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VALIDATION OF THE ITALIAN VERSION OF THE 5-ITEM COMPLIANCE QUESTIONNAIRE FOR RHEUMATOLOGY (I-CQR5) AND A CROSS-SECTIONAL STUDY ON TREATMENT ADHERENCE IN RHEUMATOID ARTHRITIS PATIENTS

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Index

Abstract

Background

The 5-item Compliance Questionnaire for Rheumatology (CQR5) allows the identification of patients likely be high adherers (HA) to anti-rheumatic treatment (i.e. taking ≥80% of their medications correctly), or "low" adherers (LA). The objective of the entire study was to validate an Italian version of I-CQR5 in rheumatoid arthritis (RA) patients. Furthermore, a cross-sectional analysis was conducted to investigate what factors are associated with high treatment adherence.

Methods

RA patients (with disease duration >1 year, undergoing treatment with ≥1 self-administered biological disease-modifying anti-rheumatic drugs (bDMARDs) or conventional synthetic DMARDs (csDMARDs), willing and capable of completing the questionnaire unaided) were enrolled in the study. The cross-cultural adaptation into Italian and validation of I-CQR5 followed standardized guidelines. The I-CQR5 was completed by patients on one occasion. Data were subjected to Partial Credit model Parametrisation (PCM) to assess the construct validity and reliability of I-CQR5. Patients who gave consent to retrieve their clinical data were included in the analysis of factors associated with high adherence to anti-rheumatic treatment. Factors included were demographic and social characteristics of the patients, and clinical and treatment information. Factors achieving a $p<0.10$ in univariate analysis were included in a multivariate regression analysis. Separate models were conducted in the entire cohort and in the csDMARD only- and bDMARD- treated groups.

Results

Among 604 RA patients, 401 were eligible for the analysis: 274 patients were included in the validation analysis and 328 in the cross-sectional analysis. Median age of the patients was 57 years (48-134), most were females (232, 82%), median disease duration was 12 years (7-19); 64.3% (193/300) of patients was treated with bDMARDs and 54.6% (107/300) with csDMARD treatment; 90.3% (270/299) of the patients was in low disease activity or

remission.

Issues regarding the adaptation of CQR5 were discussed and solved by an expert committee assessment. The I-CQR5 was well understood by patients. Factor analysis and PCM confirmed the construct validity, unidimensionality and internal consistency of the I-CQR5.

HA were found to be 35.2% (109/310) of the patients: 40.2% (79/193) in patients treated with bDMARDs and 22.4% (24/107) with csDMARDs only. 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. Older age, lower education level, higher prednisone daily dose, use of a csDMARD (particulary hydroxychloroquine and sulfasalazine) and higher patient-VAS were significantly more frequent in LA compared with HA but the association was not confirmed by the multivariate analysis. No independent predictors were found in the group of patients treated with csDMARDs only. Employment was also positively and significantly associated with high adherence considering patients treated with bDMARDs: OR 2.89 (1.3-6.44), p=0.009.

Conclusions

Only one third of Italian RA patients were found to be highly adherent to treatment according to the I-CQR5. Treatment with bDMARDs and employment status were the major determinants, increasing by almost 3-fold the likelihood of being adherent. Age, education level, PDN daily dose, and patient global assessment on a visual analogic scale, might contribute in explaining adherence in RA patients.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by persistent synovitis, which leads to joint disruption and disability. Optimisation of treatment strategies and introduction of highly effective treatments, namely biological disease-modifying anti-rheumatic drugs (bDMARDs), improved RA outcomes in the last 30 years. Conventional synthetic DMARDs (csDMARDs) are recommended as first line treatment due to their efficacy, safety profile and relatively low cost[1,2,3]. Addition of a bDMARD is recommended in patients with inadequate response to csDMARDs or poor prognostic factors[2,3].

csDMARDs can take months to exhibit noticeable therapeutic benefits and can have side-effects that prompt patients to be less adherent[4]. Adherence to csDMARDs was reported to be poor, with proportions of adherent patients of 10-60%[5,6]. Despite the rapid onset of action, the high efficacy and the favourable safety profile of bDMARDs, adherence to this class of treatments is still sub-optimal[7,8].

Non-adherence to anti-rheumatic treatment is responsible for disease progression, unnecessary treatment escalation, increase in the number of assessments and hospitalisation[6,9,10,11]which result in increased costs and decreased quality of life[12,13,14]. Optimisation of patients' adherence is recognised as an unmet need in RA[15] and recommendations for disease management advocate the investigation of potential implications of poor treatment adherence[1,3].

Measuring adherence is complex and no standardised technique is available. The "gold standard" is electronic medication event monitoring (eMEMs). However, eMEMs is unsuitable for clinical practice, as it requires numerous resources from both the patient and researcher to be implemented effectively. In large scale clinical studies, self-reported questionnaires are the most common methods of assessing medication adherence and also 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[16]. The Compliance-Questionnaire-Rheumatology (CQR) is a 19-item questionnaire developed in 1999 in the Netherlands. CQR predicts the potential for non-adherence in rheumatology patients[17]. However, CQR can be considered lengthy at 19 items for use in a clinical setting. A study by Hughes et

al., tested the factor structure of the CQR and reduced the number of items to 5[18]. CQR5 increases the clinical utility by diminishing the patient burden.

Only a few reports on adherence measured the 5-item CQR (CQR5) are available in RA to date[19,20] and no report on treatment adherence, assessed by the means of a validated questionnaire, is available for Italian patients. The objective of this study was to validate an Italian version of the CQR5 (I-CQR5) in RA patients. A cross-sectional analysis was then conducted to investigate what factors might be associated with high adherence in patients treated with csDMARDs and bDMARDs.

Methods

Design

The study was conducted in two phases. The first phase comprised the cross-cultural adaptation of the CQR5 into Italian and validation of the adapted tool, I-CQR5, in RA. The adaptation followed standardized guidelines for cross-cultural adaptation of patient-reported outcome measures[21]. The validation was conducted using a cross-sectional survey in a cohort of RA patients who completed adapted version of the CQR5 (I-CQR5) on one occasion. Data were subjected to Rasch analysis to assess the construct validity and reliability of the translated tool.

The second phase investigated what factors are associated with high adherence to anti-rheumatic treatment, measured with the I-CQR5. Factors included demographic and social characteristics of the patients and clinical and treatment information.

