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Treatment of rheumatoid arthritis with biologic and targeted synthetic disease-modifying anti-rheumatic drugs in 2022 – real-world data from the Romanian Registry of Rheumatic Diseases

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ABSTRACT

Objective. The study aimed at characterizing the evolution of RA treatment with b/tsDMARDs in Romania, since the end of the SARS-CoV-2 pandemic and the national approval of JAKi.

Methods. Data on RA patients was obtained from the Romanian Registry of Rheumatic Diseases database between January 1st, 2022, and December 31st, 2022, encompassing all Romanian RA patients fulfilling the national criteria for b/tsDMARD initiation.

Results. The RRBR database contained 5,396 active RA patients: 83.2% female, 59.9 years mean age, 13 years median disease duration, 86.7% RF positive, 81.7% ACPA positive, with a high prevalence of cardiovascular comorbidities, 89.8% receiving at least one csDMARD, most often methotrexate (48.7%), with 6.3% on glucocorticoids, 78.8% on bDMARDs (especially etanercept - 27.6%, adalimumab - 18.1% and tocilizumab - 14.0%) and 21.2% on JAKi (most often on baricitinib - 11.4%), with a 58.2% DAS28-defined remission rate and a 34.3% SDAI-defined remission rate.

Conclusion. The Romanian cohort of RA patients on b/tsDMARDs observed the both classical phenotypic characteristics of RA and local cohort characteristics. JAKi prescription has gained a significant increase. Capturing data on real-world patients filtered by stringent criteria for high disease activity and poor prognosis factors, the RRBR database proves to be an extremely useful insight into the evolution of RA pharmacologic treatment.

Keywords: rheumatoid arthritis, Romanian Registry of Rheumatic Diseases, biologic treatment

INTRODUCTION

Modern treatment of rheumatoid arthritis (RA), in terms of new therapeutic molecules and management strategies, has the ability to stop or to reduce the radiographic progression of the disease, controlling systemic inflammation and pain. In so doing, it increases the quality of life of RA patients and it preserves their functional ability, maintaining workforce and lowering health costs. In Romania, apart from conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD), the National Insurance House and its regional branches reimburse

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treatment with modern pharmaceutical molecules, being biological DMARDs (bDMARDs, namely abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, either in their original or biosimilar forms) and targeted synthetic DMARDs (tsDMARDs, namely Janus kinase inhibitors – JAKi, baricitinib, tofacitinib and upadacitinib), for active RA patients failing csDMARDs (either because adverse events, contraindication or inefficacy). The specific criteria to be fulfilled by RA cases for b/tsDMARD reimbursement have been previously published elsewhere [1-3]. These national criteria include fulfillment of the American College of Rheumatology (ACR) and European Leagues against Rheumatism (EULAR) criteria for classification of RA cases [4] and they require RA disease activity (high disease activity defined by DAS28, at least 5 swollen and painful joints and acute phase reactants above specified thresholds) in the context of failure of 2 distinct csDMARDs. Instead, EULAR recommendations allow for b/tsDMARD treatment after the failure of the first csDMARD in the presence of poor prognosis factors (autoantibodies, high disease activity, early erosions or failure of two csDMARDs) [5], without establishing cutoffs for joint counts and acute phase reactants. The intended economic benefit of the more stringent Romanian criteria for b/tsDMARD initiation selects more aggressive RA phenotypes, limiting the randomness of sampling the real RA population.

The data form all RA patients in the country fulfilling the criteria of b/tsDMARD initiation are collected in the electronic database of the Romanian Registry of Rheumatic Diseases (RRBR). RRBR data input for each patient is performed by all senior attending physicians in the country, amounting to 469 users, of whom 416 rheumatologists, at the end of 2022. Every 6 months, with the written informed consent of patients, users record efficacy and safety information for RA patients initiating, continuing or switching their b/tsDMARD treatment, thus creating a nation-wide prospective cohort study design. Even though it includes data on radiographic progression, the fields are not mandatory and are often not filled in.

