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Discordance between doctor and patient assessments and non-adherence to subcutaneous biological drugs

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Abstract

To estimate the agreement level between patient and physician assessment of disease activity and to explore whether agreement is associated with adherence to subcutaneous (SC) biological drugs in rheumatoid arthritis (RA). Cross-sectional study of RA patients who had been prescribed a SC biological drug in the past 12–18 months was performed. Patients and physicians global disease activity on visual analogue scale (VAS) were collected. Disagreement was defined as an absolute difference ≥ 3 points between VAS scores. Adherence was assessed by the Medication Possession Ratio (MPR), considering adherence an MPR > 80%. We analysed 360 patients of whom 15.5% presented disagreement with their physicians. The mean patient global VAS was 5.75 ± 1.8 (median 5.5 [5–7]) in the disagreement group versus 2.7 ± 2.2 (median 2 [1–4]) in the agreement group ($p < 0.001$). There were also differences in physicians global VAS between groups ($p = 0.01$). The non-adherence to SC biological drugs rate was 10.7% and 14.5% in the disagreement and agreement groups ($p = 0.45$). No association between adherence and discordance was found. Disagreement in the global disease activity between patients and physicians was detected in 15.5% of patients. In general, patients perceived higher disease activity. No associations between patient-physician disagreement in VAS and adherence were observed.

Keywords Adherence · Compliance · Biological drugs · Patient perspective · Disease activity · Discordance

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Abbreviations

CI	Confidence intervals
DAS28	Disease activity score
ICC	Intraclass correlation coefficient
MPR	Medication possession ratio
OR	Odds ratio
RA	Rheumatoid arthritis
Sc	Subcutaneous
VAS	Visual analogue scale

Introduction

Adherence to a medication regimen is "the extent to which patients take medications as prescribed by their health providers" [1]. Poor adherence to long-term therapy for chronic diseases, including rheumatoid arthritis [RA], is a major health problem worldwide [2]. In developed countries, mean adherence rates to long-term therapy for chronic illnesses are estimated in approximately 50%, with even lower rates in developing countries [2, 3]. Adherence in patients with RA is not well understood, in contrast with other chronic

diseases [4], with rates ranging from 30 to 93% depending on the study [2, 4].

Adherence to therapy is an individual patient behaviour that is difficult to objectively measure [5]. Common barriers to adherence on the patient side include forgetfulness, other priorities, decision to omit doses, lack of information or understanding, and emotional factors or beliefs [6]. Physicians contribute to patients' poor adherence by showing a poor interaction with them and by prescribing complex regimens, or poorly explained regimens and/or side effects [7, 8].

Biological drugs have changed the course of RA, but information on their non-adherence rate is scarce [9]. In the ARCO (Study on Adherence of Rheumatoid arthritis patients to subCutaneous and Oral drugs) study, we observed a 14.3% rate of lack adherence for new subcutaneous (SC) biological drug [defined as a Medication Possession Ratio (MPR) of ≤ 80%]. We performed a post hoc analysis aiming to explore how patient-physician disagreement by the global visual analogue scale (VAS) may explain non-adherence to SC biological drugs.

Patients and methods

The ARCO study was a multicentre, non-interventional retrospective study involving 42 hospitals throughout Spain between May 2014 and September 2015 [9]. The study was approved by all corresponding clinical research ethics committees.

Selection of participating subjects

Adult patients with established RA (EULAR-ACR 2010 criteria) and who had started a new SC biological drug in the last 12–18 months were screened consecutively and invited to participate. The exclusion criteria were: difficulties for participation (rejection, mental disorders, or linguistic difficulties that prevent adequate completion of questionnaires); concomitant clinical conditions having a serious or unfavourable status advising against, in the judgment of the investigator, participation in the study; participation in other studies and/or clinical trial at enrolment and lack of possibility to obtain reliable registries from pharmacy on dispensation and return of biological subcutaneous vials.

Procedures, data collection and definitions

Medical records reviews, as well as direct interviews and physical examination served to collect sociodemographic characteristics, disease activity (DAS28) and treatment information. Comorbidities were collected according to the ICD-9 code (International Classification of Diseases).

