Non-adherence to subcutaneous biological medication in patients with rheumatoid arthritis: a multicentre, non-interventional study

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Abstract

Objective

To evaluate non-adherence to prescribed subcutaneous biologicals in rheumatoid arthritis (RA) patients in Spain.

Methods

ARCO (Study on Adherence of Rheumatoid Arthritis patients to SubCutaneous and Oral Drugs) was a multicentre, non-interventional retrospective study involving 42 rheumatology clinics from representative hospitals throughout Spain. The primary objective was to assess the percentage of patients (aged ≥18 years with an established RA diagnosis) with non-adherence to prescribed subcutaneous biologicals using clinical records and hospital pharmacy dispensing logs as the primary information sources. Adherence was assessed using the Medication Possession Ratio (MPR). Additionally, patients completed the Morisky-Green Medication Adherence Questionnaire.

Results

A total of 364 patients (77.5% females, mean age 54.9 years, median RA duration since diagnosis 7.8 years) were enrolled in ARCO. Non-adherence (MPR ≤80%) was reported in 52/363 evaluable patients (14.3%), and was lower in patients receiving initial monthly drug administration (6.4%) than with weekly (17.4%; p=0.034) or every two weeks (14.4%; p=0.102) administration. By multivariate analysis, non-adherence was positively associated with RA duration above the median and with using induction doses. Monthly administration, compared to weekly administration, was inversely associated with non-adherence. Age, gender, order of administration, and changes in the interval of administration, showed no association with non-adherence. Compared with the MPR, the Morisky-Green questionnaire performed poorly in detecting non-adherence.

Conclusion

Non-adherence to the prescribed subcutaneous biological drug occurred in 14.3% of patients with RA. Patients using the most convenient administration period (i.e. monthly) had better adherence than those using more frequent dosing schedules.

Key words

adherence, biological, non-adherence, rheumatoid arthritis, subcutaneous

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Introduction

Access to safe and efficacious medications is necessary for the successful treatment of disease; however, in itself, access to medications is insufficient. Poor adherence to long-term therapy for chronic diseases (including hypertension, infectious diseases, and rheumatoid arthritis) is a major problem worldwide (1). In developed countries, mean adherence rates to long-term therapy for chronic illnesses are estimated to be approximately 50%, with even lower rates in developing countries (1, 2).

Poor adherence to long-term therapies severely compromises treatment effectiveness and safety outcomes, making adherence a critical issue in population health from the perspective of patient quality of life and health economics (3). Indeed, non-adherence to drug therapy has been shown to increase mortality, hospital admissions, morbidity, and results in increased costs (3-5). Interventions aimed at improving adherence would provide a significant positive return on investment through primary prevention (of risk factors) and secondary prevention of adverse health outcomes (1).

Strategies to enhance patient adherence have focused on factors which include: simplifying regimen characteristics; imparting knowledge; modifying patient beliefs; patient communication; leaving the bias (*e.g.* gender, race, sociodemographics); and evaluating adherence (6). Simplification of treatment regimens (*e.g.* reducing the number of pills taken daily) has been shown to improve adherence in a range of chronic diseases including hypertension, heart failure, and human immunodeficiency virus infection (7-9).

Studies on adherence to classical and biological disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatic diseases have reported suboptimal adherence rates, although with highly variable results. Some authors have reported adherence rates of 30–80% for patients with rheumatoid arthritis receiving DMARD therapy (10). A 2009 systematic review on adherence in different rheumatic diseases included 11 studies conducted in patients with rheumatoid arthritis (11). Adherence rates were variable according to the type of medication (49%–68% for salicylates and non-steroidal anti-inflammatory drugs; 65% for steroids; 59% for DMARDs; 81% for sulfasalazine; 55–64% for methotrexate; 68% for etanercept; and 81% for infliximab) (11). Similarly, in more recent reviews of adherence in patients with rheumatoid arthritis, variable results were also obtained for different therapies (12), with adherence rates of approximately 80% reported for different biological DMARDs (13).

