Rheumatology International
https://doi.org/10.1007/s00296-018-3933-4

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Variability in the prescription of biological drugs in rheumatoid arthritis in Spain: a multilevel analysis

Francisco Javier López-Longo[1] · Daniel Seoane-Mato[2] · María A. Martín-Martínez[2] · Fernando Sánchez-Alonso[2] · emAR II Group

Received: 22 August 2017 / Accepted: 12 January 2018

Abstract
To describe variability in the prescription of biologics (B-DMARDs) for patients with rheumatoid arthritis (RA) in hospitals in Spain, and to explore which characteristics of the patient, the doctor and the hospital are associated with this variability. Cross-sectional multicentric study in 46 rheumatology services of the National Health System. Medical records of 1188 randomly selected patients were reviewed. The association of each variable with B-DMARD prescription was analyzed using simple logistic regressions. Multilevel logistic regression models were created to analyze variability among centers. 36.8% of patients had received B-DMARD. The proportion of patients being treated with B-DMARDs varied between 3.6 and 71.4% depending on the center. Association of prescription of B-DMARD with patient age (OR = 0.958, 95% CI = 0.947–0.968, $p < 0.001$), longer disease duration (OR = 1.05, 95% CI = 1.032–1.069, $p < 0.001$), higher CRP levels (OR = 1.022, 95% CI = 1.003–1.042, $p = 0.023$), and higher number of hospitalizations (OR = 1.286, 95% CI = 1.145–1.446, $p < 0.001$) was observed. With regard to the center characteristics, the existence of telephone consultations (OR = 1.438, 95% CI = 1.037–1.994, $p = 0.03$) and the number of beds (OR = 1.045, 95% CI = 1.001–1.091, $p = 0.044$) were positively associated with prescription of B-DMARDs. Patient variables explained 34.04% of the variability among centers. By adjusting for patient and hospital characteristics, it went up to 83.71%. There is variability in the prescription of B-DMARDs for patients with RA among hospitals which is associated, to a greater extent, with the center characteristics. B-DMARDs prescription could be partly explained by other factors not covered by the current study including the provider's attitudes towards biologics and other hospital characteristics.

Keywords Biologic therapies · Rheumatoid arthritis · Variability · Healthcare resources

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune rheumatic disease, resulting in irreversible joint damage and a decline in patient's quality of life [1]. The therapeutic objective is a remission of the disease, or at least, a higher control of inflammation to reduce or prevent joint damage, morbidity, and mortality [2]. This close control of inflammation is possible thanks to the early administration and optimization of doses of non-biologic disease-modifying antirheumatic drugs (NB-DMARDs), such as methotrexate, and the introduction of biologic DMARDs (B-DMARDs) [2–4].

Variations in clinical practice (VCP) are defined as the differences observed in the assistance process and/or in the outcome of care provided for a specific clinical problem, once demographic and sociocultural factors, as well as those related to state of health, have been controlled. These variations depend on factors related to the demand for health care, the provision (existing scientific evidence on procedures, characteristics of healthcare professionals, prevalence of doctors in favor of a specific procedure), and the health care system. Likewise, they have negative consequences in patient care and resource usage [5–8].

VCP have also been observed in the management of RA patients in different countries, having repercussions on health and costs [9–15]. In this regard, data from the United

✉ Francisco Javier López-Longo
fjlopezlongo@hotmail.com

[1] Rheumatology Service, Gregorio Marañón General University Hospital, C/Dr. Esquerdo, 46, 28007 Madrid, Spain

[2] Research Unit, Spanish Society of Rheumatology, C/Marqués del Duero, 5-1A, 28001 Madrid, Spain

Published online: 24 January 2018

Kingdom General Practice Research Database showed that many individuals with RA had not been treated appropriately [15]. Stratification by hospital type in the Swedish Rheumatoid Arthritis Register for the period 1997–2001 showed that patients in district hospitals were less likely to be prescribed NB-DMARDs than those in university hospitals, independently of confounding factors [14].

In Spain, results of the *Estudio sobre la variabilidad en el Manejo de la Artritis Reumatoide en España* (emAR I), which was carried out at the end of the 90s, showed differences in the use of healthcare, diagnostic, and therapeutic resources regarding the care of RA patients in hospital centers of the national health system. This variability was in many cases independent of patient characteristics or severity of the disease [16–20]. Since then, RA management has experienced a revolution due to the incorporation of biologic therapy. As in other countries [21–23], the use of B-DMARDs to treat RA in Spain has been increasing. Variability in the use of this type of drugs depends on patient and disease characteristics, but it could also depend on the characteristics of the healthcare system.

In Spain, most patients are treated in public hospitals that belongs to the universal public health system. All these hospitals have available the treatment protocols recommended by the Spanish Society of Rheumatology. Precisely, during study period, the "2011 GUIPCAR update of the clinical practice guideline for the management of rheumatoid arthritis in Spain" (3). The aim of this study was to describe variability in the prescription of B-DMARDs for RA patients among different public hospitals in Spain, and to explore which characteristics of the patient, the doctor, and the hospital were associated with this variability. The data could be useful to develop future studies and strategies to get low levels of VCP.

Methods

Design

The design is multicentric cross-sectional descriptive study. This study is part of emAR II [Study on the management of RA and spondyloarthritis (SpA) in Spain], promoted by the Spanish Society of Rheumatology and performed in 2010 to assess the variability in the management of RA and SpA in Spain. This study only included the RA arm of emAR II.

Population: selection criteria

The following were considered inclusion criteria: medical records of patients older than 16 years old, diagnosed with RA according to ACR 1987 criteria [24], and attended at Rheumatology Units of public hospitals in Spain at least once within 2 years before the date of the study (2010). Failure to locate the patient medical record or failure to gather the necessary information contained in it was exclusion criteria.

