CLINICAL SCIENCE

Multilevel factors predict medication adherence in rheumatoid arthritis: a 6-month cohort study

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ABSTRACT
Non-adherence challenges efficacy and costs of healthcare. Knowledge of the underlying factors is essential to design effective intervention strategies.
Objectives To estimate the prevalence of treatment adherence in rheumatoid arthritis (RA) and to evaluate its predictors.
Methods A 6-month prospective cohort study of patients with RA selected by systematic stratified sampling (33% on first disease-modifying rheumatic drug (DMARD), 33% on second-line DMARD and 33% on biologics). The outcome measure was treatment adherence, defined by a score greater than 80% both in the Compliance Questionnaire in Rheumatology and the Reported Adherence to Medication scale, and was estimated with 95% CIs. Predictive factors included sociodemographic, psychological, clinical, drug-related, patient–doctor relationship related and logistic. Their effect on 6-month adherence was examined by multilevel logistic models adjusted for baseline covariates.
Results 180 patients were recruited (77% women, mean age 60.8). The prevalence of adherence was 59.1% (95% CI 48.1% to 71.8%). Patients on biologics showed higher adherence and perceived a higher medication need than the others; patients on second-line DMARDs had experienced more adverse events than the others. The variables explaining adherence in the final multivariate model were the type of treatment prescribed (second-line DMARDs OR=5.22, and biologics OR=3.76), agreement on treatment (OR=4.57), having received information on treatment adaptation (OR=1.42) and the physician perception of patient trust (OR=1.58). These effects were independent of disease activity.
Conclusion Treatment adherence in RA is far from complete. Psychological, communicational and logistic factors influence treatment adherence in RA to a greater extent than sociodemographic or clinical factors.

Key messages

What is already known about this subject?
► Non-adherence is a common problem in chronic diseases such as rheumatoid arthritis that impacts on the costs and outcome of the disease.
► Most studies on adherence focus on patient-related determinants, neglecting other elements of the process, such as the attitude of the professionals, or system barriers.

What does this study add?
► The only way to measure the contribution of the various factors is to include all in the same study.
► This strategy helped confirm an interplay between patient-related and physician-related factors, highlighting the importance of communication and information as main determinants of adherence.

How might this impact on clinical practice or future developments?
► These findings support the need to train clinicians on trustworthy doctor–patient relationships, shared decision making and on providing information on practical aspects.

INTRODUCTION

Non-adherence, defined as the extent to which a person's behaviour does not correspond with the agreed prescription,[1] is a common problem and has a significant impact on treatment efficacy and healthcare costs in patients with chronic diseases, such as rheumatoid arthritis (RA).[2–4]

The first problem in the study of adherence is the difficulty and variability of its definition and terminology. The term compliance, one of the first to be used and based on a purely clinical perspective, is defined as the 'degree to which the patient's behaviour coincides with medical recommendations' (not only treatments but also scheduled visits, health programmes, lifestyle modification, etc). However, the concept of adherence incorporates physician–patient collaboration in decision making, which includes the patient's 'active and voluntary participation in treatment adherence-related behaviour', accepted by mutual agreement, with a healthcare professional.[5]

The importance of patient involvement in decision making underlines the need to study the concept of adherence in chronic diseases. In RA, non-adherence can lead to treatment failure, delayed recovery, accelerated disease progression and the need for more aggressive treatment.[6–8] In addition, patients with RA often have associated comorbidity and thus are frequently polymedicated, which only worsens the situation of adherence.[9]

Knowledge of the factors underlying non-adherence is essential to design effective intervention strategies. Multiple barriers, defined as modifiable factors that limit or restrict adherence to a given regimen, can mediate treatment adherence. These barriers or factors can be grouped under (1) sociodemographic data; (2) patient characteristics,

including patients' beliefs and attitudes toward medication; (3) diseases; (4) treatments; (5) physician–patient relationship; and (6) relationship with the social and healthcare environments.[3][10–12]

Studies on adherence focus mainly on patient-related determinants, often neglecting other elements of the process, such as the attitude of the professionals, or system barriers. The combined contribution of all levels to adherence has seldom been quantified.[10] Our team conducted a systematic review[13] and several focus groups with the various stakeholders involved in the adherence process—that is, patients, nurses, physicians and pharmacists—with which we elaborated a list of major determinants of adherence. These factors affect patient and physician attitudes, and their components constitute the hypotheses for this study.

The main objectives of this longitudinal study were (1) to estimate the prevalence of medication adherence in patients with RA—overall and by whether the patient was on the first conventional disease-modifying rheumatic drug (csDMARD), second-line csDMARD (second csDMARD after the failure of the first one, for each patient), or biological disease-modifying rheumatic drug (bDMARD) or targeted synthetic disease-modifying rheumatic drug (tsDMARD) treatment; and (2) to study the association of adherence with factors related to the patient, the rheumatologist, the patient–doctor relationship, and the logistic factors, to better understand and quantify the contribution of the different levels to the burden of non-adherence.

