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RESEARCH ARTICLE

Adherence to Antirheumatic Treatments in Patients with Chronic Inflammatory Rheumatic Disease

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Abstract

Objectives: To evaluate the prevalence of non-adherence to corticosteroid, disease-modifying antirheumatic drug (DMARD) and biologic treatments in patients managed for chronic inflammatory rheumatic disease (CIRD), to identify socioeconomic and demographic factors, and factors linked to the disease or treatment affecting adherence, to look for possible correlations between non-adherence and negative opinions about drugs, doctors or medicines and between non-adherence and negative perceptions of disease and health in general.

Methods: A medical record review study performed between January 2014 and December 2017 on patients followed for CIRD and treated with biologics and/or with DMARDs and/or corticosteroids for at least three months. The patients completed a questionnaire concerning adherence to treatment comprising the Morisky-Green adherence questionnaire (MMAS-4) the medication possession ratio (MPR) for each immunomodulatory treatment underway, and questionnaires relating to the patient's opinions about drugs (18-item BMQ), disease perception (BIPQ) and health in general (PHQ-2). Poor treatment adherence was defined as an MPR < 80% and/or a score of 2/4 for the MMAS-4. Patients with an MPR < 100% were included in secondary uni- and multivariate analyses.

Results: Complete responses were obtained from 177 patients, 70% of whom reported general adherence to their treatment. The overall adherence rates were 69.6% for biologics, 66.3% for DMARDs and 63.6% for corticosteroids. In multivariate analysis, being male and having multiple antirheumatic treatments emerged as factors independently associated with poor treatment adherence.

Conclusion: Two factors predictive of poor treatment adherence were identified: being male and multiple treatments. Therapeutic education is particularly recommended for this at-risk population.

Keywords: Ankylosing Spondylitis; Rheumatoid Arthritis; Psoriatic Arthritis; DMARDs (synthetic); DMARDs (biologic); Adherence

Introduction

Adherence to treatment is the willingness of the individual to manage his or her disease. It combines two notions: observance and persistence [1]. Observance is the capacity of the individual to follow the treatment correctly. It concerns the taking of any drugs prescribed, but also the overall behavior of the patient with respect to treatment. Persistence takes into account the notion of duration and respect for recommendations and the intake of prescribed drugs [2]. These concepts are of particular importance in chronic diseases.

There is currently no "gold standard" for measuring adherence to treatment. Several methods are used, the most reliable being based on the determination of a clinical or biological marker, variations of which reflect the application of a recommendation, or treatment intake. Other more sophisticated methods, such as the use of electronic pills, have also been developed [3]. Some simpler methods appear to be just as reliable, such as the checking of injections delivered by nurses or the patient's relatives, or the cross-checking of prescriptions against drug dispensing and health insurance reimbursement data [4,5,6].

Finally, declarations made by patients on self-completed questionnaires are also widely used in a number of diseases. There are five principal questionnaires for evaluating treatment adherence: the compliance questionnaire for rheumatology (CQR-19) [7], which has been validated but is very long and therefore difficult to use in everyday practice, the medication adherence rating scale (MARS-10/MARS-9) [8], which has been adapted for patients with rheumatoid arthritis [9], but has only one threshold defining poor adherence and has not been validated for general use in rheumatology, the medication adherence self-report inventory (MASRI) [10,11], both versions of the Morisky Green adherence scale (MMAS-4/8) which has been validated for use in rheumatology, but there is still no validated version of the four-item form in French [12,13] and medication possession ratio (MPR) which is a visual analog scale score expressed as a percentage of the prescribed treatment actually taken over the last three months (0-100%) [2].

The principal objective of this study was to evaluate the prevalence of adherence in the principal CIRD encountered. The secondary objective was to identify factors favoring poor adherence, which could serve as levers for action to reverse the trend.

Materials and Methods

We performed a medical record review study, from January 2014 to Juin 2017, at the rheumatology department of the Centre Hospitalier Sud Francilien of Corbeil-Essonnes. In accordance with the législation at the time of the study, no ethics committee approval was required for this non interventional declaratory survey. The 'Jardé' law was only published in France on November 17, 2016. It became effective from that date. Written consent signed by the patient for the use of his data was routinely collected.

Inclusion criteria

The included patients were followed for rheumatoid arthritis (RA; ACR/EULAR criteria, 2010), spondylarthritis (AS; ASAS criteria), psoriatic arthritis (PsA; CASPAR criteria) or systemic lupus erythematosus (SLE; ACR criteria, 1997). They were seen in consultations or during day or conventional hospitalization. For inclusion, patients had to have an intravenous or subcutaneous biologic treatment and/or oral or injected Disease-modifying antirheumatic drugs (DMARD) treatment, and/or corticosteroid treatment of at least three months' duration.