Sample and sampling

Medical records from the different Spanish regions and hospitals were randomly selected through a stratified sampling process in two stages: hospital and patient. First, a list of public hospitals (first stage units) was established for each region from the National Catalogue of Hospitals [25], along with the number of beds at each center. For this first step, a probability of selection proportional to a given center's size was established; in the second step, a random equiprobabilistic selection of 25–30 patients in each center was performed. For this selection, participating hospitals provided a list with the clinical record number of eligible patients.

The change in the percentage of orthopedic surgery between emAR I and II was taken as a response variable of interest to calculate the sample size [20]. In that regard, assuming a power of 80% for the detection of differences in the hypothesis test comparing two population proportions, with a significance level of 5%, and assuming that the proportion of patients in need of orthopedic surgery changed from 26% (emAR I) to 18% (emAR II), a design effect of 2.5, and 15% of not localized or non-completed clinical histories, we calculated a sample requirement of 1351 medical records.

Variables

The primary endpoint is B-DMARDs prescription through disease evolution. The following were considered as independent variables:

1. Individual characteristics: socio-demographic characteristics (age, gender, level of education, work activity in the last 2 years, episodes of work leave which were caused by RA, and distance from the patient's home to hospital); clinical characteristics [age at onset of symptoms. Disease duration. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score (DAS28) [26], functional capacity measured with Health Assessment Questionnaire (HAQ) [27], and number of swollen and painful joints, within 2 years before the inclusion in the study; rheumatoid factor, anticitrullinated protein antibodies (ACPAs), ACR functional class at the last visit, Articular erosions, RA complications, comorbidity]; use of healthcare facilities (hospital admissions, referrals to other specialists or professionals, laboratory tests, imaging tests, or other tests); and

prescription of corticosteroids and NB-DMARDs within 2 years before the inclusion in the study.
2. Doctor in charge (responsible for more than 50% of a patient´s evolution) characteristics: age, gender, position (fellow, specialist, head of section, and head of service), public or private professional activity, years of professional practice.
3. Characteristics of the rheumatology service: number of employed doctors, number of fellows, number of hospitalization beds and number of hospitalizations per year; mean time to first visit, drug monitoring system (by the rheumatology service, primary care, rheumatology service + primary care, or other specialties), type of consultation provided (nursing consultation, monographic RA unit, telephone consultation, multidisciplinary consultation, early arthritis units), and participation in clinical trials.
4. Characteristics of the hospital centers: number of beds, population attended, percentage of urban population, level of complexity (less than 200 beds; general hospital; reference hospital, if bigger than general hospitals and with some referral services; high-technology hospital, if higher complexity with all the services).

The study has been carried out according to the principles of the Helsinki Declaration. In addition, international rules related to epidemiological studies (International Guidelines for Ethical Review of Epidemiological Studies, Council for the International Organizations of Medical Sciences-CIOMS-Geneva, 1991), and the recommendations by Spanish Society of Epidemiology [28] have been followed. The study has been approved by the Clinical Research Ethics Committee of *Hospital Clínico de San Carlos* in Madrid (E-09/104), as the reference Ethics Committee, and by all the participating centers.

Statistical analysis

Means and standard deviations or medians and interquartile ranges (IR) for numeric variables, as well as absolute and relative frequencies for qualitative variables were calculated. The association of each independent variable with the dependent dichotomized variable (B-DMARD prescription or not) shown in Table 2 was assessed by calculating the crude odds ratios via logistic regression.

To study the variability in B-DMARD prescription between centers, two random intercept multilevel logistic regression models were done. In each of them, the dependent variable was B-DMARD prescription vs no B-DMARDs and prescription of 1 B-DMARD vs more than 1, respectively. In each of the multilevel analyses, two levels were established: the individual or patient level (Level 1) and the hospital and physician level (Level 2). The multilevel regression was developed in three steps: (1) Model 1 (null or empty model) that included only the dependent dichotomized variable and a service level (service or hospital where the patient was treated); (2) Random Effects Model 2, which was based on the previous model adjusted for individual variables; (3) Random Effects Model 3, which was adjusted for both individual and hospital variables to obtain a global multivariable model. Intraclass correlation coefficients (ICC, which represents the proportion of variance that lies between centers) for the three models, and the percentage of explained variance (PVE, which represents the percentage of variance between centers explained by the variables included in the model) for Models 2 and 3 were then assessed.

In Models 2 and 3, analyzed independent variables were those that had a statistically significant result in the bivariate analysis, were clinically relevant, or were deemed confounders; however, if included variables showed significant correlation, one was excluded from the analysis depending on their contribution to the model.

All analyses were performed using STATA 11.0 software (StataCorp.2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Statistical significance was assumed as $p < 0.05$.

Results

Descriptive analysis

100 centers were invited, of which 46 from all Spanish regions agreed to participate and were included in the study. All centers (participating and not participating) were asked to submit information about administrative characteristics. 7 non-participating centers submitted this information, with no significant differences between them and the participating centers.

1188 medical records were included. The clinical characteristics of the patients as well as those of the centers taking part in the emAR II project are already published [29, 30]. Table 1 shows the results of the descriptive analysis. Patients had a mean age of 62 years (SD = 14.5), and a predominance of women was observed (74%). 74.9 and 69.6% of patients showed positivity to rheumatoid factor and ACPAs, respectively. 31.8% of patients suffered from some complication of RA, the most frequent ones being rheumatoid nodules (11.9%) and Sjögren's syndrome (10.3%). 74.7% of patients were in functional class I or II.

