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Effectiveness of a Second Biologic After Failure of a Non–tumor Necrosis Factor Inhibitor As First Biologic in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** In rheumatoid arthritis (RA), evidence regarding the effectiveness of a second biologic disease-modifying antirheumatic drug (bDMARD) in patients whose first-ever bDMARD was a non–tumor necrosis factor inhibitor (TNFi) bDMARD is limited. The objective of this study was therefore to assess the outcome of a second bDMARD (non-TNFi: rituximab [RTX], abatacept [ABA], or tocilizumab [TCZ], separately; and TNFi) after failure of a non-TNFi bDMARD as first bDMARD.

Methods. We identified patients with RA from the 5 Nordic biologics registers who started treatment with a non-TNFi as first-ever bDMARD but switched to a second bDMARD. For the second bDMARD, we assessed drug survival (at 6 and 12 months) and primary response (at 6 months).

Results. We included 620 patients starting a second bDMARD (ABA 86, RTX 40, TCZ 67, and TNFi 427) following failure of a first non-TNFi bDMARD. At 6 and 12 months after start of their second bDMARD, approximately 70% and 60%, respectively, remained on treatment, and at 6 months, less than one-third of patients were still on their second bDMARD and had reached low disease activity or remission according to the Disease Activity Score in 28 joints. For those patients whose second bMDARD was a TNFi, the corresponding proportion was slightly higher (40%).

Conclusion. The drug survival and primary response of a second bDMARD in patients with RA switching due to failure of a non-TNFi bDMARD as first bDMARD is modest. Some patients may benefit from TNFi when used after failure of a non-TNFi as first bDMARD.

Key Indexing Terms: biologics, disease-modifying antirheumatic drugs, rheumatoid arthritis, therapy

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In rheumatoid arthritis (RA), the first-line biologic disease-modifying antirheumatic drug (bDMARD) is often a tumor necrosis factor inhibitor (TNFi). This is mainly due to clinical experience and the availability of long-term data.[1,2] However, in clinical practice non-TNFi bDMARDs, with different mechanisms of action, are also used as first-line bDMARD, especially in the presence of absolute or relative contraindications for choosing a TNFi, such as history of malignancy.[3] Regardless of the choice of first bDMARD, many patients will eventually discontinue treatment.[4]

In contrast to the existing evidence guiding the choice of treatment in patients who have failed a TNFi as first bDMARD, evidence regarding the effectiveness of another non-TNFi, or a TNFi bDMARD, in patients who have failed a non-TNFi as first bDMARD is limited, as highlighted in the latest recommendations on the treatment of RA from the European Alliance of Associations for Rheumatology (EULAR).[5]

This clinically relevant question has not been explored in randomized trials; thus, observational data from real-life registers are necessary. Further, due to the predominance of TNFi as first bDMARDs, such an observational study necessitates a collaborative effort, where data from several registers are combined.[6] We took advantage of a Nordic collaboration across biologics registers to characterize patients with RA who, after failure (regardless of reason) of a non-TNFi bDMARD as first-ever bDMARD, switched either to a new non-TNFi or to a TNFi as second bDMARD, as outlined in Figure 1. Specifically, we aimed at assessing, overall and for each bDMARD, the drug survival and primary response of this second bDMARD.

METHODS

Study population. From the 5 Nordic biologic registers (SRQ, Sweden; DANBIO, Denmark; ROB-FIN, Finland; NOR-DMARD, Norway; and ICEBIO, Iceland) we identified patients ≥ 18 years of age with a rheumatologist-based diagnosis of RA who had started a non-TNFi (rituximab [RTX], abatacept [ABA], or tocilizumab [TCZ]) as first-ever bDMARD between January 1, 2010, and December 31, 2018. Since all 5 TNFi (infliximab, adalimumab, etanercept, certolizumab pegol, or golimumab) have the same cytokine target and similar overall effectiveness, we combined these in 1 group. The study period was selected to ensure that all 3 non-TNFi bDMARDs were approved and available for prescription. Patients had to have at least 12 months of potential follow-up in the registers for all treatment episodes under study. Further, patients had to have started their second bDMARD within 3 months after the discontinuation of the first, with the exception of RTX, for which a 6-month window was used. Patients switched to either an alternative non-TNFi bDMARD or to a TNFi.