Questionnaire-based evaluation of the prevalence of adherence and of the factors influencing treatment adherence

The patients were asked to complete self-reported questionnaires. The patients completed two questionnaires relating to treatment adherence: the MMAS-4 and the MPR.

Good adherence to treatment was defined as an MPR > 80% and an MMAS-4 score of 1/4 or lower. An MPR below 80% or an MMAS-4 score of 2/4 or higher was considered to indicate poor adherence.

For evaluation of the factors likely to influence treatment adherence, we recorded demographic and socioeconomic factors and factors linked to the disease, and the patients were asked to complete the following three questionnaires:

The specific Beliefs about Medicines Questionnaire (BMQ) [15.16], which contains two scales of five items each for evaluating the strength of belief that the medicines prescribed are essential to control the disease and to explore the patient's concerns relating to

the potential adverse effects of treatment. The responses of the patients to the specific medical items are evaluated with a five-point Likert scale (1 = strongly disagree to 5 = strongly agree). The scores obtained for each section are added together, generating a total global score of 10 to 50. Higher scores indicate a greater faith in the drugs prescribed.

The Brief Illness Perception Questionnaire (BIPQ) [17] has eight items, each scored from 0 to 10. A cognitive disease can be represented in five ways, which are analyzed in five of the items of this scale: consequences (how much does your disease affect your life?), chronology (how long do you think your disease will last?), personal control (what control do you have over your disease?), control by treatment (how much do you think your treatment can help you with your disease?) and identity (to what extent do you feel the symptoms of your disease?). This scale also includes two items dealing with emotional representations: concern (how concerned are you about your disease?) and emotional responses (to what extent does your disease affect you emotionally?). The final item is a standalone element concerning the patient's comprehension of his or her disease. The score for this item ranges from 1 (disease considered to be benign) to 10 (disease considered to be very serious).

Depressive symptoms were evaluated with the Patient Health Questionnaire-2 (PHQ-2) [18], which contains two questions: 1) Do you have little interest in or derive little pleasure from things? 2) Are you sad, depressed or desperate?). For each item, the possible responses are "not at all" (score 0), "on some days" (score 1), "more than half the time" (score 2) and "almost every day" (score 3). The total score is the sum of scores for the two items, and therefore ranges from 0 to 6.

Patients with a poor knowledge of the French language were helped by a doctor or nurse from the unit, enabling them to complete the questionnaires correctly.

Statistical analysis

Qualitative variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as medians and interquartile ranges. The analysis was performed for each of the two definitions of poor treatment adherence retained (MPR < 80% and MPR < 100%). Adherent and non-adherent patients were then compared in Fisher's exact tests for qualitative variables and Wilcoxon tests for quantitative variables.

The factors associated with poor treatment adherence were investigated by logistic regression analysis. Variables for which the odds ratio had a p-value below 0.25 in univariate analysis were included in the multivariate model, with stepwise forward and backward selection.

All tests were two-tailed, with an alpha risk of 5%. The analysis was performed with R software (R version 3.5.0 ©2018 The R Foundation for Statistical Computing).

Results

The questionnaires were completed in a satisfactory manner by 177 patients: 127 women (72%) and 50 men (28%). The mean age of these patients was 56 years [44-65 years]; 71% were living with a partner and 29% were single. Just over half (57%) had a low level of education (did not complete high school) and 43% had a high level of education (higher education).

More than half the patients met the ACR/EULAR 2010 criteria for RA (57%, n=100), about a third (32%, n=57) met the ASAS criteria for AS and 11% (n=20) were followed for other rheumatic or connective tissue diseases (PsA n=18, and SLE n=2). More than half the patients were treated with DMARDs (n=98), and 44% (n=77) were taking corticosteroids. The vast majority of patients were treated with biologics (n=165; 93%). The biologics were administered subcutaneously in 40% of patients (n=71) and intravenously in 60% (n=106).

The patients were on monotherapy in 32% of cases (DMARD or biologic), doble therapy in 44% of cases (DMARD + biologic) or triple therapy in 24% of cases (biologic + DMARD + corticosteroid). The scores obtained for the specific BMQ, PHQ-2 and BIPQ scales were noted (Table 1). A PHQ-2 score ≥3, considered suggestive of depression, was found in 42% of patients.

