

Treatment adherence to disease-modifying antirheumatic drugs in Chinese patients with rheumatoid arthritis

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Objective: Nonadherence in rheumatoid arthritis (RA) patients using disease-modifying antirheumatic drugs (DMARDs) may lead to joint damage and function loss. The aim of this cross-sectional study was to explore Chinese RA patients' adherence rates and investigate potential risk factors for nonadherence.

Methods: A total of 122 RA patients were recruited from the Affiliated Hospital of Nantong University from January 2014 to April 2015. Patients were asked to complete a set of standardized self-report questionnaires (Compliance Questionnaire on Rheumatology, Health Assessment Questionnaire, Short Form-36 questionnaire, 28-joint Disease Activity Score, Hospital Anxiety and Depression Scale, and Visual Analog Scale). Independent samples *t*-tests, chi-square analyses, and logistic regression modeling were used to analyze these data.

Results: Based on Compliance Questionnaire on Rheumatology, 38% of the patients adhered to DMARDs. Adherence was associated with education, income, depression, and the total number of DMARDs. Other demographic and clinical characteristics were not associated with adherence. Logistic regression models identified income, depression, and the total number of DMARDs as predictors of medication nonadherence.

Conclusion: In this study, 62% of patients with RA were not adherent to their DMARD prescription. Education, income, depression, and the total number of DMARDs were associated with medication adherence, and income, depression, and the total number of DMARDs were independent predictors of medication adherence in patients with RA. These findings could help medical personnel develop helpful interventions to improve adherence in RA patients by paying more attention to the patients with these accompanying risk factors and, finally, improve RA patients' quality of life.

Keywords: rheumatoid arthritis, disease-modifying antirheumatic drugs, adherence

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, debilitating autoimmune disease, which is most prevalent in middle-aged and old women, with an incidence rate in the range of 0.32%–0.38%. In the course of disease development, recurrent joint pain, swelling, and deformities, which seriously influence patients' quality of life, appear among partial patients. Over the last decade, great advances have been made in the treatment of RA with the development of new biologic therapies.¹ Despite these advances, oral disease-modifying antirheumatic drugs (DMARDs), most commonly methotrexate, and others, such as leflunomide, hydroxychloroquine, and sulfasalazine, remain the cornerstone of therapy in RA and are invariably used as initial therapy.² Since there is increasing evidence that earlier and more aggressive treatment of RA

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with nonbiologic and biologic DMARDs reduces symptoms of the condition and slows disease progression,^{3,4} it is crucial to ensure that patients take DMARDs regularly and correctly following the clinicians' prescription to maintain joint function to the fullest extent.⁵ However, adherence rate to medication in patients with RA is low, varying from 30% to 80%.⁶ A study from the USA, using the Medication Event Monitoring System, reported that only one fifth of patients with RA had an overall adherence to DMARDs.² Another study from the Netherlands presented that 32%–40% of the patients did not adhere to their DMARD prescription.⁷ Previous studies have reported that DMARD nonadherence results in more disease activity/radiological damage, loss of function, and a lower quality of life.^{8–10} This indicates that it is very necessary to strengthen the study of medication adherence and its risk factors. Although previous studies in RA identified a variety of sociodemographic, psychological, and/or clinical variables related to adherence, none of these variables was consistently related in all studies.^{7,8,11–14} Additionally, to our knowledge, there are currently no data from mainland China.

The aims of this descriptive study were 1) to evaluate the extent of treatment adherence to DMARDs in Chinese patients with RA and 2) to explore demographic, clinical (drug use and biochemical criterion), and psychological (anxiety and depression) risk factors for nonadherence using a representative sample of RA patient population from Nantong, People's Republic of China.