Data collection. We collected data on demographics and clinical characteristics (age, sex, disease duration, rheumatoid factor, anticitrullinated protein antibodies [anti-CCP]) from the biologics registries. Information about concomitant use of conventional synthetic DMARDs (csDMARDs) such as methotrexate, sulfasalazine, leflunomide, as well as use of glucocorticoids (GCs), was also collected at initiation of the second bDMARD (considered as baseline). We collected disease activity scores based on the Disease Activity Score in 28 joints (DAS28) and Clinical Disease Activity Index (CDAI) for all patients at baseline and after 3 and 6 months' treatment. To comply with the visit pattern in clinical practice, we defined the time window for the evaluation timepoints as 60–150 days from baseline for the 3-month visit (with preference to the visit closest to 90 days), and 150–240 days from baseline for the 6-month visit (with preference for the visit closest to 180 days). Information on reasons for switching/stopping the first bDMARD (e.g., lack/loss of effect, intolerance) was collected.

Endpoints. Drug survival of the second bDMARD was based on the start and stop dates in the clinical register, with the following edits: the drug was assumed to be discontinued at the start of another (third) bDMARD; and a stop with recorded reason "remission" was not counted as stopping, but the patient was considered to remain on therapy until starting another bDMARD. A switch between originator and biosimilar (of the same compound) was not considered discontinuation. Stops due to pregnancy or death were treated as censoring events. We analyzed all drugs combined, as

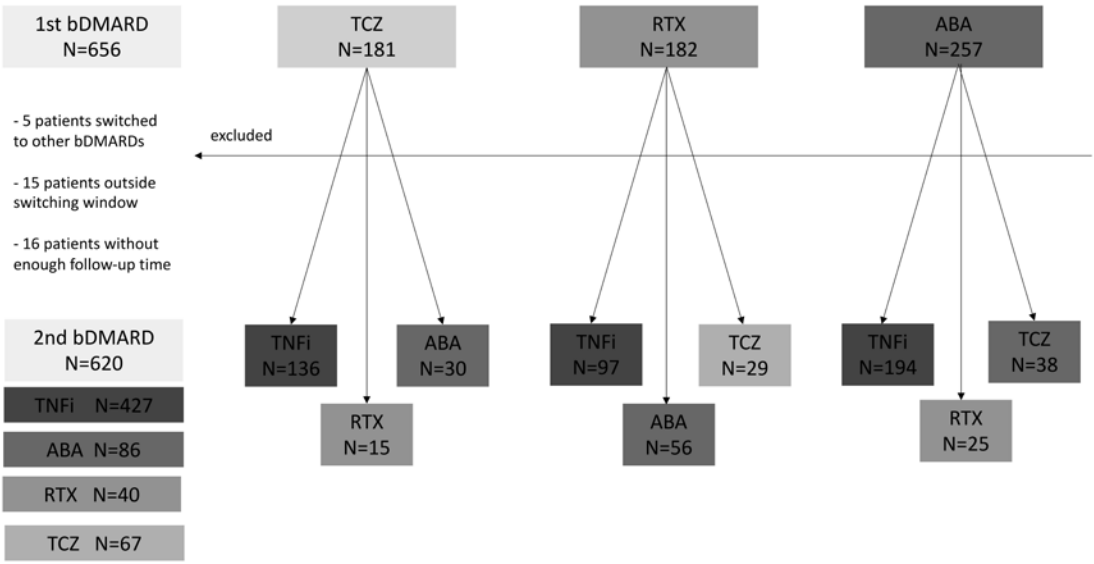

Figure 1. Flowchart of the 620 patients with RA from the 5 Nordic countries who started a second bDMARD (TNFi [infliximab, adalimumab, etanercept, golimumab or certolizumab pegol], RTX, ABA, or TCZ) after failure of a non-TNFi as first-ever bDMARD. ABA: abatacept; bDMARD: biologic disease-modifying antirheumatic drug; RA: rheumatoid arthritis; RTX: rituximab; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor.

well as each non-TNFi bDMARD separately, but merged the 5 TNFi into 1 group

We assessed crude response rates at 6 months for EULAR DAS28 response, DAS28 low disease activity (LDA) or remission, and CDAI LDA or remission. For the 6-month evaluation of treatment outcome, we prioritized 6-month data over 3-month data when available, but when no such data were available, we used data from the 3-month visit carried forward.

