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Are women with rheumatoid arthritis treated with biologicals adherent to treatment?

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Summary. *Introduction.* The Italian 5-item Compliance Questionnaire for Rheumatology (I-CQR5) identifies 'high' adherers (HAs) to treatment (i.e. taking ≥80% of their medications correctly), and 'low' adherers (LAs). The aim of this study was to evaluate factors associated with adherence in rheumatoid arthritis (RA) patients treated with biologicals (bDMARDs). We conducted separate analyses in females and males. *Methods.* RA patients (with disease duration >1 year, undergoing treatment with ≥1 self-administered bDMARD, willing and capable of completing the questionnaire unaided) were enrolled. I-CQR5s were anonymous. Demographic and clinical variables achieving a p <0.10 in univariate analysis were included in multivariate analysis. *Results.* A total of 191 patients (142 females) were included in the study. HAs were 41.4% of patients, 36.6% of females and 55.1% of males. Compared to men, women more often had a positive rheumatoid factor and/or anti-citrullinated peptides, more often had fibromyalgia and less likely to be employed. An independent association was found between HAs and employment: OR 2.81 (95% CI 1.29;6.05), p = 0.009. A gender-dependent trend in treatment adherence was observed: the OR of being HAs for female gender was 0.47 (95% CI 0.21;1.04), p = 0.064. Factors associated with HAs were, among females, employment (OR 2.71, 95% CI 1.17;6.27, p = 0.020) and, among males, patients' perception of the disease (OR 0.73, 95% CI 0.54;0.98, p = 0.038, per 10-unit worsening). *Conclusions.* Adherence to biological drugs in RA is suboptimal. Employment is a predictor of HAs to treatment. Inadequate control of pain might be responsible for poor adherence in women.

Key words. Rheumatoid arthritis, biologicals.

Le donne affette da artrite reumatoide curate con i farmaci biologici sono aderenti al trattamento?

Riassunto. *Introduzione.* La versione italiana del questionario sull'aderenza a 5 domande/quesiti per la reumatologia (I-CQR5) permette di identificare i pazienti 'ben' aderenti (HA) alla terapia antireumatica (ovvero coloro che assumono ≥80% delle loro terapie correttamente), o 'poco' aderenti (LA). L'obiettivo di questo studio era quello di individuare fattori associati con l'aderenza al trattamento, misurandoli con l'I-CQR5 in pazienti trattati con farmaci biologici (bDMARDs). Ci siamo rivolti in modo specifico alle differenze di genere e abbiamo condotto analisi separate per i fattori associati all'aderenza nel genere femminile e nel genere maschile. *Metodi.* Sono stati arruolati pazienti affetti da artrite reumatoide (con durata di malattia >1 anno, in terapia con ≥1 bDMARD autosomministrati, in grado di completare il questionario senza aiuto). Gli I-CQR5 erano anonimi e i dati clinici sono stati recuperati in forma anonima dal database locale. I fattori che abbiamo incluso erano demografici e sociali, oltre a quelli riguardanti informazioni cliniche e sulla terapia. I fattori che hanno raggiunto una p <0,10 all'analisi univariata sono stati inclusi nell'analisi di regressione multivariata. *Risultati.* Tra i 604 pazienti affetti da AR della nostra coorte, 191 sono stati inclusi nello studio e di questi 142 (73,4%) erano di sesso femminile. Il 41,4% (79/191) dei pazienti totali era HA: di questi, il 36,6% erano femmine e il 55,1% maschi. Dopo la correzione per fattori confondenti, rispetto ai maschi le pazienti femmine (totali) avevano una probabilità 3 volte maggiore di avere positività per fattore reumatoide e antipeptidi citrullinati (OR 3,18, IC 95% 1,21;8,35, p = 0,019); probabilità 6 volte maggiore di essere affette da fibromialgia (OR 6,68, IC 95% 1,43;31,12, p = 0,016); probabilità 3 volte minore di avere un impiego (OR 0,34, IC 95% 0,8;0,8, p = 0,014). Un'associazione indipendente è stata confermata solo tra alta aderenza e impiego lavorativo: OR 2,81 (IC 95% 1,29;6,05), p = 0,009. È stata evidenziata un'associazione tra genere e aderenza ai limiti della significatività, con la probabilità di essere altamente aderenti al trattamento ridotta del 50% per le femmine rispetto ai maschi: OR 0,47 (IC 95% 0,21;1,04), p = 0,064. Tra le femmine l'unica variabile associata con alta aderenza era l'impiego lavorativo: OR 2,71 (IC 95% 1,17;6,27), p = 0,020. La possibilità di essere altamente aderenti si riduceva del 25% nei maschi per ogni riduzione di 10 unità nella VAS pazienti (che sta a significare una peggiore percezione della malattia valutata su una scala da 0 a 100): OR 0,73 (IC 95% 0,54;0,98), p = 0,038. *Conclusioni.* L'aderenza al trattamento ai farmaci biologici in pazienti affetti da artrite reumatoide è subottimale. L'impiego lavorativo, che è più frequente nel sesso maschile, è predittore di buona aderenza al trattamento. L'inadeguato controllo del dolore e l'attività di malattia potrebbero essere responsabili di una bassa aderenza nelle pazienti con artrite reumatoide.

