Adherence in rheumatoid arthritis patients assessed with a validated Italian version of the 5-item Compliance Questionnaire for Rheumatology

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Abstract

Objective

The 5-item Compliance Questionnaire for Rheumatology (CQR5) proved reliability and validity in respect of identification of patients likely to be high adherers (HAs) to anti-rheumatic treatment, or low adherers (LAs), i.e. taking<80% of their medications correctly. The objective of the study was to validate an Italian version of CQR5 (I-CQR5) in rheumatoid arthritis (RA) patients and to investigate factors associated with high adherence.

Methods

RA patients, undergoing treatment with ≥1 self-administered conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) or biological DMARD (bDMARD), were enrolled. The cross-cultural adaptation and validation of I-CQR5 followed standardised guidelines. I-CQR5 was completed by patients on one occasion. Data were subjected to factor analysis and Partial Credit model Parametrisation (PCM) to assess construct validity of I-CQR5. Analysis of factors associated with high adherence included demographic, social, clinical and treatment information. Factors achieving a p<0.10 in univariate analysis were included in multivariable analysis.

Results

Among 604 RA patients, 274 patients were included in the validation and 328 in the analysis of factors associated with adherence. Factor analysis and PCM confirmed the construct validity and consistency of I-CQR5. HAs were found to be 109 (35.2%) of the patients. bDMARD treatment and employment were found to be independently associated with high adherence: OR 2.88 (1.36-6.1), p=0.006 and OR 2.36 (1.21-4.62), p=0.012, respectively.

Conclusion

Only one-third of RA patients were HAs according to I-CQR5. bDMARDs and employment status increased by almost 3-fold the likelihood of being highly adherent to the anti-rheumatic treatment.

Key words

rheumatoid arthritis, compliance

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Introduction

Optimisation of treatment strategies and introduction of highly effective treatments, namely biological disease-modifying anti-rheumatic drugs (bDMARDs), improved rheumatoid arthritis (RA) outcomes in the last 30 years. Conventional synthetic DMARDs (csDMARDs) are the first line treatment in RA due to their safety profile and relatively low cost (1-3). Addition of a bDMARD is recommended in patients with inadequate response to csDMARDs (2, 3). Adherence to csDMARDs is poor, with a proportion of adherent patients of 10–60% (4, 5). Despite the rapid onset of action, the high efficacy and the favourable safety profile of bDMARDs, adherence to this class of treatments is also sub-optimal (6, 7). Non-adherence to anti-rheumatic treatment is responsible for disease progression, unnecessary treatment escalation and increase in the number of assessments and hospitalisation (5, 8-10). which result in increased costs and decreased quality of life (11, 12). Better understanding of patients' adherence is an unmet need in RA and recent recommendations for disease management advocate the investigation of potential implications of poor treatment adherence (1, 3, 13).

Measuring adherence is complex and no standardised technique is available. In large-scale clinical studies, self-reported questionnaires are the most common methods of assessing medication adherence and explore causes of poor adherence. Of the self-reported measures that have been developed to monitor medication adherence, most have limited sensitivity and have not been specifically developed for rheumatic diseases. The Compliance-Questionnaire-Rheumatology (CQR) is a 19-item questionnaire developed in 1999 in the Netherlands. It identifies non-adherent patients and is specific for rheumatic diseases (14). However, CQR is lengthy at 19 items for use in a clinical setting. Hughes *et al*. tested the factor structure of CQR to reduce the number of items to 5 and performed a reliability and validation assessment of the resulting questionnaire, the 5-item CQR (CQR5) (15). CQR5 increases the clinical utility by diminishing the patient burden. Only a few reports on adherence measured with CQR5 are available (16, 17) and no report on treatment adherence, assessed by the means of a validated questionnaire, is available in Italian patients.

The purpose of this study was to validate an Italian version of CQR5 (I-CQR5) in RA patients. Furthermore, we investigated what factors are associated with high adherence in patients treated with csDMARDs and bDMARDs.

