

ORIGINAL ARTICLES

The influence of patient's perspective in therapeutic adherence in rheumatoid arthritis: a case study from Spain

Ahijón-Lana M¹, Gutiérrez-Ortega C², Robles-Sánchez I³, Veiga-Cabello R¹, De La Cruz-Tapiador C¹, Carreira-Delgado P⁴

ABSTRACT

Objectives: The main objective is to study the contribution of illness and medication beliefs to treatment adherence in patients with rheumatoid arthritis.

Methods: The design was a cross-sectional study. The compliance Questionnaire for Rheumatology (CQR) was used to measure therapeutic adherence. The beliefs about medicines questionnaire (BMQ) and the brief illness perception questionnaire (IPQ-b) were used to assess patient's beliefs about medicines and about the disease. Other factors studied were treatment satisfaction, patient's demographic and clinical characteristics.

Results: 144 patients were included in the study, 113 (78.4%) patients showed good treatment adherence. Patients with poor adherence presented higher scores in the BMQ harm domain (13 ± 5 vs. 11 ± 3 , $p= 0.013$). Meanwhile, patients with good adherence presented higher scores in the necessity BMQ domain (21 ± 3 vs. 20 ± 3 , $p= 0.015$), increased feeling of treatment control (8.8 ± 1.5 vs. 7.7 ± 2.1 , $p= 0.008$), higher emotional response (6.2 ± 3.1 vs. 4.8 ± 3.4 , $p= 0.042$) and a higher level of treatment satisfaction (77.2 ± 12.4 vs. 69.9 ± 12.5 , $p=0.004$). In a multivariable analysis for each unit of increase in the score of BMQ's harm domain, adherence was reduced by 20% (CI 95% 0.08-0.3, $p= 0.001$); for each unit of increase in treatment control item of the IPQ-b, adherence increased 1.4 times (CI 95% 1.1-1.8, $p= 0.006$); and for each unit of increase in the emotional response item of the IPQ-b, adherence increased 1.3 times (CI 95% 1.1-1.5, $p= 0.002$).

Conclusion: In our cohort of RA patients, good adherence is associated with stronger treatment necessity perception, stronger feeling of treatment control, higher emotional response and higher level of treatment satisfaction; on the other side, patients with poor adherence had stronger beliefs of medicines as harmful substances

Keywords: Therapeutic adherence; Rheumatoid arthritis; Perception.

INTRODUCTION

Therapeutic adherence has become a topic of central interest for medical research. The World Health Organization (WHO) defines therapeutic adherence as the extend to which the patient's behaviour coincides with the agreed recommendations by their prescribing physician¹. Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease resulting in progressive irreversible joint damage and functional impairment². Adherence to therapy in developed countries among

patients with chronic diseases averages 50%¹. Therapeutic adherence rates reported in RA vary between studies, ranging from 30% to 80%. Despite this heterogeneity, results from these studies show that adherence to disease-modifying antirheumatic drugs (DMARDs) is suboptimal, ranging from 22% (underuse) to 107% (overuse)³. Besides having a negative impact on disease outcomes, poor adherence implies a high economic burden for every health system.

It is necessary to know what factors are involved in medication-taking behaviour to develop appropriate intervention strategies to minimize this problem. Adherence-implicated factors can be classify in five dimensions: socioeconomic related factors, health care team and/or system factors, condition related factors, therapy related factors and patient related factors¹. Some of these factors are not modifiable and different studies have found conflicting results regarding their impact on medication-taking behaviour. This suggests that therapeutic adherence is a complex process, which

¹Rheumatology Department, University Hospital Central de la Defensa Gómez Ulla; ²Preventive Medicine Department, University Hospital Central de la Defensa Gómez Ulla; ³Department of Academic Psychology, University Hospital Central de la Defensa Gómez Ulla; ⁴Rheumatology Department, University Hospital 12 de Octubre.

