

Data from the Romanian Registry of Rheumatic Diseases for patients with rheumatoid arthritis treated with biologic and targeted synthetic disease-modifying anti-rheumatic drugs during 2019

Catalin Codreanu^{1,2}, Corina Mogosan^{1,2}, Claudiu C. Popescu^{1,2}

¹“Dr. Ion Stoia” Clinical Center for Rheumatic Diseases, Bucharest, Romania

²“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

The number of rheumatoid arthritis (RA) patients with visits introduced in the Romanian Registry of Rheumatic Diseases (RRBR) has been steadily increasing within the last 3 years. Included patients display the classical phenotype of established RA, with a relatively high prevalence of extra-articular manifestations, cardiovascular comorbidity and a high burden regarding early retirement due to RA. Data regarding treatment showed a very low prevalence of monotherapy with biologic and targeted synthetic disease-modifying drugs (b/tsDMARD) and a low prevalence of glucocorticoid-therapy. Approximately a fifth of the patients started b/tsDMARD-therapy early during disease course (under 2 years from diagnosis). The most frequent prescribed bDMARD was etanercept, followed by adalimumab and rituximab. Treatment decisions trends in 2019 showed that some molecules present a negative balance, such as abatacept and rituximab, while others present a positive balance such as bDMARD biosimilars and tsDMARDs. Overall, b/tsDMARD achieved treatment target (DAS28-defined remission and LDA) within the first 6 months of treatment in 81.4% 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 RA management in a real-life national setting of rheumatology healthcare.

Keywords: rheumatoid arthritis, Romanian Registry of Rheumatic Diseases, biologics

INTRODUCTION

The Romanian Registry of Rheumatic Diseases (in Romanian, RRBR) is a national electronic database comprising all rheumatoid arthritis (RA) patients treated with reimbursed biological and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs, tsDMARDs) [1]. RRBR was launched in February 2013 and it was designed as a prospective observational study. 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 both b/tsDMARD therapy and scientific use of their RRBR data. A consenting patient is included in the RRBR and begins treatment with b/tsDMARDs if all of the following 4 criteria are fulfilled:

- their RA diagnosis fulfills the 2010 RA classification criteria [2];
- there is significant RA activity according to DAS28 [3], defined simultaneously as:
 - DAS28 above 5.1, irrespective of disease duration, or DAS28 above 3.2 in early RA (defined as a disease duration shorter than 2 years) with at least 5 poor prognosis factors from the following: age below 45 years; rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) more than 10 times the upper limit of normal; erythrocyte sedimentation rate (ESR) above 50 mm/h or C-reactive protein (CRP) more than 5 times the upper limit of normal; erosions on conventional radiographs of hand and feet, ultrasound or

Corresponding author:

Claudiu C. Popescu

E-mail: claudiu.popescu@reumatologiedrstoia.ro

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magnetic resonance imaging; a score of 1.5 or above on the health assessment questionnaire (HAQ); the presence extra-articular manifestations;

- 5 or more tender/swollen joints from the DAS28 count;
- at least 2 of the following 3 supplementary criteria: morning stiffness above 60 minutes, ESR above 28 mm/h, CRP more than 3 times the upper limit of normal, according to each local laboratory.
- failure to achieve DAS28 remission or low disease activity with at least 2 conventional synthetic DMARDs (csDMARDs, usually methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, alone or in combinations), used for at least 12 weeks each at maximum indicated or tolerated doses;
- there are no contraindications according to summaries of product characteristics and physician evaluations.

The RRBR can capture several types of treatment decisions: *initiations* (RA patients naïve to b/tsDMARDs who fulfill the above criteria and who will henceforth receive b/tsDMARDs with classical posology, reimbursed by the National Health Insurance House), *initial monitoring* (RA patients currently treated with b/tsDMARDs not reimbursed by the National Health Insurance House, for example patients from clinical trials or patient initiated on b/tsDMARDs in other countries, using classical or tapered regimens, who will henceforth receive reimbursed b/tsDMARDs), *continuations* (visits at every 6 months of RA patients from the first categories who will continue their previous reimbursed b/tsDMARD either with classical regime, tapered regime or revert levels of tapering) and *switches* (RA patients with adverse events, primary or secondary non-responders who will not continue with their previous reimbursed b/tsDMARD, but with another).

RA CHARACTERISTICS OF 2019 RRBR PATIENTS

The number of RA patients with visits introduced in the RRBR has been increasing within the last 3 years (Figure 1): starting from 4,171 patients in 2017, increasing with 5.7% in 2018 and reaching 4,755 patients in 2019 (14.0% increase compared to 2017 and 7.9% increase compared to 2018). In 2019,

there were 752 cases (15.8%) without RRBR data for more 12 months and 404 cases (8.5%) were lost to follow-up.