36.8% of patients had received B-DMARD. The median time from diagnosis to the start of treatment was 60.8 months (IR 24.6–129.4) and the median treatment duration was 25.3 months (IR 8.2–54.8). 80.3% of patients received a combination of biologic therapy with NB-DMARD. The

Table 1 Descriptive data for patients, physicians, and centers

Demographic data		Disease characteristics	
Age, years	62.0 (SD:14.5)	NB-DMARD use, *n* (%)	1051 (88.5)
Sex, female, n (%)	875 (74)	Numbers of NB-DMARDs used	1 [1–2]
		NB-DMARD type, *n* (%)	
		Methotrexate	827 (78.7)
Comorbility, *n* (%)		Leflunomide	319 (30.4)
Hypertension	359 (28.2)	Hydroxychloroquine	177 (16.8)
Diabetes	130 (10.2)	Sulfasalazine	46 (4.4)
Ischemic cardiomyopathy	75 (5.9)	Gold	21 (2.0)
Ictus	48 (3.8)	Azathioprine	7 (0.7)
Ulcus	74 (5.8)	Others	8 (0.8)
Neoplasm	84 (6.6)	B-DMARD, *n* (%)	437 (36.8)
Chronic kidney disease	41 (3.2)	Numbers of B-DMARD used, *n* (%)	
Hepatic diseases	52 (4.1)	None	751 (63.2)
Infections	112 (8.8)	One	277 (23.3)
Anticoagulation	63 (5.0)	Two	96 (8.1)
Chronic heart failure	41 (3.2)	Three	39 (3.3)
		Four	16 (1.3)
		Five	9 (0.8)
Use of healthcare services		B-DMARD, *n* (%)	
Referrals to other specialists or professionals	2 [0–7]	Abatacept	19 (1.6)
Procedures	37 [25–52]	Adalimumab	196 (16.5)
Hospital admissions, *n* (%)	354 (32.7)	Anakinra	5 (0.4)
Number of hospitalizations	0 [0–1]	Etanercept	207 (17.4)
		Infliximab	159 (13.4)
		Rituximab	60 (5.1)
Physician characteristics		Tocilizumab	16 (1.3)
Female, *n* (%)	468 (38.9)	Exposure to biological, months	25.3 [8.2–54.8]
Age, years	47.5 (SD:8.5)	Corticoid prescription, *n* (%)	804 (67.7)
Years of experience	21 [11–25]	Disease duration, years	7.9 (3.8–14.0)
Public work activity, *n* (%)	749 (63.7)	CRP, mg/dl	1.0 [0.4–2.5]
Private and public work activity, n (%)	427 (36.3)	ESR, mm/h	23.5 [13.0–35.5]
Physician categories		HAQ	0.72 [0.25–1.25]
Fellow, *n* (%)	11 (0.9)	DAS28	3.5 (SD:1.3)
Specialist, *n* (%)	957 (79.6)	RA complications, *n* (%)	378 (31.8)
Section or Division Chief, *n* (%)	234 (19)	Number of RA complications	0 [0–1]
		Global functional status	
		Class I, *n* (%)	448 (51.4)
Center characteristics		Class II, *n* (%)	203 (23.3)
Atended population, people	345,000 [223, 355–450, 000]	Class III, *n* (%)	140 (16.1)
% of urban population	75 [40–90]	Class IV, *n* (%)	80 (9.2)
Center bed number	666 [460–1071]	Positive rheumatoid factor, *n* (%)	930 (74.9)
Number of doctors in rheumatology service	5 [3–9]	ACPA positive, *n* (%)	511 (69.6)
Number of beds in rheumatology service	4 [1–6]	Structural joint damage, *n* (%)	722 (61.2)
Number of hospitalizations/year	80 [20–152]	Maximum number of painful joints	
Mean time to first visit (months)	1 [1–2]	None, *n* (%)	649 (56.2)
Presence of nursing consultation, *n* (%)	19 (42.2)	1–15, *n* (%)	433 (37.5)
Presence of RA uni-disciplinary unit, *n* (%)	16 (35.6)	6–10, *n* (%)	46 (4.0)
Presence of telephone consultation, *n* (%)	17 (37.8)	11–15, *n* (%)	16 (1.4)
Early arthritis unit, *n* (%)	21 (46.7)	> 16, *n* (%)	11 (1.0)

Table 1 (continued)

Demographic data		Disease characteristics	
Clinical trial realization, *n* (%)	38 (84.4)	Maximum number of swelling joints	
Hospital level, *n* (%)		None, *n* (%)	753 (65.0)
< 200 beds	68 (5.7)	1–15, *n* (%)	354 (30.6)
General	217 (18.3)	6–10, *n* (%)	32 (2.8)
Reference hospital	295 (24.8)	11–15, *n* (%)	13 (1.1)
High tech. hospital	608 (51.2)	> 16, *n* (%)	6 (0.5)
Drug monitoring system, *n* (%)			
Rheumatology department	687 (59.3)		
Rheumatology department + PCP	371 (32.0)		
Other specialists	100 (8.6)		
Multidisciplinary attention, *n* (%)	347 (29.2)		

Data expressed as mean (SD: standard deviation) or median (interquartile range). Dichotomous variables are expressed as n and percentage

Global function status categories:

Class I: completely able to perform usual activities of daily living (self-care, vocational, and avocational)

Class II: able to perform usual self-care and vocational activities, but limited in avocational activities

Class III: able to perform usual self-care activities, but limited in vocational and avocational activities

Class IV: limited in ability to perform usual self-care, vocational, and avocational activities

Procedures include laboratory tests, imaging tests, other tests (EKG, EMG. Mantoux, lung function tests) and arthrocentesis during 2008–2009

NB-DMARD use refers to 2008–2009. B-DMARD use refers to the evolution of the disease

DMARD disease-modifying antirheumatic drugs, *NB-DMARD* non-biologic DMARD, *B-DMRAD* biologic DMARD, *ACPA* anti-cyclic citrullinated peptide antibodies, *CRP* c-reactive protein, *DAS28* disease activity score, *ESR* erythrocyte sedimentation rate, *HAQ* health assessment questionnaire, *PCP* primary care physician, *STD* short-term disability

median number of NB-DMARD before the first B-DMARD was 2 (IR 2–3).