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Correspondence to: María Ahijón-Lana
E-mail: maria_ahijon26@hotmail.com

cannot be predicted based only on clinical or patients characteristics⁴.

In the last decades, patient's participation in health-care has changed from a passive to an active role. In this context it is necessary to differentiate between adherence, which refers to an active choice of the patient to follow the instructions agreed with the health provider, and compliance, that refers to a passive attitude of the patient⁵. Traditional medicine has focussed on clinical outcomes from the treatments, whilst for the patient other issues are relevant when deciding to follow a prescription, such as their relationship with the health provider, fear to side effects or a hope for a normal life^{6,7}. People should be able to manage their lives with RA through patient education, effective communication and shared decision-making between patients and their health provider⁸. Several studies from the health psychology field, trying to understand how patients cope with disease, have established psychological models to explain adherence behaviour. One of the key constructs with a wider recognition, is that sustained health behaviour change is a process, which involves constant adaptation. Adherence is a dynamic feature that is not stable over time⁹.

The problem of non-adherence has persisted so far, although there are interventions available to diminish it. Therefore, there is an area of uncertainty in the components within the patient's perspective to develop successful interventions. This study aims to analyse the influence of the patient's beliefs about his/her disease and medication, in treatment adherence, in a sample of Spanish population with RA from a single centre. We also investigate the relevance of other factors, such as treatment satisfaction, socio-demographic and disease characteristics, in therapeutic adherence.

PATIENTS AND METHODS

Study design

This observational cross-sectional study was conducted in the university hospital Central de la Defensa Gómez Ulla, which serves a population of 120,442 in Madrid, Spain. This study was conducted in accordance with Good Clinical Practice and the current version of the revised Declaration of Helsinki (World Medical Association Declaration of Helsinki), was approved by the ethics committee and all participants signed informed consent.

Patients

Patients were selected by consecutive sampling in the outpatient clinic of the Rheumatology Department, between January 2018 and January 2019. Inclusion criteria were patients aged > 18 years and with a diagnosis of RA based on ACR /EULAR 2010 criteria¹⁰. Patients

were excluded if they had mental disorders or linguistic difficulties that could prevent the comprehension of the questionnaires. Demographic and clinical variables were collected by semi-structured interview and revision of medical records.

Main outcome variable

To assess the main outcome we used the Spanish validated version of the Compliance Questionnaire for Rheumatology (CQR)¹¹. This 19-item questionnaire is a rheumatology-specific instrument to measure adherence to treatment and to identify possible factors implicated in suboptimal therapeutic adherence. It was validated against an electronic medication monitoring system and showed an estimated sensitivity and specificity to detect good compliance of 95% and 62% respectively^{12,13}. Unsatisfactory adherence was defined as a score ≤80% in the CQR.

Study factors

Demographic and clinical variables

Demographic data included in the study were: age, sex, origin, educational level, marital and working status. Clinical data collected were RA duration, actual treatment for RA and other diseases, number of tender and swollen joints, disease activity (measured using DAS28 with ESR activity index¹⁴) and level of pain (measured with a 0-to-10 analogue visual scale). According to the DAS28 score patients were classified in remission (<2.6), low disease activity (2.6-3.2), moderate disease activity (>3.2-5.1) or high disease activity (>5.1). Comorbidity was recorded by revision of medical records. Counted comorbidities were: arterial systemic hypertension, diabetes mellitus, cardiovascular disease, hyperlipemia, end-stage renal disease, chronic liver disease, major depression, fibromyalgia, osteoporosis and chronic pulmonary disease. These data were recorded into a dichotomous comorbidity variable (comorbidity, yes/no).

