

Data from the Romanian Registry Of Rheumatic Diseases (RRBR) for patients with axial spondyloarthritis treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs) during 2019

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ABSTRACT

The Romanian Registry of Rheumatic Diseases (RRBR, in Romanian) is an electronic application that includes data of all patients with inflammatory rheumatic diseases treated with biologics in Romania. First patients with axial spondyloarthritis (axSpA) were included in 2015 and the registry collected multiple variables like demographics, axSpA therapies, disease activity, adverse events, in order to provide data for patients in our country.

The number of axSpA patients introduced in RRBR has been steadily increasing within the last 3 years. The patients included in the registry are with the two types of ax SpA (non-radiographic and radiographic spondyloarthritis) with a relatively high prevalence of extra-skeletal manifestations and a lot of comorbidities. Data regarding treatment showed a prevalence of monotherapy with biologic disease-modifying anti rheumatic drugs (bDMARDs), TNF-alpha inhibitors being used by 91% of the patients. 41% of the patients started bDMARD-therapy early during disease course (under 2 years from diagnosis). The most frequent prescribed bDMARDs was adalimumab, followed by etanercept. Treatment decisions trends in 2019 showed that some molecules present a positive balance such as bDMARD biosimilars and secukinumab. Overall, bDMARDs achieved treatment target (ASDAS defined remission and LDA) within the first 6 months of treatment in 87.6% of treated patients. Also, RRBR data indicate a slow but significant increase in tapered regimens. Thus, the RRBR has proved to be a very valuable tool in capturing data regarding axial spondyloarthritis management in a real-life national setting of rheumatology healthcare.

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

INTRODUCTION

Axial spondyloarthritis (axSpA) is a disabling inflammatory arthritis of the spine, presenting frequently as chronic back pain, typically before the age of 45. It is associated with one or more of several articular features, including synovitis, enthesitis, and dactylitis. It may also be associated with uveitis, psoriasis, and inflammatory bowel diseases. Axial SpA includes non-radiographic axial SpA (nr-axSpA), without plain radiographic changes on sacroiliac joints and ankylosing spondylitis with radiographic changes of sacroiliitis (1).

The Romanian Registry of Rheumatic Diseases (RRBR) is a national electronic database comprising all patients with axial spondyloarthritis (axSpA) treated with reimbursed biological (bDMARDs) [1]. RRBR was launched in February 2013 as a prospective observational study for patients with rheumatoid arthritis and in 2015 were included for observational study patients with axSpA. Efficacy and safety data are uploaded for each patient usually every 6 months by attending physicians. Prior to treatment and inclusion in the RRBR, all patients give written informed consent for bDMARD therapy and scientific use of

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their RRBR. Long-term efficacy, safety, drug survival and switch were evaluated and presented every year.

The guidelines for biological treatment in axSpA are represented by inclusion criteria:

- Confirmed axial SpA diagnosis according to ASAS/EULAR (2009) criteria;
- Active disease: ASDAS > 2.5 or BASDAI > 6; for patients with extrascheletal manifestations or coxitis ASDAS > 2.1, BASDAI > 4, elevated C-reactive protein (CRP) > 3xN or erythrocyte sedimentation rate (ESR) > 28 mm/1 h
- Failure to standard treatment (2 NSAIDs > 6 weeks, Sulphasalazine (SSZ) for peripheral involvement, local steroid injection
- Second opinion

The RRBR can capture several types of treatment decisions:

- *initiations* (ax SpA) patients naïve to bDMARDs who fulfill the above criteria and who will henceforth receive bDMARDs with classical posology, reimbursed by the National Health Insurance House,
- *initial monitoring* (axSpA patients currently treated with bDMARDs not reimbursed by the National Health Insurance House, for example patients from clinical trials or patient initiated on bDMARDs in other countries, using classical or tapered regimens, who will henceforth receive reimbursed bDMARDs
- *continuations* (visits at every 6 months of axSpA patients from the first categories who will continue their previous reimbursed bDMARD either with classical regime, tapered regime or revert levels of tapering)
- *switches* (axSpA patients with adverse events, primary or secondary non-responders who will not continue with their previous reimbursed bDMARD, but with another).