The proportion of patients treated with B-DMARDs varied between 13.3 and 71.4% depending on the region (etanercept 3.3–46.7%, adalimumab 8.7–26.7%, and infliximab 0–18.9%), and between 3.6 and 71.4% depending on the center (etanercept 0–57.1%, adalimumab 3.3–53.6%, and infliximab 0–36.7%).

There were 517 hospital admissions. Most of them were due to surgery (36.4%) or comorbidity (19.1%).

Univariate analysis of prescription of B-DMARDS

B-DMARD prescription decreased significantly as the age of patients became higher. It was more frequent in patients with more than 50% of work activity in the last 2 years and with a higher level of education. Regarding clinical characteristics, the prescription increased with disease duration, number of swollen joints and painful joints, articular erosions, HAQ score increase and class III global functional status, positive rheumatoid factor and ACPAs, comorbidity, RA complications, and clinical activity (CRP, DAS28) (Table 2). NB-DMARDs, but not corticosteroids, were associated with prescription of B-DMARD. The number of hospitalizations and number of tests showed a positive association with biologic therapy.

With regard to doctor characteristics as well as those of the organization of healthcare in the centers, B-DMARD prescription was associated with gender and type of professional activity developed by the doctor, mean time to first visit, number of beds in the center, number of doctors in rheumatology service, number of beds assigned for hospitalization, number of hospitalizations/year, drug monitoring system, and the presence of RA uni-disciplinary unit, telephone consultation, and early arthritis unit (Table 2).

Multilevel variability analysis of prescription of B-DMARDS

Variability between hospitals represents 8.4% of total variability in biologic prescription (Variance 0.303; Standard Error (SE) 0.108; $p < 0.001$) (Table 3). This percentage was reduced to 5.7%, ($p = 0.029$) when adjusting for the patient characteristics (Level 1), and it was reduced to 1.5% ($p = 0.184$) when adjusting for both the patient and the center characteristics (Level 1 + Level 2).

An association of biologic drugs prescription with the age of the patients (OR = 0.958; 95% CI = 0.947–0.968; $p < 0.001$), with longer disease duration (OR = 1.05; 95% CI = 1.032–1.069; $p < 0.001$), with higher levels of CRP (OR = 1.022; 95% CI = 1.003–1.042; p = 0.023), and with a higher number of hospitalizations (OR = 1.286: 95%

Table 2 Logistic regression univariate analysis for B-DMARD use

Demographic data	OR [95%CI]	*p*	Disease characteristics	OR [95%CI]	*p*
Age, years	0.968 [0.960–0.976]	< 0.001	NB-DMARD use	3.267 [1.118–9.543]	0.030
Female	1.316 [0.999–1.733]	0.051	Number of NB-DMARDs used	0.953 [0.813–1.117]	0.552
Level of studies			NB-DMARD type		
None	Reference		Methotrexate	1.031 [0.798–1.333]	0.815
Primary school	1.793 [0.732–4.389]	0.201	Leflunomide	1.402 [1.079–1.823]	0.011
High school	3.031 [1.113–8.250]	0.030	Hydroxychloroquine	2.303 [0.513–10.339]	0.276
University	3.143 [1.124–8.789]	0.029	Sulfasalazine	0.826 [0.441–1.547]	0.550
Distance from hospital			Gold	0.281 [0.082–0.961]	0.043
0 km (same locality)	Reference		Azathioprine	1.291 [0.288–5.795]	0.739
< 20 km	0.934 [0.660–1.320]	0.698	Corticoid prescription	1.248 [0.967–1.612]	0.088
20–50 km	1.141 [0.820–1.588]	0.434	Disease duration, years	1.039 [1.024–1.054]	< 0.001
> 50 km	0.993 [0.660–1.493]	0.973	Age at symptom onset, years	0.963 [0.954–0.972]	< 0.001
Work activity bigger than 50% of the last 2 years	1.720 [1.139–2.596]	0.010	CRP, mg/dl	1.019 [1.002–1.036]	0.025
			ESR, mm/h	1.003 [0.997–1.010]	0.299
Comorbility	0.731 [0.577–0.926]	0.009	RA complications	1.532 [1.193–1.968]	0.001
Hypertension	0.79 [0.606–1.031]	0.082	Number of RA complications	1.409 [1.189–1.670]	< 0.001
Ischemic cardiomyopathy	0.403 [0.222–0.732]	0.003	HAQ	1.888 [1.389–2.566]	< 0.001
Neoplasm	0.533 [0.313–0.907]	0.020	DAS28	1.286 [1.127–1.469]	< 0.001
Infections	1.855 [1.241–2.774]	0.003	Global functional status		0.100
Anticoagulation	0.532 [0.294–0.964]	0.037	Class I	Reference	
Chronic heart failure	0.391 [0.170–0.898]	0.027	Class II	1.324 [0.931–1.883]	0.118
			Class III	1.508 [1.007–2.259]	0.046
			Class IV	1.522 [0.927–2.497]	0.097
Physician characteristics			Maximum number of swelling joints		0.006
Female	1.407 [1.097–1.805]	0.007	None	Reference	
Age, years	1.000 [0.985–1.015]	0.997	1–5	1.237 [0.897–1.707]	0.194
Years of experience	1.003 [0.989–1.017]	0.680	6–10	2.011 [1.341–3.018]	0.001
Private and public work activity	1.328 [1.030–1.712]	0.029	11–15	3.069 [1.722–5.468]	<0.001
Physician categories			≥ 16	4.253 [2.182–8.292]	< 0.001
Fellow	Reference				
Specialist	2.127 [0.449–10.077]	0.342	Maximum number of painful joints		0.015
Section Chief	2.632 [0.544–12.733]	0.229	None	Reference	
Division Chief	4.267 [0.778–23.404]	0.095	1–5	1.220 [0.839–1.774]	0.298
			6–10	1.996 [1.292–3.083]	0.002
			11–15	2.400 [1.391–4.142]	0.002
Center characteristics			≥ 16	3.075 [1.810–5.224]	< 0.001
Attended population, people	1.000 [1.000–1.000]	–	Structural joints damage	2.427 [1.850–3.184]	< 0.001
% of urban population	1.000 [0.995–1.005]	0.910	Positive rheumatoid factor	1.400 [1.052–1.864]	0.021
Center beds number	1.001 [1.000–1.001]	0.001	ACPA positive	2.427 [1.850–3.184]	< 0.001
Doctors in rheumatology service	1.053 [1.019–1.090]	0.002			
Hospitalization beds number	1.068 [1.022–1.115]	0.003			
Number of hospitalizations /year	1.002 [1.001–1.003]	0.004	Use of healthcare services		
Mean time to first visit (months)	0.813 [0.720–0.917]	0.001	Referrals to other specialists or professionals	1.000 [0.987–1.012]	0.954
Number of fellows in the service	0.949 [0.702–1.283]	0.734	Procedures	1.032 [1.026–1.039]	< 0.001
Presence of nursing consultation	1.003 [0.790–1.273]	0.982	Hospital Admissions	1.407 [1.085–1.825]	0.010
Presence of RA uni-disciplinary unit	1.457 [1.143–1.859]	0.002	Number of hospitalizations	1.248 [1.132–1.375]	< 0.001
Presence of telephone consultation	1.408 [1.105–1.793]	0.006			
Early arthritis unit	1.306 [1.031–1.654]	0.027			

