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HEALTH DISPARITIES AND HEALTH EQUITY IN THE RHEUMATIC DISEASES

Female Sex, Age, and Unfavorable Response to Tumor Necrosis Factor Inhibitors in Patients With Axial Spondyloarthritis: Results of Statistical and Artificial Intelligence–Based Data Analyses of a National Multicenter Prospective Registry

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Objective. Real-world studies are needed to identify factors associated with response to biologic therapies in patients with axial spondyloarthritis (SpA). The objective was to assess sex differences in response to tumor necrosis factor inhibitors (TNFi) and to explore possible risk factors associated with TNFi efficacy.

Methods. A total of 969 patients with axial SpA (315 females, 654 males) enrolled in the BIOBADASER registry (2000–2019) who initiated a TNFi (first, second, or further lines) were studied. Statistical and artificial intelligence (AI)–based data analyses were used to explore the association of sex differences and other factors to TNFi response, using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), to calculate the BASDAI50, with an improvement of at least 50% of the BASDAI score, and using the Ankylosing Spondylitis Disease Activity Score, calculated using the C-reactive protein level (ASDAS-CRP).

Results. Females had a lower probability of reaching a BASDAI50 response with a first line TNFi treatment at the second year of follow-up ($P = 0.018$) and a lesser reduction of the ASDAS-CRP at this time point. The logistic regression model showed lower BASDAI50 responses to TNFi in females ($P = 0.05$). Other factors, such as older age ($P = 0.004$), were associated with unfavorable responses. The AI data analyses reinforced the idea that age at the beginning of the treatment was the main factor associated with an unfavorable response. The combination of age with other clinical characteristics (female sex or cardiovascular risk factors and events) potentially contributed to an unfavorable response to TNFi.

Conclusion. In this national multicenter registry, female sex was associated with less response to a first-line TNFi by the second year of follow-up. A higher age at the start of the TNFi was the main factor associated with an unfavorable response to TNFi.

INTRODUCTION

The term spondyloarthritis (SpA) encompasses a number of inflammatory diseases that share epidemiologic, pathogenic, genetic, clinical, radiographic, and therapeutic response features (1). It can be divided into predominantly axial SpA and peripheral forms (2). Within axial SpA, 2 forms are defined according to the Ankylosing Spondylitis Assessment Society classification criteria: ankylosing spondylitis (AS) or radiographic axial SpA and nonradiographic axial SpA (1,2), classified by the presence/absence of

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SIGNIFICANCE & INNOVATIONS

- The use of anti-tumor necrosis factor inhibitors (TNFi) as therapy in patients with axial spondyloarthritis (SpA) has raised the need to identify possible gender differences in response to this therapy.
- We analyzed patients with axial SpA enrolled in the BIOBADASER registry from 2000 to 2019 who initiated a TNFi as first- or second-line therapy.
- Female sex and higher ages at the start of treatment were associated with less response to first-line TNFi by the second year of follow-up.

radiographic sacroiliitis, according to the modified New York criteria (3). Patients who have axial SpA must be treated effectively, because the disease can lead to irreversible damage of the spine and joints, resulting in chronic pain, disability, and a negative impact on the patient's quality of life (4). Data from early studies have indicated that AS is more prevalent in males, while more recent data focused on axial SpA patients have shown a more homogeneous sex prevalence. However, axial SpA is still underrecognized among women, resulting in a delay in diagnosis and treatment, even when all the clinical forms are considered together (5). As a result, females are still underrepresented in studies of patients with axial SpA, and analyses stratified by sex are often not performed or disclosed. Available studies on sex differences in patients with axial SpA point out that females have different disease manifestations, and that disease activity (measured through the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) and quality of life (measured with the Ankylosing Spondylitis Quality of Life index) are significantly worse in females (5–8).

The introduction of effective biologic agents targeting tumor necrosis factor (TNF) has been a major advance in the management of axial SpA. New biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) that target interleukin 17 (IL-17i) and JAK, respectively, now offer a wider range of options for axial SpA patients. Gender differences regarding response to the treatment have been found. For example, female patients have lower response rates to TNF inhibitors (TNFi) and a lower adherence to the treatment (4,7,8). Regarding IL-17i, fewer data are available, and while sex was not an independent predictor of treatment response to secukinumab in 1 study (9), another study disclosed that male sex was associated with a lower risk of secukinumab discontinuation in patients with axial SpA and psoriatic arthritis (10). Several studies on sex differences in patients with axial SpA have revealed different biologic mechanisms that could hypothetically contribute to the observed differences in disease manifestations and treatment response (5,6). For these reasons, a greater understanding of the differences between female and male pathogenesis and bDMARD response is required. Real-world evidence studies addressing gender differences in response to bDMARDs might add evidence to this topic.

