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Treatment of axial spondyloarthritis patients with biologic disease-modifying anti-rheumatic drugs in 2022 - data from the Romanian Registry of Rheumatic Diseases

Laura Muntean[1,2], Razvan Ionescu[3,4], Corina Mogosan[4,5], Maria-Magdalena Tamas[1,2], Claudiu C. Popescu[4,5], Elena Rezus[6], Razvan-Constantin Ionitescu[4], Ana Maria Ramazan[7], Andrei Eugen Martin[8], Catalin Codreanu[4,5]

[1]Rheumatology Clinic, Cluj-Napoca, Romania
[2]"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]3rd Internal Medicine Department, Colentina University Hospital, Bucharest, Romania
[4]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[5]"Dr. Ion Stoia" Clinical Center for Rheumatic Diseases, Bucharest, Romania
[6]Clinical Recovery Hospital, Iasi, Romania
[7]"Sf. Apostol Andrei" Clinical Emergency Hospital, Constanta, Romania
[8]"Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania

ABSTRACT

Objective. The objective of this cross-sectional study was to analyze data available in the Romanian Registry of Rheumatic Diseases (RRBR) in 2022 for axial spondyloarthritis (axSpA) patients treated with biologic disease modifying anti-rheumatic drugs (bDMARDs).

Methods. From the RRBR electronic database were collected multiple variables, including patient's demographic and clinical characteristics, treatment characteristics, patterns of treatment use (initiations, continuations, switching, tapering), and treatment efficacy data of axSpA patients, from 1 January 2022 to 31 December 2022.

Results. In 2022, a total of 4,315 axSpA patients were registered in the RRBR database: 70% were men, 48.4 years mean age, 13.3 years mean disease duration, 90% with radiographic axSpA, with high prevalence of extra-musculoskeletal manifestations and cardiovascular comorbidities. Most patients (88%) were treated with a tumor necrosis factor inhibitor (TNFi), usually in monotherapy. The most frequently prescribed bDMARDs were adalimumab (36%), etanercept (32%) and secukinumab (12%). The uptake of biosimilars reached one third of patients from molecules with available biosimilars in 2022. Most patients had a good clinical response, irrespective of clinical form, disease duration, type of medication or line of treatment. Medication switching was needed in 10% of patients, the main reason for switching was secondary loss of efficacy. Medication tapering was implemented in 11% of patients, and it was successful in 90% of cases.

Conclusion. Data from RRBR provide a valuable real-world view of clinical practice at the national level regarding biologic treatment of axSpA patients.

Keywords: axial spondyloarthritis, biologics, Romanian Registry of Rheumatic Diseases

INTRODUCTION

The treatment of axial spondyloarthritis (axSpA) has changed dramatically, especially with the use of biologic disease modifying anti-rheumatic drugs (bDMARDs) and, more recently, of targeted synthetic DMARDs (tsDMARDs, i.e., Janus kinases inhibitors). Data from controlled studies, cohort studies, including data from national registries are essential to doc-

Corresponding author:
Razvan Ionescu
E-mail: tane67@gmail.com

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ument the efficacy and safety of these drugs [1]. In 2022, the Assessment of Spondyloarthritis International Society (ASAS) and the European Alliance of Associations for Rheumatology (EULAR) have updated the recommendations for the management of axSpA. According to this guideline, in axSpA patients with high disease activity despite conventional treatment, tumor necrosis factor inhibitors (TNFi), inteleukin-17 inhibitors (IL-17i) or Janus kinases inhibitors (JAKi) are recommended. Current practice is to start with TNFi or IL-17i, and to switch to another b/tsDMARD in case of treatment failure [2].

The Romanian Registry of Rheumatic Diseases (RRBR) is a national prospective cohort which includes patients treated with b/tsDMARDs from both subgroups of axSpA patients according to ASAS criteria [3]: radiographic axSpA (r-axSpA or ankylosing spondylitis - AS) and non-radiographic axSpA (nr-axSpA). Patients are enrolled at the time of starting a b/tsDMARD therapy according to the national guideline, which is updated regularly, and are followed up prospectively until treatment discontinuation. In 2022, bDMARDs reimbursed in Romania for the treatment of active axSpA included original and biosimilar TNFi (adalimumab, certolizumab, etanercept, golimumab and infliximab) and IL17i (secukinumab). This analysis does not include axSpA patients treated with tsDMARDs, as this class of medication was not reimbursed for axSpA in Romania at that time. The specific criteria to be fulfilled by axSpA patients for bDMARDs reimbursement and the type of data collected in the RRBR have been previously published [4].