However, to date, limited information is available regarding non-adherence to subcutaneous biological drugs in patients with rheumatoid arthritis, with most of the information coming from administrative databases and/or an evaluation of secondary non-adherence (*e.g.* discontinuation of therapy after filling a prescription) rather than primary non-adherence (*e.g.* failure to fill the index prescription) (14-16).

Medication adherence can be assessed using numerous subjective (*e.g.* self-reporting, physicians' assessment), direct (*e.g.* biomarkers), or indirect (*e.g.* pharmacy refill, tablet counts, electronic monitors, questionnaires) measurements, each with potential advantages or disadvantages (12). Measurement of adherence in patients with rheumatoid arthritis can be complicated further in the case of biological drugs because these compounds have dosing regimens and dosing frequencies that may change during treatment.

Therefore, at present, and despite recognition that treatment non-adherence is a common problem, solid conclusions cannot be drawn regarding the magnitude of non-adherence to subcutaneous biologicals in rheumatic diseases due to the use of different definitions, designs, populations, treatments, and measurement methods. The current study reports non-adherence rates to prescribed subcutaneous biologicals in patients with rheumatoid arthritis, with data obtained directly from clinical records and hospital pharmacy dispensing logs in Spain.

Patients and methods

The ARCO study (Study on Adherence of Rheumatoid Arthritis patients

to SubCutaneous and Oral Drugs) was a multicentre, non-interventional retrospective study involving 42 rheumatology clinics from representative hospitals throughout Spain. The study was approved by the corresponding clinical research ethics committees. Patients were recruited between May 2014 and September 2015. The primary study objective was to assess the percentage of patients with a lack of adherence to prescribed subcutaneous biological drugs using clinical records and hospital pharmacy dispensing logs as the primary sources of information.

Selection of participating subjects

Patients from rheumatology hospital clinics were screened consecutively to reduce inclusion bias, and were included in the study after signing an informed consent form. The study included patients aged ≥18 years with an established diagnosis of rheumatoid arthritis according to EULAR-ACR criteria, who had been prescribed a new subcutaneous biological drug 12 to 18 months before the study visit and had an identifiable follow-up period of at least 12 months. The subcutaneous biological drug could be the first (naïve), second or third (switches) biological agent received by the patient. To be valid for the study, patients had to have been treated with the same biological drug during the study period, but patients with changes made to the interval of administration were not excluded. Patients were excluded if they rejected participation, had mental disorders or linguistic difficulties preventing adequate understanding and completion of questionnaires or, according to investigator judgment, a serious or unfavourable status precluding study participation. Patients who were participating in other studies and/or clinical trials at enrolment or during the retrospective study period were also excluded. Hospital sites at which there was no possibility of obtaining reliable registries from the hospital pharmacy on the dispensation and return of biological medication were also excluded from the study.

Procedures

After inclusion of the subject in the study, data collection was carried out in a structured manner based on a direct interview, physical examination, review of the medical history and review of biological drug dispensing logs from the hospital pharmacy. Demographic data, educational level, working status, smoking status and risk of alcoholism (AUDIT questionnaire) were recorded. Assessment of rheumatoid arthritis status included the DAS-28 calculated using the erythrocyte sedimentation rate or the C-reactive protein concentration. The following data regarding the subcutaneous biological drug were obtained: initial dosing schedule (weekly, every other week or monthly), use of induction doses (yes/no), device (syringe, pen, other), periods of interruption during the administration of the subcutaneous biological drug due to medical reasons (start/end dates) changes in the initial dosing schedule (dates), and the order of administration of the subcutaneous biological drug (first, second or third biological drug). Comorbidities were collected according to the ICD-9 code (International Classification of Diseases). Patients responded to the Morisky-Green Medication Adherence Questionnaire (4-question version) (17) and completed the Spanish version of the Beliefs about Medicines Questionnaire (18).