Patient reported outcomes

Medication beliefs were evaluated using the Spanish validated version of Beliefs about Medicine Questionnaire (BMQ)¹⁵. The BMQ has two components BMQ-general, that assesses cognitive representations of medicines in general, and BMQ-specific, that assesses beliefs about medication prescribed for personal use. The BMQ-general has two subcomponents ("general-overuse" and "general-harm"); higher scores indicate strong beliefs in potentially harmful and addictive effects of medicines and strong belief that doctors are overusing medicines. The BMQ-specific has another two sub-components ("specific-necessity" and "specific-concerns"), higher punctuation indicates stronger perception of treatment necessity and stronger concern

towards medicine use¹⁶. Illness beliefs were assessed using the Spanish validated version of the brief-illness perception questionnaire (IPQ-b)¹⁷. This measure is a 9-item questionnaire that captures illness cognitive and emotional representations. The higher the score is in this questionnaire, the more threatening the disease is perceived¹⁸. The Spanish version of the arthritis treatment satisfaction questionnaire (ARTS) was used to assess the level of patient satisfaction¹⁹. This questionnaire is composed of 4 dimensions: satisfaction with the medical care, with the treatment's efficacy, convenience and tolerability. Higher scores indicate higher level of satisfaction.

Other measures used were the Short Form Health Survey 12 version 2(SF12v2) to assess quality of life^{20,21}, and the modified HAQ (mHAQ) to assess physical disability²².

Statistical analysis

To describe continuous variables we used measures of central tendency and dispersion: mean and standard deviation or median and interquartile range, according to the distribution of the data. Categorical variables were reported as numbers and percentages.

The normal distribution of the main outcome variable was verified using Kolmogorov-Smirnov test.

Continuous variables were compared using the Student's t-test; meanwhile categorical variables were compared using Chi-squared test or the Fisher exact test. Statistical significance was inferred at a level of $p<0.05$.

Logistic regression models were constructed to study the association between lack of adherence and risk factors. To evaluate the proportion of the variance in the dependent variable that is predictable from the independent variables the R squared adjusted was calculated. Those factors with a p value <0.250 in the univariate analysis²³ were included in the forward multivariable logistic regression analysis. Although there is a great variability between studies, age and sex have been associated with therapeutic adherence of RA patients in other studies conducted in spanish population^{24,25}. These variables were considered clinically relevant to be included in the multivariable analysis.

The Cohen's delta was used to calculate the effect size of those cognitive variables with a statistical significance in the univariate analysis. A result of 0,2 to 0,4 was considered a small size effect, a result of 0,5 to 0,8 a medium size effect and a result > 0,8 a large size effect. Statistical analysis was performed using IBM SPSS Statistics version 24.

RESULTS

Patient's characteristics

We invited 186 patients to participate in the study, of which 144 responded to all the questionnaires. Demo-

graphic and clinical characteristics of the sample are shown in Table I. Mean age was 62 years (SD 12) and 106 patients (73.6%) were women. The median disease duration was 5 years (interquartile range 25-75: 9). Most patients were seropositive for rheumatoid factor (RF), anti-citrullinated peptides antibodies (anti-CCP) or both. According to DAS-28 results, 53 patients (36.8%) were in remission, 28 (19.4%) presented low disease activity, 53 (36.8%) presented moderate disease activity and 10 (6.9%) had high disease activity. Combination therapy with DMARDs was prescribed in 85 patients (59.4%) whereas monotherapy with DMARDs was prescribed in 58 patients (40.6%). Only 18 patients (12.5%) were receiving biologic DMARD (bDMARD). Subcutaneous DMARDs were the most frequently used [67 patients (46.8%)], followed by oral DMARDs [48 patients (33.5%)] and only 7 (4.8%) patients were receiving an intravenous DMARD.

Therapeutic adherence levels and associated factors

According to CQR results, 113 patients (78,4%) showed good adherence to treatment.

Demographics and clinical factors

No significant statistical differences were found between adherent and non-adherent patients regarding age, gender, origin, educational level, marital or working status. They also did not differ significantly regarding disease duration, RA activity, autoantibody status, disability degree or quality of life. Good adherence was slightly higher amongst patients with a subcutaneous DMARD, but this difference was not statistically significant (83.6 versus 74%, $p= 0.164$). No differences were found regarding treatment strategy (combination versus monotherapy), or the type of DMARD (conventional versus biologic).