METHODS

Design and population

This was a 6-month multicentre observational longitudinal prospective study. To obtain the necessary sample size and to facilitate the logistic of the study, 10 centres were selected at random from the list of tertiary or secondary care centres with rheumatology listed at the Spanish Society of Rheumatology. In general, the patients seen in hospital clinics are representative of all patients with the diagnosis under study, since the Spanish National Health System has universal access, and most rheumatology centres are connected to a hospital service. Although patients attending hospital clinics are somewhat more severe than those seen outside hospitals, the aforementioned conditions allow us to state that the probability of obtaining a representative sample of patients is very high.

Patients were then selected at each centre by systematic stratified sampling for 2 months, starting July 2019 (the last centre ended the study in November 2020). Every third patient of the day with RA was assigned to a stratum as defined by the current treatment: (1) first csDMARD, (2) second-line csDMARD and (3) bDMARD/tsDMARD. Strata had to be balanced at the centre level (33% per stratum). To participate in the study, patients were required to have a diagnosis of RA according to the European Alliance of Associations of Rheumatology and the American College of Rheumatology (EULAR-ACR) criteria,[14] and be treated with disease-modifying rheumatic drug (DMARDs), either bDMARDs, tsDMARDs or csDMARDs, irrespective of the activity or duration of their disease. All participants gave their written informed consent.

Variables and measurements

The primary endpoint was adherence at 6 months of follow-up, evaluated by the Compliance Questionnaire Rheumatology (CQR)[15–17] and the Reported Adherence to Medication (RAM) scale.[18] The CQR is a rheumatology-specific instrument to measure patient compliance to drug regimens. It consists of 19 items and reflects statements about drug-taking behaviour. The instrument is well accepted by patients, has adequate psychometric properties and has been validated against electronic medication event monitoring systems. The total score can vary from 0 (complete non-compliance) to 100 (perfect compliance).[15] The RAM scale is a four-item composite self-report scale that assesses two aspects of adherence behaviour: active non-adherence (eg, tendency to deliberately alter the dose of mediation) and passive non-adherence (eg, the tendency to forget to take medication). The total score ranges from 4 to 20 but can be standardised to obtain a scale between 0 and 100.[18] Adherence was defined as a score over 80% on both scales.[15]

Explanatory factors included (1) sociodemographic; (2) psychological: perception of the need for treatment and concerns with the Beliefs about Medicines Questionnaire (BMQ),[19] adjustment to expectations, feeling privileged by the treatment prescribed (yes/no), anxious or depressed mood (taking medication for anxiety or depression), feeling of support (Visual Analogue Scale (VAS)); (3) clinical: previous DMARDs, previous adverse events to RA medication (yes/no), comorbidity, disease activity with the Disease Activity Score with 28 joint counts (DAS-28)[20] and impact with the Rheumatoid Arthritis Impact of Disease index (RAID)[21 22]; (4) drug-related: route and mode of administration, posology and type of drug; (5) patient–doctor relationship: trust in the physician (VAS), information received (VAS), visit times, accessibility (VAS), participation in shared decision making (yes/no); and (6) logistic factors: accessibility to the drug, costs and distance to point of treatment. In addition, summary variables on the number of RA independent comorbidities and treatments were created. The information was collected separately from the patient (blinded to the rheumatologist) and the responsible rheumatologist; some variables were collected from both sides and cross-checked. All variables were measured at baseline and the 6-month follow-up visit.

In addition, we collected variables at the centre level, such as access to a rheumatology nurse, or the possibility to choose dates for infusion or collection of medication at the hospital pharmacy. The rheumatology nurse has a key role to improve and/or increase self-management, self-efficacy and effective coping with the disease to promote patient independence. The main nursing care roles are vigilance of physical and psychological symptoms, drug toxicity and comorbidities; and providing information about treatment recommendations and ensuring continuity of care by acting as a contact person for the patient.

A secure and certified online platform was developed to facilitate data collection and monitoring. Each investigator from the participating centres entered their patient's clinical and examination data into the online platform. Questionnaires completed by patients were filled in on paper and returned to their respective physicians in a sealed envelope, who sent them to a central facility where a data manager entered the data. Data on drug administration (dates of administration and delivery, coverage periods, etc) were obtained from medical and pharmacy records. All variables were measured at the initial visit and a final visit at 6 months. The total number of visits per patient was two.

Statistical analysis

The study sample was described by using summary statistics: mean, median, SD and IQR for continuous variables, and absolute and relative frequencies for categorical ones. Differences across the three treatment strata were refuted with parametric (analysis of variance) or non-parametric tests (Kruskal-Wallis, χ^2), according to the distribution of the variables.

The prevalence of adherence as per the working definition was estimated with 95% CIs using a Poisson distribution.

The association between baseline factors and 6-month adherence by the working definition (score >80% on the CRQ and the RAM scale) was initially explored by bivariate logistic regression models and quantified by OR with 95% CI.