AXSPA CHARACTERISTICS OF 2019 PATIENTS

The number of axSpA patients with visits introduced in the RRBR has been increasing within the last 3 years (Figure 1): 3,187 patients in 2017, 3,417 patients in 2018 (7.2% increase compared to 2017) and 3,651 patients in 2019 (6.9% increase compared to 2018). In 2019, there were 417 cases (11.4%) without RRBR data for more 12 months and 137 cases (3.8%) were lost to follow-up.

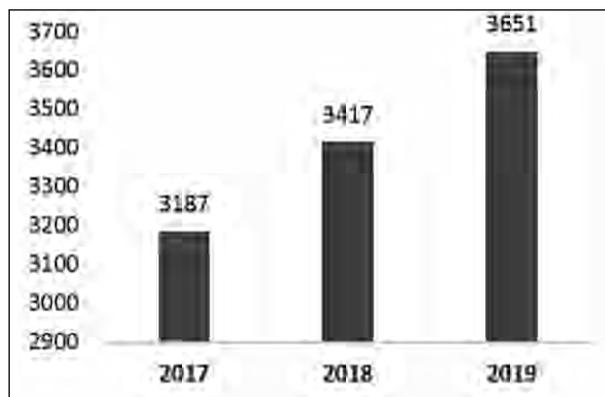


FIGURE 1. Number of axSpA patients with visits in RRBR in the last 3 years

Demographically, the predominant patient profile was that of urban-dwelling overweight young non-smoking man, with a mean age of 46.8 years and with established axSpA (mean disease duration of 12.23 years – Table 1). Of note, 967 patients were retired because of axSpA meaning 26% the entire sample.

TABLE 1. Characteristics of ax SpA patients in 2019 from RRBR (n = 3,651)

| | |
|---|---------------|
| men (n, %) | 2,796 (76.5%) |
| age (mean ± SD; years) | 46.8 ± 11.1 |
| body mass index (mean ± SD; kg/m ²) | 27 ± 5.0 |
| urban dwelling (n, %) | 2,513 (69%) |
| higher education (n, %) | 1,158 (31%) |
| employed (n, %) | 2,394 (66%) |
| AxSpA-retired (n, %) | 967 (26%) |
| age-retired (n, %) | 290 (8%) |
| smoking (n, %) | 430 (12%) |
| AxSpA duration (mean ± SD; years) | 12.23 ± 5.6 |

AxSpA – axial spondyloarthritis; RRBR – Romanian Register of Rheumatic Diseases; SD – standard deviation.

Regarding age distribution, patients from 2019 showed a very low prevalence of patients below 25 years of age (%), with a predominance of patients aged 46-65 years (%), followed by patients aged above 65 years (%) and patients aged 26-45 years (Figure 2).

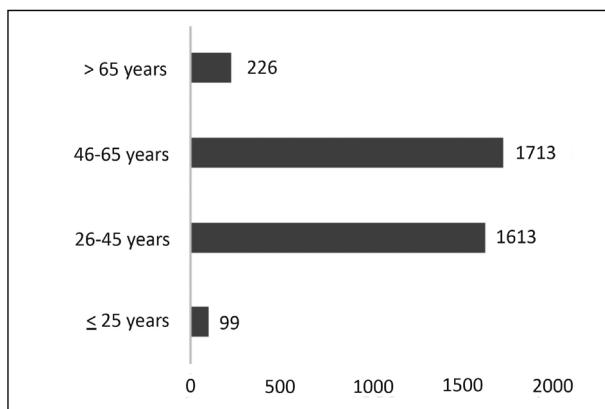


FIGURE 2. Age distribution of axSpA patients from RRBR in 2019

HLA-B27 was tested in 2,160 patients (59%) and 1,992 patients (92%) were HLA-B27 positive.

According to ASAS/EULAR 2009 classification criteria for axial SpA, of the 3,651 patients in 2019 RRBR database, 335 patients (9%) were without plain radiographic changes, but with bone edema on MRI and they were classified as non-radiographic axial SpA (nr-axSpA), while 3,316 patients (91%) were with radiographic changes of sacroiliitis (sacroiliitis fulfilling the New York criteria). Surprisingly, 407 patients reported with axSpA (12.3%) had no RRBR records of imaging sacroiliitis (Figure 3).