Patients and methods

The study was conducted in two phases. The first phase comprised the cross-cultural adaptation and validation of I-CQR5. The second phase was a cross-sectional analysis conducted to identify factors associated with high adherence, defined by I-CQR5.

Patients

Patients were recruited in the outpatient clinic of Padova University Hospital between September 1, 2017 and January 15, 2018. The inclusion criteria were: (1) diagnosis of RA according to the American College of Rheumatology 1987 classification criteria (18); (2) disease duration>1 year; (3) aged 18 years or above; (4) ongoing treatment with at least one self-administered csDMARD or bDMARD (either oral, subcutaneous or intramuscular administration) (5) duration of the current treatment ≥6 months. Inability to complete the questionnaire (*i.e*. patients with cognitive impairment or lack of proficiency in the Italian language) was an exclusion criterion. All participants provided written informed consent before inclusion in the study. An additional consent was asked to the patients to retrieve anonymised clinical data from the local database. The study was carried out in accordance with the ethical standards of the Declaration of Helsinki (1983) and was approved by the Ethics Committee for the clinical trials of the province of Padova.

CQR5

CQR5 is a 5-item, self-administered questionnaire that derives from the CQR. The original CQR has 19 items, and identifies patients as low adher-

ers (LAs), *i.e.* taking <80% of their medication correctly, and high adherers (HAs) (14, 15, 19). The statements of the CQR were identified through focus groups and clinician's expert opinion of the likely barriers to medication taking. The four point Likert answering scale ranges from: "definitely don't agree" (scored 1) to "definitely agree" (scored 4), with lower scores indicating lower levels of adherence. The CQR was validated against electronic medication event monitoring (eMEMs) devices to assess adherence and was found to correctly identify 62% of LA (19).

CQR5 was developed after factor analysis of the CQR (15). Like the original CQR, CQR5 identifies LAs and HAs. The number of items was reduced to 5, whilst retaining robust explanation of non-adherence to anti-rheumatic treatment. Items included in CQR5 are reported in Table I. A structure matrix identified the optimal linear combination of the CQR5 questions to maximise the discriminant ability. Fisher's classification function coefficients resulted into two equations that allow computing one binary result (LA or HA). A spreadsheet was provided to compute the result of CQR5 by entering the score of each answer (15). CQR5 showed to explain 50.3% of the variance in adherence, it has good internal consistency and fit to the data and detects 69% of LAs among RA patients (15).

Cross-cultural adaptation and validation of I-CQR5

CQR5 was translated from English into Italian using the cross-cultural adaptation process described by Beaton *et al*. (20). The process comprised five stages.

• *I. Forward translation*

The translation from English into Italian was carried out by two independent translators whose mother tongue was Italian (RP, EZ). Each translator provided a written report of the translation (T1 and T2) highlighting difficult phrases or uncertainties along with the rationale for their word choices.

• *II. Synthesis of the translations*

A synthesis of the two translation was produced by the 2 translators together (RP, EZ) with an unbiased moderator (LF) who mediated the discussion of translation differences arising from T1 and T2. One common translation (T12) was obtained together with a report documenting the process and how issues were resolved.

• *III. Back-translation*

Back-translation of T12 was undertaken by 2 independent translators whose mother tongue was English and who were blinded to the original versions (CC, JK). They produced 2 English translations (BT1 and BT2) (Table I).

• *IV. Expert committee assessment*

The expert committee included all the people involved in the previous stages of the adaptation, together with a methodologist (MF), 3 health professionals (2 doctors, CB and DA and 1 nurse, MM), and a member of the original CQR5 developing group (JD). The expert committee reviewed all translated versions (T1, T2, T12, BT1, BT2) in order to reach an agreement on all items and produce a provisional version of I-CQR5.