The present study consists of a secondary analysis of the BIOBADASER database, the Spanish registry of patients with rheumatic diseases starting bDMARDs and tsDMARDs (11). The objectives were to assess sex differences in response TNFi in patients with axial SpA and to explore possible risk factors associated with TNFi efficacy, making use of statistical analysis and an artificial intelligence (AI) approach.

MATERIALS AND METHODS

Study design and setting. This was a retrospective analysis of BIOBADASER, the Spanish multicenter prospective observational registry aimed at assessing safety in patients with rheumatic diseases who start treatment with bDMARDs or tsDMARDs. The registry was established in 2000 and has been comprehensively described in previous reports (12). BIOBADASER 3.0 is the third stage of the registry, an adaptation made in December 2015 (11) by adding to its objectives the systematic assessment of efficacy by commonly accepted indexes. The BIOBADASER registry is promoted by the Spanish Society of Rheumatology and supported by the Spanish Agency of Drugs and Medical Devices and several pharmaceutical companies. For the assessment of data consistency and quality, strict measures are implemented. The full database is monitored online, and additionally, a random sample of patients is selected and audited in situ annually in all 28 participating centers. The recruitment of new patients is dynamic and remains indefinitely open. Further details about design and conduct of the BIOBADASER 3.0 registry, such as the complete protocol and relevant documentation, are available at the BIOBADASER website (11).

All procedures and materials comply with the principles of the Declaration of Helsinki and with Spanish regulations on data protection and research. The project was approved by the Ethics Review Committee of the Hospital Clinic (Barcelona), acting as reference committee (approval code FER-ADA-2015-01).

All patients signed an informed consent to be included in the BIOBADASER registry, covering subsequent analyses such as the present study. Patients' information was managed as anonymized aggregated data and as approved by the Clinical

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Research Committee, and specific informed consent for this analysis was not required.

Patients. All adult patients diagnosed with axial SpA, including radiographic axial SpA/AS and nonradiographic axial SpA, according to their rheumatologist, treated with at least 1 TNFi for at least 12 weeks before inclusion and with available BASDAI results, registered from January 1, 2000 (starting date of BIOBADASER) to October 11, 2019, were included in this analysis.

Variables. Disease activity was measured using BASDAI. In addition, the Ankylosing Spondylitis Disease Activity Score, calculated using the C-reactive protein level (ASDAS-CRP) was calculated, through a recently proposed modification to calculate ASDAS-CRP, when the individual items of the BASDAI are missing (13). The clinical response (primary outcome) was defined as favorable when BASDAI50 was achieved, defined as an improvement of at least 50% of the BASDAI score between baseline and follow-up visits. Also, the change in the ASDAS-CRP scores was analyzed. The clinical responses were analyzed by treatment line (first, second, or further lines of treatment) and at different time points. Time points of interest were defined as the start of treatment as the date of starting biologic therapy; 1 year of treatment as the first visit registered between 6 and 18 months of follow-up; and second year and further as the first visit registered from 18 months and beyond. This analysis included the following variables: demographic information (sex, age at diagnosis, and age at the start of the treatment) and clinical characteristics, including 1) diagnosis according to the rheumatologist (radiographic axial SpA/AS and nonradiographic axial SpA); 2) disease duration, calculated as the time since the diagnosis date reported by physicians and study date in years; 3) BASDAI and ASDAS-CRP scores; 4) body mass index (BMI); 5) comorbidities, such as cardiovascular events (ischemic cardiopathy, myocardial infarct, congestive heart failure, peripheral vascular disease, and cerebrovascular disease); 6) cardiovascular risk factors (hypercholesterolemia, arterial hypertension, diabetes mellitus without organ damage, diabetes mellitus with organ damage, smoking status, and obesity, defined as a BMI ≥30); and 7) comorbidity burden, assessed through the Charlson Comorbidity Index (14).

The presence of each comorbidity was registered, considering the comorbidity diagnoses and/or treatments registered in the clinical charts and confirmed with the patients at the moment of the study visits. Smoking status was categorized as never smoking, past smoking, or current smoking. Clinical characteristics also included laboratory results (HLA–B27, CRP level, and erythrocyte sedimentation rate [ESR]) and treatment data: dates of initiation and discontinuation of TNFi therapy, follow-up time points (start of treatment, 1 year follow-up, and ≥2 years of follow-up), previous biologic treatments, and concomitant treatments. All the analyses were performed for the whole sample of axial SpA patients. In addition, secondary exploratory analyses were made for each subgroup of axial SpA patients (AS/radiographic axial SpA and nonradiographic axial SpA).