Patients and physicians independently scored disease activity on VAS. Patients and doctors were asked to indicate numerically from 0 to 100 their global situation of the disease, being 0 no symptom and 100, the worst situation. Disagreement was defined as a difference of ≥ 3 (this cut-off figure was chosen from the 2.5 reference that can be found in other studies [10, 11] and given that for our study, VAS values were taken as an integer number).

To evaluate non-adherence to SC biological drugs, individual-patient MPR was calculated based on the recommended dose and the hospital pharmacy registries. The MPR is the ratio between the number of days covered by the medication and the total number of days of follow-up.

$$\begin{aligned}\text{MPR} = (&\text{Number of effective} - \text{treatment days} \\ &- \text{patient has taken the drug} \\ &/ \text{number of days theoretically covered by the medication prescribed}) \times 100\end{aligned}$$

Non-adherence was defined as a MPR ≤ 80% [9].

Statistical analysis

Summary measures (mean, median, standard deviation, interquartile range, and percentages) were used to describe the sample. Clinical and socio-demographic characteristics between agreement groups were tested through mean or median differences, in the case of non-normal variables (t for Student and ANOVA or U for Mann–Whitney and Kruskal–Wallis), and proportions (Chi square) for quantitative and qualitative variables, respectively. No imputation was done for missing data.

The association between adherence and disagreement was studied using bi and multivariate logistic regression models with covariates-adjustments. Odds ratio (OR) and 95% confidence intervals (CI) are provided.

The concordance between patient and doctor was further tested with the intraclass correlation coefficient (ICC) from an ANOVA.

Results

The sample comprised 360 patients (mean age: 55.3 ± 12.4 years, 279 [77.5%] women). Regarding VAS assessment, 182 patients (50.5%) scored higher than their

Table 1 Sociodemographic characteristics in relation to the agreement or disagreement in the VAS score (in 3 or more points)

Variables	VASp = VASd ($n = 304$)	VASp ≠ VASd ($n = 56$)	p
Sex, *n* (%)			
Men	64 (21.0)	17 (30.4)	0.12
Women	240 (78.9)	39 (70.0)	
Age, mean (SD)	54.5 (12.5)	59.0 (11.4)	**0.01**
Race, *n* (%)			
White	281 (92.4)	55 (98.2)	0.11
Other	55 (7.6)	1 (1.8)	
RA duration, mean (SD); median [IQR]	11.4 (12.2); 8.4 [3.7–15.7]	9.4 (8.8); 6.1 [3.0–15.7]	0.18
Educational level			
Primary school	124 (40.8)	34 (60.7)	**0.02**
Secondary school	64 (21.0)	11 (19.6)	
Professional studies	56 (18.4)	7 (12.5)	
University degree	60 (19.7)	4 (7.1)	
Comorbidity, *n* (%)			
Yes	189 (62.2)	43 (76.8)	**0.03**
No	115 (37.8)	13 (23.2)	
Depressive syndrome or anxiety/insomnia			
Yes	75 (24.7)	18 (32.1)	0.24
No	229 (75.3)	38 (67.9)	
Classification of disease activity, *n* (%)			
Remission	150 (53.8)	13 (24.1)	**< 0.0001**
Low disease activity	53 (19.0)	15 (27.8)	
Moderate disease activity	65 (23.3)	25 (46.3)	
High disease activity	11 (3.9)	1 (1.8)	
DAS[a] 28 m mean (SD); median [IQR]	2.6 (1.2); 2.5 [1.8–3.4]	3.2 (1.1); 3.1 [2.6–4.0]	**0.0003**
Frequency of administration			
1/every week	134 (44.0)	26 (46.4)	0.496
1/every 2 weeks	120 (39.5)	18 (32.1)	
1/month	50 (16.4)	12 (21.4)	

Values in bold show statistical significance

VASp patient visual analogue scale, *VASd* doctor visual analogue scale, *RA* rheumatoid arthritis, *DAS* disease activity score

[a]Disease activity definition: remission: disease activity score (DAS < 2.6); low disease activity (2.6 to < 3.2); moderate disease activity (3.2 to < 5.1) and high disease activity: DAS ≥ 5.1

physicians, 156 (43.3%) scored equal, and 22 (6.1%) scored lower than their doctors. Considering the definition of disagreement (difference ≥ 3 points), there were 56 (15.5%) cases of disagreement and 304 (84.4%) of agreement. Of the 56 discrepancies, only 4 (7.1%) patients scored lower than their physicians, whilst 52 (92.8%) scored 3 or more points higher.