Evaluation of the primary objective

The primary objective of the ARCO study was to assess the percentage of patients who were non-adherent to the subcutaneous biological medication dosing scheme prescribed by the rheumatologist. Adherence was assessed retrospectively from the information available in the hospital records; for this purpose, the Medication Possession Ratio (MPR) during the study period was calculated for each patient using the following formula:

MPR = (number of days actually covered by the medication administered by the patient/number of days of the study period –theoretically covered by the medication prescribed-) × 100

A patient was defined as having a lack of adherence if the MPR value was ≤80%.

The first day of the study period was the day that the patient administered the first injection of the biological medication after prescription by the physician, and the last day was the day before the first injection outside the study period. The length of the study period was the difference (in days) between the last day and the first day. In the event that the patient had interruptions in the administration of the biological drug (due to incident infection, surgery, or other reasons), the number of days during which the drug was interrupted was subtracted from the length of the study period to obtain the actual number of days that should have been covered by the prescribed medication. Due to differences in dosing schemes and interruption periods, the length of the study period for each patient could differ.

The number of days of the study period that were actually covered by the medication administered by the patient was calculated according to the prescribed dosing schedule and the number of vials taken by the patient from the hospital pharmacy during the study period. In the Spanish National Health System, the hospital pharmacy is the only place from which patients can collect the prescribed medication, and they can only collect it monthly or every other month from the same hospital where it was originally prescribed, and only when previous dispensed medication has been used. Information on the vials collected by the patient is tracked in the hospital pharmacies using drug dispensing logs. The dosing schedule initially prescribed, need for induction doses, and changes in the dosing schedule (*i.e.* increasing or shortening of the administration interval), were taken into account to calculate the period actually covered by the taken medication.

Statistical analysis

Previous studies have described differing percentages for the lack of adherence to subcutaneous and oral drugs. A recent systematic review reported a lack of adherence in one-third of rheumatoid arthritis patients; however, a wide range of variation was reported among studies (12). Therefore, we took a conservative approach, using 50% as the percentage to calculate sample size. For an expected 50% lack of adher-

ence, assuming a confidence interval (CI, level 1-alpha) of 95% and 5% precision, the calculated sample size was 384 patients. The 363 patients recruited and validated for the study allows 5% precision for the frequency of non-adherence found in the study.

For the description of the sample, we used measures of central tendency and dispersion (mean, median, standard deviation, interquartile range) for continuous variables, and distribution of percentages for categorical variables. The Student's *t*-test or ANOVA was used to compare continuous variables (expressed as mean ± standard deviation [SD]), while categorical variables were compared using the chi-squared test. Chi-squared test, linear trend chi-squared test, or Fisher exact test, was used for the comparison of proportions. No imputation was done for missing data.

The primary variable (non-adherence to subcutaneous biological drug) was assessed using the MPR with an 80% cut-off point to define lack of adherence (*i.e.* an MPR ≤80% identifies a lack of adherence). The percentage of non-adherence is provided with the 95% CI. A logistic regression analysis was used to determine the variables associated with lack of adherence. Odds ratio (OR) and 95% CIs are provided. The performance of the 4-item Morisky-Green adherence scale was compared against the MPR. For this purpose, the results of the 4-item Morisky-Green adherence scale were dichotomised to "high" or "moderate-low" adherence, and compared to the MPR results (adherent *versus* non-adherent patients). The percentage of agreement and the Cohen's kappa coefficient were calculated to correct for the agreement expected by chance, with the following interpretation: poor (<0), slight (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–0.99). The R version 3.1.3 Statistical Package was used for the statistical analysis.

Table I. Characteristics of the 364 patients included in the ARCO study.