Statistical analysis. Descriptive analyses were performed for the demographic and clinical variables. The distribution of the variables was evaluated through measures of central tendency. The continuous variables are expressed as mean ± SD and the categorical variables as frequencies and percentages. We used *t*-test and chi-square tests to test differences between men and women and favorable and unfavorable response.

Logistic regression was performed to study factors associated with the risk of achieving the BASDAI50 response. Adjusted variables were age at the beginning of TNFi, sex, comorbidities (Charlson Comorbidity Index), and the line of treatment. Logistic regression results were evaluated considering the adjusted odds ratio (OR) and 95% confidence interval (95% CI). The results of all statistical analyses were evaluated as significant for *P* values less than or equal to 0.05. Statistics were performed by using STATA software.

With the aim of identifying classifiers able to distinguish patients with favorable and unfavorable response to TNFi, Anaxomics AI Data Science software (15) was used as a data mining approach to evaluate the variables describing axial SpA patients at the second year of follow-up of a first-line TNFi. This data mining approach combines a series of statistical and AI methods to extract knowledge from large data sets. It uses a combination of feature selection approaches to reduce the search space by identifying subsets of data that contain relevant features (in this case, clinical or demographic variables), with a set of base classifier methodologies, which generate the final classification models. Here, a brute force feature selection algorithm was used for single feature or variable classification models (16) (i.e., analyzing 1 feature at a time, and considering all features in the data set). For identification of multiple feature classifiers (2- and 3-feature models were explored), the following feature selection and extraction algorithms were applied, to both reduce the computational costs and to improve the performance: CHOW-LIU (17), a tree-like approach finds an optimum set of n – 1 first-order dependence relationship among n variables; minimum redundancy maximum relevance (18) focuses on reducing the search space by removing redundant features bearing similar information; RELIEFF (19) uses weights to rank the features and discard the less important ones; recursive feature elimination–support vector machine (20) discards redundant or low-impact features and ranks features; sequential forward floating selection (21) selects an optimal subset of features by adding 1 feature at a time to the new subset and discarding noninformative ones; and Wilcoxon with correlation (22) uses the Wilcoxon-Mann-Whitney test to evaluate the different features and discard redundant ones. Two different base classifier methodologies were then used to evaluate all distinct feature combinations resulting from the feature selections step:

GLM binomial (23), which is similar to an ordinary linear regression but uses a link function to generalize to nonlinear responses, here to a binomial (1 or 0) response; and naive Bayes (24), a probabilistic classification approach based on applying Bayes' theorem, using the assumption that all variables are independent. To enhance the generalization capability of the conclusions, a 10-fold cross-validation procedure was applied.

Classification models with a cross-validated *P* value less than 0.05 were considered significant (15). Once the classification models are generated, they can be used to classify or identify a group (in this case, patients with an unfavorable response), and the following concepts can be computed: true and false positives (TP and FP), patients correctly and incorrectly classified in the positive group, respectively; and true and false negatives (TN and FN), patients correctly and incorrectly classified as not pertaining to the positive group, respectively. According to this definition, the following quality parameters were calculated for each classifier, in cross-validation: sensitivity (SNS), defined as TP/(TP + FN); specificity (SPC), defined as TN/(TN + FP); and balanced accuracy (BACC), defined as (SNS + SPC)/2. BACC was used as a measure of the predictability of the resulting classifiers. All statistical analyses were performed without imputation of missing values.

RESULTS

Baseline demographic and clinical characteristics. A total of 969 patients with axial SpA treated with TNFi were identified from the BIOBADASER III database, of whom 315 (32.5%)

Table 1. Baseline demographic and clinical characteristics of the patients with axial SpA treated with TNFi by sex*