Patient reported outcomes

Patients with poor adherence presented higher scores in the BMQ harm domain (13 ± 5 vs. 11 ± 3 , $p= 0.013$), whereas patients with good adherence presented higher scores in the BMQ necessity domain (21 ± 3 vs. 20 ± 3 , $p= 0.015$). From the illness perception measures, adherent patients had higher feeling of treatment control (8.8 ± 1.5 vs. 7.7 ± 2.1 , $p= 0.008$) and higher emotional response (6.2 ± 3.1 vs. 4.8 ± 3.4 , $p= 0.042$). Patients with early RA had higher scores in the BMQ harm domain than patients with established RA ($13,38 \pm 4,76$ vs. $11,23\pm 3,59$, $p=0,013$). No other differences were observed in the BMQ and IPQ-b scores between patients with early and established RA.

A higher level of satisfaction with treatment was observed among adherent patients (77.2 ± 12.4 vs.

Table I. Baseline characteristics of the 144 patients with RA included in the study

	Adherent (n=113)	Non-adherent (n=31)
Age at disease onset (years) Mean (SD)	54 (12.0)	56 (13.2)
Age (years) Mean (SD)	62.3 (12.0)	62 (13.0)
Disease duration (years) Median (IQR 25-75)	5.2 (2-12)	3.9 (1-10)
Gender n (%)	Female	82 (72.6)
	Spain	89 (78.8)
Origin n (%)	South America	20 (17.7)
	East Europe	3 (2.7)
Marital status n (%)	Married	65 (57.5)
	Single	19 (16.8)
	Widowed	14 (12.4)
	Divorced	15 (13.3)
Educational level n (%)	No studies	4 (3.5)
	Primary school	38 (33.6)
	Secondary school	37 (32.7)
	Professional studies	12 (10.6)
	University degree	21 (18.6)
Working status n (%)	Working	45 (39.8)
	Studying	3 (2.7)
	Retired	41 (36.3)
	Disabled for work	1 (0.9)
	Unemployed	5 (4.4)
	Home care	18 (15.9)
At least one comorbidity n (%)		77 (68.1)
Smokers n (%)		24 (21.2)
DAS-28 result n (%)	Remission	40 (35.4)
	Low activity	19 (16.8)
	Moderate activity	45 (39.8)
	High activity	9 (8.0)
RF n (%)	Positive	86 (76.1)
	Negative	27 (23.9)
Anti-CCP n (%)	Positive	74 (65.5)
	Negative	34 (30.1)

SD: standard deviation IQR: interquartile range. RF: rheumatoid factor. Anti-CCP: Anti-cyclic citrullinated peptide antibodies. Information not available: Origen (2 patients); Educational level (1 patient); Anti-CCP (7 patients)

69.9±12.5, p=0.004), with higher scores in the dimensions of efficacy (28.8±4.9 vs. 26.3±6.1, p= 0.015) and convenience (12.9±2.1 vs. 11.7±2.7, p=0.030) of the ARTS questionnaire.

According to the results of the Cohen's delta, medication necessity and treatment's efficacy satisfaction had a small size effect, meanwhile beliefs in treatment's potential harm, treatment control, emotional response, total satisfaction and satisfaction with the convenience of the treatment showed a medium size effect (Table II).

In the multivariable analysis, the model that better adjusts with adherence, includes age, sex, DMARD route of administration, scores in BMQ harm and necessity domains, scores in treatment control item and emotional response item of the IPQ-b, scores of the ARTS efficacy and convenience domains. The result shows BMQ's harm domain reducing adherence by 20% for each unit of increase (CI 95% 0.08-0.3, p= 0.001); IPQ-b treat-

ment control increasing 1.4 times adherence for each unit of increase (CI 95% 1.1-1.8, p= 0.006); and IPQ-b emotional response, that increases adherence 1.3 times for each unit of increase (CI 95% 1.1-1.5,p= 0.002). The R-squared adjusted was 0.216 (Table III).

