscheduled outpatient visits due to disease flares. RA medication was also recorded. Prednisolone was the most commonly used drug (77.04%), followed by NSAIDs (66.54%), sulfasalazine (40.86%), hydroxychloroquine (36.19%) and methotrexate (34.24%).

Table I - Demographical and clinical characteristics of rheumatoid arthritis.

Variables	Number (%)	Mean, SD
Age (mean, SD)		43.22, 12.21
Gender		
Female	206 (80.2)	
Marital status		
Single	41 (16)	
Married	202 (78.6)	
Widow or divorced	14 (5.4)	
Education level		
Uneducated	16 (6.2)	
Less than or equal to high school	59 (23)	
High school graduate	85 (33.1)	
College or university	97 (37.7)	
Economical condition		
Excellent	1 (4)	
Good	34 (13.2)	
Moderate	159 (61.9)	
Bad	63 (24.5)	
Occupational status		
Employed	58 (22.6)	
Unemployed	33 (12.8)	
Retired	21 (8.2)	
Student	4 (1.6)	
Housekeeper	141 (54.9)	
Place of residence		
Rural	19 (7.4)	
Urban >100000	50 (19.5)	
Urban <100000	188 (73.2)	
Underlying disease		
Yes	145 (56.4)	
Diabetes mellitus	14 (5.44)	
Hypertension	44 (17.12)	
Hyperlipidemia	65 (25.29)	
Chronic heart disease	3 (1.16)	
Chronic lung disease	12 (4.66)	
Chronic kidney disease	7 (2.72)	

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Variables	Number (%)	Mean, SD
Disease duration (years)		10.23, 7.61
Number of tablets used in one day		
≤5	120 (46.7)	
5<number≤10	103 (40.1)	
10<number≤20	30 (11.7)	
>20	4 (1.6)	
Number of hospitalizations in the recent year due to disease flares		
0	235 (91.4)	
1	14 (5.4)	
2	2 (8)	
≥3	6 (2.3)	
Number of outpatient visits in the recent year due to disease flares		
0	101 (39.3)	
1	63 (24.5)	
2	50 (19.5)	
3	12 (4.7)	
≥4	31 (12.1)	
Are your treatment costs affordable?		
Yes	147 (57.2)	
Have you ever stopped taking your drugs due to financial problems?		
Yes	124 (48.2)	
Have you ever had to replace one of your main drugs due to financial problems?		
Yes	83 (32.3)	
Total score of MMAS-8		5.50, 1.78
Total score of CQR		75.1, 12.5
Type of medications		
Prednisolone:	198 (77.04)	
Conventional DMARDs:		
Hydroxychloroquine	93 (36.19)	
Methotrexate	88 (34.24)	
Sulfasalazine	105 (40.86)	
Leflunomide	39 (15.17)	
Azathioprine	41 (15.95)	
Mycophenolate mofetile	13 (5.06)	
Cyclosporine	1 (0.38)	
Tacrolimus	1 (0.38)	
Biologic/ targeted synthetic DMARDs:		
Adalimumab	30 (11.67)	
Etanercept	10 (3.89)	
Infliximab	9 (3.5)	
Tofacitinib	1 (0.38)	
Rituximab	4 (1.56)	
NSAIDs	171 (66.54)	

SD, standard deviation; MMAS-8, eight-item Morisky questionnaire; CQR, compliance questionnaire for rheumatology; DMARDs, disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

The mean total score of the MMAS-8 was 5.528 (SD=1.79). The answer of the patients to each question of the Morisky questionnaire is shown in Table II.

The mean total score of the 19-item CQR questionnaire was 75.1 (SD=12.5). 105 patients (40.9%) achieved a CQR score ≥80 and were recognized as adherent to treat-

ment. Participants were divided into two groups of adherent and non-adherent to treatment according to the results of the CQR questionnaire. Variables were compared between the two groups in Table III. There was no significant association between demographical and clinical variables and adherence to treatment except for the level of education in univariate analysis. Having tertiary education (college or university) was correlated with non-adherence to treatment [27 (25.71%) vs 70 (46.05%), $p=0.004$]. Results from regression analysis are presented in Table IV. The results suggest that demographical and clinical variables are not associated with adherence to treatment.