Baseline characteristic	Male (n = 654)	Female (n = 315)	Total (n = 969)	*P*
Continuous†				
Age at diagnosis, years	36.01 ± 12.34	39.96 ± 12.87	37.30 ± 12.64	<0.001‡
Disease duration, years	9.38 ± 9.86	7.79 ± 9.28	8.86 ± 9.70	0.017‡
Age at treatment start, years	45.39 ± 12.71	47.75 ± 12.67	46.16 ± 12.74	0.007‡
C-reactive protein	9.18 ± 14.79	9.60 ± 21.27	9.33 ± 17.38	0.017‡
Erythrocyte sedimentation rate	23.19 ± 22.45	27.39 ± 23.89	24.73 ± 23.05	0.096
Charlson Comorbidity Index	1.68 ± 1.21	1.67 ± 1.04	1.68 ± 1.16	0.926
Body mass index	27.41 ± 6.80	26.96 ± 5.54	27.25 ± 6.39	0. 346
BASDAI	5.44 ± 2.15	5.76 ± 2.19	5.55 ± 2.17	0.030‡
ASDAS-CRP§	3.12 ± 1.34	3.55 ± 1.46	3.24 ± 1.39	0.020‡
Categorical, no. (%)¶				
HLA–B27				
Unknown	57 (8.73)	20 (6.39)	77 (7.97)	0.002‡
Positive	489 (74.89)	213 (68.05)	702 (72.67)	–
Negative	107 (16.39)	80 (25.56)	187 (19.36)	–
Peripheral involvement	115 (17.58)	55 (17.46)	170 (17.54)	0.962
Uveitis	82 (12.54)	49 (15.56)	131 (13.52)	0.198
Ischemic cardiopathy	25 (3.87)	1 (0.32)	26 (2.72)	0.002‡
Myocardial infarct	19 (3.43)	1 (0.37)	20 (2.43)	0.007‡
Congestive heart failure	1 (0.18)	1 (0.37)	2 (0.24)	0.608
Peripheral vascular disease	9 (1.63)	4 (1.48)	13 (1.58)	0.875
Cerebrovascular disease	3 (0.54)	1 (0.37)	4 (0.49)	0.736
Hypercholesterolemia	143 (22.03)	53 (16.99)	196 (20.40)	0.069
Arterial hypertension	138 (21.36)	64 (20.58)	202 (21.11)	0.781
DM without organ involvement	35 (5.35)	11 (3.49)	46 (4.75)	0.202
DM with organ involvement	4 (0.73)	1 (0.37)	5 (0.61)	0.535
Smoking status				
No	319 (51.70)	199 (67.00)	518 (56.67)	<0.001‡
Yes	212 (34.36)	76 (25.59)	288 (31.51)	–
Former	86 (13.94)	22 (7.41)	108 (11.82)	–
Cardiovascular events#	35 (5.35)	6 (1.90)	41 (4.23)	0.013‡
Cardiovascular risk factors**	395 (60.40)	156 (49.52)	551 (56.86)	0.001‡

* Values are the mean ± SD, unless indicated otherwise. ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score based on C-reactive protein level; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DM = diabetes mellitus; SpA = spondyloarthritis; TNFi = tumor necrosis factor inhibitors.
† *P* values calculated using *t*-test.
‡ $P < 0.05$.
§ ASDAS-CRP calculated as described in reference 13.
¶ *P* values calculated using chi-square test.
# Cardiovascular events defined as ischemic cardiopathy, myocardial infarct, congestive heart failure, peripheral vascular disease, and cerebrovascular disease.
** Cardiovascular risk factors defined as hypercholesterolemia, arterial hypertension, diabetes mellitus without organ damage, diabetes mellitus with organ damage, smoking status, and body mass index ≥30.

Table 2. Sex differences in treatment response (BASDAI50) in patients with axial SpA treated with TNFi by line of treatment*

Response to treatment (BASDAI50)	Male	Female	P†
First line treatment			
First year of treatment			
Favorable	101 (41.6)	37 (39.8)	0.767
Unfavorable	142 (58.4)	56 (60.2)	–
Missing	0	0	–
Second year and further			
Favorable	92 (44.7)	20 (28.6)	0.018‡
Unfavorable	114 (55.3)	50 (71.4)	–
Missing	2	0	–
Second and further lines			
First year of treatment			
Favorable	44 (22.8)	18 (21.2)	0.765
Unfavorable	149 (77.2)	67 (78.8)	–
Missing	6	2	–
Second year and further			
Favorable	40 (29.2)	23 (34.3)	0.456
Unfavorable	97 (70.8)	44 (65.7)	–
Missing	9	1	–

* Values are the number (%) unless indicated otherwise. Values in the missing category were the number of patients excluded at year 1 and year 2 because of missing Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) data. BASDAI50 = improvement of at least 50% of the BASDAI score between baseline and follow-up visits; SpA = spondyloarthritis; TNFi = tumor necrosis factor inhibitors.
† Calculated using chi-square test.
‡ $P < 0.05$.

were female and 654 (67.5%) were male. Significant differences in several baseline factors between male and female populations were identified (Table 1). Female patients had higher values at baseline for age at diagnosis and age at the start of the TNFi, CRP levels, and BASDAI and ASDAS-CRP scores among female patients. In contrast, baseline parameters significantly higher among male patients were disease duration, HLA–B27 positivity, smoking, the presence of cardiovascular risk factors and cardiovascular events in general, and ischemic cardiopathy and myocardial infarct in particular. Similar differences were also detected in the subgroup of patients with AS (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25048).