Comparison of demographic data through agreement groups is displayed in Table 1. In the disagreement group, patient were slightly older, had lower educational level and more comorbidities. Besides, a low or moderate disease activity was more frequent in this group (low disease activity 27.8% vs 19.0%; moderate disease activity 46.3% vs 23.3%, Table 1). The mean patient-VAS was 2.7 (± 2.2), and the median 2 [interquartile range (IQR) 1–4] in the agreement group and 5.7 (± 1.8) median 5.5 (IQR 5–7) ($p < 0.001$) in the disagreement group, while physician-VAS was, respectively, 2.2 (± 2.0) (median = 2, IQR = 1–3) and 2.7 (± 1.8) (median = 2, IQR = 2–3) ($p = 0.01$).

The percentage of patients with non-adherence to their SC biological drug was 10.7% in the disagreement group and 14.5% in the agreement group ($p = 0.450$). Regression analysis showed no association between adherence and VAS disagreement (Table 2). Monthly dosing of the SC biological drug was associated with better adherence whilst need of induction therapy was associated with lower adherence rate.

The ICC between patient and physician VAS was 70% (95% CI 45.4–81.9). Greater difference was evident among intermediate scores, while the least difference occur among extreme values (Fig. 1).

Table 2 Bi and multivariate logistic regression models with covariates-adjustments

	Bivariate model		Multivariate model (adjusted)	
	OR (CI 95%)	*p*	OR (CI 95%)	*p*
Sex				
Men	1			
Women	1.03 (0.51–2.07)	0.93		
Age	1.00 (0.97–1.02)	0.78		
Race	0.61 (0.22–1.71)	0.35		
Comorbidities	1.17 (0.64–2.15)	0.60		
Depressive syndrome or anxiety/insomnia	2.06 (0.93–4.57)	0.07	2.05 (0.91–4.61)	0.08
Agreement/disagreement	1.41 (0.57–3.50)	0.45	1.26 (0.50–3.17)	0.62
Need of induction of SC biological drug	0.55 (0.28–1.07)	0.08	0.42 (1.18–0.97)	**0.04**
Frequency of administration				
1/every week	1			
1/every 2 weeks	1.25 (0.67–2.34)	0.08	1.85 (0.84–4.10)	0.12
1/month	3.10 (1.04–9.25)	**0.04**	4.19 (1.21–14.54)	**0.02**

Values in bold show statistical significance

Factors related to adherence to the biological medication

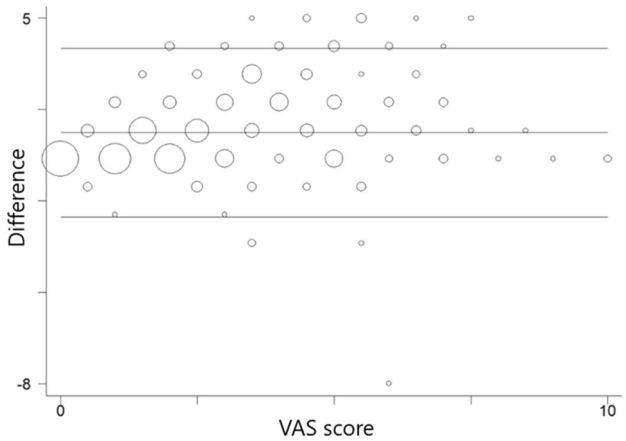

Fig. 1 Bland Altman graphic showing the concordance between VAS scores of patients and doctors

Discussion

In this work, we have attempted to explore the relationship between disease perspective (from both the physician's and the patient's point of view) and adherence. Other studies have evaluated discordance through other measures (questionnaires, or direct questions). Our analysis shows a low rate of disagreement in the perception of disease activity between patients and physicians. Most of the disagreement was due to higher values in the patients VAS compared to physicians VAS. Almost two thirds of patients with disagreement had mild or moderate activity according to DAS28.