■ DISCUSSION AND CONCLUSIONS

This study on RA patients in Kermanshah City (Iran) showed that the prevalence of adherence to treatment is 40.9% based on the 19-item CQR questionnaire results which are lower than adherence rates reported by most of the previous studies in different countries (5-9). Previous studies resulted in inconsistent data about preva-

Table II - Result of Morisky questionnaire.

Variable	Results by number (%)
Total score of MMAS-8 by mean and SD	5.528, 1.78
1. Do you sometimes forget to take your pills? Yes	179 (69.6)
2. Over the past 2 weeks, were there any days when you did not take your medicines? Yes	100 (38.9)
3. Have you stopped taking medications because you feel worse when you took it? Yes	75 (29.2)
4. When you travel or leave home, do you sometimes forget to bring along your meds? Yes	77 (30)
5. Did you take your medicine yesterday? Yes	236 (91.8)
6. When you feel like your rheumatic disease is under control, do you sometime stop taking your meds? Yes	30 (11.7)
7. Do you feel hassled about sticking to your treatment plan? Yes	125 (48.6)
8. How often do you have difficulty remembering to take all your medicines? Never Hardly ever Sometimes Usually Always	144 (56) 88 (34.2) 15 (5.8) 7 (2.7) 3 (1.2)

MMAS-8, eight-item Morisky questionnaire; SD, standard deviation.

Table III - Different variables compared between adherent and non-adherent patients (patients are divided into two groups based on compliance questionnaire for rheumatology questionnaire).

Variables	Adherent 105 (40.9%)	Non-adherent 152 (59.1%)	P value
Age (mean, SD)	44.82, 12.14	42.11, 12.17	0.08
Gender Female	88 (83.80)	118 (77.63)	0.22
Marital status Single Married Widow or Divorced	10 (9.52) 89 (84.76) 6 (5.71)	31 (20.39) 113 (74.34) 8 (5.26)	0.65
Education level Uneducated Less than or equal to high school High school graduate College or university	5 (4.76) 29 (27.62) 44 (41.90) 27 (25.71)	11 (7.24) 30 (19.74) 41 (29.97) 70 (46.05)	0.004
Economical condition Excellent Good Moderate Bad	1 (0.95) 12 (11.43) 69 (65.71) 23 (21.90)	0 22 (14.47) 90 (59.21) 40 (26.31)	0.42