Parole chiave. Artrite reumatoide, farmaci biologici.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by persistent synovitis, which leads to joint disruption and disability.[1] Women are almost 3 times more likely than men to develop RA. The contribution of hormones, particularly oestrogens, is involved in the development of immune diseases.[2] There are diverging reports regarding disease activity differences across genders. Some studies report higher disease activity in women and a poorer response to treatment. These poorer assessments seem to be due to a worse perception of the disease in women, who report lower scores in subjective measures, such as pain and function.[3]

Conventional synthetic DMARDs (csDMARDs) are the first-line treatment for RA.[4] The addition of a biological or targeted synthetic DMARD (b/tsDMARDs) is recommended in patients with inadequate response to csDMARDs or poor prognostic factors.[4] Despite the high efficacy of current DMARDs, adherence to anti-rheumatic treatments is sub-optimal.[5] Non-adherence is responsible for disease progression and unnecessary treatment escalation.[6] Measuring adherence is complex. Self-reported questionnaires are the most common methods for assessing adherence. The Compliance-Questionnaire-Rheumatology (CQR) is a questionnaire developed specifically for rheumatic diseases[7] and a reduced version of this questionnaire (CQR5) was subsequently developed to be more suitable for clinical practice.[8] Our study group at the University Hospital of Padua validated an Italian version of this questionnaire (I-CQR5) in RA patients.[9] High adherence was associated with bDMARD use and with employment. A poorer adherence trend was observed in females, but the difference was not significant.

The aim of this study was to evaluate factors independently associated with treatment adherence, measured with I-CQR5 in patients treated with bDMARDs at the University of Padua Hospital cohort. We specifically addressed the gender differences and we conducted separate analyses for factors associated with adherence in females and males.

Methods

Patients

Patients were recruited from the outpatient clinic of Padua University Hospital. The inclusion criteria were: 1) diagnosis of RA according to the 1987 American College of Rheumatology classification criteria; 2) disease duration >1 year; 3) aged 18 years or above; 4) undergoing treatment with at least one self-administered csDMARD or bDMARD (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 criterion. Clinical information was collected from the local database. A code allowed the questionnaire result to be linked with the patients' information by a blinded investigator. The data collected were: gender, age, social status, education level, employment, smoking habits, BMI, distance from the outpatient clinic, number of assessments per year, seropositivity (i.e. positive rheumatoid factor - RF - and/or anti-citrullinated protein antibodies - ACPA), disease duration, fibromyalgia; bDMARD (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, tocilizumab), route and frequency of administration, treatment duration, concomitant treatment with csDMARDs (methotrexate, leflunomide, hydroxychloroquine or sulfasalazine), prednisone, non-steroidal anti-inflammatory drugs, painkillers, other chronic treatments, 28-joint disease activity score (DAS28), health assessment questionnaire, patients' and physicians' global health measured on a visual analogue scale (patient- and physician-VAS), self-reported disease flares.[10] Information was collected on the day of questionnaire completion. All participants gave written informed consent before inclusion in the study. 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 Padua.

Assessment of adherence with I-CQR5

Adherence was defined according to the I-CQR5 and patients were classified as HA or LA. I-CQR5 is a 5-item, self-administered questionnaire that identifies patients as 'low' adherers, i.e. taking <80% of their medication correctly[8,9,11] and has a four point Likert answering scale. A spreadsheet was provided to compute the result of CQR5 by entering the score for each answer.[8]

Factors associated with gender and high adherence

To evaluate the influence of gender on adherence we analysed: i) characteristics independently associated with gender in the cohort; ii) predictors of high adherence in the entire cohort; iii) predictors of high adherence in males and females separately.

Statistical analysis

Continuous variables were compared using Mann-Whitney test or Wilcoxon-Kruskal-Wallis test; qualitative variables 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. Multivariate analysis was run to assess the independent association of demographic and clinical variables with

gender and the association of the variables with adherence. The 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 were reported as the odds ratio (OR) with corresponding 95% confidence interval (CI). Analyses were performed using SPSS version 24.0.

Results

Patients

Of 381 consecutive RA patients receiving a bDMARD, 28 were excluded due to a lack of proficiency in the Italian language, 34 due to cognitive impairment or inability to complete the questionnaire unaided, and 126 were not willing to participate to the study. One hundred ninety-three patients met the enrolment criteria; 2 questionnaires were not completed and could not be used for the purposes of this study, leaving 191 patients eligible for analysis. 142 females were included (74.3%), median age was 57 years (46;65); disease duration 14 years (9;21); duration of the bDMARD treatment 88 months (47;123) and 38.5% of the patients had already had a bDMARD failure in the past (Table 1).

Factors associated with gender

Characteristics of all patients in the entire cohort and according to gender are detailed in Table 1. Following univariate analysis, the females were significantly older, more frequently seropositive, less frequently employed, more often had fibromyalgia, and reported worse functionality (measured with HAQ). After adjustment for confounding factors, females were 3 times more likely to be seropositive (OR 3.18, 95% CI 1.21;8.35, p = 0.019); 6 times more likely to have fibromyalgia (OR 6.68, 95% CI 1.43;31.12, p = 0.016); and 3 times less likely to be employed (OR 0.34, 95% CI 0.8;0.8, p = 0.014) (regression model p-value = 0.008).