The present cross-sectional study evaluated the clinical characteristics, treatment characteristics and the efficacy of bDMARDs in patients with axSpA from the 2022 RRBR database.

METHODS

From the RRBR electronic database were collected from 1 January 2022 to 31 December 2022 many variables including: demographics (sex, age, body mass index, active smoking, habitat, educational level, professional status), comorbidities, axSpA characteristics (disease duration, extra-musculoskeletal manifestations - EMMs, HLA-B27 status, axSpA phenotype according to ASAS 2009 classification criteria [3]). Regarding axSpA treatments, data collected included molecule type, treatment decisions (initiations, continuations, switching, tapering), reasons for switching/discontinuation.

Disease activity status at baseline and after biologic treatment was assessed according to Bath Ankylosing Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). Studies showed that ASDAS more reliably indicates disease activity, since it incorporates C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) as objective measures of inflammation, is sensitive to change and has good discriminatory properties [5]. To appreciate the efficacy of a drug using the BASDAI score, a major clinical response must be achieved. This was defined as a reduction of initial BASDAI score with at least 50% (BASDAI50) and/or an absolute decrease of 2 points (on a scale of 0 to 10) of the initial BASDAI score, plus the opinion of a clinical expert that the patient has improved [6]. ASDAS has validated cut-off levels for disease activity states: inactive disease < 1.3; low disease activity ≥ 1.3 and < 2.1; high disease activity ≥ 2.1 and < 3.5; and very high disease activity ≥ 3.5. When using the ASDAS score, inactive disease is the desirable state to attain when treating axSpA patients or at least low disease activity. The ASDAS cutoff for "clinical important improvement" between evaluations is a decrease of at least 1.1 from baseline, and a decrease of at least 2.0 in the ASDAS score is considered "major improvement" [7,8].

Patient demographics and clinical characteristics at baseline were summarized using counts and percentages for categorial variables, and means and standard deviations for continuous variables. Descriptive statistics was performed using IBM SPSS Statistics for Windows, version 26.0.

RESULTS AND DISCUSSIONS

AxSpA patients characteristics

The number of axSpA patients with visits introduced in RRBR increased steadily over time (Figure 1).

In 2022, there were 4,315 axSpA patients in RRBR, of whom 3,861 (89.5%) and 454 (10.5%) were diagnosed with AS (r-axSpA) and nr-axSpA, respectively. The demographic of axSpA patients included in the national registry are shown in Table 1. Among the 4,315 axSpA patients from RRBR in 2022, the mean age was 48.4 years, the mean disease duration was 13.3 years, 70% were men and 67.5% were employed. Regarding age distribution, the prevalence peaked at age group 46-65 years (49%), followed by 26-45 years (40%). The proportions of patients aged bellow 25 years and over 65 years were 2.2% and 8.8%, respectively. Most patients belonged to urban areas and completed elementary or high school education. The reported permanent work disability was 24%.

The median disease duration at initiation of bDMARD was 7 years. Overall, 1,849 patients (43%) initiated a bDMARD during the first 2 years of diagnosis, while in 24% patients (n = 1040) initiation of bDMARD was after 10 years of follow-up.

The clinical characteristics of axSpA patients included in the national registry are shown in Table 2.