Sex differences in disease activity scores. Disease activity was assessed through BASDAI50 (Table 2). Also, the change in ASDAS-CRP versus the baseline ASDAS-CRP score was calculated (Table 3). Regarding BASDAI50 responses, we identified more unfavorable responses in female patients in the second year after the start of the first-line TNFi ($P = 0.018$). In addition, we observed higher ASDAS-CRP scores both at baseline ($P = 0.005$) and at the second year and further ($P = 0.002$) among women and a lower change in the ASDAS-CRP score at this time point ($P = 0.048$). Similar differences were also detected in the subgroup of patients with AS (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25048).

Factors associated with an unfavorable response to TNFi. Patients with unfavorable and favorable responses to TNFi present some significant clinical differences (Tables 4 and 5 and Supplementary Tables 3–5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25048). The age at diagnosis was higher among patients with unfavorable responses, both in the total group ($P = 0.007$) and the female group ($P = 0.032$). Disease duration was higher in males with unfavorable responses ($P = 0.040$). The age at the beginning of the treatment was higher among patients with unfavorable responses, both in the whole group ($P < 0.001$) and in the group of male patients ($P = 0.003$). Lower baseline ESR values were observed in patients with unfavorable responses in all groups, but no differences were identified for CRP levels. Finally, cardiovascular risk factors were higher among patients with

Table 3. Sex differences in disease activity (ASDAS-CRP) in patients with axial SpA treated with TNFi at different time points*

Time points of TNFi treatment	ASDAS-CRP score†			Change in ASDAS-CRP score‡		
	Male	Female	P§	Male, no., mean ± SD	Female, no., mean ± SD	P§
First line treatment						
Start	130 (318), 3.08 ± 1.37	39 (163), 3.75 ± 0.89	0.005¶	–	–	–
First year	87 (156), 1.78 ± 0.92	25 (68), 2.09 ± 1.12	0.162	47, −1.05 ± 1.14	7, −0.87 ± 1.09	0.694
Second year	72 (136), 1.60 ± 0.74	19 (51), 2.28 ± 1.10	0.002¶	43, −0.99 ± 1.39	9, −0.94 ± 1.04	0.049¶
Second and further lines						
Start	93 (239), 3.11 ± 1.33	50 (116), 3.28 ± 1.75	0.499	–	–	–
First year	55 (144), 2.03 ± 1.13	28 (59), 2.07 ± 0.96	0.874	27, −1.14 ± 1.51	18, −0.92 ± 0.91	0.68
Second year	42 (104), 2.13 ± 1.16	23 (45), 2.16 ± 0.75	0.907	19, −0.37 ± 1.88	11, −1.06 ± 1.24	0.186

* Values are the number (missing number), mean ± SD unless indicated otherwise. ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score based on C-reactive protein level; SpA = spondyloarthritis; TNFi = tumor necrosis factor inhibitors.
† ASDAS-CRP calculated as described in reference 13.
‡ Change in ASDAS-CRP: initial ASDAS-CRP score minus the ASDAS-CRP score at each time point.
§ Calculated using *t*-test.
¶ $P < 0.05$.

Table 4. Clinical differences (continuous variables) of axial SpA patients treated with TNFi with unfavorable and favorable responses according to BASDAI50 response, considering sex*

Continuous characteristics by sex	Favorable	Unfavorable	P†
Age at diagnosis			
Male	35.09 ± 12.37	36.55 ± 12.37	0.17
Female	37.20 ± 11.99	40.93 ± 12.87	0.032‡
Total	35.64 ± 12.28	38.08 ± 12.71	0.007‡
Disease duration			
Male	8.17 ± 9.28	9.91 ± 10.15	0.040‡
Female	8.33 ± 10.65	7.58 ± 8.92	0.556
Total	8.21 ± 9.64	9.09 ± 9.80	0.211
Age at start of treatment			
Male	43.26 ± 13.23	46.46 ± 12.45	0.003‡
Female	45.53 ± 12.08	48.50 ± 12.76	0.085
Total	43.85 ± 12.96	47.18 ± 12.59	<0.001‡
C-reactive protein			
Male	9.23 ± 13.30.	9.20 ± 15.63	0.990
Female	11.77 ± 20.33	8.89 ± 21.62	0.509
Total	9.95 ± 15.56	9.08 ± 18.21	0.661
Erythrocyte sedimentation rate			
Male	28.80 ± 21.49	20.01 ± 22.48	0.004‡
Female	34.81 ± 26.56	25.02 ± 22.60	0.043‡
Total	30.46 ± 23.04	22.07 ± 22.62	0.001‡
Charlson Comorbidity Index			
Male	1.60 ± 1.12	1.73 ± 1.6	0.207
Female	1.62 ± 1.15	1.68 ± 1.01	0.668
Total	1.60 ± 1.13	1.71 ± 1.18	0.193
Body mass index			
Male	27.69 ± 10.73	27.31 ± 4.31	0.569
Female	25.99 ± 5.70	27.25 ± 5.47	0.126
Total	27.21 ± 9.60	27.29 ± 4.79	0.888