Patients

Patients were recruited from the outpatient clinic of Padova University hospital. The inclusion criteria were: (1) diagnosis of RA according to the American College of Rheumatology 1987 classification criteria[22]; (2) disease duration >1 year; (3) aged 18 years or above; (4) undergoing treatment with at least one self-administered csDMARD or bDMARD (either oral, subcutaneous or intramuscular administration). Inability to complete the questionnaire (i.e., patients with cognitive impairment or lack of proficiency in the Italian language) was an exclusion criteria.

All participants provided written informed consent before inclusion in the study. For the purposes of the analysis of factors associated with adherence, an additional consent was asked to the patients, in order to retrieve their 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.

Measures

CQR5 is a 5-item, self-administered questionnaire that derives from the CQR. The original CQR has 19 items, and identifies patients as "low" adherers, i.e. taking <80% of their medication correctly[17,23]. 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 eMEMs and was found to correctly identify 62% of LA[23].

The CQR5 version was developed after factor analysis of the CQR[18]. The number of items was reduced to 5, whilst retaining robust explanation of non-adherence to anti-rheumatic treatment. A structure matrix was developed, which identifies the optimal linear combination of the CQR5 questions to maximise its discriminant ability. Fisher's classification function coefficients resulted in the following equations:

$D_0 = -27.611 + (4.407*Q2) + (0.939*Q3) + (6.101*Q5) + (2.366*Q6) + (2.531*Q17)$

$D_1 = -33.304 + (2.801*Q2) + (5.008*Q3) + (6.471*Q5) + (1.215*Q6) + (3.252*Q17)$

Given the two parameters D0 and D1, if D0 is greater than D1 then the respondent should be classified as likely to be a "low" adherer (LA), i.e. likely to take <80% of the medication correctly. Conversely, if D1 is greater than D0 then the respondent should be classified as likely to be highly adherent (high adherer, HA), i.e. likely to take ≥80% of the medication correctly.

The CQR5 and explains 50.3% of the variance in adherence. It has good internal consistency and fit to the data which can detect 69% of LA to anti-rheumatic treatment among RA patients[18]. Together with the CQR5 publication, a spreadsheet was provided. The spreadsheet allows the computation of the CQR5 result by inserting the score of each answer.

Cross-cultural adaptation of CQR5

The original (English) CQR5 was translated into Italian using the cross-cultural adaptation process described by Beaton et al.[21]. The process comprises five stages: forward translation, synthesis of the translations, back- translation, expert committee assessment

and field-testing.

The forward translation stage from English into Italian was carried out by two independent professional translators whose mother tongue was Italian. 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. A synthesis of the two translation was produced by the two translators together with a third unbiased person 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. Back-translation was undertaken by two translators whose mother tongue was English and blinded to the original versions. They worked from the T12 version of the questionnaire, producing English translations (BT1 and BT2).

The expert committee included a methodologist, 3 health professionals (2 doctors, 1 nurse), all the translators, the moderator of the translations and a member of the CQR5 developing group. The expert committee reviewed all translated versions (T1, T2, T12, BT1, BT2), discussing discrepancies raised in previous stages, and a consensus was reached on all items. A provisional version of the I-CQR5 was then administered for field-testing to 30 RA patients. Patients completed the I-CQR5 unaided. Afterwards they were interviewed to probe what they thought was meant by each questionnaire item. Both the meaning of the items and responses were explored.

Validation of I-CQR5

The final version of the I-CQR5 was completed by a consecutive 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). The original CQR5 showed to fit the Rasch model or Partial Credit Model parametrisation (PCM)[24]. Then, PCM was used to test whether the I-CQR5 had retained its psychometric properties following the adaptation process. A Martin-Loef Likelihood ratio test was performed in order to assess the scale invariance for gender, age, education, social status and disease duration.

Cross-sectional analysis: factors associated with high adherence

HA and LA were defined according to I-CQR5. Patients' and clinical information was

collected from the local database. A code allowed the association of the questionnaire result with patients' information by a blinded investigator. Only patients who provided consent to retrieve their clinical data were included in this analysis.

Data collected were: gender, age, social status, education level, employment, smoking habits (reported by the patients), 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, conventional and bDMARD treatment, route and frequency of administration, treatment duration (≤ or > 24 months), combination treatment (≥2 synthetic and/or bDMARDs), previous bDMARD failures, mean prednisone (PDN) daily dose, non-steroideal antinflammatory 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 analogic scale (patient- and physician-VAS) and self-reported disease flares in the three months before the assessment[25]. Clinical information was referred to the most recent assessment of the patient.

Considered csDMARDs were: methotrexate (MTX) (10– 25 mg weekly), leflunomide (LFN) (20 mg daily or every 2 days), or *other*, i.e. hydroxychloroquine (HCQ) 200-400 mg/day or sulfasalazine (SSZ) 2-3g /day. Considered bDMARDs were: abatacept (ABA), adalimumab (ADA), anakinra (AKN), certolizumab pegol (CZP), etanercept (ETA), golimumab (GLM) and tocilizumab (TCZ). 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 and continue on low-dose until remission is maintained. Low-dose treatments were ABA 125 mg or TCZ 162 mg or ETA 50 mg every ≥10 days, ADA 40 mg or CZP 200 mg every ≥3 weeks; AKN 100 mg every ≥2 days, ETA 25 mg every ≥1 week, GLM 50 mg every ≥45 days. PDN was used at a dose of ≤7.5 mg daily.

Statistical analysis

Data are presented in all patients and in HA and in LA. Continuous variables had a non-normal distribution and were compared using Mann-Whitney test or Wilcoxon-Kruskal-Wallis test. Qualitative variables were compared using Pearson's Chi-square test or Fisher's exact test. Data were reported as medians and interquartile range (IQR) for continuous variables, and absolute numbers and percentages, for qualitative variables.

Rasch model (Partial Credit Model parametrisation)

PCM is based on the assumption of unidimensionality. A factor analysis was conducted in order to identify the number of latent dimensions, useful to explain the questionnaire response variability. The Chi-square statistic and p-value in factor analysis were computed to test the hypothesis that the model, with the identified number of latent dimensions, perfectly fitted 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 to assess the assumption of unidimensionality in PCM. PCM was estimated, 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 Measure. Computations were performed using R 3.3.3[26] with rms[27] and eRm[28] packages.