In a treat-to-target paradigm, drug survival may be used to approximate treatment response, as individuals who do not respond will often be moved to an alternative therapy. We therefore chose response endpoints that combined treatment response and drug discontinuation, essentially imputing response for those no longer on therapy at a specific timepoint as "nonresponse." The following combined endpoints (yes/no) were used: (1) remaining on drug at 6 and 12 months after initiation of therapy (reason for discontinuing was also tabulated); (2) a combined endpoint of remaining on drug and reaching EULAR good response; (3) a combined endpoint of remaining on drug and achieving DAS28 LDA or remission; and (4) a combined endpoint of remaining on drug and achieving CDAI LDA or remission. In addition, the LUNDEX-corrected responses ([fraction of initiators still on drug at 6 months] × [fraction responding at 6 months]) were calculated.[7]

Statistical analysis. Country-specific data were pooled. Descriptive statistics for continuous variables (age, disease duration, DAS28, CDAI, Health Assessment Questionnaire) are presented as mean ± SD for normally distributed variables and medians (IQR) for non-normally distributed variables. Categorical variables (sex, rheumatoid factor, anti-CCP, percent of concomitant csDMARDs [yes/no], and percent of oral concomitant GCs [yes/no]) are presented as frequencies and percentages. These data were tested as predictors for treatment assignment, drug survival, and treatment response. Differences between groups were analyzed using Kruskal-Wallis, ANOVA, and chi-square tests.

We used Kaplan-Meier estimates to assess drug survival. We also performed Cox regression analyses to adjust for baseline differences across groups. Sequences such as ABA-ABA could not occur. For all analyses, we used SPSS (version 25; IBM Corp.). The appropriate ethical committees and/or data protection committees in each country approved of the study (Sweden: 2015/1844-31/2; Denmark: RH-2015–209, I-suite 04145; Norway: 2011/1339 and 2017/243; Finland: 73/13/03/00/2014; Iceland: VSNb2017010049/03.01). Individual patient consent was not required; patients give their consent before inclusion in the registries.

RESULTS

We identified 656 patients who switched from a non-TNFi as first bDMARD to a second bDMARD. Among these, 36 patients were excluded for various reasons, leaving 620 patients eligible for analysis: 86 starting ABA, 40 starting RTX, 67 starting TCZ, and 427 starting a TNFi as second bDMARD (Figure 1). Patient characteristics at the time of start of the second bDMARD are summarized in Table 1. Patients starting ABA as their second bDMARD were older and had longer disease duration compared to initiators of the other bDMARDs. Patients starting TCZ had higher disease activity as assessed by DAS28, and were less likely to have concomitant csDMARDs but more likely to have concomitant GCs (Table 1). The number of patients with available information is shown in Supplementary Table 1 (available from the authors on request). Reason for discontinuation of the first bDMARD is summarized in Supplementary Table 2.

Drug survival. The percentage of patients remaining on treatment after 6 and 12 months from start of second bDMARD was 69% and 56%, respectively, for all bDMARDs (Table 2, Figure 2). Drug survival for the whole observation period was similar for TNFi, RTX, TCZ, and ABA ($P = 0.6$; Figure 2). In the multivariate Cox regression model (including the bDMARD started as second drug [ABA, RTX, TCZ, any TNFi], disease duration, concomitant csDMARDs, concomitant GCs, and DAS28 at baseline), concomitant csDMARD was the only covariate that in itself was statistically significantly associated with drug survival (risk ratio 0.81, 95% CI 0.65–0.95). In each of the 4 bDMARD groups, approximately 50% of patients discontinued due to lack of effectiveness (Table 3).

Table 1. Patient characteristics at start of second bDMARD after failure of a non-TNFi bDMARD as first ever bDMARD in 5 Nordic RA registers during 2010–2018.