Since the last update on RRBR RA patients [3], the end of the SARS-CoV-2 pandemia and the national approval of JAKi have created the premises of a new therapeutic setting which warrants exploration, bearing in mind the importance of real-world data regarding post-marketing evolution of approved pharmacological agents.

METHODS

Data from the RRBR database was electronically retrieved between January 1st, 2022, and December 31st, 2022, including demographics (sex; age; body mass index; active smoking; dwelling; education status; professional status), comorbidities, RA characteristics (date of diagnosis; rheumatoid factor – RF; anti-citrullinated protein antibodies – ACPA; extra-articular manifestations; ACR/EULAR 2010 classification criteria), RA activity (according to the Disease Activity Score – DAS28 calculated with 4 variables [6,7], where remission was defined as DAS28 < 2.6, low disease activity - LDA as 2.6 ≤ DAS28 ≤ 3.2, moderate disease activity - MDA as 3.2 < DAS28 ≤ 5.1 and high disease activity HDA as DAS28 > 5.1; respectively according to the Simplified Disease Activity Index – SDAI [8], where remission was defined by SDAI ≤ 3.3, LDA as 3.3 < SDAI ≤ 11, MDA as 11 < SDAI ≤ 26 and HDA as SDAI > 26) and RA treatment molecules (glucocorticoids, csDMARDs, bDMARDs, tsDMARDs). Data distribution normality was assessed using descriptive statistics, normality, stem-and-leaf plots and the Lillefors corrected Kolmogorov-Smirnov tests. Continuous variables are reported as "mean ± standard deviation" if normally distributed, or as "median (minimum-maximum)" if non-normally distributed, while nominal variables are reported as "absolute frequency (percentage of group or subgroup)". The difference of continuous variables among subgroups were assessed by independent-sample t tests, while associations of dichotomous categorical variables were assessed using $\chi 2$ tests, all performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., released 2019, Armonk, NY).

RESULTS AND DISCUSSION

Demographics and RA phenotype

The RRBR database contained 5,396 active RA patients, amounting 50.6% of all RRBR patients. The typical patient in this sample was female, with an average age of 59.8 years, overweight, non-smoker, with urban dwelling, high school education and even employment status (Table 1). Compared to men, women had a significantly lower rate of smoking and of current employment, but a significantly higher rate of urban dwelling (Table 1). The 83.2% prevalence of women among RA patients is significantly higher than that reported by western epidemiological studies of RA [9,10]. Similarly, age-prevalence of RA cases is skewed to younger ages compared to the same sources, probably following national age distributions.

The typical RA case was of established disease, initiating b/tsDMARD long after RA diagnosis, with both RF and ACPA positive (both with higher prevalence compared to other national sources in the literature [11], suggesting a filtering convergent effect of Romanian inclusion criteria for prognostically severe cases), having rare extra-articular manifestations (the most frequent being rheumatoid nodules,

TABLE 1. Demographics of RA patients (n = 5396)

variable	all	women	men	p
sex	59.9±12.2	4487 (83.2%)	909 (16.8%)	-
age (years)		60.0±12.1	59.4±12.7	0.224
age categories:				
≤ 25 years	74 (1.4%)			
26-45 years	569 (10.5%)			
46-65 years	2766 (51.3%)			
> 65 years	1987 (36.8%)			
BMI (kg/m^2)	26.6±5.0	26.6±5.2	26.7±4.4	0.381
active smoking	572 (10.6%)	382 (8.5%)	190 (20.9%)	0.000
urban habitat	3458 (64.1%)	2904 (64.7%)	554 (60.9%)	0.031
no education	19 (0.4%)			
elementary education	1370 (25.4%)			
high school education	2875 (53.3%)			
university education	1132 (21.0%)	921 (20.5%)	211 (23.2%)	0.070
employed	1804 (33.4%)	1014 (22.6%)	272 (29.9%)	0.000
age-retired	1712 (31.7%)			
RA early retirement	1880 (34.8%)			

Notes: continuous variables are reported as "mean ± SD"; nominal variables are reported as "absolute frequency (percentage of group)" (n = 5396) or as "absolute frequency (percentage of subgroup)" in case of sex comparisons; p values represent the significance of t and χ2 tests.
Abbreviations: BMI – body mass index; RA - rheumatoid arthritis; SD - standard deviation.