Regression analysis

Multivariate analysis was run to assess the potential of demographic and clinical variables (independent variables) to affect treatment adherence (dependent variable). Due to the high number of variables significantly associated with adherence in the univariate analysis, variables included in the multivariate analysis were all those with a $p < 0.10$. Collinearity was assessed by the variance inflation factor (VIF), adopting a cut off of VIF = 2 as an exclusion criterion. A logistic regression model was used, with a backward elimination approach. The results of multivariate logistic regression analysis are presented as the odds ratio (OR) with the corresponding 95 % confidence interval (CI). Analyses were performed using SPSS version 24.0.

Results

Patients

Among 604 consecutive Italian RA patients, 36 were excluded because of lack of proficiency in the Italian language, 52 because of cognitive impairment or inability to complete the questionnaire unaided, and 115 were not willing to complete the questionnaire. Four hundred one patients fulfilled the enrolment criteria (Fig.1). Thirty patients were included in the cross-cultural adaptation phase, 274 in the cross-cultural validation phase. Of these, 231 gave consent to the association of the questionnaire result and their clinical information, together with 97 additional patients and were included in the cross-sectional analysis. Among the collected questionnaires, 24 were not completed or partially completed and could not be used for the purposes of this study (6 in the validation phase and 18 in the cross-sectional analysis). Demographic and clinical characteristics of the patients are described afterwards.

Cross-cultural adaptation of CQR5

Issues regarding translation included: multiple meanings of certain concepts, type of language style and idiomatic expressions. These were solved in the expert committee assessment. In the field-testing, the I-CQR5 provisional version was well understood by patients and no changes in the treatment domain were needed. A summary of issues arising from the translations and the agreements for each is presented in Table 1. The final questionnaire is reported in Figure 2. The expert committee deemed that the aim of proposing an accurate Italian version of the CQR5 was achieved.

Validation of I-CQR5

Data used for the validation phase and the patients' information are reported in Table 2. Some of the self-reported information on the patients were missing and in 6 cases some of the answers to the questionnaire were missing and could not be used for the PCM.

Factor analysis

Assessment of the response structure in the 5 items, revealed ordered thresholds in most items, indicating that the 4-point category response structure was working as expected. Test of the hypothesis showed that 2 factors were sufficient to explain the overall variability. The Chi-square statistic was 0.46, p=0.5 (Table 3).

Rasch model (Partial Credit model Parametrisation)

PCM was estimated including responses with at least one valid response per item (268 responses). Item-fit statistics showed an overall agreement of items with proposed parametrisation, as the Infit statistics were comprised between 0.6-1.4 (excluding item no.5), according to Wright & Linacre (1994) for Likert scales. The Chi-square test showed agreement with PCM parametrisation by item (excluding the first item). Martin-Loef likelihood ratio test 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 (Patient Separation Index 0.91) (Table 4). Martin-Loef Likelihood ratio test was used to assess the scale invariance for gender, age, education level and social status. 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 Martin-Loef test was significant for gender (Chi-square = 25.39, df= 14, p= 0.031).

Cross-sectional analysis: factors associated with high adherence

Among 328 patients included in the cross-sectional analysis, 18 had an incomplete questionnaire and had to be excluded. Most unanswered item was item no. 2 in 12 (66.7%) cases. Items no. 1 and 5 were unanswered in 9 cases (50%) each, items no. 3 and 4 in 3 (16.7%) cases each. In 3/18 cases no item had been completed.

Characteristics of the patients are detailed in Table 5. Median age of the patients was 57 years (48-134) and most of them were females (232, 82%) (Table 5). Patients had a disease duration of 12 years (7-19), the duration of the current treatment was 7 years (3.3-10.1) with 79.5% (178) of patients with a duration of ≥ 24 months. Most of the patients was treated with bDMARDs (193, 64.3%) and half of them with csDMARD treatment (165, 54.5%). Mean PDN daily dose was 1 mg (0-5). Almost two thirds of the patients used NSAIDs (185, 65.6%)

and one third used painkillers (76, 28.6%) either as chronic or *as-needed* treatment. Half of the patients (156, 53.1%) was undergoing a concomitant chronic treatment. Ninety per cent of the patients was in LDA or in remission (270, 90.3% and 173, 57.9% respectively). Details of the csDMARD and bDMARD treatment are reported in Table 6.

Thirty-five per cent of the patients (109/310, 35.2%) resulted to be HA to the anti-rheumatic treatment according to the I-CQR5 result (Table 5). HA were significantly younger compared to LA: 54 (46-64.8) vs 59 years (49-66), p =0.011; and were more frequently employed 58, 62.4% vs 69, 35.4%, p<0.001. Education level was reported both according to each education level and as a qualitative variable. Low adherence to treatment was associated with primary/middle school education which was observed in 70% of LA compared with 30% of HA, p=0.016. A significant larger proportion of patients in treatment with a bDMARD was observed among HA compared LA: 76.7% (79) vs 57.9% (114) respectively, p=0.001. The use of a csDMARD was associated with low adherence to treatment: 44, 40.7% of HA vs 121, 62.1% of LA were using a csDMARD, p<0.001. Particularly, MTX and HCQ/SSZ were significantly associated with low adherence. HA assumed less PDN compared with LA: median daily dose was 1 (0-2.5) and 1.5 mg (0-5) respectively (p=0.011). Patient–VAS was lower in HA compared with LA: 20 (6-54) vs 40 (20-56.3), p=0.003. Distance from the outpatient clinic was higher among HA: 30 (20-50) vs 25 km (9-45) in LA, p=0.037. LA were more frequently females, had a positive RF and/or ACPA and a higher DAS28 compared with HA but the difference was not significant (Table 5). Moreover, the rate of HA among 114 patients taking MTX (28.1%) and 26 taking LFN (23.1%) was not significantly different (p=0.605). No significant difference in adherence was observed between different administration routes of MTX either: 35.1% (13/37) HA in oral MTX and 25% (18/72) in subcutaneous/intramuscular MTX (p=0.265).