Questionnaire	Median score [IQR]
Specific BMQ	
Biologics	36 [31-40]
DMARDs	35[31-39]
Corticosteroids	36[31-50]
Mean	36[31-39]
PHQ-2	2[1-4]
BIPQ	6.12 [5.5-6.62]

BMQ: Beliefs about Medicines Questionnaire; PHQ-2: Patient Health Questionnaire-2; BIPQ: Brief Illness Perception Questionnaire; DMARDs: Disease-modifying antirheumatic drugs

Table 1: Global BMQ, PHQ-2 and BIPQ scores

Study of the prevalence of treatment adherence

If we define treatment adherence as an MPR of more than 80%, corresponding to the administration of more than 80% of the treatment prescribed over a period of three months, then 70% of our patients may be considered adherent. The adherence rates were 69.6% for biologics (i.v. or s.c.), 66.3% for DMARDs and 63.6% for corticosteroids.

The percentage of patients not adhering to biologic treatment was higher for those with subcutaneous administration (35.2%), but there was no significant difference in adherence to treatment between administration routes. The simultaneous use of several treatments favored poor adherence (p=0.037). Adherence rates were 82.4% for monotherapy, but only 58.3% for doble or triple therapy.

Treatment adherence rates were higher for women than for men (p=0.038). Treatment adherence was better among patients living with a partner than among those who were single or living alone (p=0.048).

No significant differences were found in among diseases (RA, AS, PsA and SLE).

Mean BMQ, PHQ-2 and BIPQ scores were similar between adherent and non-adherent patients. Adherence was good for 65.3% of patients with a depressive tendency based on PHQ-2 score (at least 3).

If we wish to be more stringent and define good adherence to treatment as an MPR of 100%, corresponding to the administration of 100% of the treatments prescribed, over a period of three months, then the prevalence of adherence decreases from 70% to 66.1%. The sex and family situation of the patient are no longer independent factors affecting treatment adherence, and only monotherapy with biologics remains significantly associated with good treatment adherence.

Analysis of the factors linked to poor treatment adherence

In multivariate analysis, being male and having multiple treatments (doble or triple therapy) were associated with poor treatment adherence (p=0.007, OR=3.06, 95% CI [1.37-7.03], and p=0.005, OR=4.16, 95% CI [1.72-11.01], respectively).

Age, level of education, profession, family situation, type of CIRD, subcutaneous administration and BMQ, PHQ-2 and BIPQ scores had no effect on adherence to treatment (Table 2).

Variable	Univariate analysis		Multivariate analysis	
	Crude OR [95% CI]	*p*-value	Adjusted OR [95% CI]	*p*-value
Age	0.99 [0.97-1.02]	0.59		
Sex		0.034		0.007
Female	1		1	
Male	2.17 [1.06-4.44]		3.06 [1.37-7.03]	
Level of education		0.54		
Pre-high school	1			
Higher education	0.81 [0.42-1.57]			
Profession		0.93		

Retired/unemployed	1			
Manager/employee	0.95 [046-1.91]			
Laborer/craftsman	1.16 [0.40-3.12]			
Family situation		0.043		0.059
Living with a partner	1		1	
Single	2.03 [1.02-4.05]		2.09 [0.97-4.51]	
Disease		0.70		
RA	1			
AS	0.77 [0.37-1.58]			
PsA/SLE	1.16 [0.40-3.14]			
Subcutaneous administration	1.51 [0.78-2.92]	0.22		
Number of treatments		0.03		0.005
Monotherapy	1		1	
Doble therapy	2.84 [1.28-6.73]		4.16 [1.72-11.01]	
Triple therapy	2.27 [0.90-5.92]		3.21 [1.20-9.13]	
Treatment				
Biologics	1.30 [0.37-6.06]	0.70		
DMARDs	1.50 [0.78-2.92]	0.23		
Corticosteroids	1.71 [0.90-3.30]	0.10		
Specific BMQ				
Biologics	1.02 [0.96-1.07]	0.57		
DMARDs	0.96 [0.90-1.02]	0.17		
Corticosteroids	0.98 [0.92-1.05]	0.64		
Mean BMQ	1.00 [0.94-1.05]	0.91		
Depression score				
PHQ-2	1.07 [0.90-1.27]	0.43		
PHQ-2 ≥ 3	1.57 [0.81-3.06]	0.18		
Disease perception				
BIPQ global score	1.10 [0.80-1.51]	0.57		