• *V. Field-testing*

The provisional version of the I-CQR5 was administered to 30 RA patients. Patients completed the I-CQR5 unaided. Cognitive interviews followed the questionnaire completion. During the interviews, both the meaning of the items and responses were explored. A report of the field-testing was presented to the expert committee to discuss potential issues and, if needed, modify the questionnaire accordingly.

The final version of I-CQR5 was completed by a first sample of patients fulfilling the inclusion criteria. The questionnaires were anonymous but contained self-reported data (gender, age, social status, education level and disease duration). Validation of the construct of I-CQR5 was tested on the first sample of patients completing the questionnaire.

Analysis of factors associated with high adherence

To analyse factors associated with high adherence, I-CQR5 was administered to the patients who provided consent to retrieve their clinical data. HAs and LAs were defined according to I-CQR5. Patients' information was collected from the local database. A code allowed the association of the questionnaire result with patients' information by a blinded investigator.

Data collected were: gender, age, social status (defined as: living with parents and family/living /alone/living with partner and family/other), education level, employment, smoking habits, BMI, distance from the outpatient clinic, number of rheumatologic assessments per year, positive rheumatoid factor (RF) and/or anti-citrullinated peptides antibodies (ACPA), disease duration, concomitant fibromyalgia, csDMARD and bDMARD treatment and dose, route and frequency of administration, treatment duration (≤ or >24 months), combination treatment (≥2 synthetic and/or bDMARDs), previous bDMARD failures, mean corticosteroid daily dose, non-steroideal anti-inflammatory drugs (NSAIDs) use, painkillers use, concomitant chronic treatments, 28-joint disease activity score (DAS28), Health Assessment Questionnaire (HAQ), patients' and physicians' global health measured on a visual analogue scale (patient- and physician-VAS) and self-reported disease flares in the three months before the assessment (21). DAS28 was calculated using C-reactive protein; remission was defined as a DAS28<2.6, low disease activity as a DAS28≤3.2 (22). Demographic, clinical and treatment information was collected the day of the questionnaire completion.

Corticosteroids were used at a dose of ≤7.5 mg prednisone-equivalents. Considered csDMARDs were: methotrexate (10–25 mg weekly), leflunomide (20 mg daily or every 2 days), or *other csDMARDs* (*i.e.* hydroxychloroquine 200–400 mg/day or sulfasalazine 2–3 g/day). Considered bDMARDs were: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab and tocilizumab. Patients could receive either full-dose or low-dose bDMARD. In our clinical practice, patients who maintain remission for at least 6 months on a full-dose bDMARD undergo dose reduction (23). Low-dose

Table I. Report of the Expert Committee Assessment: original 5-item Compliance Questionnaire for Rheumatology (English), back-translations, issues discussed and final agreement.