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Variables	Adherent 105 (40.9%)	Non-adherent 152 (59.1%)	P value
Occupational status			
Employed	18 (17.14)	40 (26.31)	0.11
Unemployed	12 (11.43)	21 (13.81)	
Retired	10 (9.52)	11 (7.24)	
Student	0	4 (2.63)	
Housekeeper	65 (61.90)	76 (50)	
Place of residence			
Rural	5 (4.76)	14 (9.21)	0.33
Urban >100000	19 (18.09)	31 (20.39)	
Urban <100000	81 (77.14)	107 (70.39)	
Underlying disease			
Yes	52 (49.52)	93 (61.18)	0.64
Diabetes mellitus	5 (4.76)	9 (5.92)	
Hypertension	17 (16.19)	27 (17.76)	
Hyperlipidemia	23 (21.90)	42 (27.63)	
Chronic heart disease	1 (0.95)	2 (1.31)	
Chronic lung disease	4 (3.81)	8 (5.26)	
Chronic kidney disease	2 (1.90)	5 (3.29)	
Disease duration (years)	10.74, 8.33	9.88, 7.08	0.37
Number of drugs used in one day			
≤5	42 (40)	78 (51.31)	0.17
5<number≤10	48 (45.71)	55 (36.18)	
10<number≤20	12 (11.43)	18 (11.84)	
>20	3 (2.86)	1 (0.66)	
Number of hospitalizations in the recent year due to disease flares			
0	96 (91.43)	139 (91.45)	0.57
1	7 (6.67)	7 (4.60)	
2	1 (0.95)	1 (0.66)	
≥3	1 (0.95)	5 (3.29)	
Number of outpatient visits in the recent year due to disease flares			
0	48 (45.71)	53 (34.87)	0.29
1	24 (22.86)	39 (25.66)	
2	20 (19.05)	30 (19.74)	
3	5 (4.76)	7 (4.60)	
>	8 (7.62)	23 (15.13)	
Are your treatment costs affordable?			
Yes	61 (58.09)	86 (56.58)	0.81
Have you ever stopped taking your drugs due to financial problems?			
Yes	45 (42.86)	79 (51.97)	0.15
Have you ever had to replace one of your main drugs due to financial problems?			
Yes	33 (31.43)	50 (32.89)	0.8
Type of medications			
Prednisolone:	83 (79.05)	115 (75.66)	0.525
Conventional DMARDs:			
Hydroxychloroquine	33 (31.43)	60 (39.47)	0.187
Methotrexate	36 (34.28)	52 (34.21)	0.99
Sulfasalazine	41 (39.05)	64 (42.10)	0.62
Leflunomide	16 (15.24)	23 (15.13)	0.98
Azathioprine	17 (16.19)	24 (15.79)	0.93
Mycophenolate mofetile	6 (5.71)	7 (4.60)	0.69
Cyclosporine	0	1 (0.66)	>0.99
Tacrolimus	1 (0.95)	0	>0.99

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Variables	Adherent 105 (40.9%)	Non-adherent 152 (59.1%)	P value
Biologic/ targeted synthetic DMARDs:			
Adalimumab	14 (13.33)	16 (10.53)	0.49
Etanercept	3 (2.86)	7 (4.60)	0.53
Infliximab	2 (1.90)	7 (4.60)	0.32
Tofacitinib	0	1 (0.66)	>0.99
Rituximab	2 (1.90)	2 (1.31)	>0.99
NSAIDs	67 (63.81)	104 (68.42)	0.44
Administration rout of bDMARDs			
Subcutaneously	17 (16.19)	23 (15.13)	0.82
Intravenously	4 (3.81)	9 (5.92)	0.57

SD, standard deviation; DMARDs, disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; bDMARDs, biological/targeted disease modifying anti-rheumatic drugs.

Table IV - Result of logistic regression analysis of predictors of non-adherence.

Variables	β	SE	95% CI	p value
Age	.020	.015	.990 to 1.052	.19
Gender	.246	.458	.521 to 3.135	.59
Disease duration	-.010	.021	.950 to 1.031	.62
Number of drugs	-.127	.217	.576 to 1.348	.56
Marital status	-.579	.402	.255 to 1.232	.15
Occupational status	-.046	.110	.770 to 1.185	.68
Place of residence	-.273	.264	.454 to 1.277	.30
Economical condition	.069	.246	.661 to 1.737	.78
Education level	.236	.198	.858 to 1.868	.23
Underlying disease	.089	.075	.943 to 1.267	.24

SE, standard error; CI, confidence interval.

lence rate and non-adherence-related factors. This could be due to differences in demographical variables and measurement tools used to evaluate treatment adherence. Balsa et al. studied 180 RA patients in a 6-month period between 2019 and 2020 and reported that the prevalence of adherence was 59.1% (6). The adherence rate was 79% in another study on 859 RA patients from Spain in 2017-2018 (7). Omair et al. reported high treatment compliance (80.25%) of Saudi RA patients (8) and Kim et al. reported 90.4% of Korean RA patients to be adherent to treatment (9).