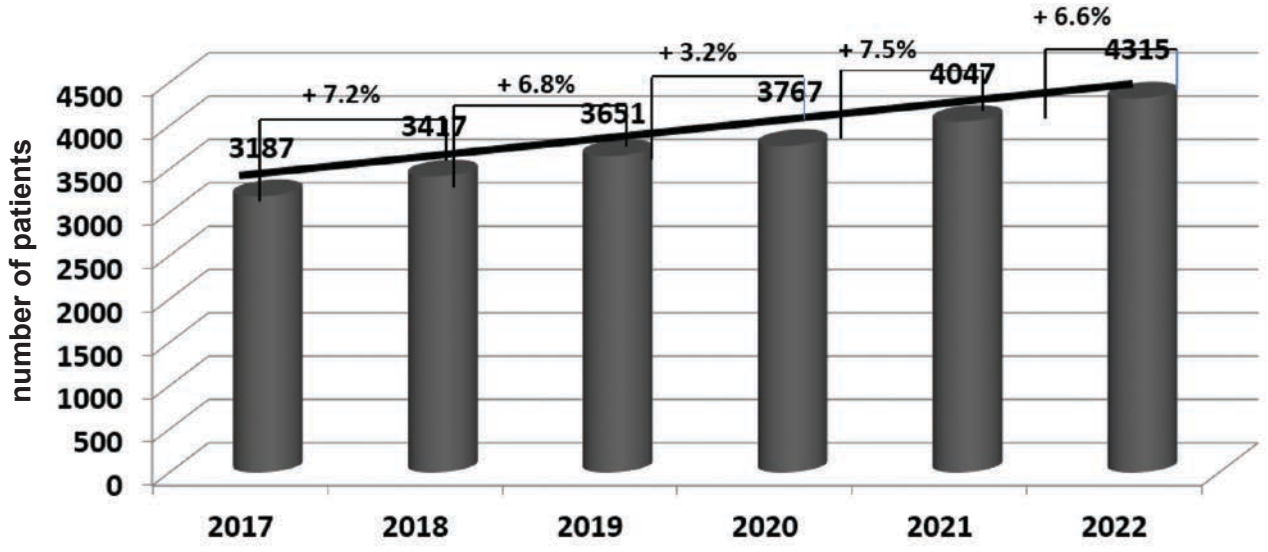

FIGURE 1. Number of axSpA patients with visits in RRBR over time (2017-2022)

TABLE 1. Demographic characteristics of axSpA patients from RRBR in 2022 (n = 4315)

Men, %	75%
Age, mean, years	48.4
BMI, mean, kg/m^2	27.1
Smoking, %	13.5%
Urban location, %	70%
Educational level	
No school completed	15 (< 1%)
Elementary school	569 (13%)
High school	2,305 (53%)
University	1,426 (33%)
Employment status	
Employed	2,918 (67.5%)
Work disability	1,028 (24%)
Retired	369 (8.5%)

AxSpA – Axial Spondyloarthritis; RRBR – Romanian Register of Rheumatic Diseases; BMI – Body Mass Index

TABLE 2. Clinical characteristics of axSpA patients from RRBR in 2022 (n = 4315)

Disease duration, mean, years	13.3
HLA-B27, n (%)	
Tested for HLA-B27	2,838 (66%)
HLA-B27 present	2,584 (91%)*
EMMs, n (%)	
Ocular	846 (20%)
Pulmonary	230 (5%)
Gastrointestinal	121 (3 %)
Psoriasis	105 (2.5%)
Cardiovascular	79 (2%)

**Percentage from patients tested for HLA-B27 (n = 2,838).*
AxSpA - Axial Spondyloarthritis; RRBR - Romanian Register of Rheumatic Diseases; EMMs - extra-musculoskeletal manifestations

Human leukocyte antigen B27 (HLA-B27) was tested in 2,838 patients (66%), and 91% of the tested patients were HLA-B27 positive. In this cohort, EMMs were present in 30% of patients. The most frequent EMMs were ocular involvement (20%), followed by pulmonary involvement (5%), gastrointestinal involvement (3%), psoriasis (2.5%) and cardiovascular involvement (2%).

As shown in Table 3, axSpA patients had a high prevalence of comorbidities. The most frequent comorbidities were arterial hypertension, cardiovascular diseases and dyslipidemia. Latent tuberculosis (defined as positive serum Quantiferon-TB GOLD Plus test) was present in 1,107 (20%) patients. Of 4233 hepatitis B surface antigen (AgHbs) negative patients, antibodies against hepatitis B core antigen (anti-HBc) were detected in 840 (19%) patients. Moreover, 82 (2%) patients had active hepatitis B infection (positive hepatitis B surface antigen – AgHbs) and 46 (1%) patients had active hepatitis C infection (positive anti-hepatitis C virus antibodies - anti-HCV).

TABLE 3. Comorbidities of axSpA patients from RRBR in 2022 (n = 4315)

Comorbidities, n (%)	
Arterial hypertension	942 (21.8%)
Cardiovascular diseases	453 (10.3%)
Dyslipidemia	630 (15%)
Liver diseases	473 (11%)
Gastroduodenal ulcer	471 (11%)
Diabetes	293 (7%)
Kidney diseases	253 (6%)
Hematologic diseases	240 (5.5%)
Osteoporosis	175 (4%)
Cancer	27 (0.6%)
Markers for hepatitis B and C, n (%)	
Positive HBs antigen	82 (2%)
Positive Total anti-HBc antibodies	840 (19%)
Positive Anti-HBs antibodies	1,095 (25%)
Positive Anti-HCV antibodies	46 (1%)
Positive QuantiFERON, n (%)	1,107 (26%)

AxSpA – Axial Spondyloarthritis; RRBR - Romanian Registry of Rheumatic Diseases; HBs - hepatitis B surface antigen; HBc - hepatitis B core antigen; HCV - hepatitis C virus.

A comparison of demographic and clinical characteristics of patients with AS and nr-axSpA is shown in Table 4. Compared with nr-axSpA, those with AS (r-axSpA) were more likely to be men, older, and had longer disease duration.