Original	Back-translation 1 (BT1)	Back-translation 2 (BT2)	Issues	Agreement
Title 5 Item version of the Compliance Questionnaire for Rheumatology	*Questionnaire on Rheumatology Compliance composed of 5 questions.*	*5-Item Questionnaire on Compliance in Rheumatology*	Uncertainty on the use of the term "*compliance*" was discussed. The Italian term "*aderenza*" seemed more appropriate to describe patients' agreement on the treatment they have been prescribed. Nevertheless, "*aderenza*" could be translated into the English term "*adherence*" while "*compliance*" allows to specifically refer to the original questionnaire version.	*Questionario sulla Compliance in Reumatologia a 5 domande.*
Acronym CQR5	–	–	–	*I-CQR5*
Introduction On the next pages you will find a number of statements made by patients with a rheumatic disease. Please indicate for each statement how far you agree, by placing a circle around the number that reflects your opinion best.	*Below there are some statements made by patients affected by rheumatic diseases. Indicate to what extent you agree with each statement by circling the number that best reflects your opinion.*	*Below there are statements made by patients with rheumatic diseases. Please, circle the number that best reflects your opinion.*	Considering the mean age of patients with rheumatoid arthritis, it was deemed more pragmatically suitable to adopt a more formal style. The first singular person statements were turned into the formal pronoun accordingly. Different options for the translation of "*to find*", "*statements*", "*how far*" are available in the Italian language. The choice has been made in order to maintain a formal style.	*Di seguito sono riportate delle affermazioni di pazienti affetti da una malattia reumatica. Indichi quanto è d'accordo con ciascuna affermazione cerchiando il numero che riflette maggiormente la Sua opinione.*
Item no. 1 I take my anti-rheumatic medicines because I then have fewer problems	*I take my antirheumatic medication so that I'll have less symptoms.*	*I take the antirheumatic medication so I can feel better.*	Translation of "*to take*" was discussed. "*Assumere*" was a suitable term according to the formal style of the questionnaire, but it usually refers to oral medications. "*Prendere*" is less formal but it was deemed appropriate as it has a broader meaning referring also to subcutaneous and intramuscular treatments.	*Prendo i farmaci antireumatici perché in questo modo ho meno disturbi.*
Item no. 2 I definitely don't dare to miss my anti-rheumatic medications	*I don't ever allow myself to skip taking my medication.*	*I never skip my medication.*	None.	*Non mi permetto mai di saltare la somministrazione dei farmaci antireumatici.*
Item no. 3 My medicines are always stored in the same place and that's why I don't forget them	*I always put my medication in the same place so that I don't forget to take it.*	*I put my medication in the same place so I don't forget to take it.*	Translation of "*to store*" was discussed. "*Mettere in un posto*" was deemed an adequate translation.	*Metto sempre le medicine nello stesso posto per non dimenticare di prenderle.*
Item no. 4 I take my medicines because I have complete confidence in my rheumatologist	*I take my prescribed medication because I have complete faith in my rheumatologist.*	*I take the medication my rheumatologist prescribed because I trust him/her completely.*	Translation of "*to take*" was discussed (see item no.2).	*Prendo i farmaci prescritti perché ho completa fiducia nel mio reumatologo.*
Item no. 5 What the doctor tells me, I hang on to	*I always follow my doctor's instructions.*	*I always follow my doctor's recommendations.*	Uncertainty has arisen on the type of doctor the item refers to, either the general practitioner or the rheumatologist. The committee deemed that the original distinction between the rheumatologist (in Item no. 4) and the doctor (Item no. 5) should be kept to ensure the same consistency of the original questionnaire. The term "*medico*" was chosen instead of "*dottore*", as "*medico*" specifically refers to the medical doctor.	*Seguo sempre le indicazioni del mio medico.*
Answers Don't agree at all Don't agree Agree Agree very much	*Don't agree at all* *Don't agree* *Agree* *Agree very much*	*Don't agree at all* *Don't agree* *Agree* *Agree very much*	Translation was chosen according to the most common Likert-scale answers adopted in the main Italian questionnaires, e.g. those used by the National Italian Institute of Statistics (ISTAT).	*Completamente in disaccordo* *In disaccordo* *D'accordo* *Completamente d'accordo*

treatments were: abatacept 125 mg or tocilizumab 162 mg or etanercept 50 mg every ≥10 days, adalimumab 40 mg or certolizumab pegol 200 mg every ≥3 weeks, anakinra 100 mg every ≥2 days, etanercept 25 mg every ≥1 week, golimumab 50 mg every ≥45 days.

Statistical analysis

• *Data description*

Descriptive statistics of data according to the result of I-CQR5 were performed. Wilcoxon-Kruskal-Wallis test was performed for continuous variables and Pearson Chi-square test for categorical ones to discriminate among stratification variables.