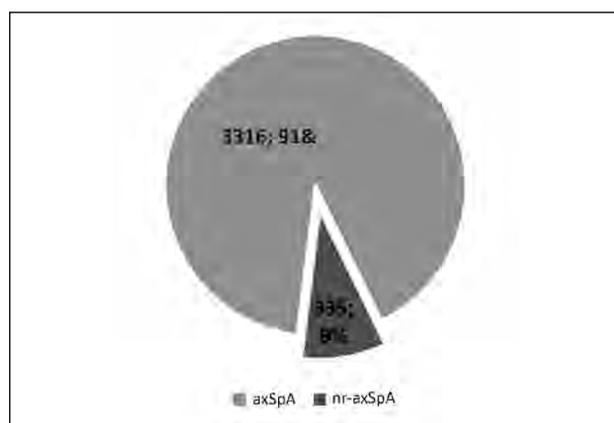


FIGURE 3. Proportion of patients with axSpA and nr-axSpA

AxSpA is more common among men, but the frequencies among women are higher in nr-axSpA with male/female ratio 2/1. There are also some other characteristics of patients with nr-axSpA. They are younger than patients with AS with a mean age of disease 42.3 and with a mean disease duration 7.2 years, lower as compared with all patients with axSpA (table 2).

Data from the RRBR showed that 1,151 axSpA patients (31.52%) had extra-articular manifestations (Figure 4). The most frequent extra-skeletal mani-

festations were ocular involvement (706 patients, 19.3%), followed by far by pulmonary involvement (213 patients, 5.8%), gastrointestinal involvement (2.3%), psoriasis (2.1%) and cardiac involvement (2.0%) (figure 4).

TABLE 2. General data comparing cases of axSpA and nr-axSpA

| | axSpA (n = 3,316) | nr-axSpA (n = 335) |
|-------------------------------|----------------------|-----------------------|
| men (n, %) | 2,571 (77.5%) | 225 (67.2%) |
| men:women ratio | 3.4:1 | 2:1 |
| mean age (years) | 47.3 | 42.3 |
| age ≤ 25 years (n, %) | 80 (2.4%) | 19 (5.6%) |
| age 26-45 years (n, %) | 1,415 (42.6%) | 198 (59.1%) |
| age 46-65 years (n, %) | 1,604 (48.3%) | 109 (32.5%) |
| age > 65 years (n, %) | 217 (6.5%) | 9 (2.6%) |
| mean disease duration (years) | 12.7 | 7.2 |
| tested for HLA-B27 (n, %) | 1,927 (58.1%) | 233 (69.6%) |
| HLA-B27 present (n, %) | 1,789 (92.8%) | 203 (60.6%) |

axSpA – axial spondyloarthritis; HLA – human leukocyte antigen;
nr-axSpA – non-radiographic axial spondyloarthritis.

The RRBR allows for data capture on comorbid conditions of ax SpA patients (Figure 5). From the 2019 reports (n = 3,651), the most frequent comorbidities were cardiovascular disease and dyslipidemia affecting 1,654 patients (45.5%) from total, including arterial hypertension, ischemic heart disease, congestive heart failure, stroke and peripheral artery disease, conditions reported as such by attending rheumatologists, followed by latent tuberculosis (25%), defined as a positive blood interferon gamma release assay, gastrointestinal disease (11%), liver disease (11.5%), diabetes mellitus (7%), hematologic disease (5%), thyroid disease (2.6%), renal disease (6%) and cancer (0.5%), including one active cancer. Notably, there was a relatively low prevalence of reported osteoporosis (3.7%) and inflamma-