The factors associated with high adherence to anti-rheumatic treatment were tested by multivariate analysis. Covariates were selected according to univariate analysis. Values achieving a p <0.10 in univariate analysis, were included in the logistic regression model: gender, age, BMI, employment, primary/middle school education, bDMARD treatment, csDMARD treatment, PDN daily dose, DAS28, patient-VAS and distance from the outpatient clinic. Age was excluded from the multivariate analysis because it was found to be collinear with employment (VIF=2.05 and 1.67 respectively). Age in employed patients

was significantly lower compared with unemployed: 50 (39-57) and 67 years (59-71), p<0.001. The final regression model is reported in Table 7. Employment and bDMARD treatment were found to be independently associated with high adherence to treatment. Treatment with a bDMARD increased by almost 3-fold the likelihood of being HA: OR 2.88 (1.36-6.1), p=0.006. Likewise, employment was positively associated with high adherence with an OR of 2.36 (1.21-4.62), p=0.012 (Table 7).

Rate of high adherence in the bDMARD group was 40.9% (79/193) while it was 22.4% (24/107) in patients treated with csDMARDs only (p=0.001). Significant differences were observed between characteristics of patients treated with bDMARDs and those treated only with csDMARDs (Table 6). Patients on bDMARDs were significantly younger, they were more often employed and had a higher education level compared with those treated with csDMARDs only. Patients in the bDMARD group compared to the csDMARD group had a longer disease and treatment duration; a higher HAQ; they took higher daily doses of PDN and less often took chronic medication other than the anti-rheumatic treatment. Lastly, patients treated with bDMARDs were usually undergoing a higher number of rheumatic assessments per year and were more distant from the rheumatology clinic.

Factors significantly associated with high adherence in patients treated with csDMARDs only were: employment (14, 60.9% of HA vs 8, 33.7% of LA, p=0.019), a lower patient-VAS (10, 0-35 in HA vs 30, 10-50 in LA, p=0.03), and a higher distance from the clinic (22.5, 15-56.5 in HA vs 15, 3-30 in LA, p=0.044) (Table 6). Factors positively associated with high adherence in the bDMARD group were employment (41, 64.1% in HA vs 40, 37% in LA, p=0.001) and higher education level (49, 62.8% vs 48, 46.2%, p=0.026). Factors negatively associated with high adherence were: female gender (52, 65.8% in HA vs 90, 80.4% in LA, p=0.024), and a higher patient-VAS (30, 10-50 in HA vs 45, 28-69 in LA, p=0.03). Patients receiving low-dose bDMARD were more likely to be HA, but the difference was not significant (29, 49.4% vs 43, 37.7%, p=0.091) (Table 6).

Separate multivariate analysis was run to assess factors associated with high adherence in each group (synthetic and bDMARDs). Covariates included were those achieving a p value <0.10 in univariate analysis.

In the model for patients treated with csDMARDs only, covariates were: age, employment, patient-VAS and distance from the clinic. Age was collinear with employment (VIF=2.221

and 2.038, respectively) and was excluded from the model. The logistic regression analysis did not find a significant model explaining factors associated with adherence in patients treated with csDMARDs only (Table 8).

Covariates included in the model for patients treated with bDMARDs were: gender, employment, education, positive RF and/or ACPA, low-dose bDMARD, treatment with HCQ/SSZ and patient-VAS. No variable was excluded because of collinearity. The final model included 3 variables. Only employment was positively and significantly associated with high adherence: OR 2.89 (1.3-6.44), p=0.009 (Table 8).

Discussion

This is the first study evaluating adherence in RA patients by the means of I-CQR5, a validated Italian version of the CQR5 questionnaire. Only 35.2% of RA patients were found to be highly adherent to treatment. Treatment with bDMARDs and employment were the major factors associated with treatment adherence, increasing by almost 3-fold the likelihood of being highly adherent. Older age, lower education level, higher PDN daily dose, use of a csDMARD (particulary HCQ and SSZ) and higher patient-VAS (i.e. worse global health) were significantly associated with poor adherence but the association was not confirmed by multivariate analysis. No independent predictors were found in the group of patients treated with csDMARDs only, while employment was positively associated with high adherence in patients treated with bDMARDs.

A direct comparison between adherence rate in this study and in other reports is difficult to perform because of the different methods used to assess adherence. None the less, the rate of HA in our analysis was lower compared to previous studies. In surveys including bDMARDs, high adherence was reported to be around 50-90% [7,8,29], although reports of adherence as low as 11% have been also described[30]. Adherence rates measured with CQR report high adherence in 20-90% of patients, but most of them describe rates around 65-90% of HA[31,32,33,34,35]. Studies using CQR5 are only a few and do not describe rated of HA in a comparable cohort of RA patients[19,20].

The 19-item CQR showed good agreement with other patient-reported outcomes, but a rather low agreement with other study-specific questionnaires on adherence. Some studies reported that CQR identifies approximately double the rate of LA compared to other questionnaires[36]. It has to be taken into account that CQR5 allows only a discrete distinction of adherence in two categories (taking correctly ≥ or < 80% of prescribed medications). Other questionnaires, like CQR, allow to score adherence on a scale with different levels of adherence entailing lower overall rates of poor adherence.

Compared to other questionnaires, CQR and CQR5 address to a wider burden of treatment adherence. Only one question on skipping of medications is included in CQR5 (item no.2). Medication Adherence Scale (MARS) and Morisky adherence questionnaire, which have

been also used in RA, have a number of questions that specifically investigate the correct intake of medication. CQR and CQR5 explore a general attitude of the patient toward the anti-rheumatic treatment and toward their rheumatologists and physicians. It has been shown that CQR5 results are strongly associated with the Beliefs on Medications Questionnaire (BMQ)[37], further supporting the evidence that CQR5 reflects patients' opinion on the treatment and on the global rheumatologic care rather than the correct medication administration.

In our cohort, rate of HA in patients treated only with csDMARDs is low, which has to be ascribed mainly to HCQ and SSZ. These two DMARDs accounted for almost one third of csDMARDs in the study. HCQ and SSZ are known to be subjected to low adherence[38]. The reason of poor adherence might be due to the number of tablet assumed per day (varying between 1 and 6) and a minor effectiveness compared to MTX and LFN[6].

A lower rate of high adherence was observed in patients treated with MTX compared to those who did not take MTX. This difference was no longer present when the csDMARD-only- and the bDMARD-treated groups were considered separately. Treatment with MTX, particularly association with MTX, has been described as undesirable by patients[39]. MTX has some adverse effect which constitute the main reason of poor adherence and can be under-recognised by the physician[8,40,41].