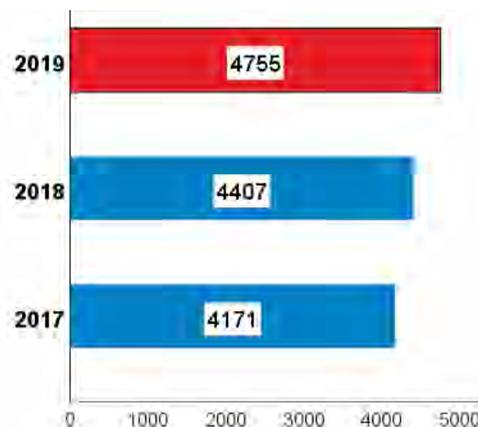


FIGURE 1. Number of RA patients with visits introduced in the RRBR in the last 3 years

Demographically, the predominant patient profile was that of urban-dwelling overweight retired non-smoking women, with a mean age of 59.4 years and with established RA (mean disease duration of 13.7 years – Table 1). Of note, 1,756 patients were retired because of RA, meaning more than a third from the entire sample (36.9%) and more than half of the retired RA patients (51.3%).

TABLE 1. Characteristics of RA patients in 2019 from RRBR (n = 4,755)

women (n, %)	4,023 (84.6%)
age (mean ± SD; years)	59.4 ± 12.1
body mass index (mean ± SD; kg/m ²)	26.7 ± 5.0
urban dwelling (n, %)	3,016 (63.4%)
higher education (n, %)	908 (19.1%)
employed (n, %)	1,334 (28.1%)
RA-retired (n, %)	1,756 (36.9%)
age-retired (n, %)	1,665 (35.0%)
smoking (n, %)	454 (9.5%)
RA duration (mean ± SD; years)	13.7 ± 8.6

RA – rheumatoid arthritis; RRBR – Romanian Register of Rheumatic Diseases; SD – standard deviation

Regarding age distribution, the 2019 showed a very low prevalence of patients below 25 years of age (1.22%), with a predominance of patients aged 46–65 years (54.4%), followed by patients aged above 65 years (33.1%) and patients aged 26–45 years (11.2%) (Figure 2).

From the total 4,755 RA patients in 2019, 4,604 (96.8%) had reports of RF tests, which were positive in 3,959 patients (86.0% from the subgroup with reported RF tests; Figure 3), according to each local

laboratory. Similarly, 3,414 (71.8%) patients had reports of ACPA tests, which were positive in 2,853 patients (83.6% from the subgroup with reported ACPA tests). Overall, 2,719 patients were both RF and ACPA positive (76.6% of tested patients).

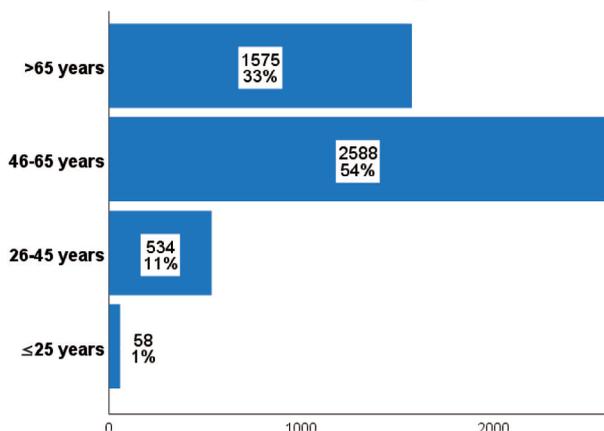


FIGURE 2. Age-distribution of RA patients from the RRBR in 2019

Data from the RRBR showed that 1386 RA patients (29.1%) had extra-articular manifestations (Figure 4): the most frequent extra-articular manifestation was the presence of rheumatoid nodules (416 patients, 8.7% from total), followed by sicca syndrome (7.7%), interstitial lung disease (6.9%), eye involvement (1.7%), Raynaud phenomena (1.6%), vasculitis (1.5%), others (1.1%, including renal involvement, Felty syndrome, serositis, lymphadenopathy).

The RRBR allows for data capture on comorbid conditions of RA patients (Figure 5). From the 2019 reports ($n = 4,755$), the most frequent comorbid category was cardiovascular disease (3,166 patients,

66.6% 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 (21.4%; defined as a positive blood interferon gamma release assay), dyslipidemia (21.3%), osteoporosis (20.6%), liver disease (14.2%), diabetes mellitus (11.8%), gastrointestinal disease (11.5%), hematologic disease (11.0%), thyroid disease (8.5%), renal disease (7.6%) and cancer (1.4%, including 2 active cancers: one case of breast cancer, currently under hormonal treatment, and one case of prostate cancer). Of note, there were 73 patients (1.5%) with positive hepatitis B surface antigen and 67 patients (1.4%) with positive anti-hepatitis C virus antibodies.