Since the data have a hierarchical structure (patients nested in physicians), the observations are not independent, which prevents the use of the common regression models and forces the construction of models that take into account the correlation structure between patients treated by the same physician. For this purpose, multilevel logistic regression analysis was used with two hierarchical levels: patient and physician. The predictors of adherence were estimated using multilevel logistic regression models with the same dependent variable as before. The inclusion of predictor variables in the models was guided by the results of the previous bivariate analysis and the conceptual model. Random intercept models were used considering random variability in average patient adherence due to the effects of the higher grouping level (physician). The best model was selected based on Akaike's information criterion and the Bayesian information criterion.

The minimum target sample size was 150 subjects, as we expected to include at least eight variables in a full model. To account for loss due to follow-up, the sample was increased by 10%, thus aiming at 165 patients. Missing data were not imputed.

RESULTS

Participating centres had access to a rheumatology nurse. In most centres (62.5%), patients with hospital-administered medication could choose the time to pick up the drug, although in 50% they could not choose the time of drug administration. For infusions, the day hospital was shared with other specialities in 87.5% of the centres and had an average of 6.7±5.6 beds.

The 10 centres recruited 180 patients, 3 of whom were lost during follow-up (1 died and 2 had logistical problems due to the COVID-19 restrictions), yielding a retention rate of 98%. Table 1 shows the description of the sample, in total and by strata. The majority were women (76.7%) with a mean age of 60.8 years, brought up in Spain (90.3%), with primary or secondary education (79.7%), and living in a couple (76.7%). A fourth (25.6%) reported economic difficulties; 19.5% were active smokers; and the median score in the alcoholic habit questionnaire was 0.

The sample is characterised by low disease activity, with median joint counts of 0; mean erythrocyte sedimentation rate and C reactive protein (mg/dL) values of 18.3 and 0.40, respectively, and a patient global VAS in the last week of 4.0±2.9. The average DAS-28 was 2.32±1.06. The impact of RA, as defined by the RAID questionnaire, was 3.9. Regarding previous toxicity, 41.3% of the patients had presented previous adverse events that required a change in medication, and 16.7% were serious. The most frequent comorbidity was cardiovascular (47.8%), and the median number of concomitant treatments was 1. The percentage of patients taking steroids and non-steroidal anti-inflammatory drugs (NSAIDs) and steroids are 38.9% and 18.3%, respectively, without differences by treatment group. The time of evolution of the disease is 10.8±9.3 (longer for the bDMARD/tsDMARD).

In terms of psychosocial variables, as many as 19.5% of the patients stated they were depressed and, in general, rated their family support high (mean 8.6 in a 0–10 VAS). The scores about medication in the BMQ were high in both the needs (mean=20.6) and the concerns (mean=14.5) scales, and the majority of patients felt privileged to receive the prescribed medication (81.9%).

As to the patient–physician relationship and logistic variables, accessibility to the rheumatologist and trust in the professional were both rated very high (9.0 and 9.3, respectively, in 0–10 VAS). A vast majority of patients stated having agreed to their treatment with their physician (82.9%), and almost all patients considered the visit times to be adequate (94.8%). Also, the majority of patients found medication easy to use (92.8%) and did not fear it (only 16.3% expressed some concern) when they were asked these questions directly and not based on questionnaires like BMQ. The information received on different aspects of the treatment, such as efficacy, practical issues or adaptation to one's own needs was perceived as adequate (mean values around 8 on 0–10 VAS), although the perception of the adequacy of the information on toxicity was slightly lower (mean=6.8). In the opinion of the physicians, their patients had a high level of trust in them as professionals (mean=8.4) and in the treatment (mean=8.2), and they felt they had given adequate information on different aspects of the treatment (mean values above 8).

As per the stratified sampling, only 88 of the 180 studied patients received in-hospital treatment, which represents 49.2% of the sample. Most of them had the possibility of choosing the time to receive the treatment (88.4%) and have some kind of appointment reminder system (64.4%). On average, hospital treatment did not cause work-related problems (only 5.1% had problems). Hospital treatment had associated costs in 52.3% of the patients, with the centre being located less than 5 km from the patient's home in 47.3% of cases.

Comparisons across treatment strata

Some baseline differences were observed across treatment groups (table 1). As expected, a history of adverse events requiring medication change was more frequent in the groups other than the first csDMARD. In terms of clinical factors, there was no variability across the groups, except for the RAID score, which was also lower in this first group in comparison to the other more experienced ones, although the DAS-28 showed no statistical differences.

Interestingly, while rheumatologists did not think they had explained better or worse depending on the groups, the patient perception of the adequacy of information was better in terms of practical aspects and adaptation to needs in the group with bDMARD/tsDMARD than in the others.

For psychological factors, patients from the bDMARD/tsDMARD had a perception of need higher than the other groups (p=0.021).