Table 2 (continued)

Demographic data	OR [95%CI]	*p*	Disease characteristics	OR [95%CI]	*p*
Clinical trial realization	1.201 [0.816–1.766]	0.353			
Hospital level					
< 200 beds	Reference				
General	0.748 [0.417–1.341]	0.329			
Reference hospital	1.286 [0.739–2.238]	0.373			
High tech. hospital	1.250 [0.737–2.120]	0.408			
Drug monitoring system					
Rheumatology service	Reference				
Rheumatology service + PCP	0.559 [0.366–0.851]	0.007			
Other specialists	0.394 [0.251–0.619]	< 0.001			
Multidisciplinary consultation	1.282[0.992–1.657]	0.058			

For abbreviations, see Table 1

Table 3 Multilevel analysis of the variability in B-DMARD prescription (dependent variable: prescription of B-DMARDs vs nonprescription) ($n = 906$)

		Hospital-level variance (SE)	ICC	Hospital-level variance explained (%VPE)	Median OR	Variables	Adjusted OR (95%CI)	*p*
Model 1	Empty model	0.303 (0.108)	0.084		1.896			
Model 2	Level 1	0.200 (0.096)	0.057	34.04	1.681			
						Age	0.958 (0.947–0.968)	< 0.001
						Female	1.142 (0.817–1.598)	0.437
						Disease duration, years	1.05 (1.032–1.069)	< 0.001
						CRP, mg/dl	1.022 (1.003–1.042)	0.023
						Number of hospitalizations	1.286 (1.145–1.446)	< 0.001
Model 3	Level 1 + Level 2	0.049 (0.063)	0.015	83.71	1.295			
						Telephone consultation	1.438 (1.037–1.994)	0.03
						Center bed number*100	1.045 (1.001–1.091)	0.044

Level 1: patient level; Level 2: hospital and physician level

Multilevel regression models: Model 1 (null or empty model); random effects Model 2 based on the previous model adjusted for individual variables; random effects Model 3 adjusted for both individual and center variables

The median OR can be conceptualized as the increased risk that (in median) a patient would have if moving to another hospital with a higher risk

SE standard error, *ICC* intraclass correlation coefficient, *OR* odds ratio

CI = 1.145–1.446; $p < 0.001$) was observed in the final model (Model 3). Regarding the characteristics of the center, the existence of telephone consultation (OR = 1.438; 95% CI = 1.037–1.994; $p = 0.03$) and number of hospital beds (OR = 1.045; 95% CI = 1.001–1.091; $p = 0.044$) were positively associated with B-DMARDs prescription.

The patient variables that were included in the model explained 34.04% of variability between centers. When adjusting for patient and hospital variables, this percentage of explained variability raised to 83.71%.

Variability between hospitals in the prescription of one B-DMARD vs more than one was not observed (data not shown).

Discussion

This study examined the variability in the prescription of B-DMARDs for RA treatment in Spain. In our analysis, we aimed to study the existence of variability between centers

and its associated variables. The multilevel analysis fits this objective and allows to separate the contribution of individual and non-individual variables to the global variability (Levels 1 and 2, respectively, in our analysis).

The results show variability in B-DMARDs prescription for patients with RA between hospitals. Part of this variability (34.04%) was associated with patient characteristics, such as the severity and activity of the disease. B-DMARDs prescription was slightly higher in younger patients, with longer disease duration and with higher levels of CRP. When interpreting the association with the number of hospitalizations, it should be taken into account that part of them were due to the administration of intravenous drugs (7.7% of the total number of hospital admissions).