RA TREATMENT CHARACTERISTICS OF 2019 RRBR PATIENTS

All 4,755 RA patients received one current bDMARD or tsDMARD, with 1.6% of patients on bDMARD or tsDMARD monotherapy and 98.4% of them with at least one current associated csDMARD (Figure 6), namely 76.7% on one current csDMARD, 20.7% on 2 current csDMARDs and 1.0% on 3 current csDMARDs.

Of the patients on 2 current csDMARDs ($n = 983$), 25.1% had a combination of methotrexate and leflunomide, 20.3% combined methotrexate and sulfasalazine, 20.2% combined leflunomide and sulfasalazine, 13.0% combined methotrexate and hydroxychloroquine, 11.8% combined leflunomide and hydroxychloroquine and 6.0% combined sulfasalazine and hydroxychloroquine.

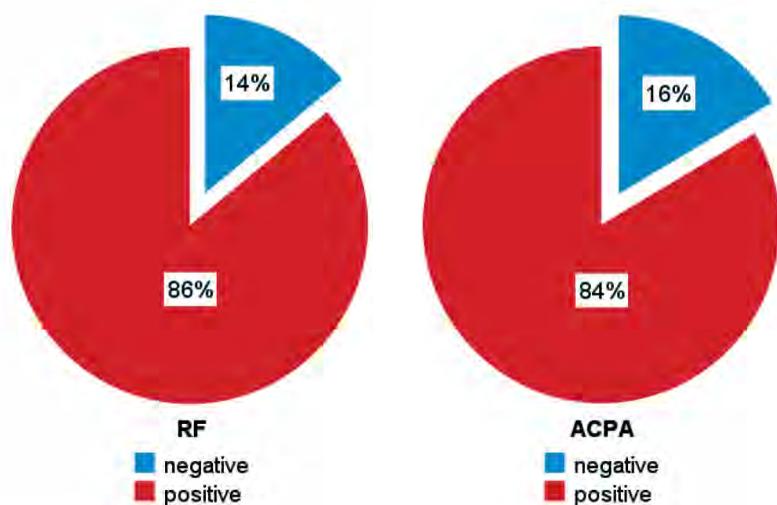


FIGURE 3. Serology of RA patients from the RRBR in 2019

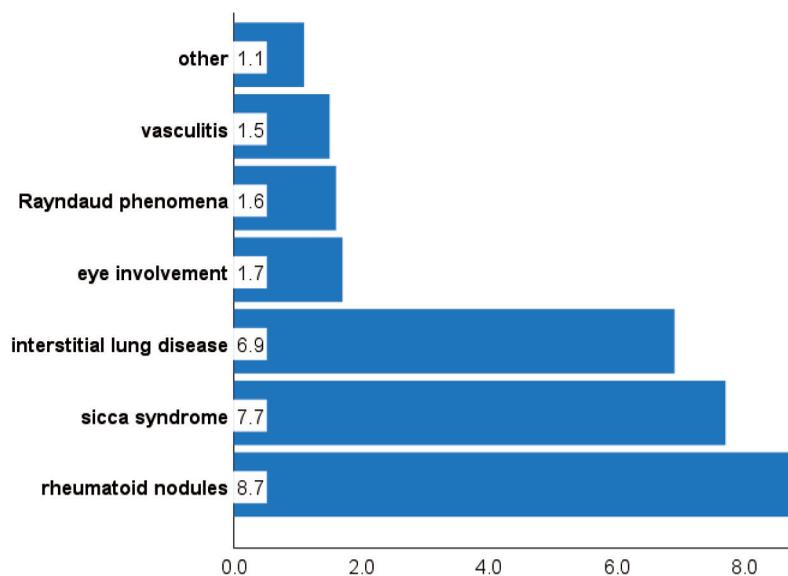


FIGURE 4. The frequency of extra-articular manifestations of RA patients from the RRBR in 2019. Reported values represent the percent from the total sample ($n = 4,755$)