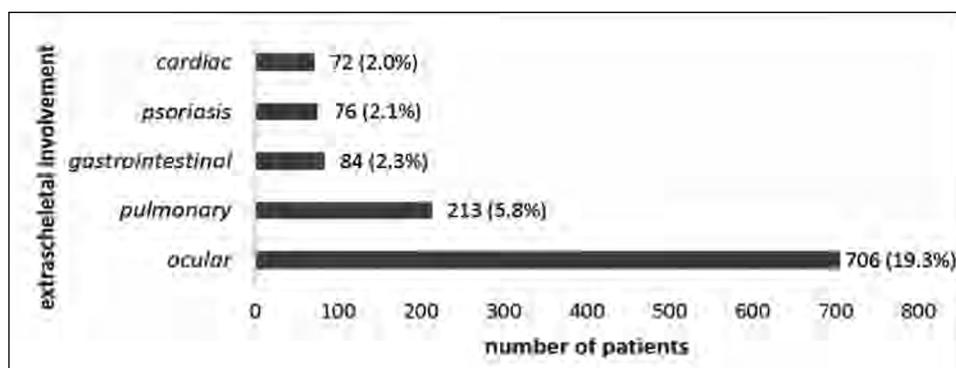


FIGURE 4. Extra-skeletal involvements in axSpA

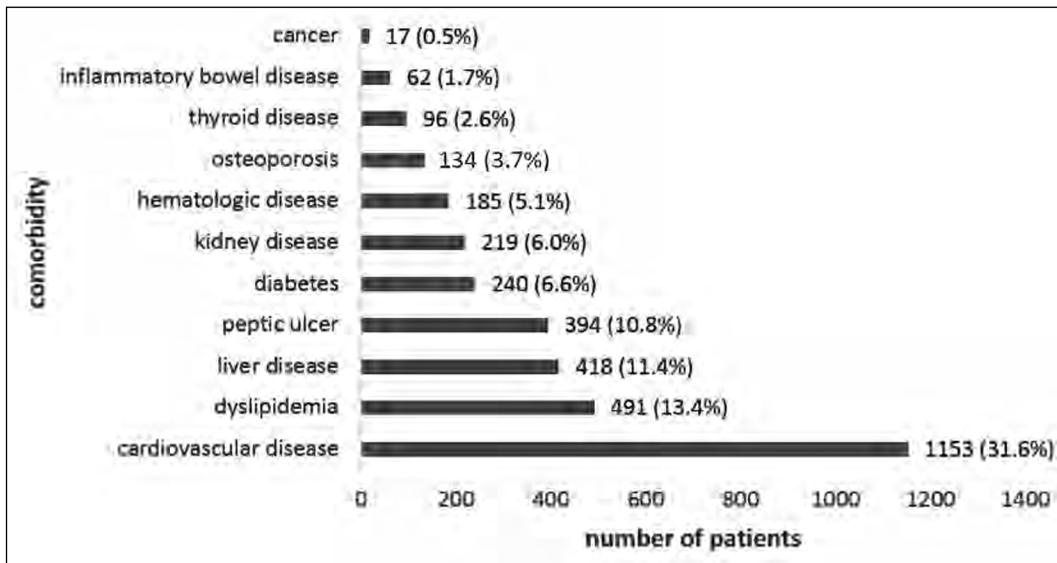


FIGURE 5. Comorbidities in patients with axSpA

tory bowel disease (1.7%). Of note, there were 65 patients (1.8%) with positive hepatitis B surface antigen and 37 patients (1%) with positive anti-hepatitis C virus antibodies.

AXSPA TREATMENT CHARACTERISTICS OF 2019 RRBR PATIENTS

All 3,651 axSpA patients received one current bDMARD, most of them in monotherapy. Regarding associated treatment only 855 patients (23.4%) were receiving csDMARD. The majority of patients were on sulfasalazine (SSZ; 20.8%), while a minority of patients were on methotrexate (MTX; 3.4%, with an average dose of 14 mg/week) (Figure 6).

In the entire sample ($n = 3,651$), only 32 patients (less than 1%) were reported to use current oral glucocorticoids (prednisone or methylprednisolone), with 22 patients on low doses (7.5 mg/day prednisone equivalent or lower). Local glucocorticoids were administered to 235 patients (6.5%).

The cohort exhibited a high prevalence of early bDMARDs treatment: 41.5% of patients started bDMARDs within the first 2 years of disease evolution, while 25% had a disease duration of over 10 years when starting bDMARDs (figure 7).

The number of initiations, continuations and switches in 2019 were quite similar to 2018 (table 3).