However, it is the differences among hospitals which enabled explanation for a higher percentage (49.67%). Overall, the variables that were included in the final model explained the majority of variability among centers (83.71%). Hospital characteristics associated with variability in B-DMARDs prescription were the presence of telephone consultation and the number of hospital beds, which could reflect a higher accessibility for patients and a higher provision of resources in these centers.

Interestingly, in the univariate analysis, not all NB-DMARDs were associated with the B-DMARD prescription. The longer disease duration and the more serious disease of 21 patients receiving gold could explain the association of gold and B-DMARDs. Nevertheless, in agreement with the guidelines, methotrexate is the first-choice treatment for RA. Patients not adequately responding to methotrexate are treated with leflunomide alone or combined with methotrexate. Therefore, the proportion of subjects that need to use B-DMARDS is much higher for leflunomide than for methotrexate. This could explain the association between leflunomide and B-DMARDs use and the lack of association with methotrexate.

Similar results have been reported by Desai et al. using health insurance claims data derived from Truven's MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits. Among monotherapy NB-DMARD users, initiation with TNF-α inhibitors was associated with enabling factors of visit to rheumatologists, health insurance type (commercial vs Medicare supplemental), RA severity, and comorbidities in this retrospective cohort study. The enabling factors of health insurance type were not found to be associated with TNF-α inhibitor initiation among NB-DMARD combination therapy users [31].

In contrast, semi-structured interviews performed by Kalkan et al. in Sweden showed that potential factors that influence individual rheumatologists' decisions when prescribing B-DMARD were experienced and perception of the evidence, structure of the department, and participation in clinical trials [32]. In a recent retrospective study using the Texas Medicaid prescription and medical claims database, younger age, Charlson Comorbidity Index scores ≥ 3, glucocorticoid use, methotrexate users (vs. SSZ and HCQ users), and NB-DMARD monotherapy users (vs. dual therapy users) were significantly associated with higher likelihood to initiate B-DMARD [33].

As previously published [34–36], emAR II is a multicenter study of a probabilistic and representative large sample of patients with RA in Spain. The participation of numerous centers from different regions of the country allows for an accurate and representative description of the variations in health care between Spanish rheumatology units and could be very helpful to identify deficiencies in healthcare delivery.

The main limitation of the study is the use of medical records as the source of information. However, this enables a larger sample size. In our study, incomplete medical records have not been included and have been taken into account in the sample size calculation; there was a 12% of lost or incomplete medical records, which is less than the 15% assumed. We also designed a type of sampling and quality control strategies to ensure the representativeness and the uniformity in data collection. The definitions of all the variables were included in the investigator´s brochure and a pilot study was conducted to detect systematic errors in the questions and to ensure comprehension. In the statistical analysis, missed values were taken into account. In this sense, variables like DAS28, ACR functional class, or HAQ were missed in a high percentage of the medical records, and this has been a limitation that could have conditioned the variables finally shown as associated with the prescription of B-DMARD in the multivariate model. The absence of some of these measures could be justified by their infrequent use in the standard clinical care [37].

B-DMARDs prescription could be partly explained by other factors not covered by the current study including the provider's attitudes towards biologics and other hospital characteristics, such as the number of consults per day, the accessibility to screening resources, and differences in hospital management or pharmacoeconomic policies.

In conclusion, our results show that, despite the universal health care system in Spain and the existence of widely spread clinical guidelines and recommendations about B-DMARDs prescription, there is variability in the prescription of biologic drugs for patients with RA between hospitals. This implies that the management of patients with severe RA does not depend only on medical criteria. The variability was associated, to a larger extent, with structural characteristics of rheumatology units and hospital centers rather than to patient characteristics, being the prescription of biologics still more likely for those attended at larger hospitals and in services with telephone consultations.