TABLE 2. RA phenotype (n = 5396)

variable	frequency
RA duration (y)	13 (0-58)
RA duration at b/tsDMARD start (y)	6 (0-48)
RF: tested and positive	5341 (99.0%) and 4629 (86.7%)
ACPA: tested and positive	4627 (85.7%) and 3781 (81.7%)
RF and ACPA: tested and positive	4623 (85.7%) and 3606 (78.0%)
extra-articular manifestations	1259 (23.3%)
- rheumatoid nodules	492 (9.1%)
- sicca syndrome	417 (7.7%)
- interstitial lung disease	386 (7.2%)
- Raynaud phenomena	98 (1.8%)
- eye involvement	94 (1.7%)
- rheumatoid vasculitis	63 (1.2%)
- others*	36 (0.7%)

*Notes: *other extra-articular manifestations include kidney involvement, Felty syndrome, serositis, lymphadenopathy; continuous variables are reported as "median (minimum-maximum)"; nominal variables are reported as "absolute frequency (percentage of group)" (n = 5396) or "absolute frequency (percentage of subgroup)" for positive RF (n = 5341), ACPA (n = 4627) and RF and ACPA (n = 4326).*
Abbreviations: ACPA - anti-citrullinated protein antibodies; RA - rheumatoid arthritis; RF - rheumatoid factor.; y - years

sicca syndrome and interstitial lung disease - Table 2, frequencies which seem in accordance with other recent reports [12,13]). In general, there was a high prevalence of comorbidities, as reported by other authors [14,15], especially cardiovascular disease [16,17] (in a Romanian background population already with a higher cardiovascular risk [18,19]), latent (non-active) tuberculosis (20.1%; again among a population with endemic disease [20,21]) and a minority of patients had active hepatitis B or C infection (Table 3; nested within a population at risk [22,23]).

TABLE 3. Comorbidities of RA patients (n = 5396)

involvement	frequency
arterial hypertension	2071 (38.4%)
dyslipidemia	1194 (22.1%)
other cardiovascular comorbidities*	1313 (24.3%)
osteoporosis	1024 (19.0%)
liver disease	749 (13.9%)
diabetes mellitus	632 (11.7%)
gastrointestinal disease	607 (11.2%)
thyroid disease	555 (10.3%)
hematological disease	529 (9.8%)
kidney disease	391 (7.2%)
psoriasis	98 (1.8%)
cancer	97 (1.8%)
positive QuantiFERON test	1082 (20.1%)
hepatitis virus B and C serology	
- positive HBs antigen	95 (1.8%)
- positive anti-HBs antibodies	1565 (29.0%)
- positive total anti-HBc antibodies	1467 (27.2%)
- positive screening anti-HCV antibodies	77 (1.4%)

*Notes: *other extra-articular manifestations include kidney involvement, Felty syndrome, serositis, lymphadenopathy; continuous variables are reported as "median (minimum-maximum)"; nominal variables are reported as "absolute frequency (percentage of group)" (n = 5396) or "absolute frequency (percentage of subgroup)" for positive RF (n = 5341), ACPA (n = 4627) and RF and ACPA (n = 4326).*
Abbreviations: ACPA - anti-citrullinated protein antibodies; RA - rheumatoid arthritis; RF - rheumatoid factor.; y - years

Conventional pharmacological treatment of RA

In the sample, there were 548 (10.2%) patients on b/tsDMARD monotherapy (without an associated csDMARD, which offers a surprisingly high rate of b/tsDMARD monotherapy despite well-established meta-analytical evidence of the superiority of combination therapy [24,25]), while the rest (4848 patients - 89.8%) had at least one csDMARD molecule as-