No other differences were found in the rest of the treatment-related, patient–doctor relationship-related or psychological factors across groups.

Prevalence of adherence

Table 2 shows the prevalence data, overall and by treatment group, as well as the mean values of the scales that define this variable (CQR and RAM). The 6-month prevalence of adherence to DMARDs was estimated at 59.1% (95% CI 48.1% to 71.8%). By treatment group, the prevalence of adherence was 43.1% (95% CI 27.9% to 63.6%) for first csDMARD, 70.4% (95% CI 49.8% to 96.6%) for the second csDMARD and 64.4% (95% CI 45.6% to 88.4%) for bDMARD/tsDMARD.

Importantly, the period of adherence was calculated as the difference between the date of the last visit minus the first one, except in patients in whom a change in the treatment had been made after the first visit and the switching date was available (n=5). This period of measurement of adherence ranged from

Table 1 Baseline factors, total and by treatment group

Factors	Total (N=180)	First csDMARD (n=61)	Second-line csDMARD (n=57)	bDMARD/tsDMARD (n=62)	P value
Clinical factors					
Female sex	138 (76.7)	43 (70.5)	45 (78.9)	50 (80.6)	NS
Age (years)	60.7±12.3	62.1±14.3	59.8±12.5	60.3±10.0	NS
Swelling joints, P_{50} (P_{25}–P_{75})	0 (0–1)	0 (0–1)	0 (0–2)	0 (0–1)	NS
Painful joints, P_{50} (P_{25}–P_{75})	1 (0–2)	0 (0–2)	1 (0–3)	1 (0–3)	NS
Erythrocyte sedimentation rate (mm/hour)	18.3±17.7	17.3±15.4	21.4±22.7	16.4±14.1	NS
C reactive protein (mg/dL)	0.4±0.7	0.5±1.0	0.3±0.5	0.4±0.7	NS
Patient Global Assessment (0–10)	4.0±2.9	3.2±2.9	4.3±2.9	4.4±2.9	NS
Physician Global Assessment (0–10)	2.5±2.5	2.2±2.3	2.7±2.7	2.5±2.6	NS
DAS-28	2.32±1.06	2.10±0.80	2.57±1.19	2.32±1.13	NS
RAID*	3.9±2.7	3.1±2.7	4.3±2.7	4.1±2.6	0.04
Number of comorbidities	1.5±1.1	1.3±1.2	1.6±1.2	1.6±1.0	NS
Time of evolution (years)	10.8±9.3	8.8±9.5	9.4±8.2	13.9±9.3	†
Treatment-related factors					
Treatment agreed	146 (82.9)	48 (81.4)	45 (78.9)	53 (88.3)	NS
Prior adverse events (patient-reported)					†
Yes, tolerable	24 (13.4)	10 (16.7)	6 (10.5)	8 (12.9)	
Yes, required medication change	74 (41.3)	8 (13.3)	30 (52.6)	36 (58.1)	
Prior serious adverse events (from eCR)	30 (16.7)	3 (4.9)	16 (28.1)	11 (17.7)	‡
Number of concomitant treatments	1.6±1.3	1.4±1.4	1.7±1.2	1.7±1.1	NS
Steroids	70 (38.9)	19 (31.1)	24 (42.1)	27 (43.5)	NS
NSAIDs	33 (18.3)	10 (16.4)	9 (15.8)	14 (22.6)	NS
Administration is felt easy	167 (92.8)	54 (88.5)	52 (91.2)	61 (98.4)	NS
Fear of medicine	29 (16.3)	11 (18.6)	9 (15.8)	9 (14.5)	NS
Patient–doctor relationship					
Accessibility to rheumatologist (0–10)	9.0±1.5	9.0±1.6	8.8±1.3	9.3±1.4	NS
Trust in the rheumatologist (0–10)	9.3±1.3	9.2±1.5	9.0±1.4	9.6±0.9	NS
Patient trust in doctor (physician, 0–10)	8.4±1.1	8.5±0.9	8.2±1.2	8.4±1.2	NS
Patient trust in treatment (physician, 0–10)	8.2±1.3	8.5±1.1	8.0±1.4	8.2±1.4	NS
Time of visit					NS
Very short	4 (2.3)	1 (1.7)	1 (1.7)	2 (3.3)	
Suitable	165 (94.8)	55 (96.5)	54 (94.7)	56 (93.3)	
Very long	5 (2.9)	1 (1.7)	2 (3.5)	2 (3.3)	
Information is felt consistent	171 (96.6)	59 (96.7)	53 (96.6)	59 (98.3)	NS
Adequacy of information (patient, 0–10)					
Efficacy	7.9±2.2	7.6±2.1	7.7±2.4	8.6±2.1	‡
Toxicity	6.8±3.0	6.5±2.9	6.6±3.1	7.4±3.1	NS
Practical aspects	8.6±1.8	8.1±2.0	8.4±1.7	9.2±1.2	†
Adaptation to needs	8.0±2.0	7.5±2.3	7.8±2.0	8.8±1.5	†
Adequacy of information (physician, 0–10)					
Efficacy	8.5±1.1	8.5±1.0	8.4±1.3	8.6±1.0	NS
Toxicity	8.4±1.4	8.3±1.5	8.2±1.3	8.6±1.3	NS
Practical aspects	8.7±1.2	8.8±1.1	8.6±1.4	8.8±1.1	NS
Adaptation to needs	8.6±1.2	8.5±1.2	8.4±1.4	8.7±0.9	NS
Access to health professionals if doubts	164 (93.2)	57 (95.0)	50 (89.3)	57 (95.0)	NS
Psychosocial factors					
BMQ score§					
Need (0–25)	20.6±3.9	19.7±3.9	20.6±3.9	21.5±3.8	0.02
Concern/damage (0–25)	14.5±4.3	15.4±4.8	14.0±5.6	14.2±4.3	NS
Feel privileged with medication	145 (81.9)	46 (78.0)	43 (76.8)	56 (90.3)	NS
Anxiety/depression	34 (17.8)	10 (17.9)	12 (21.4)	12 (20.0)	NS
Family/social support (0–10)	8.6±1.9	8.4±2.2	8.3±2.0	9.0±1.4	NS