TABLE 4. Comparison of demographic and clinical characteristics between AS and nr-axSpA

	AS (n = 3861)	nr-axSpA (n = 454)
Men, n (%) Men:women	2919 (76%) 3:1	301 (66%) 2:1
Age, mean, years	50.5	43
Age distribution, n (%) ≤ 25 years 26-45 years 46-65 years > 65 years	 67 (1.75%) 1480 (38.4%) 1952 (50.5%) 362 (9.4%)	 29 (6.3%) 253 (55.7%) 152 (33.5%) 20 (4.4%)
Disease duration, mean, years	15.6	7.8
HLA-B27, n (%) Tested for HLA-B27 HLA-B27 present	 2492 (64.5%) 2283 (92%)	 346 (76%) 301 (87%)*

** Percentage from patients tested for HLA-B27 (2492 AS patients and 346 nr-axSpA patients). AS - ankylosing spondylitis; nr-axSpA - non-radiographic axial spondyloarthritis*

TABLE 6. Pattern of bDMARDs use in 2022, by molecules

	Initiations (n = 388)*	Continuations (n = 3482)*	Single switches (n = 349)§,*	
			Exits	Entries
Adalimumab	170 (44%)	1269 (36%)	95 (27.2%)	80 (22.9%)
Original#	63 (37%)	1053 (83%)	66 (69.5%)	28 (35%)
Biosimilar 1#	56 (32.9%)	155 (12.2%)	13 (13.7%)	24 (30%)
Biosimilar 2#	42 (24.7)	57 (4.5%)	8 (8.4%)	25 (31.2%)
Biosimilar 3#	9 (5.3%)	0 (0%)	0 (0%)	3 (3.75%)
Biosimilar 4#	0 (0%)	4 (0.3%)	8 (8.4%)	0 (0%)
Etanercept	127 (33%)	1160 (33%)	69 (19.8%)	76 (21.8%)
Original#	38 (29.9%)	873 (75.3%)	42 (60.9%)	27 (35.5%)
Biosimilar 1#	70 (55,1%)	243 (20.9%)	24 (34.8)	35 (46%)
Biosimilar 2#	19 (15%)	44 (3.8%)	3 (4.3)	14 (18.4%)
Infliximab	9 (2%)	203 (6%)	92 (26.4%)	64 (18,3%)
Original#	0 (0%)	130 (64%)	21(22.8%)	1 (1.6%)
Biosimilar 1#	1 (11.1%)	3 (1.5%)	3 (3.3%)	34 (53.1%)
Biosimilar 2#	5 (55,6%)	36 (17.7%)	59 (64.1%)	4 (6.25%)
Biosimilar 3#	3 (33,3%)	34 (16.7%)	9 (9.8%)	25 (39%)
Certolizumab	21 (5.4%)	150 (4%)	17 (4.9%)	38 (10.9%)
Golimumab	2 (0.5%)	312 (9%)	25 (7.2%)	15 (4.3%)
Secukinumab	59 (15%)	388 (11%)	48 (13.8%)	73 (20.9%)

§ - multiple switches (n= 41) and non-medical switches (n = 50) are not reported in this table;
** - reported with bold text represent the fraction from the entire decision category – initiations, continuations or single switches;*
 # - reported with italic text represent fraction of originals and different biosimilars in a molecule subcategory with available biosimilars in 2022 (i.e., adalimumab, etanercept, infliximab)

TABLE 5. Patterns of bDMARDs use over time (2018-2022)

	Year of initiation of biologic therapy				
	2018	2019	2020	2021	2022
Total	n = 3417	n = 3651	n = 3767	n = 4047	n = 4310*
Initiations n (%)†	397 (11.6%)	404 (11.1%)	229 (6%)	362 (9%)	388# (9%)
Continuations n (%)†	2681 (78.5%)	2922 (80%)	3187 (84.6%)	3284 (81%)	3482§ (80.7%)
Switches n (%)†	339 (9.9%)	317 (8.7%)	329 (8.7%)	285 (7%)	440& (10.2%)

** - of the 4315 axSpA patients included in RRBR, 5 patients discontinued bDMARDs in 2022, leaving 4310 on active bDMARDs;*
† - represents fraction from the total number of patients on bDMARDs;
 # - composed of 356 bDMARDs-naïve patients and 32 initial monitoring visits (patients on bDMARDs form other sources);
§ - composed of continuations on the same regimen (n = 3000), first step tapering (n = 299), second step tapering (n = 134), and tapering reversal (n = 49);
& - composed of simple switches (n = 349), multiple switches (n = 41) and non-medical switches (n = 50);
bDMARDs - biologic disease modifying anti-rheumatic drugs