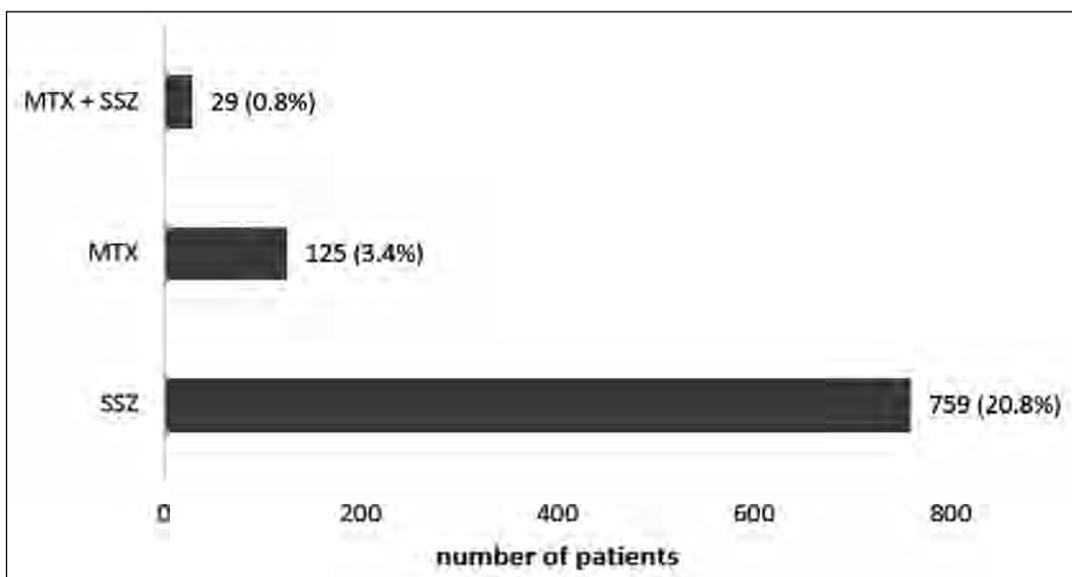


FIGURE 6. csDMARDs in combination with bDMARDs

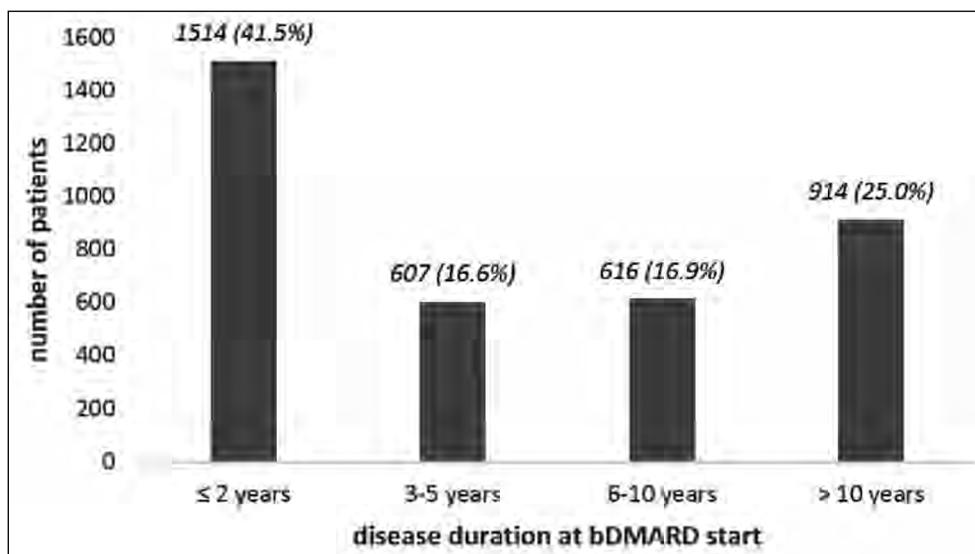


FIGURE 7. Disease duration at bDMARDs start

TABLE 3. bDMARDs used in treatment of SpA in 2019 compared to 2018

| | 2018 (n = 3,417) | 2019 (n = 3,651) |
|----------------------|------------------|------------------|
| initiations (n, %) | 397 (11.6%) | 404 (11.1%)*.# |
| continuations (n, %) | 2,681 (78.5%) | 2,922 (80.0%)& |
| switches (n, %) | 339 (9.9%) | 324 (8.9%)§ |

* initiations followed by switch = 7;

composed of 378 bDMARD-naïve patients and 26 initial monitoring visits (patients on bDMARDs from other sources;

& composed from continuations on the same regimen (n = 2,505), increased exposure (increased dose or decreased interval between administrations, n = 15), decreased exposure (decreased dose or increased interval between administrations, n = 10), first step tapering (n = 239), second step tapering (n = 111) and tapering reversal (n = 42); § composed from simple switches (n = 295), double switches (n = 28) and triple switches (n = 1).

From the total of 2,823 axSpA patients on molecules with available biosimilars in 2019 in Romania (namely adalimumab, for which biosimilars became available later in the year, and etanercept and infliximab, for which biosimilar were already available from the start of the year), 85.7% were on originator molecules and 14.3% on biosimilars. 91% of the patients treated with biologics were on TNF-alpha inhibitors and only 9% on Secukinumab (table 4).