Data are expressed as n (%) or as mean±SD unless otherwise noted.
*RAID values range from 0 to 10 with higher scores indicating worse status.
†<.001.
‡<.01.
§Higher scores indicate stronger beliefs; values range from 5 to 50 on each scale.
bDMARD, biological disease-modifying antirheumatic drug; BMQ, Beliefs about Medicines Questionnaire; csDMARD, conventional synthetic disease-modifying antirheumatic drug; eCR, electronic clinical records; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; RAID, Rheumatoid Arthritis Impact of Disease Index; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

Table 2 Adherence after 6 months

Adherence variables	Total	First csDMARD	Second-line csDMARD	bDMARD/tsDMARD
Prevalence* (%) (95% CI)	59.1 (48.1 to 71.8)	43.1 (27.9 to 63.6)	70.4 (49.8 to 96.6)	64.4 (45.6 to 88.4)
CQR score, mean±SD	86.0±9.4	83.6±9.3	87.2±9.2	86.0±9.4
RAM score, mean±SD	80.6±25.8	80.6±22.9	80.5±27.9	80.9±26.9

*Defined as a score above 80% in the CQR and RAM scales.
bDMARD, biological disease-modifying antirheumatic drug; CQR, Compliance Questionnaire Rheumatology; csDMARD, conventional synthetic disease-modifying antirheumatic drug; RAM, Reported Adherence to Medication; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

0.23 months (a patient with a treatment change in the last month) to 12.5 months (in a patient whose visit was scheduled on the first day of the COVID-19 lockdown), that is, a much greater variability than expected, since the design established a 6-month follow-up period.

Predictors of adherence: bivariate analysis

In the bivariate analysis (table 3), the only clinical or treatment-related variables with which an association was found were the current treatment (OR=3.1 for second line csDMARDs and 2.4 for bDMARDs/tsDMARDs), in-hospital delivered treatment (OR 2.1) and having agreed on the treatment (OR=2.9). Taking NSAIDs also increased the probability of adherence (OR=2.4).

In the bivariate analysis, factors related to the patient–doctor relationship associated were the trust the patient had in his/her doctor (OR=1.7), patient-perceived adequacy of the information on treatment efficacy (OR=1.3) and on the possibility of adaptation to his/her needs (OR 1.4), the level of information adequacy as perceived by the doctor (all aspects with OR >1.2) and access to a health professional to consult doubts about treatment (OR=4.3).

Among the psychosocial factors, only feeling privileged by the medication was associated with adherence (OR=3.3).

In addition, the time to measure adherence had near to significance p value in the bivariate, and so it was decided to include in all models in the multivariate.

Predictors of adherence: multivariate analysis

The results of the multilevel logistic regression are shown in table 4. The null model examines the random variability in the adherence due to the grouping level (physician) when none of the possible independent variables is taken into account; that is, heterogeneity or unobserved variability; in this model, the variance at the physician level was 0.15.

Model 1 examines the relationship between adherence and individual (patient) level variables. According to this model, the main predictor of treatment adherence was the agreement on treatment between patient and physician, with an OR of 4.32 (p=0.008). Other important factors for the patient were the prescription of hospital-administered treatment (OR=2.54, p=0.023) and receiving information on the possibility of adapting it to their needs (OR=1.44 p=0.023).

Model 2 studies the effects of the higher grouping level (physician) on adherence, after controlling for the effect of individual patient variables. The results showed that the physician variables that influence adherence are the type of treatment prescribed and the trust that patient has in his/her doctor, according to the physician's opinion. Consequently, and in comparison to first-line csDMARDs, adherence is higher in second-line csDMARDs (OR=4.24, p<0.006) and bDMARDs/tsDMARDs (OR=3.39, p=0.023). Finally, the information provided to the patient on the efficacy, assessed by the professional, increases significantly the probability that the patient will be adherent to treatment (OR=1.60, p=0.028).