Factors associated with high adherence in the entire cohort

The HA rate was 41.4% (79/191). The characteristics of HAs and LAs are reported in Table 2. HAs were more frequently males, employed, and had a better perception of disease activity (i.e. a lower patient-VAS). The factors associated with high adherence to treatment were tested by multivariate analysis. The variables that were included in the logistic regression model were: gender, seropositivity, employment, low-dose bDMARD treatment and patient-VAS. No variable was excluded due to collinearity. The multivariate regression analysis retained just two variables in the model: employment and gender

Table 1. Demographics and clinical variables according to gender

	All	Females	Males	p value
No.	191	142	49	
Females, n (%)	142 (74.3)	142 (100.0)	0 (0.0)	-
HA, n (%)	79 (41.4)	52 (36.6)	27 (55.1)	0.024
Age, years (median IQR)	57 (46;65)	58 (48.3;66.8)	50.5 (38;59)	0.006*
BMI (median IQR)	24 (22;28)	24 (21.5;27.5)	25.5 (23;28.3)	0.064
Smokers, n (%)	28 (17.6)	19 (15.8)	9 (23.1)	0.302
Employed, n (%)	80 (47.1)	50 (40.0)	30 (66.7)	0.002*
Education level				0.106
Primary school, n (%)	20 (11)	19 (14.3)	1 (2.1)	
Middle school, n (%)	64 (35.4)	46 (34.6)	18 (37.5)	
Secondary school, n (%)	68 (37.6)	46 (34.6)	22 (45.8)	
University, n (%)	29 (16)	22 (16.5)	7 (14.6)	
Social status				0.706
Living with parents and family, n (%)	13 (8.7)	8 (7.2)	5 (13.2)	
Living alone, n (%)	16 (10.7)	12 (10.8)	4 (10.5)	
Living with partner and family, n (%)	112 (75.2)	85 (76.6)	27 (71.1)	
Other, n (%)	6 (4)	4 (3.6)	2 (5.3)	

Continues

Table 1. Continued

	All	Females	Males	p value
Seropositive RA, n (%)	106 (57.6)	87 (63)	19 (41.3)	0.008*
Disease duration, years (median IQR)	14 (9;21)	14.5 (9;22)	14 (10;19)	0.550
Fibromyalgia, n (%)	38 (21.0)	36 (26.7)	2 (4.3)	0.001*
csDMARD treatment, n (%)	56 (30.3)	41 (29.9)	15 (31.3)	0.864
Methotrexate, n (%)	41 (22.2)	28 (20.4)	13 (27.1)	0.340
Leflunomide, n (%)	11 (5.9)	9 (6.6)	2 (4.2)	0.545
Other csDMARD, n (%)	6 (3.2)	6 (4.4)	0 (0.0)	0.140
Type of bDMARD				0.555
Abatacept, n (%)	13 (6.8)	10 (7)	3 (6.1)	-
Adalimumab, n (%)	33 (17.3)	22 (15.5)	11 (22.4)	-
Anakinra, n (%)	11 (5.8)	9 (6.3)	2 (4.1)	-
Certolizumab pegol, n (%)	15 (7.9)	14 (9.9)	1 (2)	-
Etanercept, n (%)	101 (52.9)	75 (52.8)	26 (53.1)	-
Golimumab, n (%)	8 (4.2)	5 (3.5)	3 (6.1)	-
Tocilizumab, n (%)	10 (5.2)	7 (4.9)	3 (6.1)	-
bDMARD administration every ≤1 week, n (%)	110 (57.6)	82 (57.7)	28 (57.1)	0.914
Low-dose of the bDMARD, n (%)	81 (42.6)	63 (44.7)	18 (36.7)	0.333
Previous bDMARD failures, n (%)	62 (38.5)	0 (0;1)	0 (0;1)	0.106
Duration of bDMARD treatment, months (median IQR)	88 (47;123)	74 (39.3;120)	104 (63;135.5)	0.136
PDN daily dose (median IQR)	1.75 (0;5)	2.5 (0;5)	0 (0;2.5)	0.112
NSAIDs, n (%)	110 (66.3)	81 (65.3)	29 (69.0)	0.562
Painkillers, n (%)	50 (31.8)	38 (32.5)	12 (30.0)	0.771
Concomitant chronic treatment, n (%)	91 (49.7)	70 (51.1)	21 (45.7)	0.523
DAS28 (median IQR)	2.29 (1.8;2.8)	2.34 (1.8;2.9)	2 (1.6;2.7)	0.057*
Remission**, n (%)	99 (52.4)	69 (48.9)	30 (62.5)	0.104
Low disease activity***, n (%)	172 (91.0)	126 (89.4)	46 (95.8)	0.176
Patient - VAS, n (median IQR)	38 (20;66)	40 (20;70)	30 (10;50)	0.131
Physician - VAS, n (median IQR)	10 (5;18.8)	15 (5;20)	10 (5;15)	0.642
HAQ (median IQR)	0.63 (0.1;1.1)	0.75 (0.4;1.3)	0.25 (0;0.8)	<0.001*
Disease flares (median IQR)	11 (27.5)	9 (31.0)	2 (18.2)	0.416
Assessments per year, n (median IQR)	4 (3;4)	4 (3;4)	3.5 (3;4)	0.273
Distance from clinic, km (median IQR)	32 (18;50)	30 (18;50)	40 (20;50)	0.557