DISCUSSION

The present research shows that 20% of the patients had a score< 80% in the CQR indicating low adherence to their treatment. Strong beliefs in medication necessity, increased perception of treatment control and strong emotional response to the disease were associated with good adherence. Perception of medicines as harmful substances was associated with poor adherence. The value of R-squared adjusted of the regression model was 0.216, that can be considered low. However, there is no rule for interpreting the strength of this statistical tool in its application to clinical relevance, as low values

Table II. Association between cognitive variables and therapeutic adherence

	Adherence (n=113)	Non-adherence (n=31)	P	Cohen's d
Beliefs about medicines (BMQ) Median (IQR)	Abuse	9 (2)	9 (3)	0.112
	Harm	11 (3)	13 (5)	0.013
	Necessity	21 (3)	20 (3)	0.015
	Concern	16 (3)	16 (4)	0.780
Illness perception (IPQ-b) Mean (SD)	Personal control	6.7 (2.7)	6.6 (2.6)	0.887
	Treatment control	8.8 (1.5)	7.7 (2.1)	0.008
	Coherence	5.6 (2.6)	7.3 (2.9)	0.647
	Consequences	6.7 (2.8)	6.1 (2.4)	0.311
	Duration	9.2 (1.6)	9 (1.8)	0.476
	Identity	6.8 (2.6)	6 (2.5)	0.130
	Concern	7.6 (2.7)	6.8 (2.1)	0.139
	Emotional response	6.2 (3.1)	4.8 (3.4)	0.042
Satisfaction level (ARTS) Mean (SD)	Total score	43.3 (10.9)	41.2 (11.7)	0.360
	Convenience	12.9 (2.1)	11.7 (2.7)	0.030
	Efficacy	28.8 (4.9)	26.3 (6.1)	0.015
	Tolerability	5.1 (2.1)	4.9 (2.5)	0.665
	Medical care	26.4 (3.7)	25.1 (4.3)	0.099
	Total score	77.2 (12.4)	69.9 (12.5)	0.004
				0.004

SD: standard deviation IQR: interquartile range. ARTS: arthritis treatment satisfaction questionnaire

can still provide a useful clinical model with respect to data trends²⁶.

Different factors within the patient's perspective have been related with therapeutic adherence. Some of which are stronger medication necessity perception, fewer treatment concerns, strong views towards illness chronicity, increased treatment control or increased knowledge about the disease²⁷⁻²⁹. Patient's beliefs have also been related with clinical outcomes and treatment delay in RA patients^{30,31}. However, differences in effect sizes are reported in chronic diseases regarding the association between patient's beliefs and therapeutic adherence. Some studies show that medication-taking behaviour depends more on patient's beliefs than on disease-related factors, meanwhile, other studies report no association. This variability can be explained in part for the lack of condition-specific questionnaires³², and it demonstrates the complexity of studying the medication-taking process. Illness and medication beliefs are modifiable factors that should be addressed with the patient in clinical practice³³.

No gold standard exists for screening non-adherence, however, the CQR is one of the questionnaires most widely validated in rheumatology³⁴. This instrument identifies possible factors implicated in suboptimal therapeutic adherence and its use in conjunction with other psychosocial measures (such as the BMQ), can help clinicians to recognize potential barriers to taking

medication³⁵. A shorter version of this questionnaire could be a useful instrument for screening of non-adherence in daily clinical practice.

Satisfaction with health care has also been related with good therapeutic adherence^{36,37}. In this study we found that higher satisfaction with treatment in general, especially with its efficacy and convenience, were associated with better adherence. However, there were no differences in the scores of the ARTS medical care dimension between adherent and non-adherent patients. As both groups presented high scores, one possible explanation for this finding is that patients satisfied with their rheumatologist could have been more prone to participate, what could account for a selection bias in our study. Neither we found differences regarding treatment tolerability, probably due to the measure used to evaluate satisfaction. The tolerability dimension of the ARTS questionnaire is composed only by 2 items and it was the dimension with the lowest internal consistency coefficient¹⁹. The level of satisfaction is a patient-reported outcome with a growing interest in health care research, although there are not yet so many validated measures as for other subjective outcomes.