Of note, the most frequently prescribed bDMARD was adalimumab, received by 1,199 patients (meaning 33% from the 3,651 patients on active bDMARD treatment), followed by etanercept received by 1,182 patients (32.5%) and infliximab (12%). TNF-alpha inhibitors were used to treat 91% of the patients and 9% of the patients were treated with the only non-TNF inhibitor approved in Romania, secukinumab, a human IgG1k monoclonal antibody that binds to the protein interleukin (IL)-17A. Treatment decisions trends in 2019 is showed in Table 5.

TABLE 4. The frequency of bDMARDs molecules in 2019 (n = 3,651)&

| | total* | originator molecule# | biosimilar molecule# |
|--------------|---------------|----------------------|----------------------|
| | | - | - |
| adalimumab | 1,203 (33%) | 1,151 (95.5%) | 52 (4.5%) |
| | | | |
| certolizumab | 116 (3.0%) | - | - |
| etanercept | 1,187 (32.5%) | 997 (84%) | 190 (16%) |
| golimumab | 366 (10.0%) | - | - |
| infliximab | 433 (12 %) | 270 (62.4%) | 163 (37.6%) |
| | | | |
| Secukinumab | 337 (9.0%) | - | - |

& of the 3,651 patients, 6 stopped bDMARDs in 2019, leaving 3,645 on active bDMARD treatment; * percentages represent fraction from the total number of patients on bDMARDs; # percentages represent fraction from the number of patients on specific molecules.

AXSPA TREATMENT EFFICACY IN 2019 IN THE RRBR DATABASE

The primary goals of management for patients with axial spondyloarthritis (AxSpA) are to optimize short- and long-term health-related quality of life. The available data suggest that therapy should be commenced at an early stage of the disease, when the process of bone repair expected to occur after an inflammatory phase has not yet started. The 2016 update of the Assessment of Spondyloarthritis International Society (ASAS) and the EULAR guidelines included a new recommendation supporting the T2T paradigm in axSpA (2). Clinical assessment should include a focused history and examination directed at the patient's known manifestations and screening for other features associated with axial spondyloarthritis (axSpA). The adequacy of the response is

TABLE 5. Treatment decisions in 2019 by therapeutic molecule

| | initiations (n = 404)* | continuations (n = 2,922) | single switches (n = 324) ^{&} | |
|---------------------|---------------------------|------------------------------|---|--------------------|
| | | | exists | Entries |
| Adalimumab | 121 (30%) | 1,021 (35%) | 86 (26.5%) | 57 (17,59%) |
| <i>Originator</i> | <i>92 (76%)</i> | <i>1,021 (35%)</i> | <i>86 (100%)</i> | <i>36 (63%)</i> |
| <i>biosimilar 1</i> | <i>17 (14%)</i> | - | - | <i>16 (28%)</i> |
| <i>biosimilar 2</i> | <i>8 (6.6%)</i> | - | - | <i>3 (5.2%)</i> |
| <i>biosimilar 3</i> | <i>4 (3.3%)</i> | - | - | <i>2 (3.5%)</i> |
| Certolizumab | 20 (5%) | 64 (2.19%) | 8 (2.4%) | 29 (8.9%) |
| Etanercept | 89 (22%) | 1,021 (35%) | 52 (16%) | 72 (22.2%) |
| <i>Originator</i> | <i>37 (41.6%)</i> | <i>926 (90.7%)</i> | <i>42 (80%)</i> | <i>32 (44.4%)</i> |
| <i>Biosimilar</i> | <i>52 (58.4%)</i> | <i>95 (9.3%)</i> | <i>10 (20%)</i> | <i>40 (55.6%)</i> |
| Golimumab | 43 (11%) | 281 (9.6%) | 30 (9.25) | 39 (12%) |
| Infliximab | 43 (10.6%) | 362 (12.4%) | 62 (19.1%) | 25 (7.7%) |
| <i>Originator</i> | <i>5 (11.6%)</i> | <i>257 (71%)</i> | <i>31 (50%)</i> | <i>7 (28%)</i> |
| <i>biosimilar 1</i> | <i>31 (72%)</i> | <i>70 (19.33%)</i> | <i>13 (21%)</i> | <i>16 (64%)</i> |
| <i>biosimilar 2</i> | <i>3 (7%)</i> | <i>35 (9.66)</i> | <i>18 (29%)</i> | <i>1 (4%)</i> |
| <i>biosimilar 3</i> | <i>4 (9.3)</i> | - | - | <i>1 (4%)</i> |
| Secukinumab | 88 (22%) | 173 (5.9%) | 57 (17.6%) | 73 (22.5%) |