*Variables included in the multivariate analysis as achieving a p <0.1; **defined as DAS28 <2.6; ***defined as DAS28 <3.2.
HA: high adherers, IQR: interquartile range, BMI: body mass index, RA: rheumatoid arthritis, csDMARD: conventional synthetic DMARD, bDMARD: biological DMARD, DMARD: disease-modifying anti-rheumatic drug, PDN: prednisone, NSAIDs: non-steroidal anti-inflammatory drugs, DAS28: disease activity score in 28 joints, VAS: visual analogue scale, HAQ: Health Assessment Questionnaire.

Table 2. Demographics and clinical variables according to high and low adherence to treatment defined by the I-CQR5 in the entire cohort

	All	HA	LA	p value
No.	191	79	112	
Females, n (%)	142 (74.3)	52 (65.8)	90 (80.4)	0.024*
HA, n (%)	79 (41.4)	79 (100)	0 (0)	-
Age, years (median IQR)	57 (46;65)	54.5 (40.8;62.8)	57.5 (47.3;66)	0.545
BMI (median IQR)	24 (22;28)	25 (23;28)	24 (21;27.3)	0.394
Smokers, n (%)	28 (17.6)	12 (21.1)	16 (15.7)	0.147
Employed, n (%)	80 (47.1)	41 (64.1)	39 (36.8)	0.001*
Education level				
Primary school, n (%)	20 (11)	8 (10.3)	12 (11.7)	
Middle school, n (%)	64 (35.4)	21 (26.9)	43 (41.7)	
Secondary school, n (%)	68 (37.6)	34 (43.6)	34 (33)	
University, n (%)	29 (16)	15 (19.2)	14 (13.6)	
Social status				0.567
Living with parents and family, n (%)	13 (8.7)	5 (9.3)	8 (8.4)	
Living alone, n (%)	16 (10.7)	6 (11.1)	10 (10.5)	
Living with partner and family, n (%)	112 (75.2)	38 (70.4)	74 (77.9)	
Other, n (%)	6 (4)	4 (7.4)	2 (2.1)	
Seropositive RA, n (%)	106 (57.6)	39 (50)	67 (63.2)	0.074*
Disease duration, years (median IQR)	14 (9;21)	14 (10;20.8)	15 (9;21)	0.762
Fibromyalgia, n (%)	38 (21)	12 (15.6)	26 (25)	0.141
csDMARD treatment, n (%)	56 (30.3)	19 (24.4)	37 (34.6)	0.124
Methotrexate, n (%)	41 (22.2)	16 (20.5)	25 (23.4)	0.693
Leflunomide, n (%)	11 (5.9)	3 (3.8)	8 (7.5)	0.225
Other csDMARD, n (%)	6 (3.2)	0 (0)	6 (5.6)	0.023
Type of bDMARD				0.541
Abatacept, n (%)	13 (6.8)	5 (6.3)	8 (7.1)	
Adalimumab, n (%)	33 (17.3)	16 (20.3)	17 (15.2)	
Anakinra, n (%)	11 (5.8)	4 (5.1)	7 (6.3)	
Certolizumab pegol, n (%)	15 (7.9)	6 (7.6)	9 (8)	
Etanercept, n (%)	101 (52.9)	39 (49.4)	62 (55.4)	
Golimumab, n (%)	8 (4.2)	2 (2.5)	6 (5.4)	
Tocilizumab, n (%)	10 (5.2)	7 (8.9)	3 (2.7)	
bDMARD administration every ≤ 1 week, n (%)	110 (57.6)	43 (54.4)	67 (59.8)	0.549

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Table 2. Continued

	All	HA	LA	p value
Low-dose of the bDMARD, n (%)	81 (42.6)	39 (50)	42 (37.5)	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 (47;123)	88 (48;127)	86 (44;119.8)	0.992
PDN daily dose (median IQR)	1.75 (0;5)	0 (0;4.7)	2.5 (0;5)	0.13
NSAIDs, n (%)	110 (66.3)	47 (67.1)	63 (65.6)	0.804
Painkillers, n (%)	50 (31.8)	22 (31.9)	28 (31.8)	0.917
Concomitant chronic treatment, n (%)	91 (49.7)	38 (50.7)	53 (49.1)	0.832
DAS28 (median IQR)	2.29 (1.8;2.8)	2.26 (1.7;2.8)	2.39 (1.8;2.9)	0.441
Remission**, n (%)	99 (52.4)	39 (49.4)	60 (54.5)	0.414
Low disease activity***, n (%)	172 (91)	73 (92.4)	99 (90)	0.595
Patient - VAS, n (median IQR)	38 (20;66)	30 (10;50)	45 (30;69)	0.03*
Physician - VAS, n (median IQR)	10 (5;18.8)	10 (2.5;15)	10 (5;20)	0.988
HAQ (median IQR)	0.63 (0.1;1.1)	0.5 (0;1)	0.75 (0.3;1.1)	0.14
Disease flares, n (median IQR)	11 (27.5)	5 (33.3)	6 (24)	0.433
Assessments per year, n (median IQR)	4 (3;4)	4 (3;4)	4 (3;4)	0.98
Distance from clinic, km (median IQR)	32 (18;50)	30 (20;50)	35 (18;50)	0.948