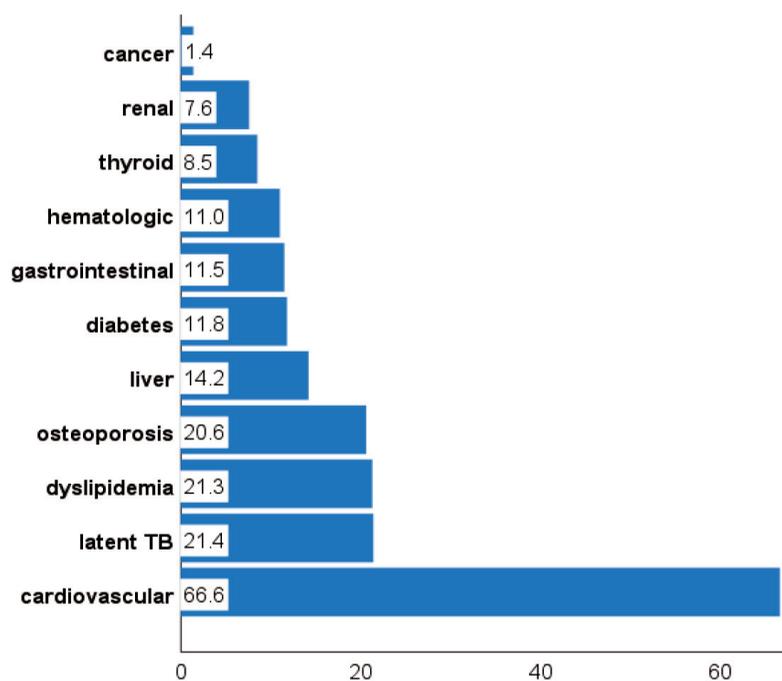


FIGURE 5. The frequency of comorbidities of RA patients from the RRBR in 2019. Reported values represent the percent from the total sample ($n = 4,755$)

Of the patients on triple current csDMARD therapy ($n = 49$), the most frequent association included either methotrexate, sulfasalazine and hydroxychloroquine (36.7%), leflunomide, sulfasalazine and hydroxychloroquine (34.7%) or methotrexate, leflunomide and hydroxychloroquine (16.3%).

As expected, methotrexate was the most frequent associated csDMARD (2,332 patients, 49.0% of total), with a mean weekly dose of 15 mg (45.8% of patients on methotrexate had 20 mg/week, 17.0% had 15 mg/week and 34.3% had 10 mg/week).

In the entire sample ($n = 4,755$), only 6.9% of patients were reported to use current oral glucocorticoids (prednisone or methylprednisolone), with

54.5% of them on low doses (7.5 mg/day prednisone equivalent or lower).

The mean RA duration at bDMARD and tsDMARD start was 8.2 years, with an approximately even distribution on disease duration categories (Figure 7), noting that 21.2% had early RA (defined as a disease duration under 2 years) when starting b/tsDMARDs, while 31.7% had a disease duration of over 10 years when starting b/tsDMARDs.

Compared to 2018, the number of initiations, continuations and switches of bDMARDs increased in 2019 with 17.0% (from 499 to 584), 6.7% (from 3,322 to 3,546) and 11.4% (from 586 to 653) respectively (Figure 8).

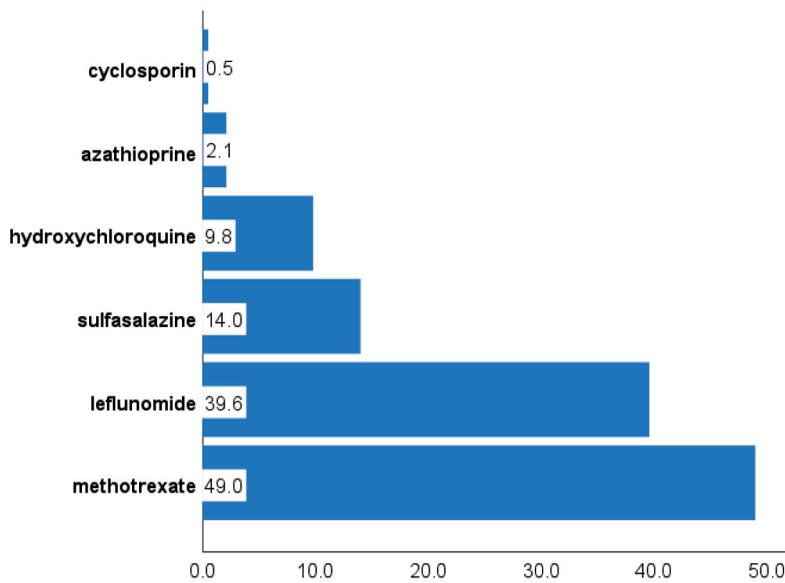


FIGURE 6. The frequency of treatment with csDMARDs of RA patients from the RRBR in 2019. Reported values represent the percent from the total sample ($n = 4,755$)

Of the 4,755 patients in the sample, 7 patients stopped b/tsDMARDs in 2019, leaving 4,748 patients on active b/tsDMARD treatment (Table 2), of which 91.3% were on bDMARDs (65.9% on TNF α inhibitors and 34.1% on non-TNF α inhibitors) and 8.7% on tsDMARDs (74.4% on baricitinib and 25.6% on tofacitinib).

From the total 2,386 RA patients on molecules with available biosimilars in 2019 in Romania (namely adalimumab, for which biosimilars became available later in the year, and etanercept and inflix-

imab, for which biosimilar were already available from the start of the year), 80.6% were on originator molecules and 19.4% on biosimilars. Reflecting the time point of availability, on one hand, RA patients on originator adalimumab were 13 times more numerous than RA patients on biosimilar adalimumab (Table 2). On the other hand, RA patients on originator etanercept were 4 times more numerous than RA patients on biosimilar etanercept, while RA patients on biosimilar infliximab surpassed 1.3 times those on originator infliximab.