Treatment characteristics

From 4,315 axSpA patients included in RRBR, 4,310 (99.8%) were currently receiving a bDMARD, with 36% receiving adalimumab, followed by etanercept (32%), secukinumab (12%), golimumab (8%), infliximab (6.5%) and certolizumab pegol (5%). Overall, 77.4% (n = 3338) patients were treated with bDMARDs in monotherapy. In 2022, 22.5% (n = 972) patients used combination therapy with a csDMARD. Of the patients receiving combination therapy, 84.2% (n = 819), were receiving sulfasalazine, followed by methotrexate (12.3%, n = 120). Thirty-three patients (3.3%) received a combination of a bDMARD with methotrexate and sulfasalazine. Systemic glucocorticoids were very rarely prescribed (less than 1%), and local glucocorticoids were administered in 298 (7%) patients.

The patterns of biologic initiations, continuations, and switches over time from 2018 to 2022 are illustrated in Table 5. The number of patients who initiated a bDMARDs was 7% higher in 2022, in comparation with 2021. Similarly, an increase with 6% was noted in the number of patients who continued the same bDMARD. The increase with 22% in switching rate in 2022 compared to the previous year reflects the increased options of biologic agents. Overall, from 4,310 patients with clinical data in RRBR 2022, 3,310 patients (77%) were on original molecules, and 1,000 patients (23%) were on biosimilars. From 3,231 patients on molecules with available biosimilars in 2022 (infliximab, etanercept and adalimumab), 69% were on original molecules, while 31% were on biosimilars. Table 6 presents the patterns of bDMARDs use in 2022, according to molecules.

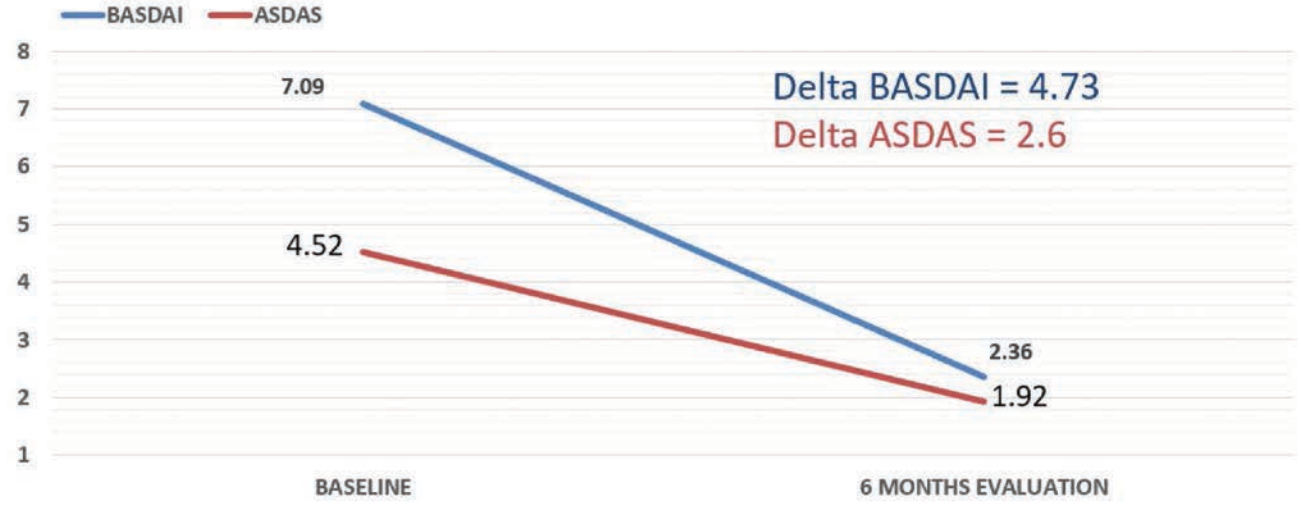

FIGURE 2. The variation of mean BASDAI and ASDAS for bDMARD of axSpA initiations in 2022 (n = 184)