Numerous reports of patients' preference for monotherapy are available[8,39,42,43]. In our study, combination of bDMARD with MTX or LFN did not affect the rate of high adherence. Among patients who completed the questionnaire, only one third was undergoing a combination treatment of a bDMARD with a csDMARD. The study sample did not adequately represent the entire RA population in our outpatient clinic. Recent analyses in our cohort found rates of combination treatment around 50-65%[25,44].

The long treatment duration (median 7 years) might explain the low rate of combination treatment. Adherence to anti-rheumatic treatments has been described to reduce over time[9,45]. Patients with long-standing treatments are prone to self-management of treatment because of tolerability issues or perception of a mild disease activity when level of pain is low[9,46]. Patients with current long-standing combination treatment might be those who well tolerated this treatment strategy and maintained it.

Furthermore, most of the patients included in the study had an adequate disease control (90% in low disease activity and 60% in remission). Self-discontinuation of the anti-rheumatic treatments has been reported in patients with low levels of pain, as they might feel that treatment is unnecessary[46]. Although we found no association with RA measures, patients with very low disease activity might have decreased and discontinued treatment on purpose.

Preference and high adherence of patients for bDMARDs has been already described[6,30,47]. Patients prefer the treatment with bDMARDs as it usually has a faster and greater effectiveness, but also because bDMARDs are innovative and costly[6,30]. Patients are in fact informed about of newly introduced medications and of the the differences in costs between csDMARds and bsDMARDs. This awareness might foster the feeling of a privileged health care with bDMARDs and the covet to rightful access to bDMARDs[30].

No association with disease activity measures was found except for patient-VAS in this study. A trend toward low adherence was found in patients with high HAQ and DAS28, positive RF and/or ACPA and high daily dose of PDN in univariate analysis. These variables are usually related with severe disease. That being so, the fact that patients with these characteristics were more frequently treated with bDMARDs may have reduced the capability of the study to show differential adherence according to disease activity.

In most studies no significant association was found between employment and adherence[13,29,35,48,49]. 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 work ability and unemployment bother considerably RA patients[50,51]. Full functionality is essential to ensure working productivity, thereby encouraging a compliant behaviour in employed patients.

In this study, a number of potential factors associated to adherence was explored and several associations emerged in the univariate analysis. Previous large reports analysing factors that drive treatment adherence have found a few and often divergent associations, especially regarding demographical and social variables[7,29,35]. The majority of these studies was conducted through multicentre, nation-wide surveys. A possible explanation of the relatively high number of association we found, is that the study was performed in one centre which collects mainly patients from the same geographical region. On one side, the

analysis conducted in a restricted area limits the generalisability of the results to the entire Italian RA population. On the other side, being limited to one area, potential confounders such as social and cultural variability, as well as accessibility to treatments, were reduced.

The study has some limits. Firstly, the use of a questionnaire to measure adherence might be subjected to some bias as questionnaires are prone to prejudiced results from socially desirable answering[52]. The adoption of anonymous questionnaires, correct item construction and validation –which was properly undertaken in this study- can overcome these issues.

Secondly, the sample was not representative of the entire RA population in our centre. About 10% of RA patients had to be excluded because of inability to complete the questionnaire. The patients not included in the analysis patients were mostly elderly or foreigners. These groups of patients are also subjected to incorrect administration of treatment because of cognitive impairment or linguistic and cultural barriers. The rate of adherence in these patients should also be assessed, being a considerable proportion of patients.

The study provided the first large cross sectional analysis of treatment adherence assessed with the validated I-CQR5 questionnaire in a monocentric cohort in Italy. The I-CQR5 was well understood and appreciated by patients. Furthermore, the I-CQR5 was easy to administer and very little time-consuming for the physician. The study reports a higher adherence to bDMARDs compared to csDMARDs which is consistent with previous reports, but a rather poor overall adherence to anti-rheumatic drugs. CQR5 and I-CQR5 address a broader patient perspective on the anti-rheumatic treatment. They might identify as LA not only patients who skip or discontinue the medication, but also patients with certain concerns and misbeliefs on medical treatment. Further studies are needed to evaluate actual administration and medical possession in LA and HA identified by I-CQR5. The potential effect of adherence, measured with I-CQR5, on treatment survival and disease outcomes on the long-term follow-up should also be determined.

Table 1. Original CQR5 version, back-translations, issues and agreement on the I-CQR5 discussed by the expert committee for each item of the questionnaire.

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, "*adherence*" meand "*adherence*". "*Compliance*" allows to specifically refer to the original questionnaire version.	**Questionario sulla Compliance in Reumatologia a 5 domande.**
Acronym				
CQR5	*CQR5*	*CQR5*	The acronym I-CQR5 specifically refers to the original questionnaire version.	**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 more 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.*	Uncertainty on the translation of "*to take*" was discussed. "*Assumere*" was a more 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 more suitable 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.*	Uncertainty on the translation of "*to store*" was discussed.	**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.*	Uncertainty on the 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. 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*" has usually a broader meaning compared with "*dottore*".	**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**

Table 2. Characteristics of the patients and questionnaires used for the cross-cultural validation.