Age, years	Mean (SD)	54.9 (12.5)	
Rheumatoid arthritis duration*, years	Median (IQR 25–75)	7.8 (3.4-15.7)	
DAS-28 at biological drug initiation*	Mean (SD)	4.7 (1.2)	
		Number	Proportion
Sex	Men	82	22.5%
	Women	282	77.5%
Race	Caucasian	340	93.4%
Smoking*	Smoker	92	25.8%
	Ex-smoker	178	50.0%
	Never-smoker	86	24.2%
Alcoholism risk (AUDIT)	Yes	24	6.6%
Educational level*	Primary school	161	44.4%
	Secondary school (graduated)	75	20.7%
	Professional studies	63	17.4%
	University degree	64	17.6%
Working status*	Currently working (out of home)	161	44.4%
	Home care	44	12.1%
	Unemployed	34	9.4%
	Retired	99	27.3%
	Disabled for work	21	5.8%
	Student	4	1.1%
Comorbidities	At least one comorbidity	261	71.7%
	No comorbidities	103	28.3%

IQR: interquartile range; SD: standard deviation.
*Information not available in the following cases: rheumatoid arthritis duration (4 patients), DAS-28 at biological drug initiation (74 patients), smoking status (8 patients), educational level (2 patients), working status (1 patient).

Results

Descriptive data

Three hundred and sixty-four patients were enrolled in the study: 282 women (77.5%), 82 men (22.5%), with a mean age of 54.9 years (SD 12.5). Other demographic characteristics and comorbidities are summarised in Table 1. The median duration of rheumatoid arthritis since diagnosis was 7.8 years (interquartile range 25–75 [IQR]: 3.4 to 15.7). According to DAS-28 values, 49.9% of patients were in remission (DAS-28 <2.6), 19.9% had low disease activity (2.6 to <3.2), 26.6% had moderate activity (3.2 to <5.1), and 3.6% had high disease activity (≥5.1). Apart from the subcutaneous biological drug, most patients (77.2%) were taking oral drugs for rheumatoid arthritis, and 31.6% were being treated with subcutaneous non-biological DMARDs.

The initial interval of administration prescribed for the subcutaneous biological drug was weekly in 161 patients (44.2%), every two weeks in 140 (38.5%) and monthly in 63 (17.3%). The subcutaneous biological drug was the first, second or third drug for 56.9%, 27.5% and 15.6% of patients, respectively. Patients were either using a syringe (59.9%) or a pen device (40.1%). The mean duration of treatment with the current subcutaneous biological drug was 14.7 months (SD 2.1). There were 49 patients (13.5%) with at least one period of therapy interruption due to medical reasons, and in 16 patients (4.4%) the interval of administration was changed by the treating physician during the studied period.

Non-adherence to subcutaneous biological drugs

The primary objective was evaluable in 363 patients; one patient did not have conclusive pharmacy drug-dispensing registries. According to such registries, 52 patients had an MPR ≤80% and were deemed to be non-adherent to the prescribed dosing schedule (14.3%; 95% CI: 11.1–18.3). There were no differences in the percentage of non-adherence by age ranges, gender or other sociodemographic factors, such as level of education, smoking habit, alcohol intake, employment status, or in patients with or without comorbidities or different

Table II. Percentage of patients non-adherent to subcutaneous biological drugs by demographic characteristics and rheumatoid arthritis characteristics.