Acknowledgements Our gratitude to Loreto Carmona, Mª Jesús García de Yébenes, and Miguel Ángel Descalzo for their role in the design of emAR II. emAR II Group: C Escudero (Hospital Virgen de Valme, Sevilla); N Chozas, I Maries, A Fernandez and F Medina (Hospital Puerta del Mar, Cádiz); M Guzman (Complejo Hospitalario Virgen de las Nieves, Granada); I Ureña, V Irigoyen, M Lopez, P Espiño and S Manrique (Hospital Carlos Haya, Málaga); E Collantes, P Font, D Ruiz, M Granados and MJ Pozuelo (Hospital Reina Sofia, Córdoba); I Moreno and A Garcia Lopez (Hospital Virgen del Rocio, Sevilla); JM Pina (Hospital de Barbastro, Barbastro); R Rosello and C Vazquez (Hospital General San Jorge, Huesca); J Beltrán, A Pecondón, E Giménez, F Jimenez, J Marzo and M Medrano (Hospital Universitario Miguel Servet, Zaragoza); J Babio, T Tinture, S Gonzalez, C Ordas and ME Garcia (Hospital de Cabueñes, Gijón); J Ballina y Alonso S (Hospital Universitario Central de Asturias, Oviedo); L Espadaler, J Fernandez and J Fiter (Hospital Son Dureta, Palma de Mallorca); S Bustabad (Hospital Universitario de Canarias, La Laguna); C Rodríguez, A Naranjo and S Ojeda (Hospital Universitario Dr Negrin, Las Palmas); J Tornero and JA Piqueras (Hospital General Universitario de Guadalajara, Guadalajara); E Judez and G Sanchez (Hospital Universitario de Albacete, Albacete); L Pantoja and C Lopez (Hospital El Bierzo, Ponferrada); J Medina, G Iglesias and M Alvarez (Complejo Asistencial de Palencia, Palencia); J Alegre, MR Colazo, JL Alonso and B Alvarez (Complejo Asistencial de Burgos, Burgos); T Perez Sandoval (Complejo Asistencial de Leon, Leon); J Del Pino, C Montilla, S Gomez, R Lopez and M Sanchez (Complejo Asistencial de Salamanca, Salamanca); FX Arasa, (Hospital Tortosa Verge de la Cinta, Tortosa); S Castro (Hospital Universitario de Tarragona Joan XXIII, Tarragona); S Ordoñez and D Boquet (Hospital Universitario Arnau de Vilanova, Lleida); J Calvet (Corporacion Sanitaria Parc Tauli, Sabadell); D de la Fuente, V Rios and M Nolla (Hospital Universitario de Bellvitge, L´Hospitalet de Llobregat); A Martinez (Hospital Universitario de la Ribera, Alzira); MA Belmonte Serrano (Hospital General de Castellon, Castellon); R Negueroles (Hospital Universitario La Fe, Valencia); J Garcia, F Gamero y E del Rincon (Complejo Hospital de Caceres, Caceres); R Veroz (Complejo Hospitalario Llerena-Zafra, Badajoz); E Perez-Pampin (Hospital Universitario de Santiago, Santiago de Compostela); L Fernandez (Complejo Hospitalario de Ourense, Ourense); R Miguelez and J Godo (Hospital de Móstoles, Móstoles); AM Ortíz, E Vicente, E Tomero, A Casado and MJ Aria (Hospital Universitario de La Princesa, Madrid); E Cuende and C Bohorquez (Hospital Universitario Principe de Asturias, Alcalá de Henares); JM Rodriguez, A Aragon, J Garcia and J Zubieta (Hospital Universitario de Getafe, Getafe); C Martinez (Hospital Clinico San Carlos, Madrid); I Mateo, A de Juanes y E Enriquez (Hospital 12 de Octubre, Madrid); FJ Lopez-Longo (Hospital General Universitario Gregorio Marañon, Madrid); J Maese (Hospital La Paz, Madrid); E Pagan, MJ Rubira and P Mesa (Hospital Los Arcos, Murcia); N Rivera (Hospital de Basurto, Basurto); C Rodriguez (Hospital Comarcal de Melilla, Melilla); B Gonzalez Alvarez (Complejo Hospital Universitario Virgen de la Candelaria, Santa Cruz de Tenerife); A Zea, C Diaz-Miguel and A Cifuentes (Hospital Ramon and Cajal, Madrid).

Funding This work was supported by AbbVie Spain. AbbVie had no role in the design, data collection, data analysis, interpretation, or writing of this report.

Compliance with ethical standards

Conflict of interest Francisco Javier López Longo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB, MSD, Actelion, and research funding from Abbvie and GSK. The other authors declare no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Carmona L, Ballina J, Gabriel R, Laffon A (2001) The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis 60:1040–1045
2. Sanmartí R, García-Rodríguez S, Álvaro-Gracia JM, Andreu JL, Balsa A, Cáliz R et al (2015) 2014 update of the consensus statement of the Spanish Society of Rheumatology on the use of biological therapies in rheumatoid arthritis. Reumatol Clin 11:279–294
3. GUIPCAR Group (2011) Update of the clinical practice guideline for the management of rheumatoid arthritis in Spain. Madrid (Spain): Spanish Society of Rheumatology. http://www.ser.es/wp-content/uploads/2016/01/GUIPCAR_31Marzo2012_ENG.pdf
4. de la Torre I, Valor L, Nieto JC, Hernández-Flórez D, Martínez L, Gonzalez CM et al (2013) Anti-TNF treatments in rheumatoid arthritis: economic impact of dosage modification. Expert Rev Pharmacoecon Outcomes Res 13:407–414
5. Keller RB, Soule DN, Wennberg JE, Hanley DF (1990) Dealing with geographic variations in the use of hospitals. The experience of the Maine Medical Assessment Foundation Orthopaedic Study Group. J Bone Joint Surg Am 72:1286–1293
6. Longo DR (1993) Patient practice variation. A call for research. Med Care 31(5 Suppl):YS81-5
7. Fernandez LA, Martin JM, Del Castillo JD, Gaspar OS, Millán JI, Lozano MJ et al (2000) Sources of influence on medical practice. J Epidemiol Community Health 54:623–630
8. Andersen R, Newman JF (1973) Societal and individual determinants of medical care utilization in the United States. Milbank Mem Fund Q Health Soc 51:95–124
9. Prodinger B, Ndosi M, Nordenskiöld U, Stamm T, Persson G, Andreasson I et al (2015) Rehabilitation provided to patients with rheumatoid arthritis: a comparison of three different rheumatology clinics in Austria, Sweden and the UK from the perspectives of patients and health professionals. J Rehabil Med 47:174–182
10. Yazdany J, Dudley RA, Chen R, Lin GA, Tseng CW (2015) Coverage for high-cost specialty drugs for rheumatoid arthritis in medicare part D. Arthritis Rheumatol 67:1474–1480
11. Zhong L, Chung KC, Baser O, Fox DA, Yuce H, Waljee Jf. Variation in rheumatoid hand and wrist surgery among medicare beneficiaries: a population-based cohort study. J Rheumatol 2015;42:429–436
12. Geens E, Geusens P, Vanhoof J, Berghs H, Praet J, Esselens G et al (2009) Belgian rheumatologists' perception on eligibility of RA patients for anti-TNF treatment matches more closely Dutch rather than Belgian reimbursement criteria. Rheumatology 48:546–550
13. Westhoff G, Schneider M, Raspe H, Zeidler H, Runge C, Volmer T et al (2009) Advance and unmet need of health care for patients with rheumatoid arthritis in the German population–results from the German Rheumatoid Arthritis Population Survey (GRAPS). Rheumatology 48:650–657
14. Carli C, Ehlin AG, Klareskog L, Lindblad S, Montgomery SM (2006) Trends in disease modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital

setting than patient or disease characteristics. Ann Rheum Dis 65:1102–1105
15. Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP et al (2005) The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology 44:1394–1398
16. Hernández-García C, González-Álvaro I, Villaverde V, Vargas E, Morado IC, Bañares AA et al (2001) Estudio sobre el Manejo de la Artritis Reumatoide en España (emAR). I. Características de los centros participantes. Rev Esp Reumatol 28:413–419
17. Hernández-García C, González-Álvaro I, Villaverde V, Vargas E, Morado IC, Pato E et al (2002) Estudio sobre el Manejo de la Artritis Reumatoide en España (emAR). II. Características de los Pacientes. Rev Esp Reumatol 29:130–141
18. Lopez-Gonzalez R, Hernandez-Garcia C, Abasolo L, Morado I, Lajas C, Vadillo C (2008) et-al. Differences between rheumatology attending physicians and training residents in the management of rheumatoid arthritis in Spain. Scand J Rheumatol 37:419–426
19. Clemente D, Hernández-García C, Abásolo L, Villaverde V, Lajas C, Loza E et al (2007) Reduction in time until first treatment until first treatment with disease modifying treatment in patients with rheymatoid arthritis. Reumatol Clin 3:245–250
20. Loza E, Abásolo L, Clemente D, López-González R, Rodríguez L, Vadillo C et al (2007) Variability in the use of orthopedic surgery in patients with rheumatoid arthritis in Spain. J Rheumatol 34:1485–1490
21. Ziegler S, Huscher D, Karberg K, Krause A, Wassenberg S, Zink A (2010) Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997–2007: results from the National Database of the German Collaborative Arthritis Centers. Ann Rheum Dis 69:1803–1808
22. Lee SJ, Chang H, Yazici Y, Greenberg JD, Kremer JM, Kavanaugh A (2009) Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. J Rheumatol 36:1611–1617
23. Söderlin MK, Geborek P (2008) Changing pattern in the prescription of biological treatment in rheumatoid arthritis. A 7-year follow-up of 1839 patients in southern Sweden. Ann Rheum Dis 67:37–42
24. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324
25. Ministry of Health, Social Policy and Equality of Spain, Health Information Institute. National Catalogue of Hospitals 2008. https://www.msssi.gob.es/ciudadanos/prestaciones/centrosServiciosSNS/hospitales/docs/CNH2008.pdf
26. Prevoo ML, Van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL (1995) Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 38:44–48
27. Esteve-Vives J, Batlle-Gualda E, Reig A (1993) Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. Grupo para la Adaptación del HAQ a la Población Española. J Rheumatol 20:2116–2122
28. Dal-Re R, Tormo MJ, Perez G, Bolumar F (1998) Ethical review of epidemiologic studies: a need and a proposal. Med Clin (Barc) 111:587–591
29. Maese J, García De Yébenes MJ, Carmona L, Hernández-García C, emAR II Study Group (2012) Management of rheumatoid arthritis in Spain (emAR II). Clinical characteristics of the patients. Reumatol Clin 8:236–242
30. Leon L, Abasolo L, Carmona L, Rodriguez-Rodriguez L, Lamas JR, Hernandez-Garcia C et al (2013) Orthopedic surgery in rheumatoid arthritis in the era of biologic therapy. J Rheumatol 40:1850–1855
31. Desai RJ, Rao JK, Hansen RA, Fang G, Maciejewski ML, Farley JF (2014) Predictors of treatment initiation with tumor necrosis factor-α inhibitors in patients with rheumatoid arthritis. J Manag Care Spec Pharm 20:1110–1120
32. Kalkan A, Roback K, Hallert E, Carlsson P (2014) Factors influencing rheumatologists' prescription of biological treatment in rheumatoid arthritis: an interview study. Implement Sci 9:153
33. Kim G, Barner JC, Rascati K, Richards K (2015) Factors associated with the initiation of biologic disease-modifying antirheumatic drugs in Texas Medicaid patients with rheumatoid arthritis. J Manag Care Spec Pharm 21:401–407
34. Silva-Fernández L, Pérez-Vicente S, Martín-Martínez MA, López-González R (2015) on behalf of the emAR II Study Group. Variability in the prescription of non-biologic disease-modifying antirheumatic drugs for the treatment of spondyloarthritis in Spain. Semin Arthritis Rheum 44(6):633–640
35. Ferraz-Amaro I, Seoane-Mato D, Sánchez-Alonso F, Martín-Martínez MA, emAR II Study Group (2015) Synthetic disease-modifying antirheumatic drug prescribing variability in rheumatoid arthritis: a multilevel analysis of a cross-sectional national study. Rheumatol Int. 35(11):1825–1836
36. Lopez-Gonzalez R, Seoane-Mato D, Perez-Vicente S, Martin-Martinez MA, Sanchez-Alonso F, Silva-Fernandez L (2016) Variability in the frequency of rheumatology consultations in patients with rheumatoid arthritis in Spain. Rheumatol Int 36(11):1525–1534
37. Bellamy N, Kaloni S, Pope J, Coulter K, Campbell J (1998) Quantitative rheumatology: a survey of outcome measurement procedures in routine rheumatology outpatient practice in Canada. J Rheumatol 25:852–858