	All	HA	LA	p value
No.	268	93	175	
Females, n (%)	201 (77)	64 (69)	137 (81)	0.025
Age, years (IQR)	57 (48-67)	55.5 (48-64.5)	58.0 (49-67.5)	0.177
Education level				0.121
Primary school, n (%)	29 (12)	9 (10)	9 (10)	
Middle school, n (%)	97 (39)	27 (30)	27 (30)	
Secondary school, n (%)	87 (35)	36 (40)	36 (40)	
University, n (%)	37 (15)	17 (19)	17 (19)	
Social status				0.76
Living with parents and family, n (%)	13 (6)	3 (5)	10 (7)	
Living alone, n (%)	30 (14)	8 (12)	22 (14)	
Living with partner and family, n (%)	159 (73)	47 (73)	112 (73)	
Other, n (%)	15 (7)	6 (9)	9 (6)	
Disease duration, years, median (IQR)	13.5(8.8-19.3)	13 (8-20)	12.0 (6.8-20)	0.365
Item no. 1				
Answer no. 1, n (%)	112 (42)	28 (30)	84 (48)	<0.001
Answer no. 2, n (%)	83 (31)	18 (19)	65 (37)	
Answer no. 3, n (%)	32 (12)	18 (19)	14 (8)	
Answer no. 4, n (%)	41 (15)	29 (31)	12 (7)	
Item no. 2				
Answer no. 1, n (%)	113 (42)	0 (0)	113 (65)	<0.001
Answer no. 2, n (%)	79 (29)	24 (26)	55 (31)	
Answer no. 3, n (%)	39 (15)	32 (34)	7 (4)	
Answer no. 4, n (%)	37 (14)	37 (40)	0 (0)	
Item no. 3				
Answer no. 1, n (%)	128 (48)	21 (23)	107 (61)	<0.001
Answer no. 2, n (%)	78 (29)	25 (27)	53 (30)	
Answer no. 3, n (%)	25 (9)	15 (16)	10 (6)	
Answer no. 4, n (%)	37 (14)	32 (34)	5 (3)	
Item no. 4				
Answer no. 1, n (%)	139 (52)	24 (26)	115 (66)	<0.001
Answer no. 2, n (%)	65 (24)	20 (22)	45 (26)	
Answer no. 3, n (%)	27 (10)	21 (23)	6 (3)	
Answer no. 4, n (%)	37 (14)	28 (30)	9 (5)	
Item no. 5				
Answer no. 1, n (%)	117 (44)	13 (14)	104 (59)	<0.001
Answer no. 2, n (%)	86 (32)	31 (33)	55 (31)	
Answer no. 3, n (%)	30 (11)	19 (20)	11 (6)	
Answer no. 4, n (%)	35 (13)	30 (32)	5 (3)	

HA high adherers, *LA* low adherers, *IQR* interquartile range.

Table 3. Factor analysis

	Loadings	
	All[†]	**HA**
Item no. 1	0.721	0.460
Item no. 2	0.629	0.522
Item no. 3	0.750	0.522
Item no. 4	0.660	0.675
Item no. 5	0.534	0.807
	Factor 1	**Factor 2**
Sum of square loadings	2.210	1.869
Proportion Variance	0.442	0.374
Cumulative Variance	0.442	0.816

Table 4. Item-fit statistics.

	Chi-square	**df**	**p value**	**Outfit mean square**	**Infit mean square**	**Outfit t**	**Infit t**
Item no. 1	224.213	183	0.020	1.219	1.111	1.96	1.05
Item no. 2	205.899	183	0.118	1.119	1.132	1.17	1.29
Item no. 3	142.900	183	0.987	0.777	0.740	-2.18	-2.65
Item no. 4	95.060	183	1.000	0.517	0.523	-4.90	-5.34
Item no. 5	131.885	183	0.998	0.7171	0.682	-3.05	-3.45

df degreees of freedom.

Table 5. Demographics and clinical variables according to high and low adherence to treatment defined by I-CQR5.

	Total	HA	LA	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 (%)	129 (43.7)	40 (38.5)	89 (46.6)	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
PDN 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)	0.49
Distance from clinic, km, median (IQR)	30 (11-45)	30 (20-50)	25 (9-45)	0.037‡

†defined as DAS28<2.6; ¥defined as DAS28<3.2; ‡variables included in the multivariate analysis as achieving a p value <0.10 in the univariate analysis.

HA high adherers, *LA* 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, *PDN* prednisone, *NSAIDs* non-steroideal antinflammatory drugs, *HAQ* Health Assessment Questionnaire, *DAS28* disease activity score in 28 joints, *VAS* visual analogic scale.

Table 6. Demographics and clinical variables according to high and low adherence to treatment defined by I-CQR5 and in the patients treated with csDMARDs only or with bDMARD.