		Percentage of non-adherence (%)	*p*-value
Age (quartiles)	Q1 (≤48 years) (n=96)	14.6	0.942
	Q2 (>48 to ≤56 years) (n=95)	13.7	
	Q3 (>56 to ≤63 years) (n=85)	12.9	
	Q4 (>63 years) (n=87)	16.1	
Sex	Men (n=82)	14.6	1
	Women (n=281)	14.2	
Race	Caucasian (n=339)	13.9	0.522
	Other (n=24)	20.8	
Smoking habit	Smoker (n=92)	10.9	0.337
	Ex-smoker (n=177)	14.1	
	Never-smoker (n=86)	18.6	
Alcoholism risk (AUDIT)	Yes (n=24)	16.6	0.970
	No (n=339)	14.2	
Educational level	Primary school (n=161)	16.8	0.411
	Secondary school (graduated) (n=75)	14.7	
	Professional studies (n=63)	7.9	
	University degree (n=63)	14.3	
Working status	Currently working (n=160)	13.1	0.654
	Other (n=202)	15.4	
Comorbidities	At least one comorbidity (n=260)	13.5	0.496
	No comorbidities (n=103)	16.5	
Number of medication units per day (overall)	0–2 (n=133)	18.0	0.124
	>2 (n=230)	12.2	
RA duration	≤7.82 years (n=179)	11.2	0.104
	>7.82 years (n=180)	17.8	
Type of device	Syringe (n=218)	14.7	0.934
	Pen-device (n=145)	13.7	
Concomitant non-biological DMARD therapy	No (biological drug in monotherapy) (n=27)	19.2	0.397
	Yes (n=336)	14.0	
Induction dose	Yes (n=74)	21.6	0.068
	No (n=289)	12.5	
Periods of interruption	Yes (n=49)	16.3	0.833
	No (n=314)	14.0	
Changes in the interval of administration	Yes (n=16)	25.0	0.378
	No (n=347)	13.8	
Order of administration	First (n=206)	13.1	0.658
	Second (n=100)	17.0	
	Third (n=57)	14.0	
Number of medication units per day (for RA)	0–1 (n=199)	16.1	0.293
	>1 (n=164)	12.2	
Subcutaneous DMARD for RA	Yes (n=248)	14.5	1
	No (n=115)	13.9	

DMARD: disease-modifying anti-rheumatic drug; RA: rheumatoid arthritis.
Information not available in the following cases: smoking status (8 patients), educational level (1 patient) working status (1 patient), rheumatoid arthritis duration (4 patients).

amounts of daily medication (Table II). The percentage of non-adherent patients was lower in those with an initial monthly administration of the biological drug (6.4%; 95% CI: 2.5–15.2) than in patients with weekly (17.4%; 95% CI: 12.3–24.0; p=0.034) or every two weeks (14.4%; 95% CI: 9.5–21.9; p=0.102) administration (Fig. 1), and slightly more frequent in those receiving induction doses (Table II). No differences were observed between patients who used syringes or pen devices, in patients who did or did not have periods of treatment interruption, and in those with or without changes in the interval of administration (Table II), or in patients with different amounts of rheumatoid arthritis medication. The percentage of non-adherent patients was higher, though non-significantly, in those with longer rheumatoid arthritis duration (Table II). There were no differences in the percentage of non-adherence with regard to the results of the Beliefs about Medicines Questionnaire. Rheumatoid arthritis activity assessment through DAS-28 yielded similar results in adherent and non-adherent patients. Mean DAS-28 before treatment initiation was 4.7 (SD 1.2) and 4.5 (SD 1.1) in adherent and non-adherent patients, respectively (p=0.302). At the study visit, mean DAS-28 was 2.8 (SD 1.2) and 2.7 (SD 1.2), respectively (p=0.544), with similar decreases in the DAS-28 (2.0 [1.4] and 1.9 [1.4], respectively, in 243 adherent and 41 non-adherent patients with data available, p=0.719).

Multivariable analysis

Variables associated with non-adherence were assessed using a multivariable model that included age, gender, rheumatoid arthritis duration, administration interval, use of induction doses, order of administration, and changes in the administration interval during the treatment period (Table IIIa). Four patients did not have data available for duration of rheumatoid arthritis and were excluded. In the resulting model, based on 359 patients, non-adherence was positively associated with rheumatoid arthritis duration above the median, whilst not using induction doses, and every two weeks or monthly administration, compared to weekly administration, appeared to be inversely associated with non-adherence (Table IIIb). Age, gender, order of administration, and changes in the interval of administration, showed no association with non-adherence.

