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Gender differences in clinical and prescribing characteristics of biologic and targeted synthetic drugs in naïve patients with rheumatoid arthritis: Data from BIOBADASER III registry

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Abstract

Background Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that can lead to progressive joint damage and irreversible disability when inadequately treated. RA is more common in women than in men. Disease characteristics differ between genders in terms of comorbidities, extra-articular manifestations, quality of life, disease activity and functional scores. There is a possibility that RA may be managed differently depending on gender: under-treated due to professional bias when prescribing advanced therapies, or over-treated due to overestimation of disease activity. Our primary objective was therefore to examine gender differences in the time course from RA diagnosis to initiation of the first biologic disease-modifying antirheumatic drug (bDMARD) or targeted synthetic DMARD (tsDMARD) and to identify factors associated with earlier or later prescribing. We also aimed to assess the differences between men and women in clinical characteristics and disease activity at initiation of the first b/tsDMARD among bio-naïve RA patients.

Methods We analyzed RA patients from the BIOBADASER III registry who began their first b/tsDMARD between 2000 and 2023, stratified by treatment start year. Clinical characteristics were compared by sex, using linear regression models for DAS28. Kaplan–Meier curves and multivariate Cox regression identified factors influencing treatment initiation timelines.

Results We included 3,384 patients (78.1% women). Males presented higher cardiovascular risk, females more osteoporosis and Sjögren Syndrome. At treatment start, females had lower mean age (54.8 vs. 57 years, $p < 0.001$) but longer disease duration (7.3 vs. 6.7 years, $p = 0.031$); higher DAS28-ESR, but not DAS28-CRP; higher subjective components of DAS28 and ESR but lower CRP and no differences in objective components. Disease duration differed

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between sexes only in the most recent cohort (≥ 2017, HR 0.9 (95% CI 0.81; 0.99), $p = 0.026$): female sex, age, and treatment with csDMARDs (other than methotrexate) were associated with later prescribing, whereas tobacco, obesity and treatment with methotrexate or glucocorticoids with earlier.

Conclusions Later prescribing in women despite higher activity rates merits reflection. Discrepancies between subjective and objective measures of DAS, and ESR and CRP, may reflect the need to establish different cut-off points for men and women, and opens a field of research worth exploring.

Keywords Arthritis, Rheumatoid, Biological therapy, Patient reported outcome measures

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that can lead to progressive joint damage and irreversible disability when inadequately treated. The current treatment strategy for RA aims to achieve remission or low activity ("treat-to-target"), with close monitoring of disease activity ("tight-control"), although therapeutic adaptation might occur when this goal is not reached [1, 2]. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate are often used as first-line therapy. Patients with adverse prognostic markers, or those who have failed to respond to csDMARDs, may opt for biologic (bDMARDs) or targeted synthetic DMARDs (tsDMARDs).

RA is more common in women than in men: its prevalence in Spain is 0.82% according to the EPISER 2016 study (0.9% in women, 0.8% in men) [3]. Disease characteristics differ between genders in terms of comorbidities, extra-articular manifestations [4, 5], and response to treatment [6–9]. In addition, female gender has been associated with poorer quality of life [10], and higher disease activity and functional scores [11–13]. Somatic symptoms are known to be reported differently between genders [14], with greater severity in women, which may hinder comparisons of disease activity measures between the two groups.

These differences between men and women, in this disease as in many others, have given rise to the so-called "gender medicine", focused on recognising and analysing not only differences based on biological sex (which would include anatomical or physiological aspects), but also on socially constructed gender (which would include psychological, social or behavioural ones) [15]. In addition to all these factors, clinician biases have been detected in the management of male and female patients, such as the delayed diagnosis of ankylosing spondylitis among females [16], or the later referral of women with RA to a rheumatologist from primary care compared to men [17–19]. Several reports in the cardiological literature were the first to indicate further disparities in the therapeutic approach, with men receiving more intensive treatment than women [20, 21]. On the other hand, the multicentre QUEST-RA study found no significant differences in the proportion of women and men taking prednisone, methotrexate and biologic agents, and the delay in starting therapies was similar in men and women, with no statistically significant results [7].

There is hence a possibility that RA may be managed differently depending on gender: under-treated due to professional bias when prescribing advanced therapies, or over-treated due to overestimation of disease activity. Therefore, our main purpose was to explore the potential gender differences in clinical characteristics and timing of prescription among rheumatoid arthritis patients initiating b/tsDMARD therapy. Specifically, the primary objective was to examine gender differences in the time course from RA diagnosis to initiation of the first bDMARD or tsDMARD, and to identify factors associated with earlier or later prescribing. We also aimed to assess the differences between men and women in clinical characteristics and disease activity at initiation of the first b/tsDMARD among bio-naïve RA patients.

