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Biosimilars in rheumatoid arthritis in 2022 – data from the Romanian Registry of Rheumatic Diseases

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ABSTRACT

Objective. The study aimed at determining whether RA patients starting or stopping biosimilars differ in any regard from those starting or stopping originals.

Methods. Data on RA patients was obtained from the Romanian Registry of Rheumatic Diseases (RRBR) database between January 1st, 2022, and December 31st, 2022, encompassing all Romanian RA patients fulfilling the national criteria for bo/bsDMARD initiation, continuation or switching.

Results. Etanercept and adalimumab predominated for initiations of biosimilars. Most entries on biosimilars originated from originals (including non-medical switches) and from bDMARDs without biosimilars. A historical effect of accumulation of patients was observed, manifested in the fact that originals still dominated the group of patients continuing their treatment, with the exception of infliximab, while biosimilars tended to be continued in younger patients and in patients with shorter disease duration. Cases categorized more severe by both patients, their doctors and their disease activity were preferably reserved for originals. In patients continuing their previous bDMARD, biosimilars exhibited higher DAS28 and SDAI remission rates.

Conclusion. RRBR data from 2022 confirm the market rise of biosimilars in RA, but also physicians' prudence in prescribing them to highly active cases. In the Romanian RA cohort, biosimilars are overall more effective in holding remission than originals.

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

INTRODUCTION

In Romania, the National Insurance House and its regional branches reimburse treatment of rheumatoid arthritis (RA) with both biological original disease-modifying anti-rheumatic drugs (boDMARDs) and their biosimilar molecules (bsDMARDs). Up to 2022, there were two bsDMARD molecules for infliximab, available starting from 2015 (CT-P13 [1-3] and PF-06438179/GP1111 [4-6]), two biosimilars for etanercept, available starting from 2017 (SB4 [7-9] and GP2015 [10-12]), seven biosimilars for adalimumab, available starting from 2019 (ABP501 [13-15]; FKB327 [16-18]; GP2017 [19-21]; SB5 [22-24]; MSB11022 [25-27]; CT-P17 [28-30] and AVT02 [31-33]), and a single biosimilar for rituximab, available since 2020 (GP2013 [34-36]). Local market conditions did not assure instant, simultaneous and unrestricted access to all of these biosimilars, some of which became commercially unavailable. The national protocol for RA treatment does not restrict the use of bo/bsDMARDs, in the sense that a RA patient fulfilling the national criteria for initiating or switching treatment could re-

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ceive either an original or a biosimilar molecule, the decisions being left to the patient-doctor relationship.

The specific national criteria to be fulfilled by RA cases for bDMARD reimbursement are more stringent than the recommendations of the European Leagues against Rheumatism (EULAR) [37]. These national criteria for initiating modern treatment have been previously published elsewhere [38-40], they include fulfillment of the American College of Rheumatology (ACR) and EULAR criteria for classification of RA cases [41] and they require RA disease activity (high disease activity defined by DAS28, at least five swollen and painful joints and acute phase reactants above specified thresholds) in the context of failure of two distinct conventional synthetic DMARDs. Continuation of treatment requires efficacy criteria (reaching DAS28-defined remission or low disease activity - LDA) and the lack of significant adverse events (AE). The data form all RA patients in the country fulfilling the criteria of bDMARD initiation are collected and followed 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 every 6 months, with the written informed consent of patients. Users record efficacy and safety information for RA patients initiating, continuing or switching their bDMARD treatment, thus creating a nation-wide prospective cohort study design.

Since the last update on RRBR RA patients [38], the end of the SARS-CoV-2 pandemic and the national approval of multiple biosimilar molecules have created the premises for a new therapeutic setting which warrants exploration, especially in determining whether patients starting or stopping biosimilars differ in any regard from those starting or stopping original.