Consequently, in the final and complete model, the variables that explain adherence are agreement on treatment between patient and physician (OR=4.29), receiving information on the possibility of adapting the treatment to the patient's needs (OR=1.54), the type of treatment prescribed (second-line csDMARDs and bDMARDs/tsDMARDs (OR=4.72 and OR=3.50, respectively), the information provided by the professional on treatment efficacy (OR=1.71) and the use of NSAIDs (OR=4.21). These effects are independent of baseline disease activity measured by the DAS-28.

DISCUSSION

This study has shown that medication adherence in patients with RA in Spain is not 100% despite achieving good control of disease and that having patient–physician agreement on the treatment, the type of treatment prescribed—in favour of second-line csDMARDs and bDMARDs/tsDMARDs—and the patient feeling privileged by the medication received are consistent predictors of adherence.

A major difficulty in studying adherence is the variability of its definition and measurement. There is no single method to measure adherence, so it is generally recommended to use several simultaneously.[23] Most authors distinguish between adherence and persistence (time during which patients follow their prescription) and use the medication possession ratio (MPR)—only measurable in health systems with centralised pharmacy records linked to clinical records, or for drugs administered at the hospital—and survival time as measurement parameters for both concepts.[3] The majority of studies use questionnaires, among which the most commonly used are the Haynes-Sackett[24] and the Morisky-Green questionnaires.[25] In the case of rheumatic diseases, there is a specific questionnaire, the CQR, used in this study and validated in patients with inflammatory rheumatic diseases against a medication electronic monitoring system.[15–17] Therefore, a first cautionary message about any study of adherence is to first understand the definition and measure used; otherwise, comparisons will be difficult.[26] We used a double source definition based on complementary questionnaires, which makes our estimates of adherence stricter than using a single questionnaire or measure. Although we also included the MPR as a secondary measure of adherence, we have not shown the results here for the sake of clarity and because a large proportion of patients did not have a reliable measure due to differences in pharmacy procedures and information systems.

Roughly half of the patients could be considered good adherers in our study. These values are in line with the WHO estimate of adherence in chronic diseases, around 50%.[1] In studies on rheumatic diseases, the prevalence of adherence varies as much as from 9% to 94%, owing to differences in the definitions and methods used to measure adherence, but also

Table 3 Predictors of adherence, bivariate analysis

Factors	n	OR (95% CI)	P value
Sociodemographic factors			
Female sex	171	0.90 (0.44 to 1.85)	0.775
Age (per year increase)	171	0.98 (0.96 to 1.01)	0.270
Level of education	165		
Primary		1	
Secondary		1.66 (0.80 to 3.42)	0.170
College		1.37 (0.37 to 5.10)	0.634
University		0.86 (0.33 to 2.19)	0.747
Economic difficulties	167	0.93 (0.45 to 1.90)	0.840
Living in a couple	167	1.38 (0.67 to 2.84)	0.381
Smoking	165		
Never smoker		1	
Ex-smoker (>1 year)		0.65 (0.32 to 1.31)	0.225
Active smoker		0.75 (0.32 to 1.76)	0.507
Clinical factors			
Swelling joints	171	0.96 (0.81 to 1.13)	0.606
Painful joints	171	0.98 (0.89 to 1.08)	0.686
Erythrocyte sedimentation rate (mm/hour)	149	1.02 (1.00 to 1.04)	0.098
C reactive protein (mg/dL)	154	1.34 (0.79 to 2.29)	0.274
Patient Global Assessment (0–10)	169	1.04 (0.94 to 1.15)	0.451
Physician Global Assessment (0–10)	171	0.93 (0.82 to 1.04)	0.214
DAS-28	147	1.17 (0.85 to 1.60)	0.329
RAID	167	0.99 (0.89 to 1.11)	0.918
Comorbidities (number)	171	1.02 (0.79 to 1.33)	0.852
Time of evolution (years)	156	1.00 (0.96 to .03)	0.912
Treatment-related factors			
Current treatment	171		
First-line csDMARD		1	
Second-line csDMARD		3.13 (1.43 to 6.85)	0.004
bDMARD/tsDMARD		2.39 (1.13 to 5.03)	0.022
Glucocorticoids	171	1.11 (0.59 to 2.08)	0.754
NSAIDs	171	2.41 (1.01 to 5.75)	0.046
In-hospital treatment	170	2.14 (1.14 to 4.01)	0.017
Treatment agreed	167	2.88 (1.26 to 6.58)	0.012
Prior adverse events (patient-reported)	170		
No		1	
Yes, but tolerable		1.07 (0.42 to 2.67)	0.891
Yes, with changes		1.89 (0.96 to 3.71)	0.065
Prior serious adverse events (from eCR)	171	1.21 (0.52 to 2.84)	0.654
Concomitant treatments	171	1.03 (0.81 to 1.31)	0.796
Administration is felt easy.	171	0.70 (0.20 to 2.44)	0.580
Fear of medicine	169	0.81 (0.35 to 1.87)	0.627
Patient–doctor relationship			
Accessibility to rheumatologist (0–10)	167	1.12 (0.91 to 1.38)	0.278
Trust in the rheumatologist (0–10)	165	1.14 (0.90 to 1.44)	0.289
Patient trust in doctor (physician, 0–10)	171	1.71 (1.25 to 2.33)	0.001
Patient trust in treatment (physician, 0–10)	169	1.22 (0.97 to 1.54)	0.095
Time of visit	165		
Very short		1	
Suitable		1.48 (0.20 to 10.7)	0.701
Very long		4.0 (0.211 to 75.6)	0.355
Information is felt consistent.	168	0.73 (0.13 to 4.09)	0.718
Adequacy of information (patient, 0–10)			
Efficacy	170	1.25 (1.08 to 1.45)	0.002
Toxicity	168	1.06 (0.95 to 1.17)	0.281
Practical aspects	169	1.14 (0.96 to 1.36)	0.137
Adaptation to needs	166	1.35 (1.14 to 1.59)	0.001
Adequacy of information (physician, 0–10)			
Efficacy	171	1.72 (1.26 to 2.35)	0.001
Toxicity	171	1.44 (1.10 to 1.87)	0.007