* Values are the mean ± SD unless indicated otherwise. BASDAI50 = improvement of at least 50% of the Bath Ankylosing Spondylitis Disease Activity Index score between baseline and follow-up visits; SpA = spondyloarthritis; TNFi = tumor necrosis factor inhibitors.
† Calculated using *t*-test.
‡ $P < 0.05$.

unfavorable responses, both in the whole sample ($P = 0.01$) and in males ($P = 0.003$).

Regarding the results of the multivariate logistic regression model carried out to identify factors associated with an unfavorable response to TNFi (measured as BASDAI50), female sex was close to being significantly associated with an unfavorable response to TNFi (adjusted OR 1.33 [95% CI 1.00–1.78]; $P = 0.05$). Moreover, the age at the beginning of TNFi (adjusted OR 1.02 [95% CI 1.01–1.03]; $P = 0.004$) and being on a second or further line of treatment (adjusted OR 1.88 [95% CI 1.44–2.46]; $P < 0.001$) were significantly associated with an unfavorable response. The Charlson Comorbidity Index was not associated with an unfavorable response (adjusted OR 0.98 [95% CI 0.84–1.15]; $P = 0.837$). The results of the subgroup of AS/radiographic axial SpA patients are shown in Supplementary Tables 3–5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25048.

Finally, to further explore both individual and factor combinations, associated with an unfavorable response at the second year of the first-line TNFi, a data mining approach for classification analysis based on AI was carried out (Table 6). Regarding individual variables, female sex, higher age at diagnosis and at the beginning of the treatment, comorbidity burden, and the presence of cardiovascular risk factors were significantly associated with an unfavorable response, although with moderate BACC. That is, these factors are able to correctly predict some patients' output, hence a mild relationship should exist between them and treatment response outcomes. Regarding the relation of factor combinations associated with an unfavorable response, the age at the beginning of the treatment was present in almost all significant variable-combination classification models. Variable combination models of 2 or 3 variables were able to increase BACCs up until 65%, meaning that these factors can be used in combination to increase predictability of the treatment response. Besides significant individual factors associated with an unfavorable response, disease duration, uveitis, cardiovascular events, and cardiovascular risk factors appeared to play a role in treatment response when combined. Among the cardiovascular risk factors associated with an

Table 5. Clinical differences (categorical variables) of axial SpA patients treated with TNFi with unfavorable and favorable responses according to BASDAI50 response, per sex*

Categorical characteristics by sex	Favorable	Unfavorable	P†
Hypercholesterolemia			
Male	38 (19.59)	103 (23.20)	0.312
Female	6 (8.70)	47 (19.75)	0.032‡
Total	44 (16.73)	150 (21.99)	0.073
Arterial hypertension			
Male	32 (16.58)	105 (23.76)	0.043‡
Female	14 (20.29)	49 (20.59)	0.975
Total	46 (17.56)	154 (22.65)	0.087
Cardiovascular risk factors§			
Male	102 (52.04)	289 (64.65)	0.003‡
Female	32 (46.38)	122 (50.62)	0.534
Total	134 (50.57)	411 (59.74)	0.01‡

* Values are the number (%) unless indicated otherwise. Only characteristics with significant differences between response in at least 1 group are shown (see Supplementary Tables 3–5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25048). BASDAI50 = improvement of at least 50% of the Bath Ankylosing Spondylitis Disease Activity Index score between baseline and follow-up visits; SpA = spondyloarthritis; TNFi = tumor necrosis factor inhibitors.
† Calculated using chi-square test.
‡ $P < 0.05$.
§ Cardiovascular risk factors defined as hypercholesterolemia, arterial hypertension, diabetes mellitus without organ damage, diabetes mellitus with organ damage, smoking status, and body mass index ≥30.