METHODS

Data and patients

Data from the RRBR database was electronically retrieved between January 1st, 2022, and December 31st, 2022, including demographics (sex; age), RA characteristics (date of diagnosis; rheumatoid factor - RF; anti-citrullinated protein antibodies - ACPA; ACR/EULAR 2010 classification criteria), RA activity (according to the Disease Activity Score – DAS28 calculated with 4 variables [42,43], where remission was defined as DAS28 < 2.6; respectively according to the Simplified Disease Activity Index – SDAI [44], where remission was defined by SDAI ≤ 3.3) and RA treatment molecules (glucocorticoids, csDMARDs, bDMARDs). Each entry for an RA patient in the RRBR database can be defined as either an initiation (a bDMARD-naïve RA patient, fulfilling the national criteria for bDMARD treatment, will start treatment), a continuation (a patient with past experience of b/tsDMARDs, fulfilling the national criteria for efficacy, will continue treatment in the absence of significant AE) or a switch (a patient with past experience of b/tsDMARDs, failing the national criteria for efficacy, experiencing significant AE or for other documented reasons, such as transitioning non-medically to biosimilars, will change their previous molecule with any other drug, original or biosimilar).

Statistics

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 (including post-hoc analysis for trichotomous variables such as use of glucocorticoids: none, bellow or above 7.5 mg/day oral prednisone-equivalent), all performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., released 2019, Armonk, NY).

RESULTS AND DISCUSSION

Group characteristics

The overlapping groups of RA patients initiating a bo/bsDMARD (n = 195), continuing the previous treatment with a bo/bsDMARD (n = 2559), switching their previous b/tsDMARD to a bo/bsDMARD (n = 294) or switching their previous bo/bsDMARD (n = 202) exhibited the classical general characteristics of established RA cohorts (Table 1): predominance of women, 60 years of age in average, overweight, urban-dwelling with low rates of employment and university education, around 10% smokers, with established disease, mostly RF and ACPA positive, with high rates of csDMARD treatment (especially methotrexate) and low levels of glucocorticoid treatment of patients exposed to b/tsDMARDs.

Naïve patients initiating bo/bsDMARD

There were 195 initiations of bo/bsDMARDs during 2022 (Table 1), of which 84.6% were on biosimilars (Table 2), with a predominance of etanercept (61.0% of initiations) and adalimumab (30.3% of initiations) on one hand, and of biosimilar etanercept (87.4% of etanercept initiations) and biosimilar adalimumab (78% of adalimumab initiations) on the other hand. Compared to patients initiated on any origi-

TABLE 1. Gender and clinical outcome of post laminectomy patients

	initiations (n = 195)	continuations (n = 2559)	switch on (n = 294)	switch off (n = 202)
men	24.6%	17.4%	19.0%	18.3%
age (y)	59.9±10.2	60.6±12.2	61.4±10.6	61.6±10.2
BMI (kg/m^2)	27.3±5.8	26.7±5.0	26.6±5.1	27.0±5.4
smoking	13.3%	10.3%	8.8%	8.9%
urban dwelling	65.6%	64.3%	66.7%	66.8%
university education	21.5%	20.3%	15.3%	13.4%
employed	23.1%	23.0%	18.7%	18.3%
disease duration (y)	5 (0-36)	15±9	15±9	15±9
RF positive	86.2%	84.8%	89.5%	89.6%
ACPA positive	76.9%	66.4%	73.1%	69.8%
EAM	17.9%	21.3%	20.7%	15.3%
csDMARDs	91.3%	95.2%	93.9%	96.0%
methotrexate	44.1%	48.9%	36.7%	38.6%
glucocorticoids	50.8%	1.7%	9.2%	7.5%
current DAS28	6.3±0.9	2.9±1.1	4.7±1.4	4.5±1.4
DAS28-remission	0	45.4%	8.8%	9.9%
current SDAI	42±13	6 (0-71)	24±14	21±14
SDAI-remission	0	28.8%	4.8%	6.4%
CRP (mg/L)	26 (0-219)	3 (0-199)	9 (0-277)	7.5 (0-277)
ESR (mm/h)	55±25	20 (0-150)	39±27	37±26

Notes: CRP normal < 5 mg/L; ESR normal < 20 mm/h; continuous variables are reported as "median (minimum-maximum)"; nominal variables are reported as "absolute frequency (percentage of group)".
Abbreviations: ACPA - anti-citrullinated protein antibodies; BMI – body mass index; CRP – C-reactive protein; csDMARD - conventional synthetic disease-modifying anti-rheumatic drug; DAS – disease activity score; EAM – extra-articular manifestations; ESR – erythrocyte sedimentation rate; RA - rheumatoid arthritis; RF - rheumatoid factor; SDAI – simplified disease activity index; y – years.