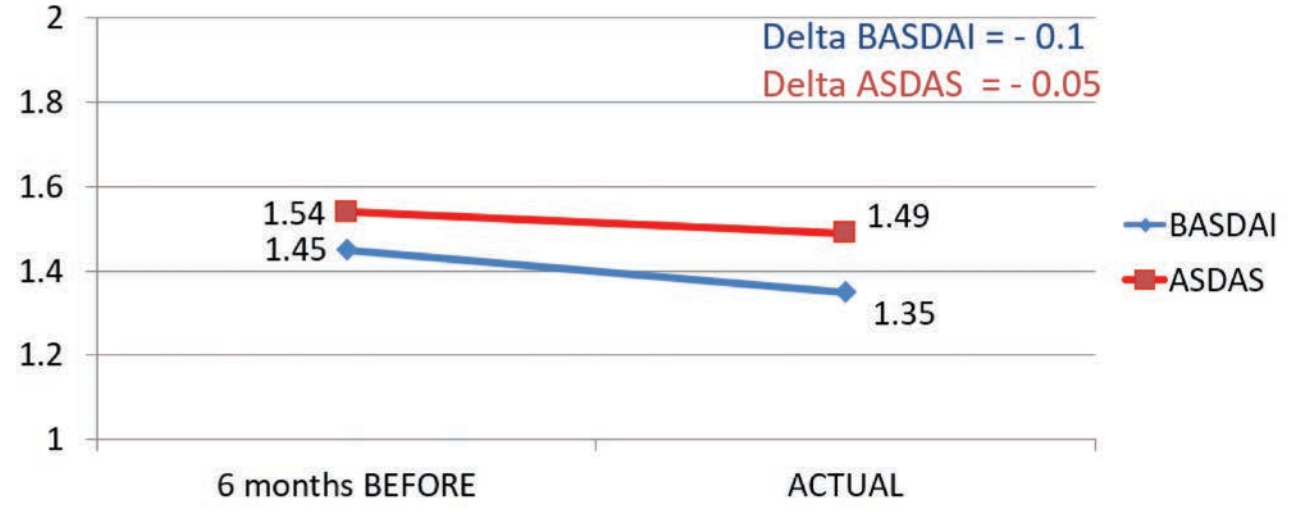

FIGURE 3. The variation of mean BASDAI and ASDAS for bDMARD continuations in axSpA in 2022 (n = 3482)

Treatment efficacy

In 2022, there were 184 new patients (initiations) in the RRBR database. The BASDAI mean score at the time of biologic therapy initiation was 7.09 and after 6 months of treatment was 2.36 (Figure 2), which corresponds to a mean delta BASDAI (ΔBASDAI) of 4.73 at 6 months. We can conclude that at the group level, any treatment used for initiation in axSpA patients from RRBR database was effective. When evaluating treatment efficacy of the same 184 patients initiated in 2022 using ASDAS, the mean baseline ASDAS score was 4.52 and at the 6 months evaluation it was 1.91 (Figure 2), corresponding to an ASDAS variation of 2.6, which represents a "major improvement". Overall, regarding initiations, even though at the group level inactive disease status in terms of ASDAS was not reached, all treatments were effective in reducing disease activity.

During 2022, 3,482 axSpA patients from RRBR continued the same treatment and their mean BASDAI score decreased from 1.45 to 1.35. This result suggests that sustained low disease activity is possible for patients achieving the treatment target and maintaining the treatment regimen. Similar evolution of ASDAS scores was observed in patients continuing the same treatment in 2022 (Figure 3). Noteworthy, mean ΔBASDAI and ΔASDAS were low, meaning that most patients already benefit from their treatments and this trend persisted throughout 2022.

Patients continuing biologics throughout 2022 were stratified according to their BASDAI values. More than 90% of patients had a BASDAI score of less than 3, and more than half of them had a BASDAI score of less than 1. A BASDAI score greater than 3, corresponding to active disease, was observed only in 8% of patients. These observations show that more than 9 out of 10 patients maintain inactive disease status as they continue their treatment.

Similar results were obtained when patients were stratified according to their ASDAS values. As shown in Figure 5, most patients that continued biologic treatment during 2022 were in inactive/low disease activity status, according to the ASDAS categories.