* the percent frequency of counts reported with bold text represent the fraction from entire treatment decision category (initiations, continuations), while the percent frequency of counts reported with italic text represent the fraction from molecule subcategories, for example: 22% of all initiations in 2019 were on etanercept, 41.6% of them using the originator molecule and 58.4% using the biosimilar molecule.

& total number of switches in 2019 was 324 (8.8% from the entire sample); multiple switches (n = 29) are not reported in this table.

based upon a combination of measures of disease activity assessment with either the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or the Ankylosing Spondylitis Disease Activity Score (ASDAS) (2). Clinically significant improvement is defined as either a 50 percent improvement of the BASDAI score (BASDAI 50) or an absolute change of ≥ 2 on a scale of 0 to 10 and a clinical „expert” opinion that a particular patient has improved. The ASDAS categorizes the disease activity as inactive, low, high, or very high. A change of ≥ 1.1 in the ASDAS score is considered a significant improvement, while a change of ≥ 2.0 is a major improve-

ment (3). ASDAS has been shown to have good discriminatory capacity and sensitivity to change because incorporates an objective measure of disease activity such as CRP or ESR. ASDAS inactive disease (< 1.3) can be considered a possible target and remission criterion in axSpA (4).

In 2019 in RRBR there were 383 initiations with monitoring visits at 6 months: for these patients, the average BASDAI decreased with 4.92 and the average ASDAS decreased with 2.72 (figure 8).

There were 2,922 continuations in the cohort: for these patients, compared to 6 months prior, the current evaluation showed that the average BASDAI

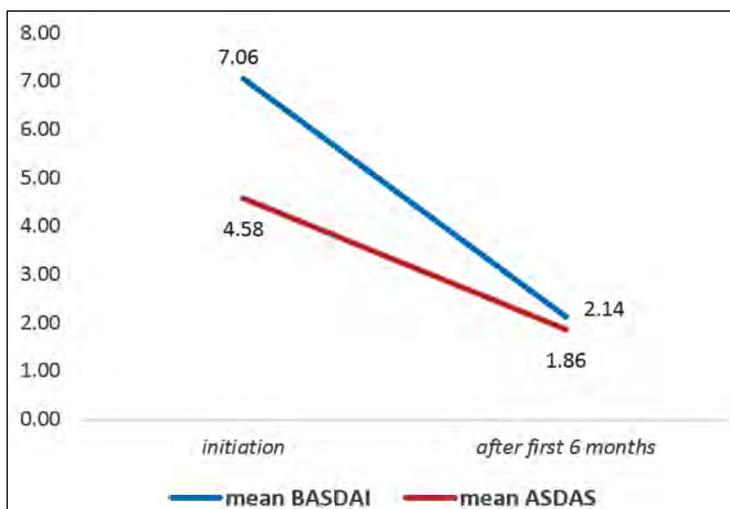


FIGURE 8. The variation of mean BASDAI and ASDAS after the first 6 months of treatment with bDMARDs

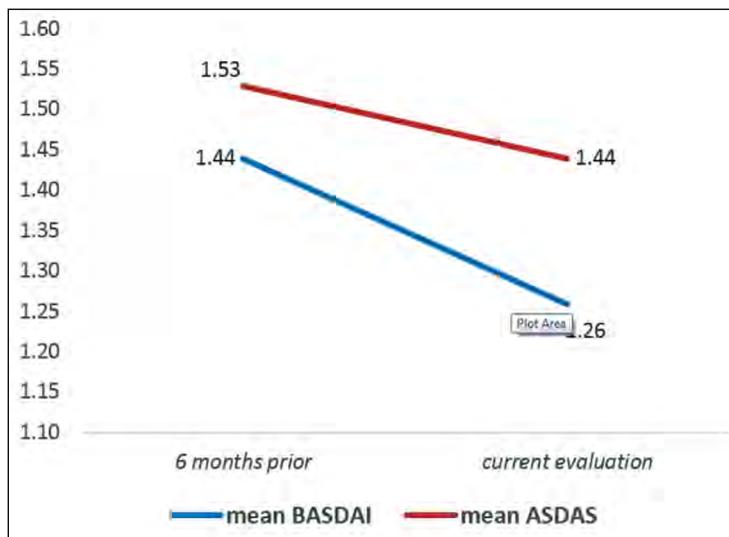


FIGURE 9. The variation of mean BASDAI and ASDAS for 2,922 continuations in the cohort

decreased with 0.18 and the average ASDAS decreased with 0.09 (figure 9).