TABLE 4. Conventional treatment of RA patients (n = 5396)

molecule/strategy	frequency
csDMARDs	
no csDMARDs	548 (10.2%)
≥1 csDMARD	4848 (89.8%)
- 1 csDMARD	4001 (82.5%)
- 2 csDMARDs	801 (16.5%)
- 3 csDMARDs	46 (0.9%)
- methotrexate*	2363 (48.7%)
- leflunomide	1991 (41.1%)
- sulfasalazine	701 (14.5%)
- hydroxychloroquine	571 (11.8%)
- azathioprine	92 (1.9%)
- cyclosporine A	24 (0.5%)
glucocorticoids[#]	340 (6.3%)

*Notes: *methotrexate dose (n = 2363; % of subgroup): 20 mg/week or above (989; 41.9%), 15 or 17.5 mg/week (428; 18.1%), 12.5 mg/week or less (946; 40.0%); [#]dose of glucocorticoids (prednisone-equivalent; n = 340; % of subgroup): < 7.5 mg/day (160; 47.1%) or ≥ 7.5 mg/day (180; 52.9%); nominal variables are reported as "absolute frequency (percentage of group)" (n = 5396 for "no csDMARDs", "≥1 csDMARD" and "glucocorticoids") or "absolute frequency (percentage of subgroup)" (n = 4848 patients on ≥1 csDMARD, for the rest).*
Abbreviations: csDMARD - conventional synthetic disease-modifying anti-rheumatic drug; RA - rheumatoid arthritis.

sociated with the b/tsDMARD treatment (Table 4). Of the patients treated with csDMARDs, most often they would receive a single csDMARD molecule (82.5%) and this csDMARD would usually be either methotrexate (48.7%) or leflunomide (41.1%). Of note, 6.3% of RA patients were also receiving oral glucocorticoids, a rate which can be considered low and probably under-reported.

Treatment with b/tsDMARDs of RA

Of the whole sample, only 41 patients (0.8%) stopped b/tsDMARDs altogether in 2022, while the rest of the patients (99.2%) either continued their previous b/tsDMARD, initiated it or switched it at least one time (Table 5). Regarding treatment types, bDMARDs were the most frequent (78.8%, compared to 21.2% for tsDMARDs). The most frequent bDMARDs in terms of molecular target were TNF inhibitors (68.9% of bDMARDs and 54.3% of patients on b/tsDMARDs), and the most frequent bDMARDs in terms of molecule type were etanercept (27.6% of bDMARDs), adalimumab (18.1%) and tocilizumab (14.0%). Regarding JAKi molecules, baricitinib lead the subgroup (53.8% of JAKi), followed by upadacitinib (28.5%) and tofacitinib (17.7%).

TABLE 5. Treatment with b/tsDMARDs of RA patients (n = 5396)

molecule/class	frequency
no b/tsDMARD	41 (0.8%)
b/tsDMARD	5355 (99.2%)
bDMARDs	4222 (78.8%)
abatacept	58 (1.1%)
adalimumab	967 (18.1%)
certolizumab	268 (5.0%)
etanercept	1479 (27.6%)
golimumab	95 (1.8%)
infliximab	98 (1.8%)
rituximab	507 (9.5%)
tocilizumab	750 (14.0%)
TNFi	2907 (54.3%; 68.9%)
non-TNFi	1315 (24.6%; 31.1%)
tsDMARDs (JAKi)	1133 (21.2%)
baricitinib	610 (11.4%)
tofacitinib	200 (3.7%)
upadacitinib	323 (6.0%)

Notes: nominal variables are reported as "absolute frequency (percentage of group)" (5396 RRBR patients only for "no b/tsDMARD",) or "absolute frequency (percentage of subgroup)" (5355 patients on b/tsDMARDs for treatment categories, 4222 patients on bDMARDs, or 1133 patients on JAKi). Subgroups represent the number of patients on active b/tsDMARD treatment (5396 – 41 = 5355), and, in the case of TNF and non-TNF inhibitors, the number of patients on bDMARDs (4222).
Abbreviations: b/tsDMARD - biological or targeted synthetic disease-modifying anti-rheumatic drug; JAKi - Janus-kinase inhibitors; RA - rheumatoid arthritis; RRBR – Romanian Registry for Rheumatic Diseases; TNFi - tumor necrosis factor inhibitors.