	csDMARD treatment				bDMARD treatment			
	All	**HA**	**LA**	**p value**	**All**	**HA**	**LA**	**p value**
No.	107	24 (22.4)	83 (77.6)		193	79 (40.9)	114 (59.1)	
HA, n (%)*	24 (22.4)	-	-	-	79 (40.9)	-	-	-
Females (%)	72 (72)	18 (75)	54 (71.1)	0.707	142 (73.4)	52 (65.8)	90 (80.4)	0.024‡
Age, years, median (IQR)*	62 (51-70.8)	53.5 (48.5-65)	64.5 (52.5-71)	0.082‡	57 (46-65)	54.5 (39.8-28)	57.5 (47-66.3)	0.491
BMI, median (IQR)	24 (23-28)	24 (23-28)	24 (23-27.5)	0.801	24 (22-28)	25 (23-28)	24 (21-27.8)	0.545
Smokers, n (%)	17 (18.1)	1 (5.6)	16 (21.1)	0.125	28 (17.6)	12 (21.1)	16 (15.7)	0.394
Employed, n (%)	42 (39.6)	14 (60.9)	28 (33.7)	0.019‡	81 (47.1)	41 (64.1)	40 (37)	0.001‡
Education level				0.250				0.147
Primary school, n (%)	14 (14.3)	1 (4.5)	13 (17.1)		20 (11)	8 (10.3)	12 (11.5)	
Middle school, n (%)	45 (45.9)	11 (50)	34 (44.7)		65 (35.7)	21 (26.9)	44 (42.3)	
Secondary school, n (%)	29 (29.6)	9 (40.9)	20 (26.3)		68 (37.4)	34 (43.6)	34 (32.7)	
University, n (%)	10 (10.2)	1 (4.5)	9 (11.8)		29 (15.9)	15 (19.2)	14 (13.5)	
Primary/middle school education, n (%) **	59 (60.2)	12 (54.5)	47 (61.8)	0.538	85 (46.7)	29 (37.2)	56 (53.8)	0.026‡
Social status				0.634				0.567
Living with parents and family, n (%)	3 (3.1)	0 (0)	3 (3.8)		13 (8.7)	5 (9.3)	8 (8.3)	
Living alone, n (%)	16 (16.3)	2 (10)	14 (17.9)		16 (10.7)	6 (11.1)	10 (10.4)	
Living with partner and family, n (%)	69 (70.4)	16 (80)	53 (67.9)		113 (75.3)	38 (70.4)	75 (78.1)	
Other, n (%)	10 (10.2)	2 (10)	8 (10.3)		6 (4)	4 (7.4)	2 (2.1)	
Positive RF and/or ACPA, n (%)	44 (44.4)	9 (45)	35 (44.3)	0.955	79 (42.2)	27 (34.6)	52 (47.7)	0.074‡
Disease duration, years, median (IQR)*	8 (4-15)	6 (4-13.8)	8 (4-17)	0.409	15 (9-21)	14 (10-21)	15 (9-21.5)	0.762
Fibromyalgia, n (%)	13 (14.1)	3 (14.3)	10 (14.1)	0.981	38 (20.8)	12 (15.6)	26 (24.5)	0.141
csDMARD treatment, n (%)*	107 (100)	24 (100)	83 (100)	-	57 (30.5)	19 (24.4)	38 (34.9)	0.124
Methotrexate, n (%)*	73 (68.2)	16 (66.7)	57 (68.7)	0.852	41 (21.9)	16 (20.5)	25 (22.9)	0.693
Leflunomide, n (%)*	19 (17.8)	5 (20.8)	14 (16.9)	0.654	12 (6.4)	3 (3.8)	9 (8.3)	0.225
Other csDMARD, n (%)*	34 (31.8)	6 (25)	28 (33.7)	0.418	7 (3.7)	0 (0)	7 (6.4)	0.023
bDMARD treatment, n (%)	-	-	-	-	193 (100)	79 (100)	114 (100)	-
Type of bDMARD		-	-	-				0.541
Abatacept, n (%)	-	-	-	-	13 (6.7)	8 (7)	5 (6.3)	
Adalimumab, n (%)	-	-	-	-	35 (18.1)	19 (16.7)	16 (20.3)	
Anakinra, n (%)	-	-	-	-	11 (5.7)	7 (6.1)	4 (5.1)	
Certolizumab pegol, n (%)	-	-	-	-	15 (7.8)	9 (7.9)	6 (7.6)	
Etanercept, n (%)	-	-	-	-	101 (52.3)	62 (54.4)	39 (49.4)	
Golimumab, n (%)	-	-	-	-	8 (4.1)	6 (5.3)	2 (2.5)	
Tocilizumab, n (%)	-	-	-	-	10 (5.2)	3 (2.6)	7 (8.9)	
bDMARD administration every ≤ 1 week, n (%)	-	-	-	-	110 (57)	43 (54.4)	67 (58.8)	0.549
Low-dose of the bDMARD, n (%)	-	-	-	-	82 (42.7)	29 (49.4)	43 (37.7)	0.091‡
Previous bDMARD failures, n (%)	-	-	-	-	62 (38.5)	29 (38.7)	33 (38.4)	0.969
Duration of bDMARD treatment, months, median (IQR)	-	-	-		88 (45-61.8)	88 (47-130)	86 (41.5-120)**	0.992
Combination treatment, n (%)**	19 (17.8)	3 (12.5)	16 (19.3)	0.444	57 (30.5)	19 (24.4)	38 (34.9)	0.124
Treatment duration>24 months, n (%)*	27 (65.9)	11 (68.8)	16 (64)	0.754	149 (83.7)	63 (82.9)	86 (84.3)	0.8
PDN daily dose, median (IQR)*	1 (1-5)	1 (1-2.5)	1 (1-5)	0.211	1.5 (0-5)	0 (0-5)	2.5 (0-5)	0.13
NSAIDs, n (%)	68 (64.8)	12 (52.2)	56 (68.3)	0.153	111 (66.1)	47 (67.1)	64 (65.3)	0.804
Painkillers, n (%)	21 (21.4)	4 (17.4)	17 (22.7)	0.59	50 (31.4)	22 (31.9)	28 (31.1)	0.917
Concomitant chronic treatment, n (%)*	59 (58.4)	10 (43.5)	49 (62.8)	0.098	91 (49.7)	38 (50.7)	53 (49.1)	0.832
DAS28, median (IQR)	2.2 (2-2.8)	2.1 (2-2.5)	2.3 (2-2.8)	0.57	2.3 (1.8-2.8)	2.3 (1.7-2.8)	2.4 (1.8-3.0)	0.441
Remission†, n (%)	64 (64)	16 (66.7)	48 (63.2)	0.755	101 (52.9)	39 (49.4)	62 (55.4)	0.414
Low disease activity‡, n (%)	88 (88)	23 (95.8)	65 (85.5)	0.176	174 (91.1)	73 (92.4)	101 (90.2)	0.595
Patient - VAS, median (IQR)	26.5 (10-48.5)	10 (0-35)	30 (10-50)	0.03‡	38 (20-66)	30 (10-50)	45 (28-69)	0.03‡
Physician - VAS, median (IQR)	10 (5-20)	10 (0-20)	10 (5-20)	0.876	10 (5-15)	10 (0-15)	10 (5-20)	0.988
HAQ, median (IQR)*	0.1 (0-0.6)	0.1 (0-0.5)	0.3 (0-0.6)	0.276	0.6 (0.1-1.1)	0.5 (0-1.1)	0.8 (0.3-1.1)	0.14
Disease flares, median (IQR)	33 (37.1)	5 (31.3)	28 (38.4)	0.594	11 (26.2)	5 (33.3)	6 (22.2)	0.433
No. of assessments per year, median (IQR)*	2 (2-2)	2 (2-2)	2 (2-3)	0.104	4 (3-4)	4 (3-4)	4 (3-4)	0.98
Distance from clinic, km, median (IQR)*	18 (4-30)	22.5 (15-56.5)	15 (3-30)	0.044‡	32 (18-50)	30 (20-50)	35 (18-50)	0.948

†defined as DAS28<2.6; ‡defined as DAS28<3.2; ‡variables included in the multivariate analysis in patients treated with csDMARDs only, as achieving a p <0.1;‡ variables included in the multivariate analysis in patients treated with bDMARDs as achieving a p <0.10; *significant difference observed in the cohort between patients treated with bDMARDs and those with synthertic DMARDs only with p<0.01 and ** p<0.05.

csDMARD conventional synthetic DMARD*, bDMARD* biological DMARD*, DMARD* disease-modifying anti-rheumatic drug, *HA* high adherers, *LA* low adherers, *IQR* interquartile range, *BMI* body mass index, *ACPA* anti-citrullinated peptides, *RF* rheumatoid factor, *PDN* prednisone, *NSAIDs* non-steroideal antinflammatory drugs, *HAQ* Health Assessment Questionnaire, *DAS28* disease activity score in 28 joints, *VAS* visual analogic scale.