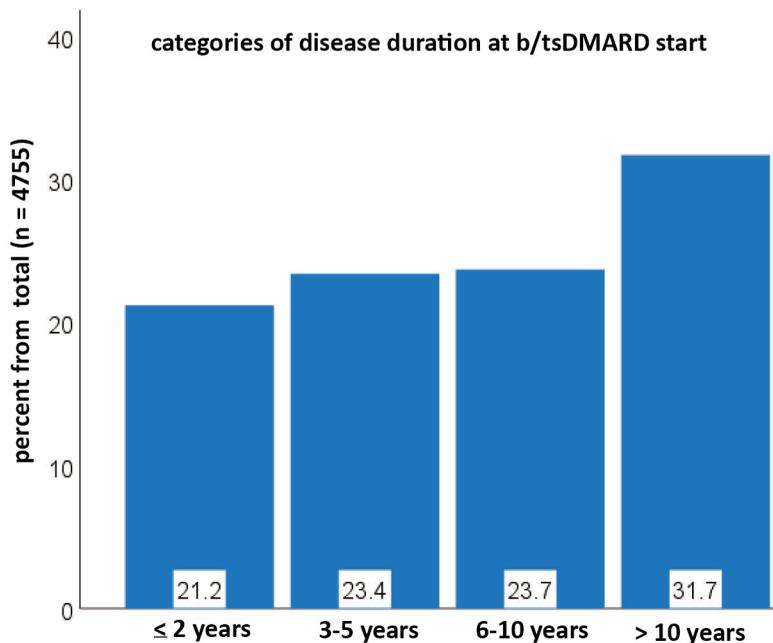


FIGURE 7. The distribution of RA patients starting b/tsDMARDs in 2019 according to disease duration sub-groups

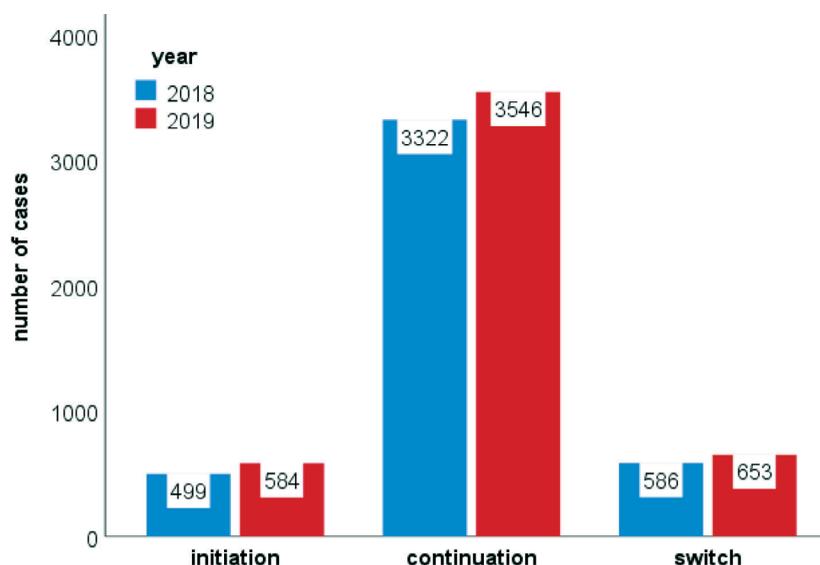


FIGURE 8. The number of RA patients from RRBR in 2019 compared to 2018, regarding treatment decisions

TABLE 2. The frequency of b/tsDMARDs molecules in 2019 (n = 4,748)[§]

	total*	originator molecule [#]	biosimilar molecule [#]
abatacept	112 (2.4%)	-	-
adalimumab	903 (19.0%)	840 (93.0%)	63 (7.0%)
baricitinib	308 (6.5%)	-	-
certolizumab	284 (6.0%)	-	-
etanercept	1,244 (26.2%)	979 (78.7%)	265 (21.3%)
golimumab	184 (3.9%)	-	-
infliximab	239 (5.0%)	103 (43.1%)	136 (56.9%)
rituximab	768 (16.2%)	-	-
tocilizumab	600 (12.6%)	-	-
tofacitinib	106 (2.2%)	-	-

& of the 4,755 patients, 7 stopped b/tsDMARDs in 2019, leaving 4,748 on active b/tsDMARD treatment; * percentages represent fraction from the total number of patients on b/tsDMARDs; # percentages represent fraction from the number of patients on specific molecules

Of note, the most frequently prescribed bDMARD was etanercept, received by 1,244 patients (meaning 26.2% from the 4,748 patients on active b/tsDMARD treatment), followed by adalimumab (19.0%) and rituximab (16.2%). In the tsDMARD category, RA patients on baricitinib were 3 times more numerous than RA patients on tofacitinib (Table 2).