Table 6. Classification models (consisting of 1, 2, and 3 features) for favorable versus unfavorable response to TNFi in patients with axial SpA, identified using an AI based–data mining approach*

Model type and features†	cVal SNS	cVal SPC	cVal BACC
Single feature			
Age at beginning of treatment	85.37	35.71	60.54
Charlson Comorbidity Index	41.46	76.79	59.12
Age at diagnosis	68.29	49.11	58.70
Arterial hypertension	26.22	87.50	56.86
Cardiovascular risk factors	65.24	48.21	56.73
Female	30.49	82.14	56.32
Multiple features			
Age at beginning of treatment; uveitis	72.81	57.61	65.21
Age at beginning of treatment; smoking	75.44	54.35	64.89
Age at beginning of treatment; disease duration	89.47	40.22	64.85
Age at diagnosis; age at beginning of treatment; disease duration	70.18	58.70	64.44
Age at beginning of treatment; cardiovascular events; smoking	72.81	55.43	64.12
Cardiovascular events; disease duration; ischemic cardiopathy	46.49	80.43	63.46
Age at beginning of treatment; Charlson Comorbidity Index; disease duration	87.72	39.13	63.42
Age at beginning of treatment; disease duration; ischemic cardiopathy	87.72	39.13	63.42
Age at beginning of treatment; uveitis; smoking	78.95	47.83	63.39
Age at beginning of treatment; ischemic cardiopathy; uveitis	76.32	50.00	63.16

* Only classifiers with cross-validated $P < 0.05$ are reported. BACC = balanced accuracy, defined as (SNS + SPC)/2; AI = artificial intelligence; cVal = cross-validated; FN = false negatives; FP = false positives; SNS = sensitivity, defined as TP/(TP + FN); SpA = spondyloarthritis; SPC = specificity, defined as TN/(TN + FP); TN = true negatives; TNFi = tumor necrosis factor inhibitors; TP = true positives.
† Classification models obtained using Anaxomics AI Data Science software (reference 15).

unfavorable response, the most frequently identified was smoking. Nevertheless, there is still much response variability unexplained, suggesting that other factors must also play a role.

DISCUSSION

In this real-world study of a national multicenter prospective observational registry, we analyzed sex differences in response to TNFi in patients with axial SpA. Overall, our results showed that females were less responsive to TNFi by the second year of the first-line TNFi, with lower BASDAI50 response rates and a lower reduction of the ASDAS-CRP scores at this time point. Sex differences were not observed at the first year of the first-line TNFi nor with second or further lines of TNFi. According to the multivariate analysis (logistic regression model), female sex was close to being significantly associated with an unfavorable response to TNFi. However, the strongest factors associated with an unfavorable response were the second or further lines of treatment and the age at the beginning of the treatment. In addition, our AI results show a potential relationship between female sex, the age at diagnosis and at the beginning of the treatment, or comorbidity (either some individual comorbidities, such as cardiovascular risk factors, or comorbidity burden), with an unfavorable response to TNFi.

Our study evaluated and characterized a broad series of patients with axial SpA, and almost a third were female. Thus, this cohort allowed us to study how disease-related factors differ among sexes. Despite the scarcity of analyses investigating differences by sex in patients with axial SpA, some studies have found that women are less responsive to TNFi (25–30), as we have disclosed in our study. Diagnosis delay is higher among women with axial SpA (26,31,32), and it has been linked to worse outcomes and unfavorable treatment responses in patients with axial SpA (33). A systematic review and meta-analysis disclosed a longer diagnostic delay among females that cannot be attributed to sex-related differences in symptoms (32). In this sense, increasing knowledge of axial SpA among nonspecialized physicians to prompt a referral of the patients with suspected axial SpA and paying more attention to women is essential to reduce this delay in diagnosis.

Immunologic and genetic data show differences in disease expression between men and women with axial SpA, and sex hormones could also contribute to differences in treatment response in these patients, as such hormones interact with the immune system and influence pain perception (5,6). Therefore, several factors could potentially contribute to sex differences in the response to TNFi.

Furthermore, diagnosis delay could be one of the reasons for an older age at the start of the treatment, which was another factor associated with an unfavorable response in our study. In this case, disease duration, instead of the time since symptom onset, was used according to the available data in the BIOBADASER registry. As women with axial SpA used to have longer diagnostic delays, the time since symptom onset possibly would have been the main factor associated with an unfavorable response to TNFi, rather than disease duration as we defined it (since diagnosis). In this regard, numerous studies have indicated that the age at the beginning of treatment is associated with the success of TNFi in patients with axial SpA (30,34,35). A possible explanation for this

finding is that TNFi target multiple immune cell pathways (36,37), and with aging the composition of immune cells changes (38). In fact, the subset of TNF-producing CD8 cells has been shown to be significantly lower in the nonresponsive patients, also correlating with age (34), which could be one explanation for the loss of response associated with age.