Table 7. Factors associated with high adherence to anti-rheumatic treatment defined by I-CQR5: a multivariate regression analysis model.

	OR (95% C.I.)	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, *C.I.* confidence interval, *bDMARD* biological DMARD*, DMARD* disease-modifying anti-rheumatic drug, *VAS* visual analogic scale.

Table 8. Factors associated with high adherence to anti-rheumatic treatment defined by I-CQR5, two separate multivariate regression models for patients treated csDMARDs only and with bDMARDs.

	csDMARD treatment		bDMARD treatment	
	OR (95% C.I.)	p value	OR (95% C.I.)	p value
Female gender			2.05 (0.9-4.66)	0.086
Employment	1.95 (0.56-6.83)	0.296	2.89 (1.3-6.44)	0.009
Patient-VAS (per 10-unit increase)	0.77 (0.55-1.06)	0.105	0.95 (0.83-1.09)	0.453
Distance from clinic, km (per 10-unit increase)	1.13 (0.89-1.44)	0.31		
Model constant		0.025		0.035

OR odds ratio, *C.I.* confidence interval, *csDMARD* conventional synthetic DMARD, *bDMARD* biological DMARD, *DMARD* disease-modifying anti-rheumatic drug, *VAS* visual analogic scale.

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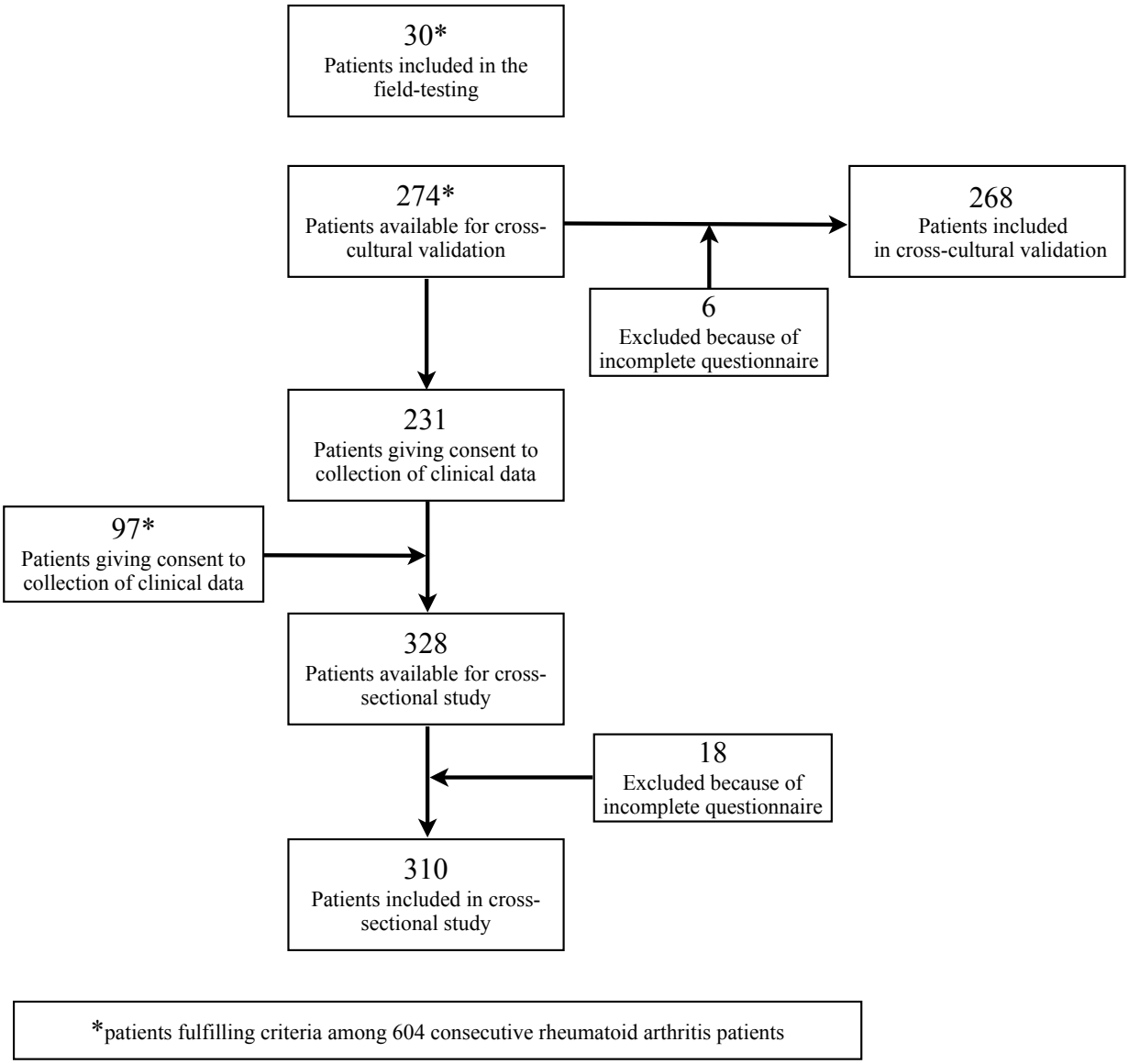

Figure 1. Schematic enrolment of the patients in the study.

Questionario sulla Compliance in Reumatologia a 5 domande (I-CQR5)

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.

1. Prendo i farmaci antireumatici perché in questo modo ho meno disturbi.

1	2	3	4
Completamente in disaccordo	In disaccordo	D'accordo	Completamente d'accordo

2. Non mi permetto mai di saltare la somministrazione dei farmaci antireumatici.

1	2	3	4
Completamente in disaccordo	In disaccordo	D'accordo	Completamente d'accordo

3. Metto sempre le medicine nello stesso posto per non dimenticare di prenderle.

1	2	3	4
Completamente in disaccordo	In disaccordo	D'accordo	Completamente d'accordo

4. Prendo i farmaci prescritti perché ho completa fiducia nel mio reumatologo.

1	2	3	4
Completamente in disaccordo	In disaccordo	D'accordo	Completamente d'accordo

5. Seguo sempre le indicazioni del mio medico.

1	2	3	4
Completamente in disaccordo	In disaccordo	D'accordo	Completamente d'accordo

Figure 2. Final I-CQR5 version.