Treatment decisions trends in 2019 showed that some molecules present a negative balance (Table 3), such as abatacept (with 95 continuations, 2 initiations, 45 entries by switch and 90 exists by switch) and rituximab (with 706 continuations, 7 initiations, 28 entries by switch and 58 exists by switch). Others present a relatively neutral balance, such as adalimumab (with 734 continuations, 124 initiations, 55 entries by switch and 118 exists by switch), certolizumab (with 223 continuations, 25 initiations, 28 entries by switch and 58 exists by switch), etaner-

cept (with 966 continuations, 182 initiations, 100 entries by switch and 108 exists by switch), golimumab (with 129 continuations, 25 initiations, 31 entries by switch and 31 exists by switch), infliximab (with 179 continuations, 42 initiations, 21 entries by switch and 67 exists by switch) and tocilizumab (with 399 continuations, 41 initiations, 149 entries by switch and 49 exists by switch). The relatively new molecules (tsDMARDs) present a highly positive balance, both baricitinib (with 64 continuations, 106 initiations, 131 entries by switch and only 19 exists by switch) and tofacitinib (with 45 continuations, 30 initiations, 30 entries by switch and 12 exists by switch).

RA TREATMENT EFFICACY IN 2019 IN THE RRBR DATABASE

The therapeutic objective in RA is to achieve a state of remission of the disease, whenever possible (most commonly in early RA, with the early initiation of treatment), or a state of low disease activity (LDA), in cases where remission cannot be obtained (most commonly in established or severe forms of RA) [4]. The national guidelines for RA treatment and consequently the RRBR use DAS28-defined categories of disease activity (DAS28 up to 2.6 for remission and up to 3.2 for LDA), with additional information regarding SDAI-defined categories of disease activity (SDAI up to 3.3 for remission and up to 11.0 for LDA) [5].

In this sense, efficacy data for patients who were initiated on b/tsDMARDs in 2019 and who had their first 6-month evaluation in 2019 (n = 259), excluding switches, showed a significant variation of mean

TABLE 3. Treatment decisions in 2019 by therapeutic molecule

	initiations (n = 584)*	continuations (n = 3,546)	single switches (n = 601) ^{&}	
			exists	entries
abatacept	2 (0.3%)	95 (2.7%)	50 (8.3%)	11 (1.8%)
adalimumab	124 (21.2%)	734 (20.7%)	118 (19.6%)	55 (9.2%)
<i>originator</i>	<i>84 (72.4%)</i>	-	<i>118 (100%)</i>	<i>33 (60.0%)</i>
<i>biosimilar 1</i>	<i>20 (17.2%)</i>	-	-	<i>10 (18.2%)</i>
<i>biosimilar 2</i>	<i>12 (10.3%)</i>	-	-	<i>9 (16.4%)</i>
<i>biosimilar 3</i>	<i>8 (6.9%)</i>	-	-	<i>3 (5.5%)</i>
baricitinib	106 (18.2%)	64 (1.8%)	19 (3.2%)	131 (21.8%)
certolizumab	25 (4.3%)	229 (6.5%)	57 (9.5%)	28 (4.7%)
etanercept	182 (31.2%)	966 (27.2%)	108 (18.0%)	100 (16.6%)
<i>originator</i>	<i>87 (47.8%)</i>	<i>854 (88.4%)</i>	<i>81 (75.0%)</i>	<i>41 (41.0%)</i>
<i>biosimilar</i>	<i>95 (52.2%)</i>	<i>112 (11.6%)</i>	<i>27 (25.0%)</i>	<i>59 (59.0%)</i>
golimumab	25 (4.3%)	129 (3.6%)	31 (5.2%)	31 (5.2%)
infliximab	42 (7.2%)	179 (5.0%)	67 (11.1%)	21 (3.5%)
<i>originator</i>	<i>6 (14.3%)</i>	<i>94 (52.5%)</i>	<i>22 (32.8%)</i>	<i>3 (14.3%)</i>
<i>biosimilar 1</i>	<i>34 (80.9%)</i>	<i>71 (39.7%)</i>	<i>27 (40.3%)</i>	<i>17 (81.0%)</i>
<i>biosimilar 2</i>	<i>2 (4.8%)</i>	<i>14 (7.8%)</i>	<i>18 (26.9%)</i>	-
<i>biosimilar 3</i>	-	-	-	<i>1 (4.8%)</i>
rituximab	7 (1.2%)	706 (19.9%)	90 (15.0%)	45 (7.5%)
tocilizumab	41 (7.0%)	399 (11.3%)	49 (8.2%)	149 (24.8%)
tofacitinib	30 (5.1%)	45 (1.3%)	12 (2.0%)	30 (5.0%)
anti-TNFα	398 (68.2%)	2,237 (63.1%)	381 (63.4%)	235 (39.1%)
non-anti-TNFα	50 (8.6%)	1,200 (33.8%)	189 (31.4%)	205 (34.1%)
tsDMARDs	136 (23.3%)	109 (3.1%)	31 (5.2%)	161 (26.8%)

* 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: 31.2% of all initiations in 2019 were on etanercept, 47.8% of them using the originator molecule and 52.2% using the biosimilar molecule.