Methods

Study design and setting

This is a Spanish multicenter observational study in a real-world setting. Information was obtained from BIOBADASER III, a national registry of patients with rheumatic diseases treated with bDMARDs and tsDMARDs and followed thereafter. Originally aimed at assessing drug safety, the registry was updated in December 2015 in order to include the appraisal of drug effectiveness as a secondary objective [17]. The registry protocol and materials of BIOBADASER III are available at https://biobadaser.ser.es. Briefly, data in BIOBADASER III are monitored once a year with a double process: online to whole database and in situ to a random sample of 20 patients in all 28 participating centers. Patients initiating a b/tsDMARD are invited to participate in the registry, and those who accept must sign an informed consent form, covering subsequent analysis such as the present study. BIOBADASER III was approved by the Hospital Clinic de Barcelona Ethics Committee (code FER-ADA-2015–01) and performed in accordance with

Good Pharmacoepidemiology Practice standards and the principles of the Declaration of Helsinki.

Specifically, the present work is a cross-sectional study, given that the analysis is focused at the time of starting the first b/tsDMARD.

Population

For this analysis, patients diagnosed with RA included in BIOBADASER III registry were selected, who initiated treatment for the first time with a b/tsDMARD (i.e., bionaïve) from January 2000 to October 2023.

Outcomes and variables of interest

Sex was the explanatory variable, and the main outcome variables are the time course from RA diagnosis to initiation of the first b/tsDMARD (i.e., disease duration), as well as the disease activity at treatment start. The year of treatment start was stratified into three periods: up to December 2006 (only three anti-tumour necrosis factor (TNF) marketed); January 2007-December 2016 (five anti-TNFs, abatacept, rituximab and tocilizumab, but no Janus kinase (JAK) inhibitors marketed yet); after January 2017 (JAK inhibitors and sarilumab emergence).

The following data were collected and considered as covariates: seropositivity, extraarticular manifestations of RA (interstitial lung disease, Sjögren Syndrome), age at RA diagnosis, age and degree of disease activity at initiation of first b/tsDMARD, comorbidities (Charlson comorbidity index, obesity, cancer, hypercholesterolemia, arterial hypertension, diabetes, chronic obstructive pulmonary disease (COPD), osteoporosis, peptic ulcer, moderate-severe chronic kidney disease), risk factors (smoking status, body mass index (BMI)) and concomitant DMARDs treatment (methotrexate, other csDMARDs, glucocorticoids).

Statistical analysis

Proportions, means and medians were reported according to distribution type. Clinical characteristics were compared between males and females using Chi-squared, t- and Kruskal–Wallis tests. Linear regression models were performed for DAS28 and its different components with sex as explanatory variable and adjusted for variables selected based on clinical and statistical relevance. Sjögren's syndrome was also taken into account as an adjustment variable, as discrepancies in ESR and CRP levels were detected in the descriptive analysis. In order to assess the timing of prescription, the time course from RA diagnosis until drug initiation was plotted using a Kaplan Meier curve and compared through log rank test, and a multivariate Cox regression model was performed to explore factors associated with disease duration until treatment start.

Analyses were performed on available data, with missing categories for those variables with missing information. Covariates for the adjusted models (linear and Cox regression) were selected using backward selection procedure, with a p-value cutoff of 0.05. Thus, all baseline characteristics were considered as covariates, but those above the cutoff were discarded from the final models. All analyses were performed using Stata version 13.1 (Stata Corp., College Station, TX 2013).

Results

At the time of the study, 3384 patients (2642 women, 78.1%) with a diagnosis of RA, enrolled in BIOBADASER III had started a first b/tsDMARD. The mean age at treatment initiation was lower in females (54.8 (SD: 12.6) vs 57 (SD: 11.5) years, $p < 0.001$), yet disease duration was higher (7.3 (SD: 7.5) vs 6.7 (SD: 7.2) years, $p = 0.031$). Males had higher BMI, Charlson comorbidity index, tobacco use, diabetes, moderate-severe chronic kidney disease, COPD, interstitial lung disease, and peptic ulcer, while females had more osteoporosis and Sjögren Syndrome. Concomitant treatment with methotrexate was more frequent in males. There were no differences in other comorbidities or clinical characteristics including seropositivity (Table 1).