• *Questionnaire validation*

A maximum-likelihood factor analysis was conducted in order to identify the number of latent dimensions underly-

ing the observed variable distribution (24). Based on the Chi-square statistics we tested the hypothesis that the model, based on the actual number of dimensions, was fitting the data with a minimal loss of information. The variables with the greater percentage of explained variance in the first two latent factors were included as subset item in the Martin-Loef test (25) to assess the assumption of unidimensionality in a Partial Credit model Parametrisation (PCM) (26). PCM was estimated to test whether I-CQR5 retained its psychometric properties following the adaptation process (26). The model was estimated including responses with at least one valid response per item and the item-fit statistics was reported in order to assess deviations from the PCM assumption for each item of the scale. Internal Consistency was analysed, including the Patient Separation Index (PSI) measure (27). PSI quantifies the error associated with the measurements of subject in this sample with values >70 indicating an adequate reliability.

• *Multivariable analysis*

A multivariable logistic regression analysis was performed to evaluate factors associated with high adherence to anti-rheumatic treatment. Variables included in the multivariable analysis were all those with a $p<0.10$. Collinearity was assessed by the variance inflation factor (VIF), adopting a cut off=2 as an exclusion criterion (28). Analyses were performed using R 3.3.3 (29) with arms (30) and eRm (31) packages.

Results

Among 604 consecutive RA patients, 401 fulfilled the enrolment criteria. Thirty patients were involved in the field testing, 274 in the cross-cultural validation and 328 in the cross-sectional analysis (Supplementary Fig. 1).

Cross-cultural adaptation and validation of I-CQR5

The expert committee assessment discussed discrepancies raised in the stages of the translations and reached a consensus on all items. Report of the assessment is reported in Table I. During the field-testing, I-CQR5 was well understood by patients and no major issue arose. Thus, the committee deemed that the aim of proposing an accurate Italian version of the CQR5 was achieved. The final I-CQR5 (Table I) was completed by 274 patients on one occasion. Characteristics of the patients and data of the questionnaires used in the validation phase are reported in Supplementary Table I.

Table II. Factor analysis: the proportions of contribution to latent factors provided by questionnaire items, the sum of square loadings, proportion and cumulative proportion of explained variance are reported for each item. Partial Credit model Parametrisation threshold analysis reports mean Square Item-fit statistics and location parameters.

	Factor analysis loadings			Partial credit model parametrisation threshold analysis		
	All†	HAs		Outfit mean square	Infit mean square	Location Parameters
Item no. 1	0.721	0.460	Item no. 1	1.219	1.111	0.44
Item no. 2	0.629	0.522	Item no. 2	1.119	1.132	0.55
Item no. 3	0.750	0.522	Item no. 3	0.777	0.740	0.91
Item no. 4	0.660	0.675	Item no. 4	0.517	0.523	0.98
Item no. 5	0.534	0.807	Item no. 5	0.7171	0.682	0.83
	Factor 1	Factor 2				
Sum of square loadings	2.210	1.869				
Proportion variance	0.442	0.374				
Cumulative variance	0.442	0.816				

• *Factor analysis*

Assessment of the response structure in the 5 items, revealed ordered thresholds in most items. Factor analysis revealed that two factors were sufficient to explain the overall variability: the cumulative percentage of explained variance was 0.82 (Table II) and it was possible to accept the hypothesis that the model fitted the data perfectly (Chi-square=0.46, p=0.5).

• *Rasch model (Partial Credit model Parametrisation)*

The assessment of the response structure revealed that, observing location parameters, thresholds were ordered in most items, implying that the 4-point category structure worked as expected (Table II). Item-fit statistics showed an overall agreement of items with proposed parametrisation as the Mean Square Error Item fit statistics were comprised between 0.6–1.4 (excluding item no. 5), according to Wright & Linacre (1994) (Table II). The Chi-square test showed agreement with PCM by item (excluding item no.1) (Table II). Martin-Loef test, without covariates, confirmed the unidimensionality of scales (Chi-square 65.8, degrees of freedom (df) 53, p=0.11). The Separation Reliability Index proved the internal consistency of the scale (PSI 0.91). Martin-Loef test for the scale invariance for gender, age, education level and social status showed that the scale was invariant to age (Chi-square=40.56, df=28, p=0.059), education level (Chi-square=49.95, df=42, p=0.187), social status (Chi-square=10.46, df=15, p=0.79) and disease duration (Chi-square=13.63, df=36, p=0.220); while the test was significant for gender (Chi-square=25.39, df=14, p=0.031).