We found that high education level was associated with low adherence to treatment. One possible explanation for this result could be the higher knowledge about drug side effects and therefore increased con-

cerns about using prescribed medications in patients with higher education. In agreement with our findings, the results of the studies by Omair et al. (8) and Kim et al. (9) showed that patients with higher education have lower treatment adherence. In contrast, a review article by Salt et al. showed a positive correlation between education level and treatment adherence (10).

We compared the type of medication and route of administration between adherent and non-adherent patients, and there was no difference. Neither cDMARDs nor bDMARDs were associated with adherence to treatment. Pombo-Suarez et al. observed the same result (7), while some previous studies showed a higher prevalence of adherence in patients using bDMARDs, especially tumor necrosis factor inhibitors (6, 11-13).

Age, gender, disease duration, number of drugs, place of residence, and marital and occupational status were not associated with treatment adherence. Previous studies revealed different results about these variables. Older age was correlated with higher adherence in some studies (8, 9, 11, 12). The number of drugs was a predictor for adherence in one study (6) and disease duration was weakly associated with adherence to treatment in another previous article (14).

In order to investigate the relationship between adherence to treatment and the economic status of participants, we asked about their economic condition [excellent (4%), good (13.2%), moderate (51.9%), and bad (24.5%)], and three specific questions about the impact of patient's economic level on their access to prescribed medications (are your treatment costs affordable? Yes: 57.2%; have you ever stopped taking your drugs due to financial problems? Yes: 48.2%; have you ever had to replace one of your main drugs due to financial problems? Yes: 32.3%). When we compared these variables between adherent and non-adherent patients, no differences were observed and we conclude that economic level is not a predictor for adherence in our study population. In contrast, Kim et al showed that higher income increased the risk of poor adherence (9).

The number of hospitalizations and outpatient visits during the previous year was asked to investigate the correlation between adherence to treatment and RA relapses, but we observed no correlation.

In addition to the 19-item CQR questionnaire, we asked our participants to complete the MMAS-8 which is used to determine adherence to treatment in various chronic diseases (15, 16). The mean obtained score was 5.5 (SD=1.78) which is defined as low adherence (8 score=high; 6-8=medium; <6=low). Non-adherence to treatment could be classified as unintentional or intentional. The first one is due to forgetfulness, regimen complexity, and physical problems. The latter is caused by the patient's own decision not to use drugs (16). According to MMAS-8 results, 69.6% of the patients re-

ported that they sometimes forget to use their pills, while 11.7% claimed that they stop their medication when their disease is under control. Therefore, we conclude that unintentional is the main type of non-adherence in our study population.

Our study has both strengths and limitations. One of the strengths is that we included various demographical and clinical variables to find non-adherence risk factors. We used two reliable and valid questionnaires and we utilized the complete form of them (19-item CQR and MMAS-8). CQR is a specific questionnaire to measure treatment adherence in rheumatologic patients (16). The self-administrating nature of the questionnaires could be considered both an advantage and a disadvantage. They are easily used by patients and allowed us to include a larger population in the study; on the other hand, they can lead to bias, because patients might pretend to be adherent. Another limitation is the cross-sectional design of the study which did not permit to measure adherence at different times since adherence is dynamic. In addition we did not measure disease activity in this study. Further studies are needed to investigate the correlation between adherence and disease activity.

Identifying RA patients at higher risk of non-adherence helps to design interventions to increase adherence. We found that the prevalence of non-adherence to treatment is 59.1% in RA patients in Kermanshah, Iran. Having a higher education level is associated with lower adherence to treatment. Other demographical and clinical characteristics could not be a predictor for treatment adherence.

Contributions

SA, conceived the idea and designed the study. SA, MP, PS, were responsible for data collection. DM, MS, were responsible for data analysis. SA, DM, drafted the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Local Clinical Research Ethics Committee. This study

was performed according to the principles of the Declaration of Helsinki.

Informed consent

Patient consent was obtained.

Conflict of interest

The authors declare no conflict of interest.

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Availability of data and materials

Data and materials are available if requested.

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