Continued

Table 3 Continued

Factors	n	OR (95% CI)	P value
Practical aspects	170	1.40 (1.07 to 1.84)	0.014
Adaptation to needs	171	1.34 (1.02 to 1.75)	0.033
Access to health professionals if there are doubts	167	4.27 (1.09 to 16.7)	0.037
Psychosocial factors			
BMQ score			
Need (0–25)	170	1.03 (0.95 to 1.11)	0.487
Concern/damage (0–25)	170	0.97 (0.91 to 1.03)	0.318
Feeling privileged by the medication	168	3.26 (1.45 to 7.37)	0.004
Anxiety/depression	163	0.73 (0.33 to 1.63)	0.447
Family/social support (0–10)	165	1.09 (0.93 to 1.28)	0.284
Time to measure adherence (months)	171		0.064
<6		1	
≥6		1.98 (0.96 to 4.07)	

bDMARD, biological disease-modifying antirheumatic drug; BMQ, Beliefs about Medicines Questionnaire; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying anti-rheumatic drug (c, conventional; eCR, electronic clinical records; NSAID, non-steroidal anti-inflammatory drug; RAID, Rheumatoid Arthritis Impact of Disease Index.

on the interventions and populations studied.[13 27–33] The average disease activity is, however, very low in our study, which would be counterintuitive, given an adherence prevalence of only 50%. A plausible explanation is that the working definition in our study was very stringent compared with other studies.

As our study also confirms, adherence is greater among bDMARD/tsDMARD users than among first-line csDMARD users[6 8 13 30 32 33]; however, although one could think this is due to the control of medication by the hospital—both bDMARDs and tsDMARD are delivered at the hospital pharmacy or are administered in-hospital[12]—users of second-line DMARDs also showed better adherence in comparison to first line. This could be in relation to the use of previous treatment that failed, making the patient feel privileged of having alternatives, an explanation that is also supported by our results.

A systematic review quantified over 700 factors involved in adherence.[31] This illustrates the complexity of the problem

Table 4 Multilevel analysis: predictors of adherence from patient and physician

Fixed effects	Model 1 (patient)	Model 2 (physician)
Individual level (patient)		
Treatment agreement	4.32 (1.48 to 12.6) (0.008)	4.29 (1.41 to 13.0) (0.010)
Information: adaptation	1.44 (1.05 to 1.98) (0.023)	1.54 (1.09 to 2.17) (0.015)
Information: practical aspects	0.74 (0.53 to 1.03) (0.071)	0.66 (0.45 to 0.96) (0.030)
In-hospital treatment	2.54 (1.08 to 6.01) (0.033)	
Time to measure adherence		
<6 months	1	1
≥6 months	3.91 (1.34 to 11.4) (0.012)	3.85 (1.22 to 12.2) (0.022)
DAS-28	1.20 (0.80 to 1.78) (0.375)	1.17 (0.77 to 1.78) (0.471)
Grouping level (physician)		
Treatment		
First-line csDMARDS		1
Second-line csDMARDS		4.72 (1.61 to 13.9) (0.005)
bDMARDs/tsDMARDS		3.50 (1.14 to 10.8) (0.029)
Information: efficacy		1.71 (1.10 to 2.64) (0.016)
NSAIDs		4.21 (1.25 to 14.2) (0.021)
Constant	0.060	0.001
Random effects		
σ^2 (variance)	0.32	0.16

Cells include ORs with 95% CIs and p values unless otherwise noted.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

and the challenge in designing one-fit-all intervention strategies.[34][35] Many studies focusing on predictors, however, have not approached the problem at multiple levels at a time, like ours. According to the WHO multidimensional framework, there are five dimensions of factors influencing medication adherence: social and economic factors, health system-related factors, therapy-related factors, illness-related factors and patient-related factors.[1] In our study, we tried to include factors from all dimensions and to measure the contribution of the different levels. For this, we used models that allowed us to quantify the magnitude of the variation in therapeutic adherence that depends on patient-related factors and the variance corresponding to the higher aggrupation level (physician).