Factor analysis showed that I-CQR5 fitted the data and proved its unidimensionality and internal consistency. I-CQR5 could be then administered to a larger sample of patients for further analyses. The final version of I-CQR5 is reported in Supplementary Figure 2.

Analysis of factors associated with high adherence

Characteristics of patients included in the cross-sectional analysis are detailed in Table III. The median duration of the current treatment was 7 years (3.3–10.1). Most of the patients were treated with bDMARDs and half with csDMARD treatment. Ninety per cent of the patients was in low disease activity or in remission: 270 (90.3%) and 173 (57.9%), respectively. HAs were 109 (35.2%) of all patients according to I-CQR5 (Table III). Variables significantly associated with high adherence to treatment were: younger age, employment, higher level

Table III. Analysis of factors associated with high adherence defined by I-CQR5: demographics and clinical characteristics of the patients according to high and low adherence (n=310).

	Total	HAs	LAs	*p*-value
No.	310	109	201	-
Females (%)	232 (82)	88 (85.4)	144 (80)	0.081[‖]
Age, years, median (IQR)	57 (48-67)	54 (46-64.8)	59 (49-66)	0.011[‖]
BMI, median (IQR)	24 (22-28)	25 (23-28)	24 (21-27.3)	0.094[‖]
Smokers, n (%)	45 (17.2)	13 (16)	32 (17.7)	0.746
Employed, n (%)	127 (44.1)	58 (62.4)	69 (35.4)	*p*<0.001[‖]
Education level				0.114
Primary school, n (%)	35 (12.1)	10 (9.4)	25 (13.6)	
Middle school, n (%)	115 (39.7)	35 (33)	80 (43.5)	
Secondary school, n (%)	101 (34.8)	45 (42.5)	56 (30.4)	
University, n (%)	39 (13.4)	16 (15.1)	23 (12.5)	
Primary/middle school education, n (%)	150 (51.7)	45 (30)	105 (70)	0.016[‖]
Social status				0.921
Living with parents and family	18 (7)	6 (7.5)	12 (6.8)	
Living alone	34 (13.2)	10 (12.5)	24 (13.6)	
Living with partner and family	187 (72.8)	57 (71.3)	130 (73.4)	
Other	18 (7)	7 (8.8)	11 (6.2)	
Positive RF and/or ACPA, n (%)	166 (56.3)	51 (49.0)	115 (60.2)	0.178
Disease duration, years, median (IQR)	12 (7-19)	12 (7.3-18)	11 (6.8-20)	0.876
Fibromyalgia, n (%)	51 (18)	15 (14.6)	36 (20)	0.252
csDMARD treatment, n (%)	165 (54.5)	44 (40.7)	121 (62.1)	*p*<0.001[‖]
Methotrexate, n (%)	114 (37.6)	32 (29.6)	82 (42.1)	0.033
Leflunomide, n (%)	31 (10.2)	8 (7.4)	23 (11.8)	0.227
Other csDMARD, n (%)	42 (13.9)	7 (6.5)	35 (17.9)	0.006
bDMARD treatment, n (%)	193 (64.3)	79 (76.7)	114 (57.9)	0.001[‖]
Treatment duration>24 months, n (%)	178 (79.5)	75 (78.1)	103 (80.5)	0.667
Prednisone daily dose, median (IQR)	1 (0-5)	1 (0-2.5)	1.5 (0-5)	0.011[‖]
NSAIDs, n (%)	185 (65.6)	62 (62.6)	123 (67.2)	0.439
Painkillers, n (%)	76 (28.6)	30 (30.6)	46 (27.4)	0.574
Concomitant chronic treatment, n (%)	156 (53.1)	51 (49)	105 (55.3)	0.307
DAS28, median (IQR)	2.3 (1.8-2.8)	2.1 (1.7-2.7)	2.3 (1.9-2.3)	0.088[‖]
Remission*, n (%)	173 (57.9)	60 (55.6)	113 (59.2)	0.544
Low disease activity[¥], n (%)	270 (90.3)	101 (93.5)	169 (88.5)	0.158
Patient - VAS, median (IQR)	30 (10-51)	20 (6-54)	40 (20-56.3)	0.003[‖]
Physician - VAS, median (IQR)	10 (5-20)	12.5 (1.3-20)	10 (5-20)	0.984
HAQ, median (IQR)	0.5 (0-1)	0.3 (0-1)	0.5 (0.1-1)	0.114
Disease flares, median (IQR)	44 (31.4)	10 (27)	34 (33)	0.501
No. of assessments per year, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	0.490
Distance from clinic, km, median (IQR)	30 (11-45)	30 (20-50)	25 (9-45)	0.037[‖]