*Variables included in the multivariate analysis as achieving a p <0.1; **defined as DAS28 <2.6; ***defined as DAS28 <3.2.
HA: high adherers, LA: low adherers, IQR: interquartile range, BMI: body mass index, RA: rheumatoid arthritis, csDMARD: conventional synthetic DMARD, bDMARD: biological DMARD, DMARD: disease-modifying anti-rheumatic drug, PDN: prednisone, NSAIDs: non-steroidal anti-inflammatory drugs, DAS28: disease activity score in 28 joints, VAS: visual analogue scale, HAQ: Health Assessment Questionnaire.

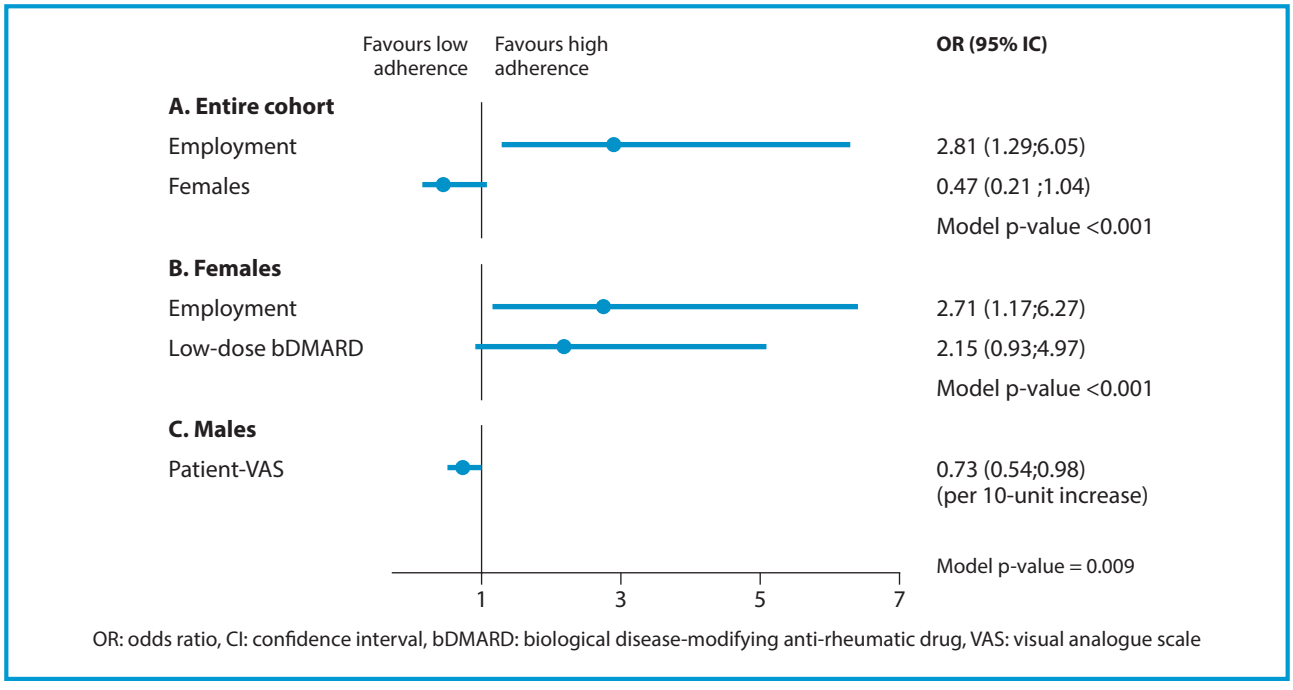

Figure 1. Factors independently associated with high adherence, results of multivariate analysis: A. Entire cohort; B. Females; C. Males.

(model p-value <0.001). An independent association was confirmed only between high adherence and employment: OR 2.81 (95% CI 1.29;6.05), p = 0.009. A gender-dependent trend in treatment adherence was observed, as the likelihood of being highly adherent was 50% lower in females than in males: OR 0.47 (95% CI 0.21;1.04), p = 0.064 (Figure 1A).

Factors associated with high adherence in females

The HA rate amongst females was 36.6% (52/142). The characteristics of HAs and LAs are reported in Table 3. Amongst females, HAs were more frequently employed, less frequently using a csDMARD in combination with the bDMARD and more frequently were receiving a low-dose of the bDMARD. The variables included in the logistic regression model were: employment, csDMARD use and low-dose bDMARD (model p-value <0.001). No variable was excluded due to collinearity. Amongst females, the only variable associated with high adherence was employment: OR 2.71 (95% CI 1.17;6.27), p = 0.020. Being on a low-dose bDMARD treatment was also included in the model but the association was not significant: OR 2.15 (95% CI 0.93;4.97), p = 0.074 (Figure 1B).