Patients and methods

Participants

Patients who fulfilled the American College of Rheumatology (1987 or 2012) criteria for RA were recruited from the Affiliated Hospital of Nantong University from January 2014 to April 2015. A total of 129 patients with RA were constantly invited to participate in a single-center cross-sectional study and 122 (94.57% of the patients) took part in and completed questionnaires in the end. All the patients have been told by the rheumatologist who prescribed the drugs the importance of adherence to DMARD therapy in controlling the disease. Patients were excluded if they were under 18-years-old, diagnosed with life-threatening disorders and severe mental disorders, or found without the use of prescribed DMARDs. All other patients were included, regardless of disease duration, seriousness of the condition, recent surgery, or comorbidity. This study was approved by the Ethics Committee of Affiliated Hospital of Nantong University, and the Clinical Trial Registration number for this study is 2014-387. Written informed consent was obtained from each participant.

Methods

Patients with RA were asked to complete a set of standardized self-report questionnaires (Compliance Questionnaire on Rheumatology [CQR], Health Assessment Questionnaire, Short Form-36 questionnaire, 28-joint Disease Activity Score [DAS28], Hospital Anxiety and Depression Scale, and Visual Analog Scale). The personal medication was gained by querying the electronic medical records combining with patients' self report. Results were totally gained by nurses blinded to study groupings and added to a computer database by two blinded research assistants who rechecked totals prior to entering the data.

Demographics and clinical characteristics

Demographic variables contain the following: age, sex, marital status, education attainment, occupation, monthly per capita income, type of medical insurance, family history, disease duration, comorbidity, hospitalization, tobacco use, and alcohol use. Clinical variables include the total number of DMARDs, which consist of biological and nonbiological DMARDs, total number of medicines, and non-steroidal anti-inflammatory drug (NSAID) use.

Self-reported adherence

Adherence was assessed using the CQR. The CQR is a 19-item, self-administered questionnaire, and was developed to correctly identify patients who were classified as "low" adherers (taking <80% of their medication correctly). The questions were identified through focus groups and clinician's expert opinion of the likely hindrances to medication taking. The 4-point Likert answering scale ranges from "Definitely don't agree" (scored 1) to "Definitely agree" (scored 4); items 4, 8, 9, 11, 12, and 19 have to be reversely recoded (4=1, 3=2, etc). Lower scores indicate lower levels of adherence. The CQR was validated against Medication Event Monitoring System and found to correctly identify 62% of low adherers without the extensive time and costs which are combined with "gold standard" medication monitoring techniques, such as pill counting or blood chemistry levels. Another advantage to the questionnaire is that the answers can indicate to us some social or cognitive reasons behind nonadherence. When used in conjunction with specialized psychosocial measures, this provides the potential for health care professionals to address problems exposed by the questionnaire as hindrances to taking medication.^{5,15–17}

Health Assessment Questionnaire

The Health Assessment Questionnaire, a total of 20 items, was used to rate activity limitation (range from 0 to 3),

where 0= “without difficulty” and 3= “unable to do” in eight domains (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and common daily activities), with higher scores indicating more disability.¹⁸

Measure of the quality of life

The general health status of each patient was measured using the Short Form-36 questionnaire, which measures eight multi-item dimensions: physical functioning (ten items); role limitations due to physical problems (four items); role limitations due to emotional problems (three items); social functioning (two items); mental health (five items); energy/vitality (four items); body pain (two items); and general health perception (five items). For each dimension, the item scores were coded, summed, and transformed on a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state).¹⁹

Disease activity

Disease activity was estimated with the valid and reliable DAS28, incorporating 28 swollen and tender joint counts, patient’s assessment of disease activity (0–100 mm Visual Analog Scale, where 0= not active at all and 100= extremely active), erythrocyte sedimentation rate (mm/hour), and C-reactive protein (mg/L). The questionnaire was also used to collect concurrent information about disease-related data and general health perception rated on visual analog scale.²⁰