Non-adherence and results of the Morisky-Green test

The 4-item Morisky-Green test yielded 76.7% of patients classified as highly-adherent and 23.3% as non-adherent (22.7% as moderately-adherent, 0.6% as low-adherent). Figure 2 shows the distribution of patients according to the MPR results and Morisky-Green

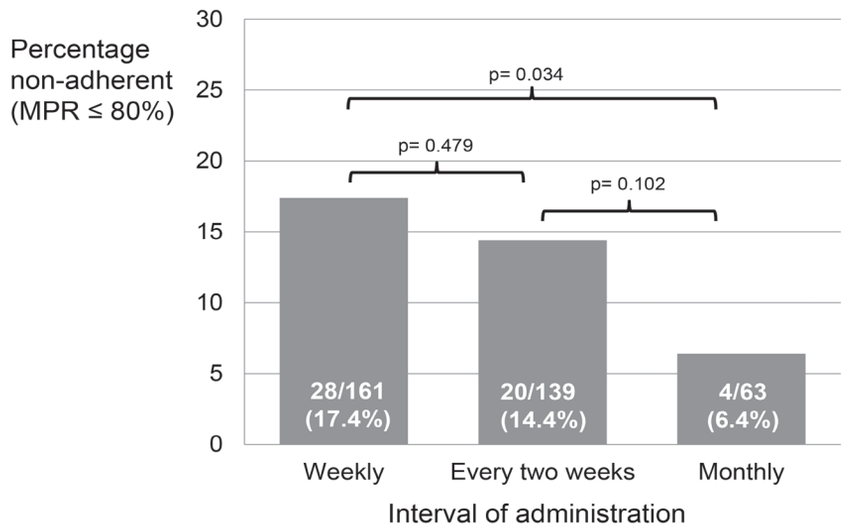

Fig. 1. Percentage of non-adherent patients (MPR ≤80%), according to the administration interval.
MPR: medication possession ratio.

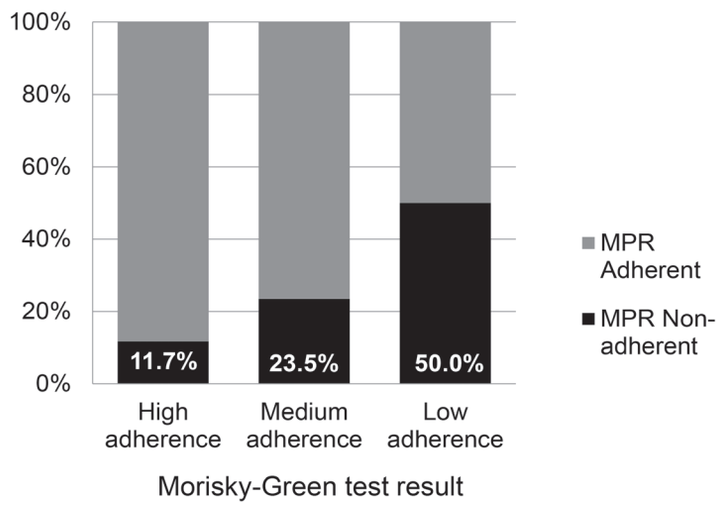

Fig. 2. The distribution of adherent and non-adherent patients according to the MPR and Morisky-Green test results.
MPR: medication possession ratio.

questionnaire results. The percentage of non-adherence according to the MPR was significantly lower in patients classified as adherent with the Morisky-Green compared with in those classified with moderate or low adherence (p=0.005). The performance of the Morisky-Green questionnaire to detect lack of adherence, compared to the MPR, is shown in Table IV. The percentage of agreement in the diagnosis of adherence or non-adherence between the Morisky-Green questionnaire and the MPR was 73.3%, but the kappa coefficient showed only a slight agreement (kappa = 0.142, 95% CI: –0.01 to 0.29, p=0.036).