& total number of switches in 2019 was 653 (13.7% from the entire sample); multiple switches (n = 52) are not reported in this table

DAS28 (from 6.35 at initiation to 3.19 after the first 6 months) and of mean SDAI (from 42.3 at initiation to 10.7 after the first 6 months), both scores barely reaching the LDA target overall (Figure 9).

Of the 3,546 patients who continued the same b/tsDMARD in 2019, there were 706 patients on rituximab which were excluded because of the particular re-administration strategy for this molecule accord-

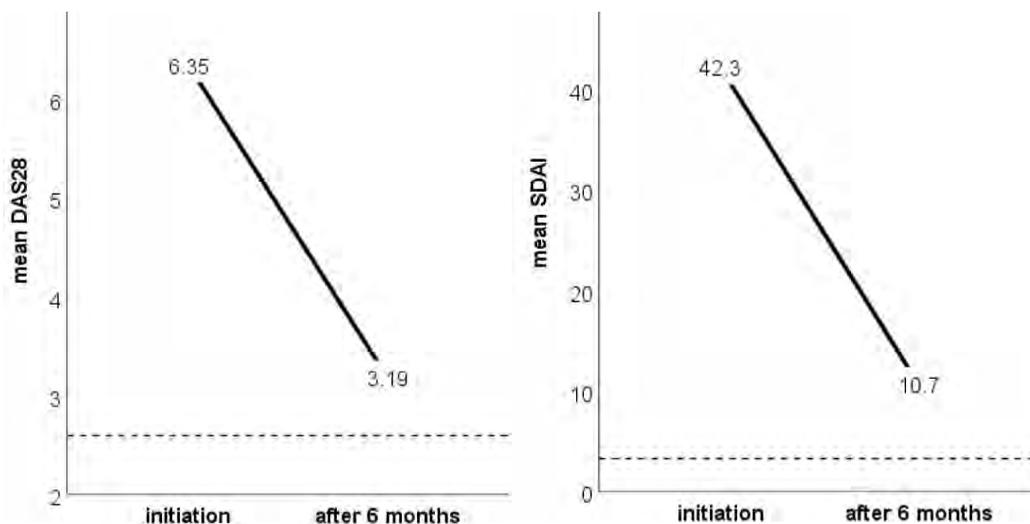


FIGURE 9. The variation of mean DAS28 (left: variation of -3.16) and mean SDAI (right: variation of -31.6) after the first 6 months of treatment with b/tsDMARDs ensuing initiation (n = 259, counting patients who were initiated in 2019 and had their first 6-month evaluation in 2019, excluding switches). Dotted lines represent the level of remission (2.6 for DAS28 and 3.3 for SDAI)

ing to the national protocol: repeated treatment will be administered after at least 24 weeks from the previous treatment cycle, only to responses (patients who previously achieved treatment target of remission/LDA) and only when one of the following conditions of disease activity is met: there is a residual active disease ($DAS28 \geq 3.2$) or there is a reactivation of the disease with an increase in DAS28 with 1.2 or more, provided the disease activity class changes to the next higher activity level (from remission to LDA or from LDA to MDA).

Excluding patients on rituximab leaved 2840 patients who continued with the same b/tsDMARD treatment in 2019 (Figure 10) which revealed that 2,312 patients were within DAS28-defined treatment target of remission/LDA (representing 81.4% of treated patients) and 2,530 patients were within SDAI-defined treatment target of remission/LDA (representing 89.1% of treated patients).

As of 2019, from the entire sample, 57.7% of RA patients were exposed to a single b/tsDMARD, 26.2% received 2 consecutive b/tsDMARDs and 16.1% received 3 or more b/tsDMARDs (Table 4). When investigating efficacy in patients who continued the same b/tsDMARD ($n = 2,840$, excluding rituximab) according to the history of b/tsDMARD exposure, the mean DAS28 revealed that patients with up to 2 different b/tsDMARD exposures tended

to be in remission, while patients with 3 or more b/tsDMARD exposures were in LDA (Table 4), suggesting the need of dynamic treatment in more severe cases in order to reach the therapeutic target.

Compared to the end 2018, when 181 (4.11%) patients were receiving tapered bDMARDs and 17 patients returned from tapered doses to the classical frequency of bDMARD administration, at the end of 2019 a total of 216 (4.54%) patients were receiving tapered bDMARDs and 19 patients reverted their tapered bDMARD regimen (Figure 11).