At the start of the first b/tsDMARD, females had a higher activity index than males measured by DAS28-ESR, but no difference was found when using DAS28-CRP. When analysing the DAS28 components individually, the subjective components (TJC and PGA-VAS) and ESR were statistically higher for women, meaning females started therapy with increased disease activity components compared to males, even when fitting the linear regression model (Tables 1 and 2). However, there were no differences in the objective component SJC, and CRP was significantly higher for men. In the adjusted linear regression models, the variable "Sjögren's syndrome" was only significant for ESR (see supplementary Table 1 for detailed linear regressions).

Figure 1 shows differences in the time course of RA until treatment start between men and women (log rank test, $p = 0.028$). This gender difference was not observed in the overall population according to the Cox regression model (Table 3), yet year of treatment start was a significant factor: female sex was only statistically significant in the most recent cohort (≥ 2017, HR 0.9 (95% CI 0.81; 0.99), $p = 0.026$). In said model (cohort 3), the initiation of the first b/tsDMARD occurred later (longer time course of RA) in females, and also among older patients and those treated with other concomitant csDMARDs (other than methotrexate). Conversely, therapy started earlier (shorter time course of RA) among smokers,

Table 1 Clinical characteristics of rheumatoid arthritis patients at baseline, stratified by sex

		Male (*n* = 742, 21.9%)	Female (*n* = 2642, 78.1%)	Total (*n* = 3384)	P
Age at diagnosis (years, mean, SD)		50.3 (12.7)	47.5 (13.3)	48.1 (13.2)	**< 0.001**
Age at treatment start (years, mean, SD)		57 (11.5)	54.8 (12.6)	55.3 (12.4)	**< 0.001**
RA duration at treatment start (years, mean, SD)		6.7 (7.2)	7.3 (7.5)	7.2 (7.4)	**0.031**
Seropositivity (n, %)		551 (74.3)	1921 (72.7)	2472 (73.1)	0.849
Cancer (n, %)		32 (4.3)	118 (4.5)	150 (4.4)	0.857
Hypercholesterolemia (n, %)		124 (16.7)	396 (15.0)	520 (15.4)	0.23
Arterial hypertension (n, %)		127 (17.1)	368 (13.9)	495 (14.6)	0.026
Diabetes (n, %)		90 (12.2)	154 (5.9)	244 (7.2)	**< 0.001**
COPD (n, %)		58 (7.9)	51 (1.9)	109 (3.2)	**< 0.001**
Interstitial lung disease (n, %)		61 (8.2)	71 (2.7)	132 (4.5)	**< 0.001**
Osteoporosis (n, %)		27 (3.6)	312 (11.8)	339 (10.0)	**< 0.001**
Peptic ulcer (n, %)		16 (0.8)	17 (1.1)	33 (1.0)	**< 0.001**
Moderate-severe chronic kidney disease (n, %)		23 (3.1)	31 (1.2)	54 (1.6)	**< 0.001**
Smoking habit (n, %)	Non-smoker	291 (39.2)	1759 (66.6)	2050 (60.6)	**< 0.001**
	Smoker	220 (29.7)	426 (16.1)	646 (19.1)	
	Former smoker	186 (25.1)	305 (11.5)	491 (14.5)	
	Unknown	45 (6.1)	152 (5.8)	197 (5.8)	
Sjögren's syndrome (n, %)		12(1.6)	159 (6.0)	171 (5.1)	**< 0.001**
Charlson comorbidity index (median, IQR)		1 [1, 2]	1 [1 - 1]	1 [1 - 1]	**< 0.001**
BMI (median, IQR)		27.1 [24.6—29.8]	26.1 [22.9—30.1]	26.4 [23.3—30.1]	**< 0.001**
BMI (n, %)	Normal weight	190 (25.6)	912 (34.5)	1102 (32.6)	**< 0.001**
	Overweight	277 (37.3)	706 (26.7)	983 (29.1)	
	Obesity	148 (20.0)	563 (21.3)	711 (21.0)	
	Unknown	127 (17.1)	461 (17.5)	588 (17.4)	
Concomitant treatment (n, %)	Methotrexate	421 (56.7)	1390 (52.6)	1811 (53.5)	**0.046**
	Other csDMARDs*	251 (33.8)	989 (37.4)	1240 (36.6)	0.072
	Glucocorticoids	480 (64.7)	1622 (61.4)	2102 (62.1)	0.102
Disease activity	DAS28-ESR (mean, SD)	4.4 (1.4)	4.7 (1.2)	4.6 (1.3)	**< 0.001**
	DAS28-CRP (mean, SD)	3.6 (1.2)	3.7 (1.1)	3.7 (1.1)	0.271
	SJC (median, IQR)	3 [1–6]	3 [1–6]	3 [1–6]	0.947
	TJC (median, IQR)	4 [2–9]	5 [2–9]	5 [2–9]	**0.009**
	PGA-VAS (median, IQR)	6 [5–7]	6 [5–8]	6 [5–8]	**0.006**
	ESR mm/h (median, IQR)	18 [8–36]	23 [12—39]	22 [11—38]	**< 0.001**
	CRP mg/L (median, IQR)	7.9 [3.4—19.4]	6 [2.2—14.2]	6.5 [2.5—15.2]	**< 0.001**