TABLE 2. Initiations of naïve patients during 2022 (n = 195)

	adalimumab	etanercept	infliximab	rituximab
number on molecule	59	119	8	9
% of initiations	30.3%	61.0%	4.1%	4.6%
number on original	13	15	0	2
original % of initiations	6.7%	7.7%	0	1.0%
original % of molecule	22.0%	12.6%	0	22.2%
number on biosimilar	46	104	8	7
biosimilar % of initiations	23.6%	53.3%	4.1%	3.6%
biosimilar % of molecule	78.0%	87.4%	100%	77.8%

TABLE 3. Patients continuing their bo/bsDMARD during 2022 (n = 2559)

	adalimumab	etanercept	infliximab	rituximab
number on molecule	826	1272	80	381
% of continuations	32.3%	49.7%	3.1%	14.9%
number on original	623	800	40	348
original % of continuations	24.3%	31.3%	1.6%	13.6%
original % of molecule	75.4%	62.9%	50.0%	91.3%
number on biosimilar	203	472	40	33
biosimilar % of continuations	7.9%	18.4%	1.6%	1.3%
biosimilar % of molecule	24.6%	37.1%	50.0%	8.7%

nal (n = 30), patients initiated on any biosimilar (n = 165) had significantly lower global evaluations, both from the patient's perspective (a median of 80 versus 88 mm; p = 0.013) and from the physician's perspective (a median of 70 versus 80 mm; p = 0.047), and a significantly higher prevalence of positive RF (89.0% compared to 76.7%; p = 0.045).

Patients continuing bo/bsDMARD

During 2022, 2,259 patients continued their bo/bsDMARD (Table 1), 29.2% on biosimilars and 70.8% on original molecules (Table 3). Again, etanercept (49.7% of continuations) and adalimumab (32.3% of continuations) dominated the prescription choices. Of note, half of the patients on infliximab (probably and effect of the poor commercial availability of the original), 37.1% of patients on etanercept and 24.6% of patients on adalimumab were on biosimilars. Compared to patients continuing original molecules, those continuing biosimilar molecules were significantly younger (59.1 years compared to 61.3 years; p < 0.001) and they exhibited other statistically significant differences and associations (Table 4): higher mean body mass index (27.2 versus 26.4 kg/m2; p = 0.001), higher mean physician global assessments (22.1 versus 20.6 mm; p = 0.046), higher mean previous DAS28 (3.5 versus 2.9; p < 0.001) and median previous SDAI (8.1 versus 5.7; p < 0.001), lower mean RA disease duration from diagnosis (11.7 versus 16.9 years; p < 0.001), higher prevalence of leflunomide treatment (45.6% versus 34.2%; p < 0.001), lower prevalence of methotrexate treatment (42.8% versus 51.5%; p < 0.001) and of urban dwelling (59.8% versus 66.2%; p = 0.002). Even though there were no significant differences in average DAS28 and SDAI, patients continuing a biosimilar had significantly higher prevalence of both DAS28 and SDAI-defined remission (52.4% compared to 42.5%, p < 0.001; respectively 33.0% compared to 27.1%, = 0.002).