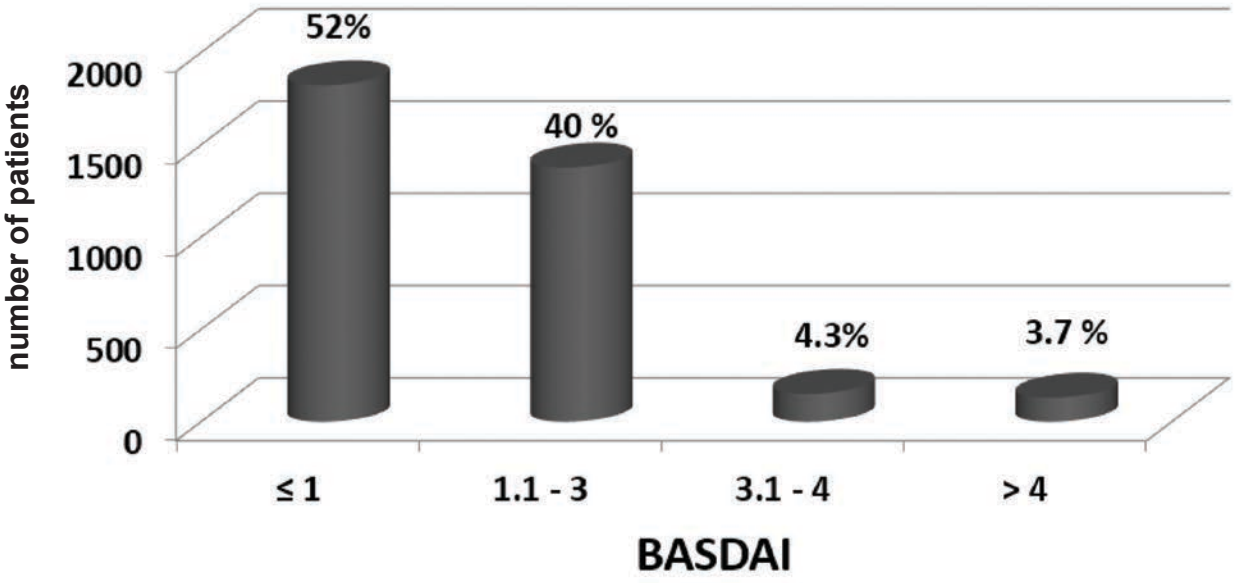

FIGURE 4. Percentage of axSpA patients who continued treatment, stratified according to actual BASDAI values

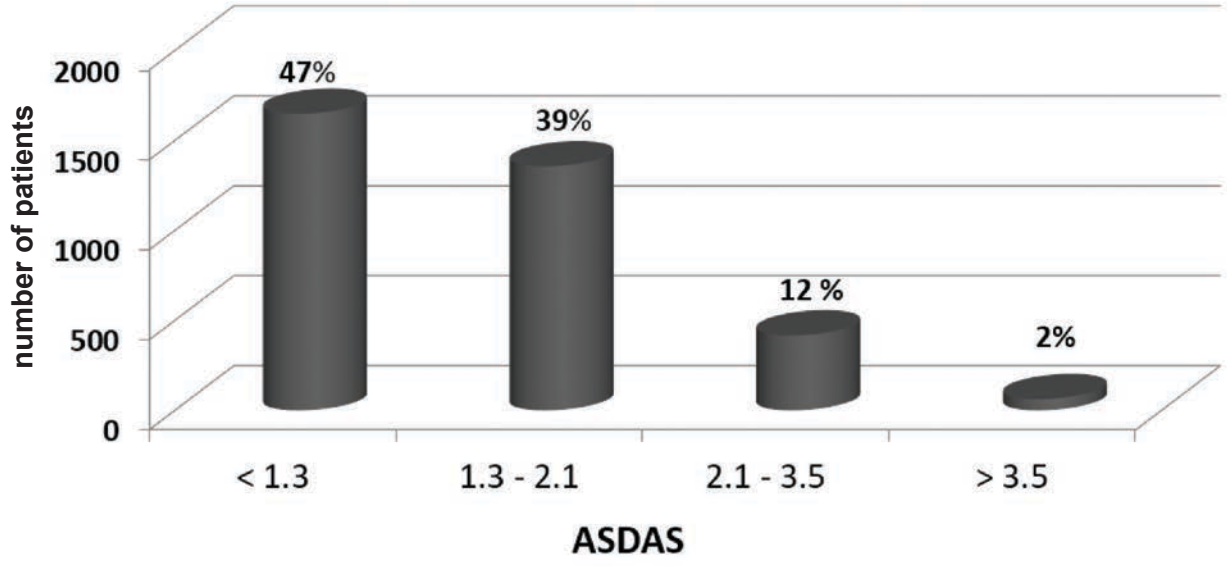

FIGURE 5. Percentage of axSpA patients who continued treatment, stratified according to actual ASDAS values