Regarding socioeconomic factors, we could not see any association with gender, age, level of education or having economic difficulties. This could reflect the health system in Spain, with universal coverage of visits, admissions and medications, highly accessible in all the territories of Spain. In countries with other types of health systems, with no universal coverage or high payment for health services, economic factors may impact directly adherence and are a source of long-term concern, even for health.[36] Another socioeconomic aspect could be work-related problems due to scheduled visits or due to the medication having been administered in-hospital. We did not detect an association as well, although it could be because only a third, or less, of the patients, had to go to the hospital pharmacy to collect the medication.

Health system-related factors, such as information about the frequency of follow-up, patient–provider communication, perceived quality of healthcare delivery, level of treatment information and a good relationship with the treating physician, all influence adherence.[29][37][38] Patients likely increase trust in the treatment efficacy if they feel they can rely on and trust the treating physician. Our results confirm these data as the privilege by the medication received, the agreement with the doctor, the good access to health professionals and the received information about different aspects of treatment increase, all of which increase treatment adherence.

Different factors related to therapy, such as type of medication used, the complexity of the treatment regimen, side effects and duration of medication, have been associated with adherence.[27][30] As already mentioned, our results support an increased adherence in second-line csDMARDs and bDMARDs/tsDMARDs, but other treatment-related factors, such as the number of medications or the ease of use, might not contribute as much to the collective adherence in the specific case of RA as the other highlighted factors. The results also show a significant effect of NSAIDs on adherence. These drugs control pain very well in the acute phase, producing an immediate response that improves the patient's clinical situation, which could reinforce treatment maintenance and increase adherence.

Patient-related factors, such as type of disease, duration, disease activity, functional disability, depressive symptoms and other comorbidities, have been studied with inconsistent results.[10] Except for the RAID in the bivariate analysis, no other clinical variables of the patient predict who will be adherent in our study. Only psychological variables, that is, the belief in the need for treatment and feeling privileged by the treatment prescribed, showed an association. Both can be modified by educating the patient in his/her disease and the treatment.

Special mention is the strong association of adherence with having agreed on the treatment. The shared decision between patient and physician about treatment is the first principle of the treat-to-target strategy.[39] Communication with the patient to clarify and agree on the treatment goal and the means to attain it is of utmost importance.[40] On the other hand, shared decision making is a right and a principle of adherence.[34] If a patient has not agreed on a specific treatment, we cannot say that the patient is not adherent, as adherence is, by definition, a volunteer decision based on an agreed prescription.[1][34] We tend to blame the patient for not being adherent, something understandable as it is a behaviour; however, there are many barriers that we can modify to help the patient. Instead of focusing on developing reminders, or assessing adherence, we should focus on training physicians on communication skills, making sure they approach the shared decision-making process efficiently and provide the practical information the patient demands.[34] Thus, our results support the concept that adherence is not just an individual characteristic but rather a complex and dynamic experience in which each part—patient, healthcare physician and the community—plays a specific role.[27][34]

Our study is not without limitations. In longitudinal studies, obtaining reliable and unbiased estimates depends, to a large extent, on complete follow-up. Because the intended follow-up in the study design was 6 months, we expected low attrition. There are two considerations: first, only three patients were lost to follow-up, representing a retention rate of 98%; second, there was significant variability in the follow-up time and adherence measurement period. We tried to control for the possible effect of these differences by introducing this variable in the multivariate models. Although we included the results of this variable in the tables, we should not draw any conclusions about its association with adherence. Also, the sample is very homogeneous, with all centres having access to a nurse in rheumatology and with a large majority of patients with low disease activity. Although with the sampling design we tried to reach a representative sample, some may find this with limited external validity. Consistently, however, studies on RA in Spain show very good control of the disease.[41][42] This control, in principle, would facilitate adherence. However, despite the use of a very stringent definition of adherence, 41% of the sample was non-adherent to treatment. Therefore, we believe that the prevalence of adherence is representative of the RA population in our country.

Finally, the hypothesis of the study was that adherence is influenced by psychological, communicational and logistic factors to a greater extent than by the sociodemographic and clinical characteristics of the patients. Our results confirm the hypothesis, since the factors that determine treatment adherence, besides the line of treatment, are those derived from the doctor–patient relationship, that is, agreement on the treatment, and receiving information on practical aspects, independently of disease activity. Our task now is to focus on improving these aspects.

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