Patients switching to bo/bsDMARDs

During 2022, there were 294 switches to bo/bsDMARDs, 67 (22.8%) to an original molecule and 227 (77.2%) to a biosimilar molecule. Of the patients

TABLE 4. Differences and associations among continuations (n = 2559)

	biosimilar (n = 748)	original (n = 1811)	p
age (y)	59.1 ± 11.7	61.3 ± 12.3	0.000
men	19.4%	16.6%	0.087
university education	17.9%	21.3%	0.056
urban dwelling	59.8%	66.2%	0.002
body mass index (kg/m^2)	27.2 ± 5.1	26.4 ± 4.9	0.001
RA duration from onset (y)	13.0 ± 8.7	18.2 ± 9.3	0.000
RA duration from diagnosis (y)	11.7 ± 8.2	16.9 ± 8.9	0.000
tender joint count	2 (0-22)	1 (0-28)	0.758
swollen joint count	0 (0-14)	0 (0-24)	0.287
PtGA (mm)	25 ± 18	24 ± 20	0.102
PhGA (mm)	22 ± 17	21 ± 18	0.046
CRP (mg/L; normal < 5)	3.1 (0-138.4)	3.0 (0-198.5)	0.176
ESR (mm/h; normal < 20)	21 (0-150)	20 (0-140)	0.120
current DAS28	2.9 ± 1.1	2.9 ± 1.2	0.588
DAS28-remission	52.4%	42.5%	0.000
previous DAS28	3.5 ± 1.6	2.9 ± 1.3	0.000
current SDAI	6.7 (0.1-46.5)	5.4 (0.1-71.3)	0.542
SDAI-remission	33.0%	27.1%	0.002
previous SDAI	8.1 (0.1-72.6)	5.7 (0.1-64.1)	0.000
methotrexate	42.8%	51.5%	0.000
leflunomide	45.6%	34.2%	0.000
glucocorticoids (≤ 7.5 mg/day)	2.0%	0.9%	0.065

Notes: p values represent the significance of t, Mann Whitney and χ2 tests. Abbreviations: CRP – C-reactive protein; DAS – disease activity score; ESR – erythrocyte sedimentation rate; LDA – low disease activity PhGA – physician global assessment; PtGA – patient global assessment; RA – rheumatoid arthritis; SDAI – simplified disease activity index; y – years.

TABLE 5. Differences and associations among patients switching to bo/bsDMARD (n = 294))

	switch to biosimilar (n = 67)	switch to original (n = 227)	p
men	15.0%	32.8%	0.001
extra-articular manifestations	18.5%	28.4%	0.080
tender joint count	6 (0-28)	8 (0-28)	0.068
swollen joint count	2 (0-18)	3 (0-23)	0.120
PtGA (mm)	49 ± 25	58 ± 26	0.006
PhGA (mm)	46 ± 24	54 ± 24	0.017
CRP (mg/L; normal < 5)	8 (0-157)	15 (0-277)	0.043
ESR (mm/h; normal < 20)	31 (2-130)	40 (1-111)	0.036
current DAS28	4.6 ± 1.4	5.1 ± 1.4	0.010
current SDAI	22.3 ± 13.5	27.6 ± 14.8	0.010
glucocorticoids (> 7.5 mg/day)	2.6%	9.0%	0.039

Notes: p values represent the significance of t, Mann Whitney and χ2 tests. Abbreviations: CRP – C-reactive protein; DAS – disease activity score; ESR – erythrocyte sedimentation rate; PhGA – physician global assessment; PtGA – patient global assessment; RA – rheumatoid arthritis; SDAI – simplified disease activity index; y – years.

TABLE 6. Reasons for stopping bo/bsDMARD (n = 202)

reason for switch off	AE (n = 13)	PNR (n = 33)	SNR (n = 51)	non-medical (n = 100)	other (n = 5)
biosimilar	6 (46.2%)	19 (57.6%)	21 (41.2%)	6 (6.0%)	2 (40.0%)
original	7 (53.8%)	14 (42.4%)	30 (58.8%)	94 (94.0%)	3 (60.0%)

Notes: variables are reported as "number of patients (percentage of subgroup)"; non-medical switch refers to changing an efficient and tolerated bo/bsDMARD with its/another biosimilar for cost reasons.
Abbreviations: AE – adverse event; bo/bsDMARD – biological original or biosimilar disease-modifying anti-rheumatic drugs; dPNR – primary non-responder; SNR – secondary non-responder.