CONCLUSIONS

The number of RA patients with visits introduced in the Romanian Registry of Rheumatic Diseases has been steadily increasing within the last 3 years. Included patients display the classical phenotype of established RA, with a relatively high prevalence of extra-articular manifestations, cardiovascular comorbidity and a high burden regarding early retirement due to RA. Data regarding treatment showed a very low prevalence of b/tsDMARD-monotherapy and a low prevalence of glucocorticoid-therapy. Approximately a fifth of the patients started b/tsDMARD-therapy early during disease course (under 2 years from diagnosis). The most frequent prescribed bDMARD was etanercept, followed by

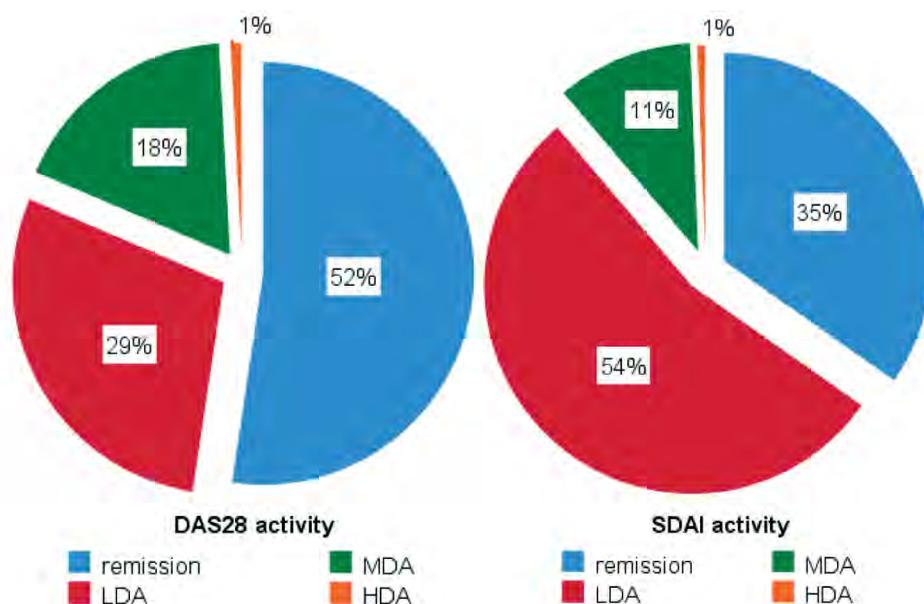


FIGURE 10. The distribution of RA patients who continued with the same b/tsDMARD treatment according to DAS28 (left: 2,312 patients within treatment target of remission and LDA, representing 81.4% of treated patients) and SDAI (right: 2,530 patients within treatment target of remission and LDA, representing 89.1% of treated patients) activity categories ($n = 2,840$ continuations in 2019, excluding patients on rituximab). L/M/HDA – low/moderate/high disease activity

TABLE 4. The distribution of RA patients according to prior b/tsDMARD exposure and DAS28-defined efficacy

number of different b/tsDMARDs	number of patients (n = 4755)	number continuations excluding rituximab (n = 2840)	mean DAS28 per category of continuations
1	2,742 (57.7%)	1,795 (63.2%)	2.54
2	1,246 (26.2%)	609 (21.4%)	2.61
3	525 (11.1%)	301 (10.6%)	2.74
4	177 (3.7%)	97 (3.4%)	2.66
5	52 (1.1%)	35 (1.2%)	2.94
6	11 (0.2%)	3 (0.1%)	2.67
7	2 (0.04%)	-	-

b/tsDMARDs – biologic/targeted synthetic disease-modifying anti-rheumatic drugs;
DAS – disease activity score; RA – rheumatoid arthritis

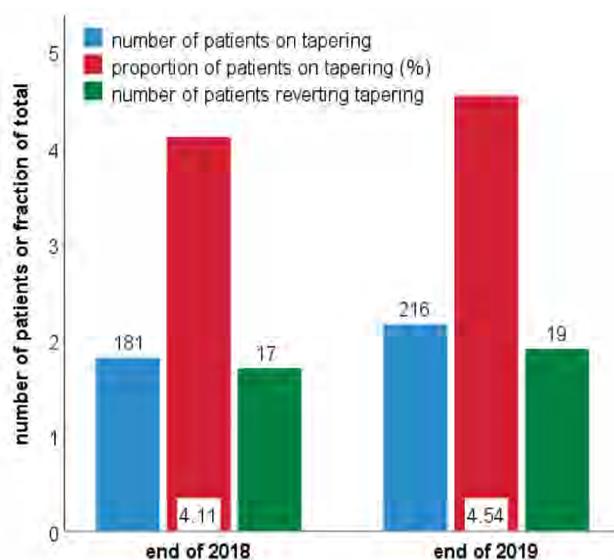


FIGURE 11. The number and proportion of patients on tapered regimens of bDMARDs at the end of 2018 (n = 4,407) compared to the end of 2019 (n = 4,755)

adalimumab and rituximab. Treatment decisions trends in 2019 showed that some molecules present a negative balance, such as abatacept and rituximab, while others present a positive balance such as bDMARD biosimilars and tsDMARDs. Overall, b/tsDMARD achieved treatment target (DAS28-defined remission and LDA) within the first 6 months of treatment in 81.4% 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 RA management in a real-life national setting of rheumatology healthcare.

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