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale is designed to assess both anxiety and depression in outpatient populations. Each subscale includes seven items which are rated on a 4-point scale and scored from 0 to 3 with total scores therefore ranging from 0 to 21 for each subscale. Scores between 0 and 7 suggest “no case”; 8 to 10 represent a “possible case”; and 11 to 21 indicate a “probable case of anxiety/depression”. These cutoff points have been validated against clinical interviews with sensitivity and specificity approximately 0.80. Recent studies have reported good internal consistency for both anxiety (0.89) and depression (0.86) subscales.^{21,22}

Data analysis

Descriptive statistics are provided using mean (\pm standard deviation) or number (percentage) depending on parametric distribution of measured variables. Potential demographic, clinical, and psychological variables were screened using univariate tests of the group difference (adherent versus nonadherent according to the dichotomized CQR) at a lenient level of significance without correction for multiple

testing ($\alpha = 0.05$). We used chi-square tests to evaluate differences in proportions. Independent sample *t*-tests were used to evaluate differences in mean. Multivariate analysis was performed to explore how a number of variables might jointly affect adherence behavior. All social demography variables with a significant association with adherence by univariate tests were entered into a logistic regression model with the dichotomous adherence evaluated by the CQR as the dependent variable. Data were analyzed using SPSS (version 21.0).

Results

Demographics and clinical characteristics

Demographic, clinical, and psychological characteristics of the study population are described in Table 1. This study group reflects a normal RA population with 86% of the patients being female, a mean (standard deviation) age of 55.20 years (11.08 years), 91% being married, and with disease duration of 8.76 years (9.20 years). Approximately half of the patients’ monthly per capita income was <1,000 yuan. The educational level was mostly medium to low. In all, 54% of the participants had secondary education, and only 11% were highly educated. Nine (7%) patients were found with family history, 7% with tobacco use, and 18% without alcohol use. A total of 99 patients with RA had an experience of being in hospital before.

As shown in Table 1, the majority of participants used two to three types of DMARDs. Leflunomide was the most prescribed DMARD (72%), followed by methotrexate (64%), hydroxychloroquine (54%), biologic drug (9%), sulfasalazine (5%), or other DMARDs. Moreover, 49% of the study population used glucocorticoid, 47% used NSAIDs, and 51% used radix paeoniae alba. This study group also reflects a normal RA population with a mean DAS28 (standard deviation) of 3.80 (1.51), erythrocyte sedimentation rate of 28.27 (26.75), C-reactive protein of 16.61 (24.45), and 69% of the patients were depressed.

Self-reported adherence

Previous studies used CQR to assess the patients’ adherence as a cutoff at 80%.^{7,23} According to this, 38% of the patients were adherent. This means that 45 (38%) patients were adherent with prescribed medicines; 77 (62%) patients’ compliance is not well, based on the CQR.

Differences between adherent and nonadherent patients

Previous studies reported that nonadherent patients had higher disease activity scores, increased radiographic damage, higher

Table 1 Demographic, clinical, and psychological characteristics of the patients with RA (n=122)