Factors associated with high adherence in males

The high adherence rate amongst males was 55.1% (27/49). The characteristics of HAs and LAs are reported in Table 3. Amongst males, HAs were more frequently using a TNF-inhibitor. The variables included in the logistic regression model were: TNF-inhibitor use, duration of the bDMARD treatment, patient-VAS, distance from clinic (Table 3). No variable was excluded due to collinearity. Amongst males, the only variable associated with high adherence was the patient's perception of disease activity, indeed, the patient-VAS was the only variable that was retained in the final regression model (model p-value = 0.009). The chances of being highly adherent decreased by 25% in males for every 10-unit increase in the patient-VAS (meaning a worse perception of the disease, with VAS measured on a 0-100 scale): OR 0.73 (95% CI 0.54;0.98), p = 0.038 (Figure 1C).

Discussion

In this study, we evaluate adherence in bDMARD-treated RA patients by means of the I-CQR5, a questionnaire specifically developed for rheumatic diseases. Notwithstanding the high effectiveness of bDMARD treatment, we observed a highly adherent (HA) rate of just 40%. Employment increased the likelihood of being HA to treatment 3-fold. Gender was also associated with poorer adherence in females than in males but, after adjustment for confounders, this difference was not significant. The main determinants of good adherence were employment in females and a better perception of disease activity in males. We also observed that females were more likely to be RF and/or ACPA-positive, and to have fibromyalgia and less likely to be employed than males.

The preference of patients for bDMARDs has been described along with a better adherence to these very effective and well tolerated treatments.[12] Nevertheless, in our study, less than half of the patients were HAs. Adherence seems lower than previous reports, although a comparison is not feasible due to the different methods used to assess adherence. Other questionnaires score adherence on a continuous scale, whereas the CQR5 and I-CQR5 provide a discrete distinction into two categories: HAs or LAs, i.e. taking correctly ≥ or <80% of prescribed medications.[7-9] Thus, the I-CQR5 might entail lower rates of good adherence.[8] In surveys including bDMARDs, high adherence was reported to be around 50-90%[5] although reports of adherence as low as 11% have been also described.[12] Studies using the CQR5 do not describe rates of HAs in a comparable cohort of RA patients.[13]

The low adherence rate might be explained by the fact that the CQR, CQR5 and I-CQR5 might reflect the patients' opinion on treatment and their perception of the disease. Indeed, compared to other questionnaires, just one question in the CQR5 regards the skipping of medication. The I-CQR5 may address the question of treatment adherence rather than correct medication administration.[9]

The long duration of treatment might contribute to the poor adherence we observed. Patients with long-standing treatments were described to be prone to self-management.[6,14] Furthermore, most of the patients were in remission. Self-discontinuation of anti-rheumatic treatments has been reported in patients with low pain levels, as they might feel that treatment is unnecessary.[14] Good RA control might be a new reason for poor adherence in the case of chronic treatment.

The major determinant for adherence was employment. This result is in line with our previous study including patients treated with csDMARDs alone.[9] In other reports on adherence no significant association was found with employment.[15,16] Full functionality is essential to ensure work ability and may encourage compliant behaviour.

In univariate analysis, females were seen to be less adherent than males: half of all male patients but just one third of females were HAs. Only a few studies on adherence were capable of identifying independent associations with gender. The first reports in rheumatology patients reported less compliant behaviour in women.[12] One Brazilian study considering medication possession revealed that women were less adherent than

Table 3. Demographics and clinical variables according to high and low adherence to treatment defined by the I-CQR5 separately in females and males