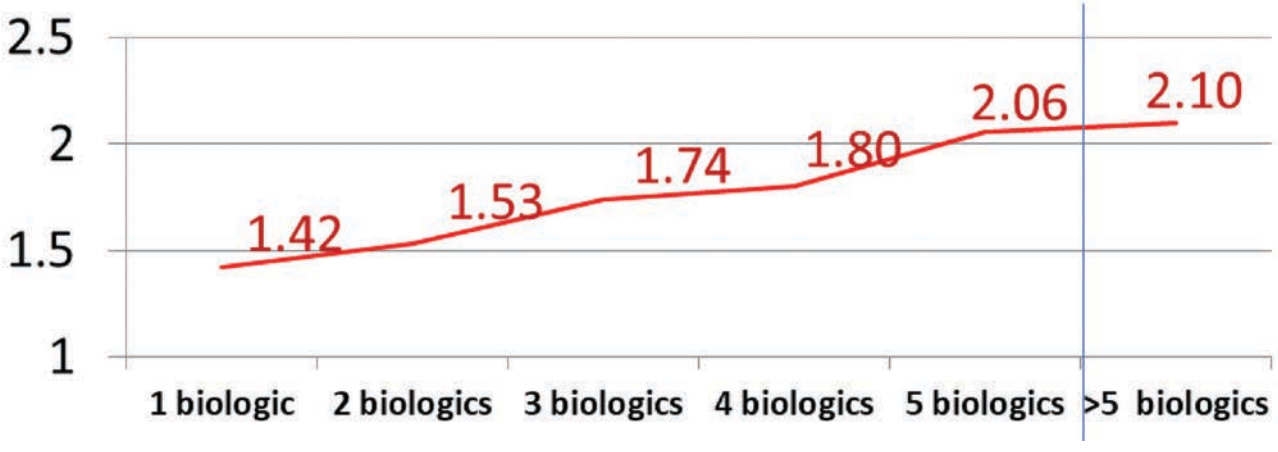

FIGURE 6. Efficacy of treatment (ASDAS score) according to the number of biologics used

FIGURE 7. Evolution of BASDAI and ASDAS scores in axSpA patients who switched therapy (n = 168)

Disease duration at the time of starting biologic therapy has no influence on treatment efficacy. Mean ASDAS score ranged between 1.46-1.53, regardless of the disease duration category (less than 2 years, between 3-5 years, between 6-10 years, or more than 10 years).

Of the 3,482 patients who continued treatment in 2022, 2,285 (65.6%) were exposed to one bDMARD only, while 809 (23.2%) received 2 bDMARDs, 248 (7.1%) received 3 bDMARDs, 84 (2.4%) received 4, 37 (1.1%) received 5 and 19 (0.5%) received more than 5 bDMARDs. Regarding treatment efficacy, with respect to their exposure history, only patients who received more than 5 bDMARDs were having high disease activity, according to ASDAS scores, while the others were in low disease activity status or remission (Figure 6).

Of the 440 patients who switched medication in 2022, 168 patients had available data of efficacy in evolution. We analyzed the evolution of BASDAI and ASDAS scores 6 months after the switching, and we observed that the mean BASDAI decreased from 3.85 to 1.75 (corresponding to a ΔBASDAI of 2.1) and the mean ASDAS decreased from 2.87 to 1.79 (corresponding to a ΔASDAS of 1.08). We can conclude that switching medication was efficacious in terms of disease activity (Figure 7).

One of the concerns when treating with biologics is the total duration of treatment. Published data indicate that tapering medication may be a useful and effective strategy in maintaining remission and/or low disease activity status in most axSpA patients. Moreover, it was shown that tapering is likely to be successful when remission has been present for at least 12 months [9]. Tapering is achieved either by reducing the dose or by increasing the interval between doses. Throughout 2022, there were 469 patients (representing 11% of all treated patients) in whom biologics were tapered. Of those patients, 206 were treated with etanercept, 194 with adalimumab, 49 with infliximab, 13 with golimumab and 7 with certolizumab. The current mean BASDAI was 0.75, compared to 0.77, 6 months earlier. The current mean ASDAS of these patients was 1.13 and 6 months earlier it was 1.14. These results suggest that tapering was efficient in most axSpA patients in sustained remission/low disease activity. Nevertheless, the tapering strategy does not always succeed. In 2022, there were 49 patients that had to revert the tapering strategy to the original treatment strategy (tapering reversal strategy).

CONCLUSIONS

The present analysis of the RRBR database showed that the number of axSpA patients treated with bDMARDs increased steadily between 2017 and 2022. The predominant demographic patient profile was that of a man with established r-axSpA, with high prevalence of EMMs and comorbidities, mainly ophthalmologic involvement and cardiovascular diseases respectively. Almost half of axSpA patients from the RRBR were initiated within two years of diagnosis. The most used bDMARD continues to be adalimumab, both the original and the biosimilar molecules. Overall, the uptake of biosimilars by Romanian rheumatologists has increased during 2022 by 6%, to almost a third of all molecules with available biosimilars. The use of bDMARDs showed efficacy in more than 90% of axSpA patients from the RRBR database. All these data demonstrate that the RRBR is a valuable data source for the management of axSpA patients in daily clinical practice.

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