The lower response rate in patients with axial SpA and older age at the start of the treatment leads to the question of the optimal age to start treatment in these patients, and thus the concept of a window of opportunity arises (39). This concept is critical in patients with rheumatoid arthritis and might also be applied to patients with axial SpA, as delays in diagnosis and the beginning of the treatment would negatively impact the outcomes of these patients. Our results reinforce the idea that age at the beginning of treatment is the main factor associated with an unfavorable response to TNFi, so that our results add evidence to support the concept of early intervention in patients with axial SpA. Also, combination of an older age at the beginning of the treatment with other patients' characteristics could contribute to an unfavorable response. The challenge in the near future will be the identification of high-risk patients and their early treatment.

Also, we disclosed that the use of successive TNFi lines was associated with an unfavorable response. In this sense, poorer treatment response and shorter drug survival among patients using second or further lines of treatment has been reported (40). Notably, patients switching TNFi were more frequently women.

We have also identified an association between comorbidity, particularly cardiovascular events and risk factors, such as smoking, and unfavorable responses to TNFi. Comorbidity is common among patients with axial SpA and reduces their functional status and quality of life (41). For example, smoking is known to be a harmful factor in patients with axial SpA, leading to worse clinical, functional, and radiographic outcomes (42), and it has also been related to an impaired response to TNFi (43). Therefore, we must pay close attention to comorbidities, and particularly to their modifiable risk factors, and patients with axial SpA should be encouraged to refrain from smoking as soon as a diagnosis of the disease is made, even though we lack evidence of specific interventions on this matter.

Among the strengths of our study, we highlight the large nationwide sample of patients with axial SpA from daily clinical practice. Thus, the results are representative of the whole spectrum of patients with axial SpA (radiographic and nonradiographic) attending rheumatology outpatient clinics. Real-world data are necessary to improve clinical practice, and the present study provides information on axial SpA patients treated with TNFi in a multicenter, coordinated, and unified registry that is periodically monitored to ensure better data quality. Also, the application of AI-based data analyses in addition to statistical methods is original. To the best of our knowledge, no studies in the whole spectrum of the disease (axial SpA) analyzing different lines of TNFi have been published yet, although a machine learning model to predict the treatment responses to the first TNFi in patients with AS has been reported (44).

Nevertheless, this study has several limitations. First, no separate analyses were made for the patients with nonradiographic axial SpA due to sample size limitations. The results for patients with radiographic axial SpA are shown in Supplementary Tables 1–5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25048. However, as both forms are part of the same disease construct and have similar disease burden, we believe that an analysis including both forms is in line with today's notion of the disease. Second, the study was focused on TNFi, and newer treatments were not analyzed due to sample size limitations. In this sense, a post hoc analysis of the pooled data from the MEASURE trials disclosed no sex differences on the response to secukinumab in axial SpA patients (9), while another study found worse responses among women (10). Third, this is an analysis of a database not specifically designed to look for sex or gender differences, so some variables with a potential influence on treatment response possibly were not collected. Finally, the long duration of the study may have caused some data dispersion, due to possible changes in clinical practice, as well as effects on missing data due to long follow-up. In this sense, we must acknowledge that the considerable number of missing data regarding ASDAS-CRP responses (used as a secondary estimate of response) preclude further interpretations of such data. Epidemiologic studies are prone to have age, period, and cohort effects (45). However, long-term studies with good planning such as the BIOBADASER registry provide very solid observational data (46).

Females were less responsive to a first-line TNFi by the second year of treatment. Age at the start of treatment was the main factor associated with an unfavorable response. These results suggest that an improvement in diagnosis is needed, especially in females, as well as a shorter delay in the start of effective treatments, to achieve the best possible response to TNFi in patients with axial SpA, and that close monitoring, prevention, and treatment of comorbidities could also improve the patients' outcomes.

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Novartis had no role in the collection, analysis, or interpretation of the data, the first drafting of the manuscript, or the decision to submit the manuscript for publication. Authors affiliated with Novartis at the time of the study had a role in the study design as well as in critically revising the manuscript, as stated in the authors contributions. Publication of this article was not contingent upon approval by Novartis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Coma had full access to all of

the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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