	Females				Males			
	All	HA	LA	p value	All	HA	LA	p value
No.	142	52	90		49	27	22	
Females, n (%)	142 (100.0)	52 (100.0)	90 (100.0)	-	0 (0.0)	0 (0.0)	0 (0.0)	-
Age, years (median IQR)	58 (48.3;66.8)	57 (48;65)	58 (49;67)	0.610	50.5 (38;59)	48 (38;58)	55 (44;59)	0.366
BMI (median IQR)	24 (21.5;27.5)	25 (22;28)	24 (21;27)	0.161	25.5 (23;28.3)	25 (23.3;28.8)	26.5 (22.8;27.8)	0.943
Smokers, n (%)	19 (15.8)	8 (21.6)	11 (13.3)	0.246	9 (23.1)	4 (20.0)	5 (26.3)	0.640
Employed, n (%)	50 (40.0)	22 (55.0)	28 (32.9)	0.019*	30 (66.7)	19 (79.2)	11 (52.4)	0.57
Education level				0.186				0.560
Primary school, n (%)	19 (14.3)	8 (15.7)	11 (13.4)		1 (2.1)	0 (0)	1 (4.8)	
Middle school, n (%)	46 (34.6)	12 (23.5)	34 (41.5)		18 (37.5)	9 (33.3)	9 (42.9)	
Secondary school, n (%)	46 (34.6)	20 (39.2)	26 (31.7)		22 (45.8)	14 (51.9)	8 (38.1)	
University, n (%)	22 (16.5)	11 (21.6)	11 (13.4)		7 (14.6)	4 (14.8)	3 (14.3)	
Social status				0.885				0.469
Living with parents and family, n (%)	8 (7.2)	2 (5.7)	6 (7.9)		5 (13.2)	3 (15.8)	2 (10.5)	
Living alone, n (%)	12 (10.8)	4 (11.4)	8 (10.5)		4 (10.5)	2 (10.5)	2 (10.5)	
Living with partner and family, n (%)	85 (76.6)	26 (74.3)	59 (77.6)		27 (71.1)	12 (63.2)	15 (78.9)	
Other, n (%)	4 (3.6)	2 (5.7)	2 (2.6)		2 (5.3)	2 (10.5)	0 (0)	
Seropositive RA, n (%)	87 (63)	27 (53)	60 (68)	0.121	19 (41.3)	10 (40)	9 (42.9)	0.943
Disease duration, years (median IQR)	14.5 (9;22)	14 (10;21)	15 (9;22)	0.703	14 (10;19)	15 (12;18.5)	14 (9.3;19.3)	0.171
Fibromyalgia, n (%)	36 (26.7)	11 (22.0)	25 (29.4)	0.347	2 (4.3)	1 (3.7)	1 (5.3)	0.798
csDMARD treatment, n (%)	41 (29.9)	9 (17.6)	32 (37.2)	0.016*	15 (31.3)	10 (37.0)	5 (23.8)	0.327
Methotrexate, n (%)	28 (20.4)	7 (13.7)	21 (24.4)	0.134	13 (27.1)	9 (33.3)	4 (19.0)	0.269
Leflunomide, n (%)	9 (6.6)	2 (3.9)	7 (8.1)	0.335	2 (4.2)	1 (3.7)	1 (4.8)	0.856
Other csDMARD, n (%)	6 (4.4)	0 (0.0)	6 (7.0)	0.054	0 (0.0)	0 (0.0)	0 (0.0)	-
Type of bDMARD				0.802				0.263
Abatacept, n (%)	10 (7)	3 (5.8)	7 (7.8)		3 (6.1)	2 (7.4)	1 (4.5)	-
Adalimumab, n (%)	22 (15.5)	9 (17.3)	13 (14.4)		11 (22.4)	7 (25.9)	4 (18.2)	-
Anakinra, n (%)	9 (6.3)	2 (3.8)	7 (7.8)		2 (4.1)	2 (7.4)	0 (0)	-
Certolizumab pegol, n (%)	14 (9.9)	5 (9.6)	9 (10)		1 (2)	1 (3.7)	0 (0)	-

Continues

Table 3. Continued

	Females				Males			
	All	HA	LA	p value	All	HA	LA	p value
Etanercept, n (%)	75 (52.8)	28 (53.8)	47 (52.2)		26 (53.1)	11 (40.7)	15 (68.2)	-
Golimumab, n (%)	5 (3.5)	1 (1.9)	4 (4.4)		3 (6.1)	1 (3.7)	2 (9.1)	-
Tocilizumab, n (%)	7 (4.9)	4 (7.7)	3 (3.3)		3 (6.1)	3 (11.1)	0 (0)	-
bDMARD administration every ≤1 week, n (%)	82 (57.7)	30 (57.7)	52 (57.8)	0.996	28 (57.1)	13 (48.1)	15 (68.2)	0.159
Low-dose of the bDMARD, n (%)	63 (44.7)	29 (56.9)	34 (37.8)	0.029*	18 (36.7)	10 (37.0)	8 (36.4)	0.961
Previous bDMARD failures, n (%)	0 (0;1)	0 (0;1)	0 (0;1)	0.647	0 (0;1)	0.5 (0;1)	0 (0;1)	0.708
Duration of bDMARD treatment, months (median IQR)	74 (39.3;120)	72 (38;120)	88 (47;120)	0.548	104 (63;135.5)	109 (72.3;140)	84 (35;105)	0.087*
PDN daily dose, n (median IQR)	2.5 (0;5)	0 (0;5)	2.5 (0;5)	0.146	0 (0;2.5)	0 (0;2.5)	0.5 (0;4.4)	0.768
NSAIDs, n (%)	81 (65.3)	31 (66.0)	50 (64.9)	0.908	29 (69.0)	16 (69,6)	13 (68,4)	0.963
Painkillers, n (%)	38 (32.5)	16 (34.8)	22 (31.0)	0.662	12 (30.0)	6 (26,1)	6 (35,3)	0.530
Concomitant chronic treatment, n (%)	70 (51.1)	27 (54.0)	43 (49.4)	0.606	21 (45,7)	11 (44.0)	10 (47,6)	0.806
DAS28 (median IQR)	2.34 (1.8;2.9)	2.27 (1.7;2.8)	2.44 (1.9;3)	0.304	2 (1.6;2.7)	1.94 (1.6;2.7)	2 (1.8;2.5)	0.561
Remission**, n (%)	69 (48.9)	25 (48.1)	44 (49.4)	0.876	30 (62,5)	14 (51.9)	16 (76.2)	0.084
Low disease activity***, n (%)	126 (89.4)	47 (90.4)	79 (88.8)	0.728	46 (95,8)	26 (96.3)	20 (95.2)	0.856
Patient - VAS, n (median IQR)	40 (20;70)	30 (10;70)	45 (30;69)	0.145	30 (10;50)	29 (10;38)	43.5 (27.5;61)	0.052*
Physician - VAS, n (median IQR)	15 (5;20)	15 (0;25)	15 (5;20)	0.847	10 (5;15)	10 (5;15)	10 (1.3;18.8)	0.886
HAQ (median IQR)	0.75 (0.4;1.3)	0.63 (0.1;1.6)	0.88 (0.4;1.3)	0.299	0.25 (0;0.8)	0.13 (0;0.8)	0.31 (0.1;0.8)	0.218
Disease flares, n (median IQR)	9 (31.0)	4 (36.4)	5 (27.8)	0.628	2 (18,2)	1 (25.0)	1 (14,3)	0.658
Assessments per year, n (median IQR)	4 (3;4)	4 (3;4)	4 (3;4)	0.522	3.5 (3;4)	3 (3;4)	4 (2;4)	0.487
Distance from clinic, km (median IQR)	30 (18;50)	28.5 (17.3;46)	35 (18;50)	0.465	40 (20;50)	40 (23;50)	30 (18;43.8)	0.092*