Achieving inactive disease may improve structural and functional outcomes and stop the development of radiographic spine damage. Data from RRBR demonstrated that 1,439 patients (49.6%) for 2,922 continuations in the cohort achieved remission according to ASDAS and 1,108 patients (38%) achieved a low disease activity with ASDAS between 1.3 and 2.1.

As of 2019, from the patients which continue the biological treatment, 2,613 axSpA patients (89.4%) were exposed to a single bDMARD and 725 (24.81%) patients received 2 consecutive bDMARDs and 10.71% received 3 or more bDMARDs (Table 6). When investigating efficacy in patients who continued the bDMARD ($n = 2,922$), according to the history of bDMARDs exposure, the mean ASDAS revealed that patients with 1 biological exposure tended to be in remission and those with 2 or more different bDMARDs exposures were in LDA (Table 6), suggesting the need of dynamic treatment in more severe cases in order to reach the therapeutic target.

Tapering strategy for anti-TNF therapy is successful in maintaining remission or LDA in most patients with axial spondyloarthritis (5). The bDMARD dosage tapering had been made in patients with a maintained remission more than 12 months and consisted of the following: increase the interval between doses for subcutaneous bDMARDs or reduction of the dose for intravenous bDMARDs. Compared to the end 2018, when 305 (8.9%) patients were receiving tapered bDMARDs and 27 patients returned

from tapered doses to the classical frequency of bDMARD administration, at the end of 2019 a total of 351 (9.6%) patients were receiving tapered bDMARDs and 42 patients reverted their tapered bDMARD regimen (Table 7).

TABLE 6. The distribution of axSpA patients according to the number of bDMARDs exposure and ASDAS-defined efficacy

| number of different bDMARDs | number of continuations patients ($n = 2,922$) | mean ASDAS per category of continuations |
|-----------------------------|--|--|
| 1 | 2,613 (89.4%) | 1.32 |
| 2 | 725 (24.81%) | 1.49 |
| 3 | 196 (6.70%) | 1.81 |
| 4 | 70 (2.4%) | 2.01 |
| 5 | 29 (1%) | 2.3 |
| 6 | 15 (0.51%) | 2.37 |
| 7 | 3 (0.10%) | 2.26 |

bDMARDs – biologic disease-modifying anti-rheumatic drugs;
ASDAS – ankylosing spondylitis disease activity score;
AxSpA – axial spondyloarthritis

TABLE 7. Tapering status in patients with SpA, comparison in 2018-2019

| | 2018 ($n = 3,417$) | 2019 ($n = 3,651$) |
|-------------------------------------|-------------------------|-------------------------|
| patients on tapering (n, %) | 305 (8.9%) | 351 (9.6%) |
| patients with tapering reversal (n) | 27 | 42 |

CONCLUSIONS

The number of axSpA patients with visits introduced in the Romanian Registry of Rheumatic Diseases has been steadily increasing within the last 3 years. Patients included in RRBR display are with a relatively high prevalence of extra-articular mani-

festations, cardiovascular comorbidity. Data regarding treatment showed a prevalence of bDMARD-monotherapy. Approximately 41% of the patients started bDMARD-therapy early during disease course (under 2 years from diagnosis). The most frequent prescribed bDMARD was adalimumab, followed by etanercept and infliximab. Treatment decisions trends in 2019 showed that some molecules present a positive balance such as

bDMARD biosimilars. Overall, bDMARDs achieved treatment target (ASDAS-defined remission and LDA) within the first 6 months of treatment in 87.6% of treated patients. Also, RRBR data indicate a slow but significant increase in tapered regimens. Thus, the RRBR has proved to be a very valuable tool in capturing data regarding axSpA management in a real-life national setting of rheumatology healthcare.

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