*Remission was defined as DAS28<2.6; [¥]low disease activity was defined as DAS28<3.2; [‖]variables included in the multivariable analysis as achieving a *p*-value<0.10 in the univariate analysis.
HAs: high adherers; LAs: low adherers; IQR: interquartile range; BMI: body mass index; ACPA: anti-citrullinated peptides; RF: rheumatoid factor; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD; DMARD: disease-modifying anti-rheumatic drug; NSAIDs: non-steroidal anti-inflammatory drugs; HAQ: Health Assessment Questionnaire; DAS28: 28-joint disease activity score; VAS: visual analogue scale.

Table IV. Factors associated with high adherence to anti-rheumatic treatment defined by I-CQR5: multivariable regression analysis model.

	OR (95% CI)	*p*-value
Female gender	0.79 (1.58-0.39)	0.501
Employment	2.36 (1.21-4.62)	0.012
bDMARD treatment	2.88 (1.36-6.1)	0.006
Patient-VAS (per 10-unit increase)	0.88 (0.78-1)	0.052
Model constant		<0.001

OR: odds ratio; CI: confidence interval; DMARD: disease-modifying anti-rheumatic drug; bDMARD: biological DMARD; VAS: visual analogue scale.

of education (secondary school/university), bDMARD treatment, lower median prednisone dose, lower patient-VAS, higher distance from the outpatient clinic. The use of a csDMARD, particularly MTX and HCQ/SSZ, was significantly associated with low adherence to treatment (Table III).

Values achieving a $p<0.10$ in univariate analysis, were included in the logistic regression model (Table IV). Age resulted collinear with employment (VIF=2.05 and 1.67, respectively). Thus, two separate regression analyses were conducted, one including age and one including employment. The model including age was not significant (Suppl. Table II). The model including employment is reported in Table IV. Treatment with a bDMARD and employment resulted predictors of high adherence increasing by 2–3-fold the likelihood of being HAs (Table IV).

Discussion

This is the first study to evaluate adherence in RA patients by means of I-CQR5, a validated Italian version of CQR5 questionnaire. I-CQR5 was well understood by patients and very little time-consuming for the physician. Only one third of RA patients was highly adherent to treatment according to I-CQR5. Treatment with bDMARDs and employment were associated with a 2-3 times increased likelihood of being highly adherent to treatment.