Discussion

The current study demonstrates that, based on the MPR, non-adherence to the prescribed subcutaneous biological drug occurred in 14.3% of patients with rheumatoid arthritis. Moreover, patients using the most convenient administration period (*i.e.* monthly) had significantly better adherence than those using more frequent dosing schedules.

The dosing interval is an important factor for adherence in chronic diseases, particularly in patients with multiple comorbidities and polypharmacy (6, 20, 21). Simplification of treatments has been shown to lead to improved adherence rates in pathologies such as hypertension (6). Indeed, our findings are not unique to the use of subcutaneous biological therapy in rheumatoid arthritis, with similar outcomes being reported in a recent systematic review and meta-analysis of studies in patients with chronic cardiovascular disease (22). In that analysis, the risk of non-adherence was reduced in patients taking once-daily medication compared with those receiving more frequent daily doses of medication (22).

Adherence rates using the MPR in our study (85.7% of patients with an MPR >80%) were slightly higher than those reported by Tkacz *et al*., with 82.0%, 70.5% and 61.8% of golimumab, adalimumab, and etanercept recipients, respectively, achieving an MPR ≥80% (p<0.001) (15). The study by Tkacz *et al*. was conducted using administrative claims data, which represents a limitation. In contrast, our study used hospital dispensing logs, a more reliable source of information moreover in Spain, because the patients collect their medication only in the pharmacy of the hospital where the drug was prescribed. Nevertheless, results from both studies appear to be coherent. The higher rate of adherence in our study can be attributed to the fact that the Spanish healthcare system, and not the patient, covers the cost of biological medication, which eliminates one of the frequent barriers to adherence; this is likely to be particularly evident in the case of expensive medication such as biological drugs.

Using the 4-item Morisky Medication Adherence Scale, 23.3% of patients in our study were classified as non-adherent, which is in line with data from a recently published cohort study which showed that 20.6% of 260 evaluable patients with rheumatoid arthritis were non-adherent to subcutaneous biological medication, assessed using the same scale (23). In that study, at least one form of non-adherent behaviour was observed in 53.1% of patients (23). Similarly, in a prospective observational study, non-adherence was self-reported in 27.0% of 286 evaluable patients with rheumatoid arthritis who received subcutaneous biologicals (24). However in our study, compared with the MPR, the Morisky-Green test

Table III. Multivariable analysis. Variables associated with non-adherence. (**a**) Full model, (**b**) Final model.

a. Full model	Odds ratio	95% CI	*p*-value
Age (year of increase)	0.99	0.96 – 1.01	0.363
Women (gender *vs*. men)	0.90	0.45 – 1.92	0.774
RA duration above median (>7.8 years)	1.74	0.88 – 3.48	0.113
No induction dose (*vs*. induction dose)	0.43	0.18 – 0.98	0.045
Every two weeks *vs*. weekly administration	0.56	0.24 – 1.21	0.153
Monthly *vs*.weekly administration	0.32	0.09 – 0.87	0.042
Order of administration (second or third *vs*. first biological drug)	1.07	0.55 – 2.08	0.836
Changes in the administration interval during the treatment period (*vs*. no change)	1.59	0.40 – 5.00	0.468
b. Final model	Odds ratio	95% CI	*p*-value
RA duration above median (>7.8 years)	1.63	0.89–3.05	0.117
No induction dose (*vs*. induction dose)	0.41	0.18–0.93	0.033
Every two weeks *vs*. weekly administration	0.54	0.24–1.16	0.125
Monthly *vs*. weekly administration	0.32	0.09–0.87	0.042

RA: rheumatoid arthritis.

Table IV. Performance of the 4-item Morisky-Green test with regard to the Medication Possession Ratio for the detection of non-adherent patients.