	Second bDMARD				
	RTX, n = 40	ABA, n = 86	TCZ, n = 67	TNFi, n = 427	Overall, n = 620
Age, yrs, mean ± SD	59 ± 16	62 ± 14	59 ± 12	58 ± 13	58 ± 13
Sex, % female	80	91	90	91	90
Disease duration, yrs, median (IQR)	5 (2–10)	9 (4–20)	6 (3–13)	5 (2–10)	5 (2–12)
RF-positive, %	84	81	80	78	79
Anti-CCP–positive, %	100	74	68	72	73
Survival-on-drug of 1st bDMARD, months, median (IQR)	12 (5–30)	11 (4–27)	8 (4–17)	8 (4–14)	8 (4–16)
Concomitant csDMARDs, %	39	42	37	56	51
MTX (% of all csDMARDs)	87	70	72	82	80
Concomitant GCs, %	28	33	46	28	30
DAS28 baseline, mean ± SD	4.3 ± 1.4	4.3 ± 1.0	5.1 ± 1.1	4.3 ± 1.3	4.4 ± 1.3
CDAI baseline, mean ± SD	22.5 ± 12.4	19.8 ± 9.7	25.7 ± 12.4	20.4 ± 11.4	20.9 ± 11.4
HAQ baseline, mean ± SD	1.2 ± 0.7	1.3 ± 0.7	1.5 ± 0.7	1.2 ± 0.7	1.3 ± 0.7

ABA: abatacept; anti-CCP: anticitrullinated protein antibody; bDMARD: biologic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; GC: glucocorticoids; HAQ: Health Assessment Questionnaire; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; RTX: rituximab; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor (infliximab, adalimumab, etanercept, golimumab, or certolizumab pegol).

Table 2. Treatment outcomes of clinical effectiveness of second bDMARD when the first bDMARD was a non-TNFi among patients with RA in the 5 Nordic registers in 2010–2018.

Patients	Second bDMARD				
	RTX, n = 40	ABA, n = 86	TCZ, n = 67	TNFi, n = 427	Overall, n = 620
Still on drug at 6 months from start of second bDMARD	73	69	66	70	69
Still on drug at 12 months from start of second bDMARD	63	49	54	57	56
EULAR good response at 6 months	8	17	25	26	24
DAS28 LDA or remission at 6 months	37	34	43	49	45
CDAI LDA or remission at 6 months	40	45	30	36	37
Still on therapy + EULAR good response at 6 months	6	12	16	22	19
Still on therapy + DAS28 LDA or remission at 6 months	30	25	31	40	37
Still on therapy + CDAI LDA or remission at 6 months	33	32	22	31	30
LUNDEX-corrected EULAR response at 6 months	6	12	17	18	17

Values are expressed as %. ABA: abatacept; bDMARD: biologic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; EULAR: European Alliance of Associations for Rheumatology; LDA: low disease activity; RA: rheumatoid arthritis; RTX: rituximab; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor (infliximab, adalimumab, etanercept, golimumab or certolizumab pegol).