Abbreviations: *SD* standard deviation, *IQR* interquartile range, *COPD* Chronic Obstructive Pulmonary Disease, *BMI* body mass index, *DAS* disease activity score, *TJC* tender joint count, *SJC* swollen joint count, *PGA-VAS* patient global assessment visual analogue scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

* Other csDMARDs include: leflunomide, sulfasalazine, gold salts, azathioprine, hydroxychloroquine, mesalazine, cyclophosphamide and cyclosporine

obese patients, and those receiving methotrexate or glucocorticoids (Table 3).

Discussion

This study provides real-world data of RA patients initiating treatment with the first b/tsDMARDs, confirming that there are gender differences in clinical characteristics and timing of prescription.

In general, males had more comorbidities (e.g., higher BMI, Charlson comorbidity index, smoking, diabetes, ...), with the exception of osteoporosis and Sjogren's syndrome, which were more frequent in females. These findings are consistent with those previously described in the literature [5]. Additionally, disease onset differed between sexes, occurring at a significantly younger age in females. A previous study designed to estimate the incidence of RA in Spain also found a significantly lower age of RA onset in women [22].

In our study, factors associated with an earlier start of b/tsDMARDs were tobacco use, obesity, and concomitant treatment with methotrexate or glucocorticoids, the latter consistent with previous findings [23, 24]. In addition, treatment was initiated earlier in the periods 2007—2016, and ≥ 2017, compared to before 2007. This could be attributed to greater confidence in the use of b/tsDMARDs by prescribers, as well as

Table 2 Linear regression models (simplified) for DAS28 and its different components, with sex as explanatory variable (adjusted for age at treatment initiation, Charlson comorbidity index, BMI, and Sjögren's syndrome)

Disease activity	Sex coefficient (ref. male)	(95% CI)	*p* value
DAS28-ESR	0.36	(0.24; 0.47)	**< 0.001**
DAS28-CRP	0.09	(−0.03; 0.20)	0.131
SJC	−0.01	(−0.42; 0.40)	0.953
TJC	0.68	(0.12; 1.24)	**0.017**
PGA-VAS	0.38	(0.16; 0.59)	**0.001**
ESR	5.22	(3.01; 7.43)	**< 0.001**
CRP	−3.63	(−6.90; −0.37)	**0.029**

Abbreviations: DAS disease activity score, *BMI* body mass index, *CI* confidence interval, *TJC* tender joint count, *SJC* swollen joint count, *PGA-VAS* patient global assessment visual analogue scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

greater availability of drugs with different mechanisms of action, in the more recent cohorts. Further research should explore the reasons behind the earlier prescription in patients with obesity and smoking habit. Assuming sex is "assigned at birth", this attribute precedes other studied characteristics (e.g., smoking, BMI, comorbidities) among which sex differences have been observed. While BMI and smoking could act as potential mediators, they were not effect modifiers of sex (data not showed): sex had an effect in timing of b/tsDMARD start regardless of BMI and smoking habit.

Conversely, the initiation of the first b/tsDMARD occurred with a longer time course of RA in females, and among older patients. To our knowledge, this is the first study to show a gender difference in the timing of prescribing the first biologic agent, among those initiated after 2017. There is only one study that prospectively analyzed factors associated with RA disease duration at the time of prescription, and no gender differences were found [23]. It should be noted that patients in said study were included from 2003 until 2015 with a relatively low sample size ($n = 178$, compared to 900 in the corresponding cohorts in our study), and we just found significant gender differences in the most recent cohort ($\geq$ 2017). The delay in initiating biologic therapy in elderly patients with chronic arthritis has been previously described [23–26] and may be explained by prescribers' reluctance to initiate b/tsDMARDs in elderly patients.