Characteristics	Descriptives
Age (years) mean \pm SD	55.20 \pm 11.08
Sex, female, n (%)	104 (86)
Marital status, n (%)	
Married	111 (91)
Other marital status	11 (9)
Education level, n (%)	
Primary (0–6 years)	43 (35)
Secondary (7–12 years)	66 (54)
Higher (>12 years)	13 (11)
Employment, n (%)	
Employed	79 (65)
Unemployed	43 (35)
Monthly per capita income, n (%)	
<1,000 yuan	60 (49)
1,000–2,999 yuan	46 (38)
3,000–5,000 yuan	12 (10)
>5,000 yuan	4 (3)
Type of medical insurance, n (%)	
With basic medical insurance	86 (71)
Self-pay, n (%)	30 (25)
Other, n (%)	6 (5)
Hospitalization, yes, n (%)	99 (81)
Tobacco use, yes, n (%)	9 (7)
Alcohol use, yes, n (%)	22 (18)
Family history, yes, n (%)	9 (7)
Disease duration, mean \pm SD	8.76 \pm 9.20
Comorbid conditions, yes, n (%)	46 (38)
Total number of DMARDs, n (%)	
One	31 (25)
Two	53 (43)
Three	33 (27)
>Three	5 (4)
ESR (mm/hour), mean \pm SD	28.27 \pm 26.75
CRP (mg/L), mean \pm SD	16.61 \pm 24.45
DAS28, mean \pm SD	3.80 \pm 1.51
HAQ, mean \pm SD	0.46 \pm 0.63
VAS global (mm), mean \pm SD	4.32 \pm 2.76
VAS pain (mm), mean \pm SD	3.94 \pm 3.18
HADS anxiety, n (%)	85 (70)
HADS depression, n (%)	84 (69)
Domains of SF-36, mean \pm SD	
PF	57.50 \pm 29.07
RP	21.31 \pm 36.46
BP	48.22 \pm 25.86
GH	42.34 \pm 21.17
VT	51.39 \pm 18.82
SF	61.17 \pm 27.07
RE	35.52 \pm 43.44
MH	61.21 \pm 18.39

Abbreviations: RA, rheumatoid arthritis; SD, standard deviation; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; HAQ, health assessment questionnaire; VAS global, visual analog scale for general health; VAS pain, visual analog scale for pain; HADS, hospital anxiety and depression scale; SF-36, short form-36 questionnaire; PF, physical functioning; RP, role limitations due to physical problems; BP, body pain; GH, general health perception; VT, energy/vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health.

degree of depression, and worse mental health, with a trend toward lower function as well, compared with adherent patients.² The differences of demographic, clinical, and psychological characteristics between adherent and nonadherent patients are presented in Table 2. Education level, monthly per capita income, depression, and the total number of DMARDs were found to be associated with adherence. With regard to age, sex, marital status, employment, disease duration, type of medical insurance, comorbid condition, hospitalization, family history, drinking, and smoking, no statistically significant differences were found between the two groups ($P>0.05$). Adherent and nonadherent patients did not differ in terms of DAS28 score, Visual Analog Scale, Health Assessment Questionnaire, erythrocyte sedimentation rate, C-reactive protein, anxiety, eight dimensions of Short Form-36, or the use of NSAID, hormone, and biological agent ($P>0.05$).

Logistic regression analysis for adherence

We used logistic regression analysis to investigate predictors of medication nonadherence, as indicated in Table 3. We found that monthly per capita income (odds ratio =2.515; $P<0.01$), depression (odds ratio =4.305; $P<0.01$), and the total number of DMARDs (odds ratio =1.843; $P<0.05$) were the predictors of medication nonadherence.

Discussion

As we know, DMARDs can obviously reduce disease activity and joint damage in patients with RA,²⁴ so it is necessary to ensure that patients take medications as prescribed by their health care providers regularly and correctly. The extent to which a patient takes medication as prescribed is termed as “adherence”.²⁵ Nonadherence has been found to be linked with poorer treatment outcomes, progression of disease symptoms, complications, increased health services utilization, and hospital admission.^{26–30} The most feasible way to identify nonadherence in clinical practice is self-report measures.⁷ Currently, there is only one validated rheumatology-specific adherence questionnaire, CQR.²⁵ Previous studies have evaluated adherence using CQR 80% cutoff scores.^{7,23} In the present study, we reported that based on the CQR, 38% of Chinese RA patients were adherent to DMARDs. The proportion of adherence is in accordance with previous studies from other countries and areas, which indicates that adherence rates to prescribed medicine regimes in people with RA varies from 30% to 80%.⁶ To our knowledge, this study is the first to estimate medication adherence and explore its risk factors in patients with RA in mainland China using a self-reported questionnaire.