RA: rheumatoid polyarthritis; AS: ankylosing spondyloarthritis; PsA: psoriatic arthritis; SLE : systemic lupus erythematosus ; DMARDs: disease-modifying antirheumatic drugs; BMQ: Beliefs about Medicines Questionnaire; PHQ-2: Patient Health Questionnaire-2; BIPQ: Brief Illness Perception Questionnaire

Table 2: Uni- and multivariate analyses of demographic, socioeconomic and psychological factors and of factors linked to the disease likely to affect adherence to treatment

Discussion

This study highlights that 70% of CIRD patients are adherent to their treatment. The percentage of patients not adhering to biologic treatment was higher for those with subcutaneous administration, but there was no significant difference in adherence to treatment between administration routes. Two factors predictive of poor treatment adherence were identified: being male and multiple treatments.

The vast majority of prevalence studies are not exhaustive. They generally investigate adherence for a particular disease, mostly RA, and/or for a particular drug class (biologics or synthetic DMARDs) [6.3].

This is the first study of adherence to all antirheumatic treatments (corticosteroids, DMARDs and biologics) for the principal forms of CIRD (RA, AS, PsA and SLE).

The rate of adherence to biologic treatment in our study was 69.6%. Mena-Vazquez et al. [19], in a study using the same instruments (MMAS-4 and MPR > 80%) on a population of similar size to that studied here (178 patients) but composed exclusively of patients followed for RA, reported an adherence rate of 76.9%. In our study, statistical analyses showed adherence to treatment to be no higher in patients with RA than in patients with the other CIRD.

Betegnie et al. [20] reported an adherence to biologics of 85.2% for CIRD. This prevalence is higher than ours because their method of assessment was based on a non-validated self-reported questionnaire.

For the route of administration for biologics (intravenous or subcutaneous), we found that a higher proportion of the patients were non-adherent in the subcutaneous administration group (35.2%), but the difference between the two groups was not significant.

Published values for adherence to DMARDs range from 30% to 107% [21]. This diversity of values can be explained by the heterogeneity of the populations studied, and differences in the definition of adherence and the methods used to assess it [22].

Surprisingly, we found no significant difference in adherence between biologics, DMARDs and corticosteroids.

Finally, the good adherence to treatment observed here may be due to most of our patients being followed in the hospital environment, with the support of a therapeutic education team.

In two recent studies, several factors were found to be likely to influence adherence to biologics. These factors included a low level of disease activity, self-administration of treatments (i.e. subcutaneous injections performed by the patient at home), the use of more than one line of biologic treatment, a poor opinion of treatments and poor medicosocial support [19,20].

Other factors have also been described as not favoring good adherence to DMARD treatment. These factors include young age, depressive mood, presence of several comorbid conditions, poor medicosocial support and the concomitant use of several treatments [23].

In our study, two factors had a statistically significant negative influence on adherence to treatment: being male (OR=3.06) and the simultaneous use of several treatments (OR=4.16).

By contrast to the studies cited above, age, subcutaneous administration, and social context had no effect on adherence.

The different methods used in these studies may account for this discordance.

A few studies have focused on mental factors and their influence on adherence to treatment in CIRD. De Thurah et al. [24] observed a significant association between a strong belief in the efficacy of methotrexate (MTX) and adherence to this treatment.

In the study by Betegnie et al. [20], negative opinions of biologics and a lack of medical and social support had major consequences for treatment adherence. Our study shows that the various scores evaluated (BMQ PHQ-2 and BIPQ) had no significant effect on adherence to treatment.

In a systematic literature review who was performed in CIRD, educational interventions had the highest level of evidence (8/13) . However, it is worth noticing that an important heterogeneity exist between the studies across the modalities (individual or collective structered programs) and the actors (physicians, pharmacists and nurses) of these educational interventions [25].

Recommendations for the assessment and optimization of adherence to DMARD in CIRD were developed by a group of rheumatologists in France in 2019 based on literature reviews and expert consensus. Key points include that adherence should be assessed at each outpatient visit, at least using an open question especially if the treatment target is not reached and before any therapeutic change. They highlight the role of patient information and education, and patient/physician shared decision [26].

Finally, we remind that non adherence in CIRD is associated with a higher disease activity which may induce intensification of the treatment strategy and therefore it may lead to an increase of costs [25].

Conclusion

Poor adherence to treatment can have many consequences in CIRD, including the persistence of high levels of disease activity, a risk of disability and structural progression and treatment intensification due to the supposed inefficacy of the treatments received. Being male and using multiple treatments are factors associated with poor adherence. Further studies are required to identify other factors associated with a risk of non-adherence to treatment.

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