Among patients initiating treatment with b/tsDMARD (n = 653), the most frequent molecules were etanercept (34.2%), upadacitinib (18.7%) and adalimumab (16.7%), while among patients continuing their b/tsDMARD treatment, the most frequent mole-

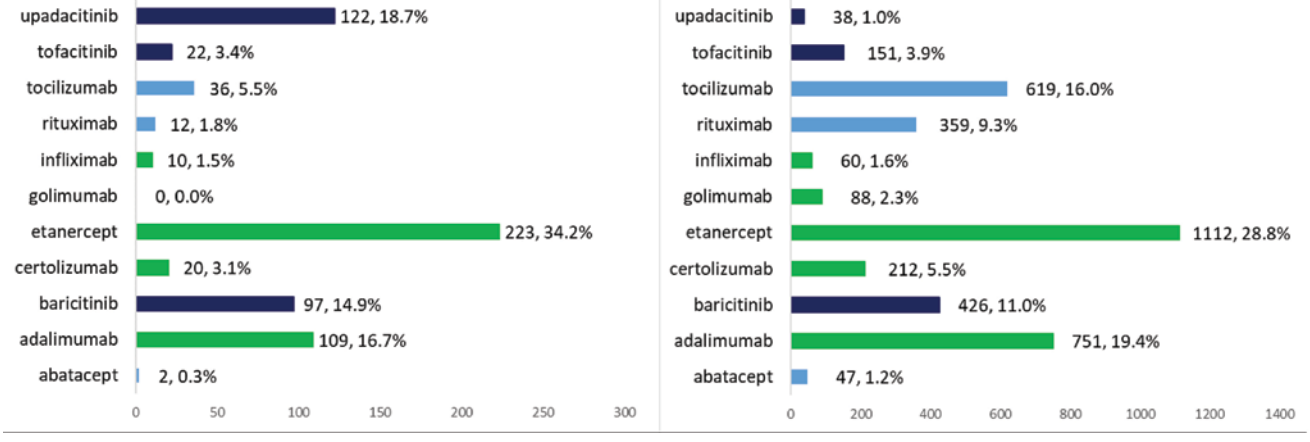

FIGURE 1. Patients initiating b/tsDMARDs (left panel; n = 653) and patients continuing their b/tsDMARD (right panel; n = 3862)

cules were etanercept (28.8%), adalimumab (19.4%) and tocilizumab (16.0%; Figure 1). Apart from patients initiating or continuing their b/tsDMARD, there were 899 patients who switched their b/tsDMARD, of which 678 simple switches (75.4%), 99 multiple switches (11.0%) and 122 non-medical switches (13.6%). The majority of medical switches were done because the patients were primary (20.5%) secondary non-responders (41.0%), while adverse events motivated 10.0% of medical switches and the rest of 28.5% were done for other reasons. Although half of the RRBR patients were only exposed to one b/tsDMARD molecule (50.9%), especially TNF inhibitors (70%), the rest of the patients were exposed to as many as 6 lines of b/tsDMARD treatment (Table 6).

TABLE 6. Exposure and type of b/tsDMARDs (n = 5396)

line	patients	TNFi	non-TNFi	JAKi
1st	2749 (50.9%)	70%	11%	19%
2nd	1425 (26.4%)	47%	35%	18%
3rd	753 (14.0%)	32%	41%	27%
4th	298 (5.5%)	24%	43%	33%
5th	111 (2.1%)	23%	46%	43%
≥ 6th	60 (1.1%)	23%	33%	43%

Notes: nominal variables are reported as "absolute frequency (percentage of group)" (5396 RRBR patients only for "patients",) or "absolute frequency (percentage of subgroup)" (number of patients in each line of treatment).
Abbreviations: b/tsDMARD - biological or targeted synthetic disease-modifying anti-rheumatic drug; JAKi - Janus-kinase inhibitors;
RRBR – Romanian Registry for Rheumatic Diseases; TNFi - tumor necrosis factor inhibitors.