Table 2 Differences between demographic, clinical, and psychological characteristics of adherent and nonadherent patients

Characteristics	Adherent n=45	Nonadherent n=77	P-value
Age (years) mean \pm SD	55.31 \pm 13.24	55.14 \pm 9.69	0.941
Sex, female, n (%)	40 (89)	64 (83)	0.386
Marital status, n (%)			0.772
Married	40 (89)	71 (92)	
Other marital status	5 (11)	6 (8)	
Education level, n (%)			0.016*
Primary (0–6 years)	22 (49)	21 (27)	
Secondary (7–12 years)	20 (44)	46 (60)	
Higher (>12 years)	3 (7)	10 (13)	
Employment, n (%)			0.218
Employed	26 (58)	53 (69)	
Unemployed	19 (42)	24 (31)	
Monthly per capita income, n (%)			0.031*
<1,000 yuan	28 (62)	32 (42)	
1,000–2,999 yuan	13 (29)	33 (43)	
3,000–5,000 yuan	3 (7)	9 (12)	
>5,000 yuan	1 (2)	3 (4)	
Type of medical insurance, n (%)			0.981
With basic medical insurance	32 (71)	54 (70)	
Self-pay	11 (24)	19 (25)	
Other	2 (4)	4 (5)	
Hospitalization, yes, n (%)	36 (80)	63 (82)	0.804
Tobacco use, yes, n (%)	3 (7)	6 (8)	1.000
Alcohol use, yes, n (%)	6 (13)	16 (21)	0.302
Family history, yes, n (%)	5 (11.1)	4 (5)	0.397
Disease duration, mean \pm SD	8.64 \pm 9.17	8.84 \pm 9.27	0.734
Comorbid conditions, yes, n (%)	20 (44)	26 (34)	0.240
Total number of DMARDs, n (%)			0.032*
One	18 (40)	13 (17)	
Two	15 (33)	38 (49)	
Three	11 (24)	22 (29)	
>Three	1 (2)	4 (5)	
ESR (mm/hour), mean \pm SD	24.42 \pm 24.86	30.52 \pm 27.70	0.129
CRP (mg/L), mean \pm SD	17.74 \pm 29.00	15.94 \pm 21.53	0.947
DAS28, mean \pm SD	3.73 \pm 1.55	3.85 \pm 1.50	0.673
HAQ, mean \pm SD	0.53 \pm 0.70	0.42 \pm 0.58	0.595
VAS global (mm), mean \pm SD	4.41 \pm 3.05	4.27 \pm 2.59	0.781
VAS pain (mm), mean \pm SD	3.92 \pm 3.34	3.95 \pm 3.11	0.951
HADS anxiety, n (%)	29 (64)	56 (73)	0.337
HADS depression, n (%)	25 (56)	59 (77)	0.015*
Domains of SF-36, mean \pm SD			
PF	54.11 \pm 31.43	59.48 \pm 27.62	0.327
RP	25.56 \pm 39.70	18.83 \pm 34.45	0.239
BP	51.67 \pm 26.54	46.21 \pm 25.41	0.262
GH	42.53 \pm 25.01	42.23 \pm 18.75	0.945
VT	53.33 \pm 23.33	50.26 \pm 15.66	0.434
SF	62.50 \pm 31.19	60.39 \pm 24.54	0.680
RE	37.78 \pm 46.38	34.20 \pm 41.88	0.729
MH	58.58 \pm 23.30	62.75 \pm 14.76	0.283

Notes: * $P < 0.05$. Adherence, measured with the Compliance Questionnaire on Rheumatology, is expressed as dichotomous (<80% or \geq 80% adherence) variable.

Abbreviations: SD, standard deviation; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, 28-Joint Disease Activity Score; HAQ, health assessment questionnaire; VAS global, visual analog scale for general health; VAS pain, visual analog scale for pain; HADS, hospital anxiety and depression scale; SF-36, short form-36 questionnaire; PF, physical functioning; RP, role limitations due to physical problems; BP, body pain; GH, general health perception; VT, energy/vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health.