*Variables included in the multivariate analysis as achieving a p <0.1; **defined as DAS28 <2.6; ***defined as DAS28 <3.2.
HA: high adherers, LA: low adherers, IQR: interquartile range, BMI: body mass index, RA: rheumatoid arthritis, csDMARD: conventional synthetic DMARD, bDMARD: biological DMARD, DMARD: disease-modifying anti-rheumatic drug, PDN: prednisone, NSAIDs: non-steroidal anti-inflammatory drugs, DAS28: disease activity score in 28 joints, VAS: visual analogue scale, HAQ: Health Assessment Questionnaire.

men, but no adjustment for confounders was performed.[17] Data from commercial claims in the US report a minor persistence with bDMARD treatment in women, which might be a consequence of poor adherence as well as inefficacy of the treatment.[18] Nevertheless, in our study the association between gender and adherence was not confirmed after adjustment for confounding variables, particularly employment. Employed patients were mainly males, which had an impact on the difference in HA rate between the genders.

To better comprehend which factors may explain the lower adherence trend in females, we investigated which characteristics were different between genders. As expected in the general population, females were more likely to be unemployed than males. Furthermore, females more often had seropositive disease and more frequently had fibromyalgia. In our study, both features were moderately associated with poor adherence. Seropositive RA is known to be more severe.[1,4] It can be assumed that patients with a more severe disease are not content and might not follow the prescriptions or, alternatively, they might have active disease because they are non-compliant. We did not find any correlation between RA activity and adherence; however, the correlation between adherence and disease activity might be non-linear. Adherence may be poor in patients in remission who do not feel they need to take the medication and also those with high activity who are not satisfied or not taking medication properly.

Fibromyalgia is well known to be a comorbidity of women rather than men.[3] RA patients may be suffering from secondary fibromyalgia, due to the persistent pain caused by the disease. This condition is characterised by widespread pain and worse self-reported disease activity scores.[19] Patients suffering pain, might not be satisfied with the treatment and be more inclined to non-adherent behaviour.

The analysis of the determinants of adherence in the female population revealed that employment is a determinant for adherence in women. Interestingly, low-dose bDMARD treatment was also associated with low adherence, although not significantly. In our cohort, reduction of bDMARD administration is started in patients who are in stable remission.[20] Thus, patients on low-dose bDMARDs might be prone to self-management of the treatment, because they believe it to be unnecessary, as discussed above.

Amongst males, employment was not significantly associated with adherence, which might be due to the fact that most of males were employed. The only variable independently associated with adherence was patient-VAS, i.e. the patient's assessment of RA. Thus, independently from employment and conditions of widespread pain, adherence measured with I-CQR5 correlates with the perception of disease activity. This finding confirms that the I-CQR5 reflects the overall opinion of the patient on disease control and medical care rather than the exact medication intake.

The study has some limitations. As in our previous study[9] a monocentric study limits the generalisability of the results. Secondly, the use of a questionnaire is subject to biased results. The adoption of an anonymous and validated questionnaire may have overcome these issues.

Conclusions

This study follows the first large analysis of treatment adherence in Italy and provides insight on gender differences in RA. Adherence to bDMARDs in RA is suboptimal. We observed a strong trend towards lower adherence in females. Females are less frequently employed, and more often present with seropositive RA and fibromyalgia. On the one hand, employment, which is more common in males, might encourage patients to be compliant, since optimal treatment control ensures full working ability. On the other hand, patients with inadequate pain control or severe disease, which are more common in females, may be more prone to non-adherent behaviour because they are not satisfied with the treatment. The I-CQR5 seems to reflect not only adherence but also the patient's perception of the disease and the treatment. The care provided to RA patients, especially women, who represent the majority of RA patients, should include a comprehensive assessment of health status and patient education to reduce concerns and misbeliefs regarding treatment.

Key messages

- Adherence to biological drugs in rheumatoid arthritis patients is suboptimal.
- Women with rheumatoid arthritis tend to be less adherent to treatment than men.
- Employment, which is more common in men, is a predictor of good adherence to treatment.
- Inadequate control of pain and disease activity might be responsible for poor adherence in rheumatoid arthritis patients.
- I-CQR5 is a simple questionnaire to assess treatment adherence and might reflect the patients' perception of the disease activity and their opinion on treatment.

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