No differences were observed regarding any of the socio-demographic factors included in this study. Results from previous works show great variability and, sometimes, contradictory results about the influence of these factors on treatment adherence⁴. For instance, younger

Table III. Results from multivariable analysis.

Initial logistic regression model	OR (CI 95%)	P
Sex	1.37 (0.44-4.24)	0.594
Age	1.00 (0.97 -1.04)	0.678
Oral DMARD	1.19 (0.31-4.54)	0.798
Subcutaneous DMARD	2.60 (0.61-11.08)	0.197
BMQ damage	0.82 (0.72-0.95)	0.007
BMQ necessity	1.05 (0.90- 1.22)	0.571
IPQ-b treatment control	1.28 (0.90-1.81)	0.169
IPQ-b emotional response	1.29 (0.98-1.70)	0.071
ARTS convenience	1.120 (0.84-1.49)	0.440
ARTS efficacy	0.99 (0.83-1.20)	0.977
Final model	OR (CI 95%)	P
BMQ damage	0.81 (0.71-0.92)	0.001
IPQ-b treatment control	1.40 (1.10 -1.80)	0.006
IPQ-b emotional response	1.30 (1.10-1.50)	0.002

R² adjusted= 0.216
OR: odds ratio, CI confidence interval, DMARD: disease-modifying antirheumatic drugs, BMQ: beliefs about medicines questionnaire, IPQ-b: brief illness perception questionnaire, ARTS: arthritis treatment satisfaction questionnaire

age has been associated both with better and worse adherence³⁸⁻⁴⁰. Similarly, women have shown association with good adherence in some studies, whereas no differences were observed between genders in others^{24,41}. This variability can be at least partially explained by regional characteristics, the study design or the different methods used to assess treatment adherence.

Simplification of treatment strategy is another factor that has been correlated with improved patient's adherence^{42,43}, however we found no differences between patients receiving combination therapy and those receiving monotherapy. It is important to highlight that previous studies were conducted in patients receiving bDMARD, which in our sample accounted only for 12,5%. Patients treated with bDMARD usually have been treated first with conventional DMARD, and therefore it could be possible that they perceived less necessity of the conventional DMARD once the biologic is started. In our study patients with a subcutaneous DMARD showed higher adherence, although this difference was not statistically significant. Previous studies have found an association between subcutaneous DMARD and good adherence, which can be explained because it usually implies a less frequent dosing schedule than oral DMARD^{44,45}.

The main advantage of the present study is that, in addition to socio-demographic and clinical data, different questionnaires have been used to assess subjective aspects that can influence adherence (BMQ, IPQ-b, ARTS and CQR). These factors will be taken into account in our

future analysis and show that CQR, in combination with other psychosocial measures, could be a useful screening tool for non-adherence, identifying possible cognitive barriers to taking medication that can be addressed with the patient during the shared-decision process.

Our study has some limitations. First, our study has a cross sectional and not a longitudinal design. A prospective longitudinal cohort would have reflected the dynamic nature of the therapeutic adherence process and would allow us to find conclusions about causality. Second, the relatively small sample size could be the cause of the lack of association between some of the variables studied and therapeutic adherence. Third, all the patients included belonged to the same health care area and, therefore, the sample could not be representative of other populations, for example, only a small percentage of patients were treated with bDMARD.

In conclusion, in our cohort of RA patients, good adherence is associated with stronger treatment necessity perception, stronger feeling of treatment control, higher emotional response and higher level of treatment satisfaction; on the other side, patients with poor adherence had stronger beliefs of medicines as harmful substances.

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