Efficacy of b/tsDMARDs

Excepting the patients on rituximab (n = 507) and the patients without b/tsDMARD (n = 41), the patients continuing their b/tsDMARD in 2022 (n = 3314) were in either remission (58.2% in DAS28-defined remission and 34.3% in SDAI-defined remission), in LDA (25.6% respectively 54.5%) or in MDA or HDA (15.4% respectively 11.1%). Of note, the DAS28-defined remission rate is slightly higher than that reported for metanalytical mean of randomized controlled clinical trials [26]. The outcome (mean DAS28) depended on the number of previous b/tsDMARDs and on the mean RA disease duration at b/tsDMARD start in patients continuing treatment (n = 3862), showing a direct proportional relationship in both cases (Figure 2).

Efficacy data, in terms of DAS28 and SDAI variations, were observable for the subgroup of patients who initiated their b/tsDMARD in 2022 (first evaluation) and who had a second visit in 2022, after the first 6 months on b/tsDMARD without switching it, amounting for 290 patients. In this subgroup, the mean DAS28 decreased from 6.2 at b/tsDMARD start to 3.0 after the first 6 months, while the mean SDAI decreased from 40.7 at b/tsDMARD start to 10.1 after

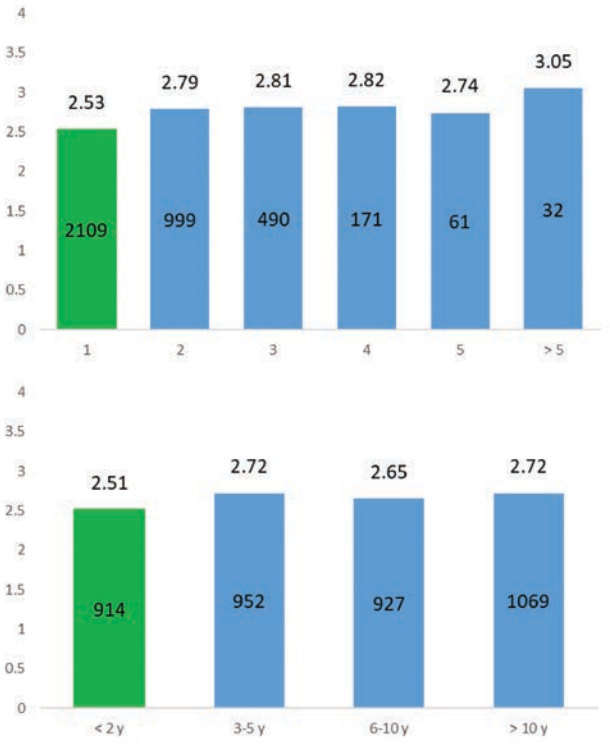

FIGURE 2. Mean DAS28 (top of columns) according to the number of previous b/tsDMARDs (upper panel, axis labels) or RA disease duration at b/tsDMARD start (lower panel, axis labels, y - years) in patients continuing treatment (n = 3862, with number of patients in each subgroup inside the columns)

the first 6 months. Similarly, patients who underwent their first switch and who also had a 6-month visit after the switch (n = 297), the mean DAS28 decreased from 4.8 at b/tsDMARD switch to 3.1 after the first 6 months, while the mean SDAI decreased from 24.8 at b/tsDMARD switch to 9.7 after the first 6 months.

At the end of 2022, there were 260 patients (4.9% of patients of b/tsDMARDs, especially patients on etanercept – 43.1%, adalimumab – 27.6% and tocilizumab – 18.5%), while 46 patients (0.9%) returned to usual posology from tapering schemes.

CONCLUSION

The Romanian cohort of RA patients on b/tsDMARDs observed the classical phenotypic characteristics of RA (female predominance; established disease; specific autoantibodies; clustering of cardiovascular comorbidities; achieving DAS28-defined remission in half of the cases; most frequently treated with methotrexate and TNFi, especially etanercept and adalimumab, even though JAKi have gained an important increase of choices for remissive strategy). Capturing data on real-world patients filtered by stringent criteria for high disease activity and poor prognosis factors, the RRBR database proves to be an extremely useful insight into the evolution of RA pharmacologic treatment.

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