Poor adherence to treatment was more common in our cohort than in previous reports, although a comparison is difficult to perform because of the different methods used to assess adherence. In surveys including bDMARDs, good adherence was reported to be around 50–90% (6, 7, 32), nevetheless reports of adherence as low as 11% were described (33). Studies using CQR5 are only a few and do not have comparable cohorts of RA patients (16, 17). Adherence rates measured with the original 19-item CQR show rates of HAs around 65–90% (34-38). CQR has been reported to identify approximately a doubled rate of LAs compared with other questionnaires (39). Lower rates of high adherence may be entailed by the discrete distinction of adherence in two

categories (taking correctly ≥ or <80% of prescribed medications, *i.e.* HAs or LAs) given by CQR and CQR5. To explain the rather low rates of good adherence, it has to be considered that CQR and CQR5 seem to explore the general attitude of the patient toward the anti-rheumatic treatment and the health-care providers. Actually, only one question of CQR5 investigates the correct medication intake (item no. 2, on skipping medication). Other questionnaires, such as the Medication Adherence Scale and the Morisky adherence questionnaire, which have been also used in RA, have several items addressing specifically the administration of medications. Furthermore, CQR proved to correlate well with patient-reported outcomes, but not with other questionnaires on adherence (41). Likewise, CQR5 results were associated with the results of the Beliefs on Medications Questionnaire, (40) which identifies patients with concerns or misbeliefs regarding the medical treatment. One reason for the low rate of high adherence observed in the study might be that almost 90% of the patients were in remission or low disease activity. In fact, self-discontinuation of anti-rheumatic treatment is described in patients with low levels of pain, as they might feel that treatment is unnecessary (41). In our study, the high rate of patients with low disease activity might be explained by the stable treatment and the large number of bDMARDs therapies. Although, we found no association with measures of RA activity, one can assume that patients with very good control of disease activity decrease treatment on purpose. That being so, LAs may include both patients not needing to comply because of low disease activity and patients with active disease who are not taking the treatment properly.

High adherence to treatment was less frequently observed in patients treated with csDMARDs compared with bDMARDs, which is consistent with previous findings (5, 7, 33, 42-46). Patients prefer bDMARDs as they usually have a faster and greater effectiveness, but also because they are innovative and costly (5, 33). This awareness might foster the feeling of a privileged health care with bDMARDs (33). No significant association has been previously reported between employment and adherence (11, 32, 47). In our cohort employed patients were younger and had a higher educational level, and both factors affected positively adherence. Nevertheless, employment was independently associated with high adherence. Concerns about reduced working ability considerably bother RA patients and full functionality is essential to ensure working productivity (48, 49), thereby encouraging a compliant behaviour in employed patients.

The study has some limits. Firstly, questionnaires are prone to biased results from socially desirable answering (50). The adoption of an anonymous questionnaire and the correct item construction and validation can overcome these issues. Secondly, the study was conducted in a monocentric cohort of patients, where a large number of patients were treated with bDMARDs. Our cohort might be not representative of the RA population in Italy. In any case, recent evidences show that a lower rate of Italian patients is treated with bDMARDs compared with the rest of Europe (51). Given trends in other countries, our centre possibly preempts a pace that other services will follow in due course. One further limitation may be that most of the patients in the cohort had a good disease control which might also have affected adherence. Nonetheless, the study suggested that also patients who respond well to the treatment might be inclined to reduced compliance.

This is the largest study to date exploring the clinical utility of this simple questionnaire. Like previous reports, this study reports a higher adherence to bDMARDs compared with csDMARDs, but a rather poor overall adherence to anti-rheumatic drugs. Addressing treatment adherence is recommended by guidelines for RA (1, 3, 13), and I-CQR5 may serve as an initial screening of patients' behavior in order to implement interventions to ameliorate adherence. I-CQR5 addresses both the compliance to treatment prescription and the attitude of the patient toward the anti-rheumatic treatment. Furthermore, the study highlighted that LAs may be not only patients who skip the medication because of concerns regarding the treatment but also patients who reduce the medication because of good disease control. The latter group of patients might increase in the future because of the broad use of effective treatments, such as targeted synthetic DMARDs, which require oral daily administration and may be more subjected to incorrect administration. Additional investigations are needed to explore different grounds for reduced compliance. Possibly, interventions to improve adherence will have to include patients' information and education. Shared decision to tailor treatment according to disease activity and patients' preferences is necessary to maximise the chances of good adherence.

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