At the start of the first b/tsDMARD, females had a higher activity index measured by DAS28-ESR, but there was no difference with males when using DAS28-CRP. In addition, ESR was significantly higher in females, while PCR was higher in males. The equivalence between DAS28-ESR and DAS28-CRP, established by Wells et al. [27], deserves some reflections: firstly, this equivalence was not assessed independently in men and women, and, secondly, when there were discrepancies in remission classification defined by DAS28, most were due to patients being classified as in remission with DAS28-CRP but not with DAS28-ESR, and the authors supported the criterion

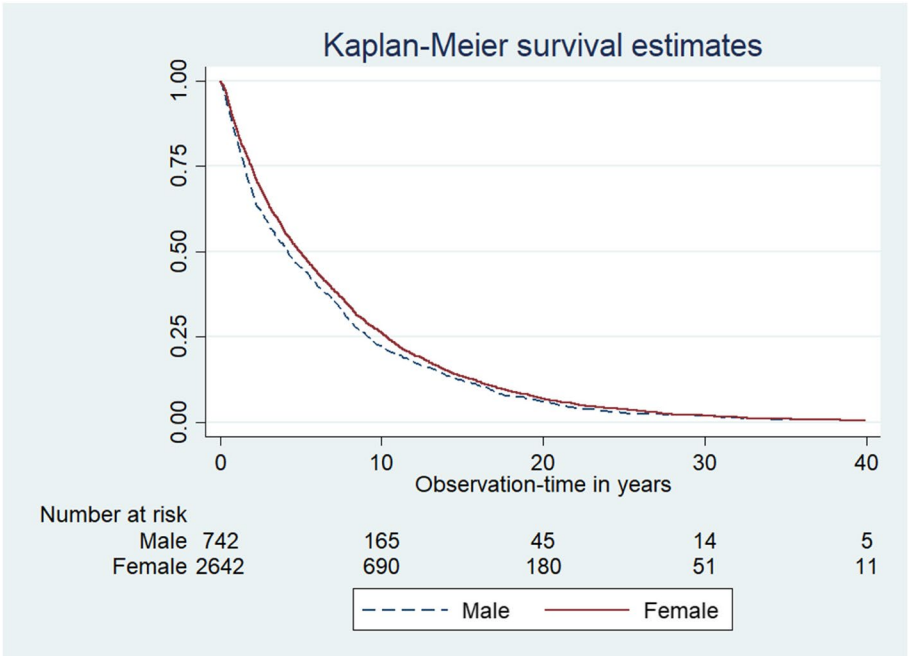

Fig. 1 Kaplan–Meier curve: time course from RA diagnosis until the first prescription of b/tsDMARD

Table 3 Cox regression model to assess factors associated with RA duration until drug initiation

	All population		Cohort 1 (< 2007) *n* = 295		Cohort 2 (2007–2016) *n* = 605		Cohort 3 (≥ 2017) *n* = 2484	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Female sex (ref. male sex)	0.93 (0.86; 1.01)	0.099	1.39 (0.97; 1.98)	0.07	0.96 (0.78; 1.19)	0.719	0.9 (0.81; 0.99)	**0.026**
Age at treatment start	0.98 (0.98, 0.98)	**< 0.001**	1.00 (0.99; 1.01)	0.806	0.98 (0.97; 0.98)	**< 0.001**	0.98 (0.98; 0.98)	**< 0.001**
Seropositivity	0.89 (0.82; 0.98)	**0.015**	0.74 (0.50; 1.09)	0.124	0.76 (0.61; 0.95)	**0.014**	0.93 (0.84; 1.04)	0.193
Year of treatment start (ref. < 2007)								
2007–2016	1.37 (1.18; 1.60)	**< 0.001**	-	-	-	-	-	-
> 2016	1.43 (1.23; 1.66)	**< 0.001**	-	-	-	-	-	-
Smoking habit (ref. non-smoker)								
Smoker	1.2 (1.10; 1.32)	**< 0.001**	1.44 (0.96; 2.14)	0.075	1.29 (1.03; 1.60)	**0.024**	1.20 (1.08; 1.33)	**0.001**
Former smoker	1.11 (1.00; 1.23)	0.053	1.89 (0.98; 3.62)	0.057	1.13 (0.83; 1.54)	0.434	1.11 (0.99; 1.24)	0.07
BMI (ref. Normal weight)								
Overweight	1.07 (0.98; 1.17)	0.119	0.85 (0.53; 1.34)	0.473	1.15 (0.91; 1.46)	0.233	1.06 (0.97; 1.17)	0.212
Obesity	1.16 (1.05; 1.27)	**0.003**	0.82 (0.48; 1.39)	0.460	1.23 (0.95; 1.59)	0.11	1.15 (1.04; 1.28)	**0.009**
Concomitant treatment								
Methotrexate	1.12 (1.04; 1.21)	**0.003**	1.21 (0.94; 1.55)	0.148	1.17 (0.97; 1.42)	0.11	1.10 (1.01; 1.20)	**0.026**
Other csDMARDs	0.94 (0.87; 1.01)	0.095	1.19 (0.91; 1.56)	0.193	1.09 (0.89; 1.33)	0.405	0.89 (0.81; 0.97)	**0.01**
Glucocorticoids	1.09 (1.02; 1.17)	**0.017**	1.06 (0.82; 1.36)	0.648	1.06 (0.89; 1.26)	0.523	1.10 (1.01; 1.19)	**0.024**