Cohen's kappa coefficient	0.142 (-0.005 – 0.290)
Overall percentage of agreement	73.3% (68.3 – 77.8)
Sensitivity	38.5% (25.6 – 53.0)
Specificity	79.3% (74.2 – 83.6)
Positive predictive value	24.1% (15.7 – 35.0)
Negative predictive value	88.3% (83.7 – 91.7)

Except for the kappa coefficient, values are percentages with 95% confidence intervals.

performed poorly in detecting a lack of adherence to subcutaneous biological drugs (Table IV), indicating that it is not a reliable alternative method. The high negative predictive value is due to the low frequency of non-adherence. Similar outcomes were noted in a recent prospective, observational study carried out in pharmacologically-treated patients with hypertension at a community pharmacy in Spain. In that study, the pill count method (reference method) revealed a non-adherence rate of 62.8% compared with rates of 36.0% and 3.1% using the Morisky-Green or Haynes-Sackett methods, respectively (25).

Although there is also acknowledgement that patients' beliefs about treatment for chronic disease influence medication engagement and adherence (26, 27), there was a lack of association between beliefs about medicines and adherence in our study. This may possibly reflect the fact that patients had been receiving subcutaneous biologicals for at least 12 months and were therefore a selected population who had benefited from taking the drug over that time period and understood the need for treatment. This selection bias, *i.e*. the need for a period of 12 months with the same subcutaneous biological drug to qualify for the study, limits the generalisability of our findings and may also explain another finding of the ARCO study, that disease activity was similar in adherent and non-adherent patients. Some studies, however, have associated non-adherence to lack of efficacy of the medication in rheumatic diseases (28, 29), and thus identification of non-adherent patients can warn the treating physician about patients at potential risk of future loss of response to biologicals. On the other hand, thorough information on use or changes of other specific medications such as DMARDs or steroids was not collected and this represents a study limitation. Moreover, the names of the active principles of the biological subcutaneous drugs were not collected either and, other than the interval of administration, specific characteristics which could also influence adherence were not captured. Additionally, in our study, some degree of "intentional" lack of adherence cannot be excluded in some patients with low disease activity or in remission who could have voluntarily delayed their subcutaneous injection for several days.

One of the main advantages of the present study is that the source of the information (hospital pharmacy registries) is reliable because the hospital pharmacy is the only place where patients can collect the prescribed biological medication and patients are not dispensed new medication if they did not use the previous medication. We also captured changes in the interval of administration and suspension periods thoroughly in order to calculate the MPR; these aspects are not captured routinely in studies where information is obtained from administrative sources. The fact that the present study design was retrospective (representing the real-life situation) rather than prospective represents an advantage because patient behaviour was not modified. In the prospective setting, individual behaviour can change because there is an understanding that patients are being observed (the Hawthorne effect) (30, 31).

A limitation of the current study acknowledges the fact that, while there is no optimal method to measure adherence to subcutaneous biologicals in patients with rheumatoid arthritis, 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 prescribed medication. Also, as noted earlier, selection bias represents a limitation of our study. As patients were required to have been prescribed the same subcutaneous biological drug for 12 to 18 months before the study visit, it is likely that patients with a better response to the medication were selected into the study. This precluded an analysis of the potential relationship between non-adherence and disease activity. Patients who failed to respond to the biological medication, or lost response, were not likely to be included in the study because they were likely to have been switched to other drugs.

In conclusion, the current study shows that the non-adherence rate to prescribed subcutaneous biological medication in patients with rheumatoid arthritis from Spanish rheumatology hospital clinics is generally low and similar to rates reported previously. Furthermore, our study shows that, in line with studies on patients with other diseases, patients using the most convenient administration schedule (*i.e.* monthly subcutaneous administration) had better adherence than patients using more frequent dosing schedules. These data contribute new insights to the limited information currently available regarding adherence to prescribed subcutaneous biologicals in patients with rheumatoid arthritis, and should serve to inform further research into non-adherence and strategies for improving adherence rates in this population.

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