switching to an original, 19.4% were previously receiving an original, 22.4% a biosimilar and 58.2% a bDMARDs without available biosimilars. Correspondingly, of the patients switching to a biosimilar molecule, 59.5% were on an original, 17.2% on another biosimilar and 23.7%% from bDMARDs without available biosimilars. Compared to patients switching to an original (Table 5), those switching to a biosimilar had a lower prevalence of men (15.0% versus 32.8%; p = 0.001), extra-articular manifestations (18.5% versus 28.4%; p = 0.080) and glucocorticoid treatment in doses above 7.5 mg/day prednisone-equivalent (2.6% versus 9.0%; p = 0.039), lower median acute phase reactants (CRP: 8 versus 15 mg/L; p = 0.043; ESR: 31 versus 40 mm/h; p = 0.036) and tender and swollen joint counts (6 versus 8; p = 0.068, respectively 2 versus 3; p = 0.120), and lower mean patient and physician global evaluations (49 versus 58 mm; p = 0.006; respectively 46 versus 54 mm; p = 0.017) and composite indices (DAS28: 4.6 versus 5.1; SDAI: 22.3 versus 27.6, p = 0.010 for both).

Patients switching off bo/bsDMARDs

During 2022, there were 202 switches off bo/bsDMARDs. Of note, 100 patients had a non-medical switch (Table 6), representing 44.1% of switches to a biosimilar and 34.0% of switches in general. Compared to patients stopping their boDMARD (Table 7), patients stopping their bsDMARD had a higher prevalence of men (29.6% versus 14.2.%; p = 0.012) and of glucocorticoids in doses above 7.5 mg/day prednisone-equivalent (9.3% versus 0.7%; p = 0.004), lower mean age (59.6 versus 62.4 years; p = 0.061) and disease duration (10.4 versus 17.2 years; p < 0.001), higher median tender and swollen joint counts (7 versus 6, p = 0.373; respectively 3 versus 2, p = 0.006) and acute phase reactants (CRP: 10.3 versus 5.9 mg/L, p = 0.013, respectively 35 versus 28 mm/h, p = 0.057).

CONCLUSION

The 2022 RRBR cohort allowed the observations of the predominance of etanercept and adalimumab for initiations of biosimilars, the fact that most entries on biosimilars originate from originals (including non-medical switches) and from bDMARDs without biosimilars and the historical effect of accumulation of patients manifested in the fact that originals still

TABLE 7. Differences and associations among patients switching from bo/bsDMARDs (n = 202)

	switch off biosimilar (n = 54)	switch off original (n =148)	p
age (y)	59.6 ± 9.8	62.4 ± 10.3	0.061
men	29.6%	14.2.%	0.012
RA duration (y)	10.4 ± 8.0	17.2 ± 8.3	0.000
tender joint count	7 (0-24)	6 (0-28)	0.373
swollen joint count	3 (0-20)	2 (0-23)	0.006
CPR (mg/L; normal < 5)	10.3 (0.3-276.6)	5.9 (0-162.8)	0.013
ESR (mm/h; normal < 20)	35 (5-130)	28 (2-130)	0.057
WBC (/µL; normal > 4)	6.9 ± 2.5	8.0 ± 3.2	0.012
glucocorticoids >7.5 mg/day	9.3%	0.7%	0.004

Notes: p values represent the significance of t, Mann Whitney and χ2 tests. Abbreviations: CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; RA – rheumatoid arthritis; WBC – white blood count; y – years.

dominate the group of patients continuing their treatment, with the exception of infliximab, while biosimilars tend to be continued in younger patients and in patients with shorter disease duration. Cases categorized more severe by both patients, their doctors and their disease activity were preferably reserved for originals, whether initiating a naïve patient or medically switching to a bo/bsDMARD or switching off their previous bo/bsDMARD. In patients continuing their previous bDMARD, biosimilars exhibited higher DAS28 and SDAI remission rates. RRBR data from 2022 confirm the market rise of biosimilars.

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