validity of DAS28-CRP. Therefore, it could be interpreted that DAS28-CRP is considered more reliable as a measure of disease activity than DAS28-ESR. ESR can be influenced by several factors unrelated to inflammation, such as age [28], gender [29] or plasma proteins. We found that Sjögren's syndrome was significantly more frequent in women and, when fitting the linear regression model for DAS28 and its different components, the variable 'Sjögren's syndrome' was only significant in the ESR model.

In our study, analysis of the individual components of DAS28 only showed significantly higher values in women in the subjective components TJC and PGA-VAS, but not in the objective component SJC. It is well known that women have a higher sensitivity to pain than men due not only to biological factors (e.g., a higher pain threshold due to testosterone in men, or the higher number of pain receptors in women with a different expression of these receptors), but also to gender-specific factors, such as the environment and social interactions, which vary between the sexes [30, 31]. Validated composite disease activity measures have been fundamental in recent decades to guide assessment of disease status and treatment response, but their limitations are well-recognized [32, 33]. Several published trials and studies have shown sex differences especially in subjective parameters: in the BARFOT study, higher DAS28 values in women were mainly dependent on higher pain scores [34]; in the Orencia and Rheumatoid Arthritis Registry, while there was no difference in response to abatacept between men and women, DAS28, TJC and PGA-VAS were consistently lower in men during follow-up [35]. In the QUEST-RA study, in patients with no SJC (no or very little clinical disease activity), gender differences were clinically and statistically significant in all other measures of the American College of Rheumatology core data set and in fatigue [7].

A possible explanation for the delay in treatment initiation in women despite a higher activity index (DAS28-ESR) could be that clinicians are aware of the predominance of subjective components such as pain or general patient assessment over components more directly related to inflammation, such as CRP or joint swelling [36]. Buch et al. [37], in a recent review, classified patients with persistent symptoms in the absence of objective inflammation as refractory non-inflammatory RA (RINRA). Misdiagnosis of persistent symptomatology as joint inflammation may lead to unnecessary treatment with b/tsDMARDs, or cycling though several therapies, but this increased perception of pain and discomfort clearly indicates an impaired quality of life that needs to be addressed.

Among the strengths of this study are the use of real-world data from BIOBADASER, a well-known registry with monitored patient information, including participating centers throughout the country. The nationwide coverage and the long-term study period encourage the generalizability of results among the Spanish population. Covariates included in the regression models were restricted to those available in the registry, therefore, the main limitation was the lack of data regarding other potential confounders that are not collected (e.g.,

hypergammaglobulinaemia, educational level or other social educational status, date of first symptoms) or difficult to measure (e.g., prescription bias) and that could have an impact in the disease activity measures or the timing of prescription. On the other hand, another important limitation could be that sex is recorded in BIOBADASER as a dichotomous biological variable (male, female) and not as self-reported gender (understood as the socially constructed norm: male, female, trans man, trans woman, non-binary, etc.). If the data had information on self-reported gender, a better approach to investigating the role of sex (biological, e.g. relevant to BMI) and gender (social, e.g. relevant to BMI and smoking) would be possible, which would serve to strengthen the study and advocate for better data collection in the sex and gender domains.

Conclusions

We have identified several factors associated with time to the first prescription of a b/tsDMARD in the most recent cohort ($\geq$ 2017): female sex, age, and combined treatment with csDMARDs other than methotrexate were associated with later prescribing, whereas smoking habit, obesity and concomitant treatment with methotrexate or glucocorticoids were associated with earlier prescribing. In addition, the prescription of b/tsDMARDs has been initiated with shorter disease duration (less advanced RA) over time.