Table 3 Logistic regression analysis of demographic, medical, and psychological characteristics in relation to adherence

	Adherence	Beta	Standard error	P-value	Exp (B)	(95% CI)
Step 1	Education level	0.510	0.390	0.191	1.665	0.776, 3.573
	Monthly per capita income	0.693	0.370	0.061	1.999	0.968, 4.128
	HADS depression	1.356	0.484	0.005	3.882	1.502, 10.031
	Total number of DMARDs	0.657	0.273	0.016	1.929	1.130, 3.295
Step 2	Monthly per capita income	0.922	0.331	0.005**	2.515	1.315, 4.812
	HADS depression	1.460	0.477	0.002**	4.305	1.689, 10.973
	Total number of DMARDs	0.611	0.266	0.022*	1.843	1.094, 3.104

Notes: * $P < 0.05$, ** $P < 0.01$.

Abbreviations: CI, confidence interval; HADS, hospital anxiety and depression scale; DMARD, disease-modifying antirheumatic drug.

Previous studies have reported that sex, age, disease duration, and education level were associated with medication adherence, and disease activity and side effects were not related to medication adherence.^{12,14,23,31} Chrzanowska et al³² reported that level of education did not significantly influence medication adherence. Lorish et al³³ found that financial status was not associated with adherence. In the present study, our group found that medication adherence had an obviously positive correlation with education level and monthly per capita income. One possible explanation for the different results is the existence of cultural diversity between Chinese and Western population.

There is an increasing evidence that depression frequently occurs in RA.³⁴ While many studies showed the association between depression and adherence in other diseases, fewer studies have been carried out in patients with RA. Julian et al³⁵ reported that patients with both rheumatologic diseases and depression were less likely to be adherent with their medications. We also found that depression had a significantly negative impact on medication adherence, which is similar to previous studies from other countries.^{36–38} This may be due to the fact that RA is currently incurable and needs continuous therapy. This finding indicates the importance of carrying out patient education for RA patients with depression so as to improve their adherence to medication.

As reported by Kristensen et al,³⁹ treating patients with more types of DMARD usage history may lead to premature treatment termination. Salt and Frazier⁴⁰ reported that total number of prescriptions was the independent predictor of medication adherence. In the current study, most patients (70%) took two to three types of DMARDs. We found that the number of DMARDs had a positive correlation with adherence in most patients, but more than three types would have a negative effect on patients' adherence.

To investigate predictors of medication nonadherence, we used logistic regression analysis. We found that monthly per capita income and depression had a significant effect on

medication nonadherence. Interestingly, we also found that the total number of DMARDs played an important role in medication nonadherence. To our knowledge, it is the first time the potential risk factors of medication adherence in Chinese patients with RA have been explored.

However, this study has several limitations. First, all patients involved in this investigation were only from one center. Second, the measurement to identify adherence was subjective, which may result in a possible overestimation or misclassification of adherence due to the absence of an objective "gold standard" for adherence. Third, a proportion of patients in our study were people with terminal RA combined with interstitial pneumonia, and the doctors took no account of the RA patients' fertility for the basic national condition of the People's Republic of China, so the current study reported leflunomide being the most prescribed DMARD, followed by methotrexate, the generally accepted anchor drug. Other limitations of the study also exist, such as problems in causal inference due to a cross-sectional design.

Conclusion

We have first reported that 38% of Chinese patients with RA were adherent to DMARDs. Education level, monthly per capita income, depression, and total number of DMARDs were significantly correlated with adherence. In mainland China, the results indicated that rheumatologists and nurses should pay attention to RA patients' medication adherence, especially those with a low degree of education, low monthly per capita income, being depressive, and/or taking more types of DMARDs by patient education or some other ways so as to improve patients' prognosis and, finally, improve RA patients' quality of life.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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