In our opinion, this finding may suggest that different aspects in the disease evaluation that are important to patients might be overlooked by physicians. Thus, a patient-doctor disagreement should prompt further assessments of patients' status before taking a therapeutic decision. The self-evaluation of patients by VAS is, therefore, vital, because physicians' score may require a "correction factor" since according to our results, those cases with significant differences in the VAS have a higher mean DAS28.

On the other hand, poor adherence severely compromises treatment effectiveness and safety outcomes, making adherence a critical issue for patient quality of life and health economics [5–7]. Previous studies have suggested that reducing disagreement between patients and physicians may be an important goal to improve adherence. As this hypothesis has not been proven [10], we decided to explore non-adherence to SC biological drugs, although we could not detect an association between disagreement in the perception of disease activity and adherence to the SC biological drugs. However, discordance in the VAS may not be a good surrogate for the patient-physician communication or empathy, both of which are better candidates for determinants of adherence [1, 12]. The variables associated to better adherence in the multivariate analysis had been described in the primary publication [9] and the introduction of the level of agreement in the model did not alter this associations.

A greater burden of comorbidities is associated with reduced adherence and persistence over time, although this data should be taken with caution, since studies conducted on the relation between age, comorbidities and adherence in rheumatic patients have yielded contradictory results [13–15].

In view of the results obtained in our multivariate analysis, it may be important for patients with poor adherence to

consider the different dosages currently available for RA, as had already been seen in other studies [16]. Neither age, nor comorbidity showed an association with adherence in our study.

This study has some limitations; mainly the study design (cross-sectional) and that, there is no optimal method to measure adherence to SC biological drugs. Its cross-sectional design prevents conclusions on the causality of the associations we observed. In addition, the dynamic nature of adherence may make it change over time. There is no optimal method to measure adherence to SC biological drugs [17]; simply collecting the medication from the hospital pharmacy might not be an accurate measure of use as it does not imply that the patient subsequently injected the drug. As only patients with 12 to 18 months of continuous and stable treatment were recruited, it is likely that mainly patients with a good response were included. Another fact is that these data may not be applicable to other types of medications. In addition, using the VAS as the single measure of disagreement may be a too narrow approach. Finally, the limited number of patients disagreeing with their doctors may have led to a small statistical power, and so will move us to reformulate the question and the study.

Conclusions

Disagreement between patients and physicians in the assessment of disease activity using a VAS does not seem frequent, and occurs predominantly in patients with low or moderate disease activity according to DAS28, a very common RA-subgroup in daily clinical practice. Disagreement does not appear to be an important determinant of non-adherence. Further studies should look at other aspects of patient-physician relationship, especially those that may be modifiable.

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Availability of data and material The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions TO was responsible con analysis, interpretation and also for drafting the manuscript. LC, MJA and LCC were responsible for conception, design, analysis and interpretation of data. AUA and JCA were responsible for acquisition of data and interpretation of data. All the authors made substantial contributions and approved the final content of the manuscript. MSD was involve in the design, analysis, and interpretation of the data and writing of the report.

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Compliance with ethical standards

Conflict of interests Teresa Otón and Loreto Carmona's institution (InMusc) has received consultancy honoraria from MSD. Outside this project, InMusc has received consultancy honoraria from Abbvie, Astellas, BMS, Eisay, Gebro Pharma, Leo Pharma, Lylly, Novartis, Pfizer, Roche, Sanofi-Aventis and UCB Pharma. Maria J. Arteaga and Luis Cea-Calvo are full time employees at Merck Sharp & Dohme of Spain. The remaining authors declare no conflict of interest.

Ethics approval and consent to participate Ethics was approved by the Clinical Research Ethics Committee of Hospital Virgen de la Arrixaca. All subjects consented to participate in the study.

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