At the start of the first b/tsDMARD, females had a higher activity index measured by DAS28-ESR, but there was no difference with males when using DAS28-CRP. ESR was significantly higher in females, while PCR was higher in males. Also, there are discrepancies between the subjective (TJC and PGA-VAS) and objective (SJC) parameters of DAS28.

These results could have important implications: the delay in treatment initiation in women despite a higher activity rate merits reflection. The discrepancies found between subjective and objective measures of DAS, as well as the lack of equivalence between ESR and CRP, may reflect the need to establish different cut-off points for men and women, and opens up a field of research worth exploring.

Abbreviations

bDMARD	Biologic disease-modifying antirheumatic drug
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
DAS	Disease activity score
ESR	Erythrocyte sedimentation rate
HR	Hazard ratio
IQR	Interquartile range
JAK	Janus kinase
PGA-VAS	Patient global assessment visual analogue scale
RA	Rheumatoid arthritis
SD	Standard deviation
SJC	Swollen joint count
TJC	Tender joint count
TNF	Tumour necrosis factor
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03571-2.

Supplementary Material 1.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Authors' contributions

PVC and LOV designed the study. LOV and FSA contributed to data management and statistical analysis. PVC and LOV drafted the publication. PVC, LOV, FSA, SGS, RCA, CCF, JCG, YPV, SMA, SB, JMR, MDRM, LRG, MJMR and IC, performed a critical review of the article, contributed to the discussion and interpretation of the results, and read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The project was approved by the Research Ethics Committee of the Hospital Universitario Clinic Barcelona (approval code FER-ADA-2015–01), while the reference committee is the Research Ethics Committee of the Hospital Universitario de Canarias. Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

PVC received grants or contracts from GSK, Abbvie, Roche, Novartis, Lilly, AstraZeneca, Pfizer; consulting fees from GSK; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, GSK, Lilly; Support for attending meetings and/or travel from Abbvie.
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The other authors declare that they have no relevant financial or non-financial interests to disclose.

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References

1. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99.
2. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2021;73:1108–23.
3. Silva-Fernández L, Macía-Villa C, Seoane-Mato D, Cortés-Verdú R, Romero-Pérez A, Quevedo-Vila V, et al. The prevalence of rheumatoid arthritis in Spain. Sci Rep. 2020;10(1):21551.
4. Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum. 1998;41:817–22.
5. Aurrecoechea E, Llorca Diaz J, Diez Lizuain M, McGwin G Jr, Calvo-Alen J. Gender-associated comorbidities in rheumatoid arthritis and their impact on outcome: data from GENIRA. Rheumatol Int. 2017;37:479–85.
6. Bergstra SA, Allaart CF, Ramiro S, Chopra A, Govind N, Silva C, et al. Sex-associated treatment differences and their outcomes in rheumatoid arthritis: Results from the METEOR Register. J Rheum. 2018;45:1361–6.
7. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: Analyses of disease activity, disease characteristics, and treatments in the QUEST-RA Study. Arthritis Res Ther. 2009;11:R7.
8. Jawaheer D, Maranian P, Park G, Lahiff M, Amjadi SS, Paulus HE. Disease progression and treatment responses in a prospective DMARD-naïve seropositive early rheumatoid arthritis cohort: Does gender matter? J Rheum. 2010;37:2475–85.
9. Hallert E, Thyberg I, Hass U, Skargren E, Skogh T. Comparison between women and men with recent onset rheumatoid arthritis of disease activity and functional ability over two years (the TIRA project). Ann Rheum Dis. 2003;62:667–70.
10. Aurrecoechea E, Llorca Díaz J, Diez Lizuain M, McGwin G Jr, Calvo-Alen J. Impact of gender on quality of life of patients with rheumatoid arthritis. J Arthritis. 2015;4:160.
11. Krasselt M, Baerwald C. Sex, Symptom Severity, and Quality of Life in Rheumatology. Clin Rev Allergy Immunol. 2019;56(3):346–61.
12. Forslind K, Hafström I, Ahlmén M, Svensson B, BARFOT Study Group. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis. 2007;66(1):46–52.
13. Ahlmén M, Svensson B, Albertsson K, Forslind K, Hafström I, BARFOT Study Group. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Ann Rheum Dis. 2010;69(1):230–3.
14. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med. 2001;16:266–75.
15. Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. Clin Chem Lab Med. 2013;51(4):713–27.
16. Jovani V, Blasco-Blasco M, Ruiz-Cantero MT, Pascual E. Understanding how the diagnostic delay of spondyloarthritis differs between women and men: A systematic review and meta-analysis. J Rheum. 2017;44:174–83.
17. Palm O, Purinszky E. Women with early rheumatoid arthritis are referred later than men. Ann Rheum Dis. 2005;64:1227–8.
18. Lard LR, Huizinga TW, Hazes JM, Vlieland TP. Delayed referral of female patients with rheumatoid arthritis. J Rheum. 2001;28:2190–2.
19. Barnabe C, Xiong J, Pope JE, Boire G, Hitchon C, Haraoui B, et al. Factors associated with time to diagnosis in early rheumatoid arthritis. Rheumatol Int. 2014;34:85–92.
20. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, French WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med. 1998;158:981–8.
21. Heer T, Schiele R, Schneider S, Gitt AK, Wienbergen H, Gottwik M, et al. Gender differences in acute myocardial infarction in the era of reperfusion (the MITRA registry). Am J Cardiol. 2002;89:511–7.
22. Carbonell J, Cobo T, Balsa A, Descalzo MA, Carmona L, SERAP Study Group. The incidence of rheumatoid arthritis in Spain: results from a nationwide primary care registry. Rheumatology (Oxford). 2008;47(7):1088–92.
23. Kedra J, Granger B, Emilie S, Gaujoux-Viala C, Rat AC, Combe B, et al. Time to initiation of biologic disease-modifying antirheumatic drugs in the French cohort ESPOIR. Joint Bone Spine. 2021;88(1): 105060.
24. Desai RJ, Rao JK, Hansen RA, Fang G, Maciejewski ML, Farley JF. Predictors of Treatment Initiation with Tumor Necrosis Factor-Inhibitors in Patients with Rheumatoid Arthritis. J Manag Care Pharm. 2014;20:1110–20.
25. Vela P, Sanchez-Piedra C, Perez-Garcia C, Castro-Villegas MC, Freire M, Mateo L, et al. Influence of age on the occurrence of adverse events in rheumatic patients at the onset of biological treatment: data from the BIOBADASER III register. Arthritis Res Ther. 2020;22(1):143.
26. Steffen A, Holstiege J, Klimke K, Akmatov MK, Bätzing J. Patterns of the initiation of disease-modifying antirheumatic drugs in incident rheumatoid arthritis: a German perspective based on nationwide ambulatory drug prescription data. Rheumatol Int. 2018;38:2111–20.
27. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68(6):954–60.
28. Beregi E, Regius O, Németh J, Rajczy K, Gergely I, Lengyel E. Gender differences in age-related physiological changes and some diseases. Z Gerontol Geriatr. 1995;28(1):62–6.
29. Alende-Castro V, Alonso-Sampedro M, Vazquez-Temprano N, Tuñez C, Rey D, García-Iglesias C, et al. Factors influencing erythrocyte sedimentation rate in adults: New evidence for an old test. Medicine (Baltimore). 2019;98(34): e16816.
30. Jawaheer D, Olsen J, Hetland ML. Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis – results from the DANBIO registry. J Rheumatol. 2012;39:46–53.
31. Maranini B, Bortoluzzi A, Silvagni E, Govoni M. Focus on Sex and Gender: What We Need to Know in the Management of Rheumatoid Arthritis. Pers Med. 2022;12(3):499.
32. Ferreira RJO, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JAP. Suppressing Inflammation in Rheumatoid Arthritis: Does Patient Global Assessment Blur the Target? A Practice-Based Call for a Paradigm Change. Arthritis Care Res (Hoboken). 2018;70(3):369–78.
33. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology. 2006;45:885–9.

34. Andersson ML, Forslind K, Hafstrom I. Comparing Five Year Out-Come in Two Cohorts of Patients with Early Rheumatoid Arthritis—A BARFOT Study. Open Rheumatol J. 2015;9:8–15.
35. Nourisson C, Soubrier M, Mulliez A, Baillet A, Bardin T, Cantagrel A, et al. Impact of gender on the response and tolerance to abatacept in patients with rheumatoid arthritis: Results from the 'ORA' registry. RMD Open. 2017;3: e000515.
36. Castrejon Fernandez I, Martinez-Lopez JA, Ortiz Garcia AM, Carmona Ortells L, García-Vicuña R, González-Álvaro I. Influence of gender on treatment response in a cohort of patients with early rheumatoid arthritis in the area 2 of Madrid. Reumatol Clin. 2010;6(3):134–40.
37. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nat Rev Rheumatol. 2021;17:17–33.

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