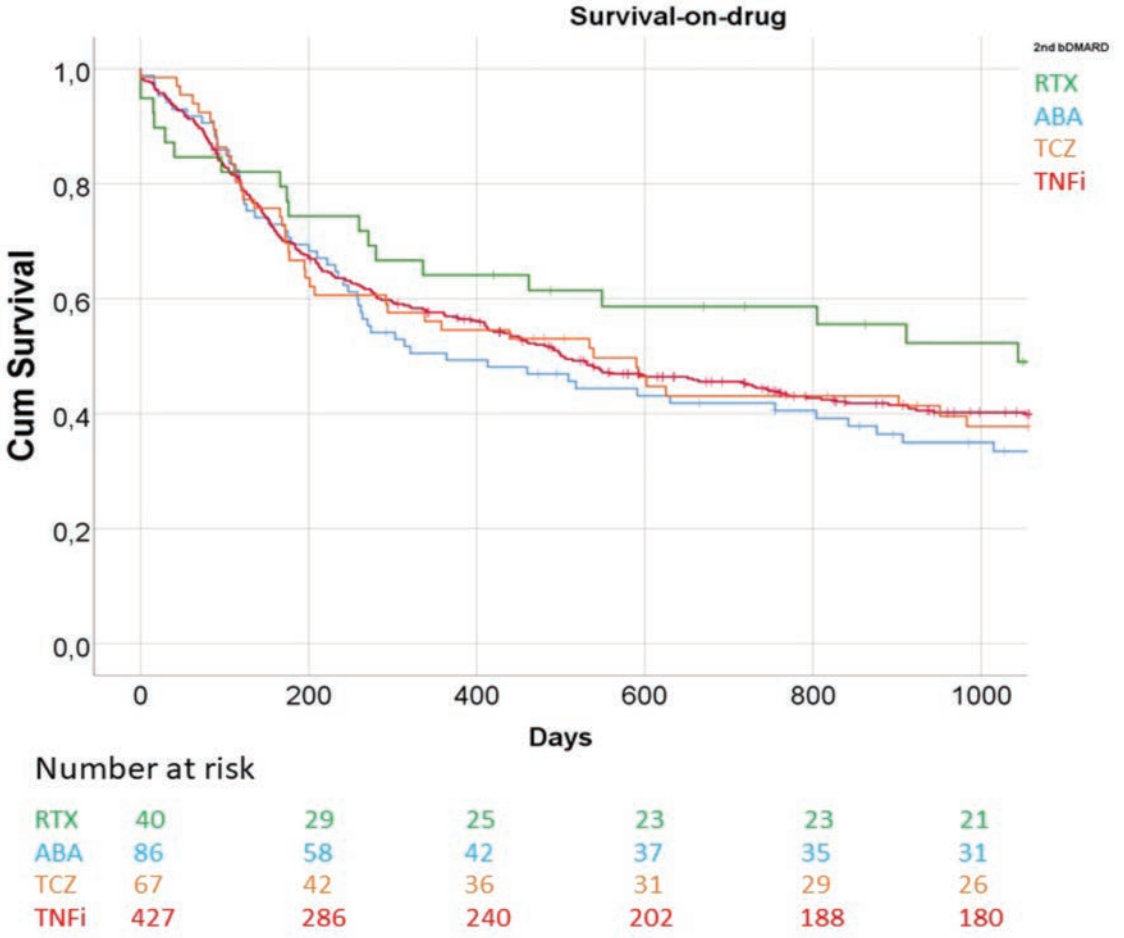

Figure 2. Drug survival for RTX, TCZ, ABA, and TNFi as second bDMARDs after the failure of a non-TNFi as first bDMARD, among 620 patients with RA identified in the biologics registers of 5 Nordic countries. ABA: abatacept; bDMARD: biologic disease-modifying antirheumatic drug; Cum: cumulative; RA: rheumatoid arthritis; RTX: rituximab; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor.

Table 3. Reason of discontinuation of RTX, ABA, TCZ and TNFi as second bDMARD in patients who failed a non-TNFi as first bDMARD.

	RTX, n = 23	ABA, n = 58	TCZ, n = 42	TNFi, n = 247	Overall, n = 371
Lack/loss of effectiveness	48	55	43	53	52
Intolerance	13	10	17	29	23
Other *	39	35	40	18	25

Values are expressed in %. * For most of these patients the reason was unknown (specified in the register as "unknown"), whereas for a minority of the patients it was the patient's decision. Other reasons could include compliance and comorbidity. ABA: abatacept; RTX: rituximab; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor (infliximab, adalimumab, etanercept, golimumab or certolizumab pegol).

Primary response. Overall, 30% of all patients were still on their second bDMARD and had reached CDAI LDA or remission at 6 months. The percentages of patients remaining on drug and having attained a EULAR good response were lower (Table 2). For all bDMARDs, less than one-third of patients were still on drug and had reached LDA or remission according to DAS28, apart from TNFi-treated patients for which the percentage was slightly higher (40%).

We performed a sensitivity analysis stratifying our cohort to 2 time periods (2010–2014 and 2015–2018), observing similar results (data not shown). The proportion of missingness of treatment outcome for DAS28 was around 20% and around 50% for CDAI. Missingness did not differ across treatment groups (Supplementary Table 3, available from the authors on request). We stratified the results per country and found similar results in each (data not shown).

DISCUSSION

According to the EULAR treatment recommendations for RA, a bDMARD should be added in patients with RA who have not reached the treatment target with the first csDMARD strategy, and all approved bDMARDs can be used without hierarchical positioning.[5,8,9] Current practice in this situation is to start with a TNFi. However, a number of patients will instead start a non-TNFi for various reasons, including contraindications to TNFi.[4] TCZ has been used as first-line bDMARD when used as monotherapy. Importantly, however, evidence regarding the effectiveness and safety of a TNFi or an alternative non-TNFi bDMARD (ABA, RTX, TCZ) after a non-TNFi bDMARD has failed is very limited. To our knowledge, this is the first study specifically assessing treatment outcomes of available bDMARDs approved and used in clinical practice for the treatment of patients with RA as second bDMARDs after the discontinuation of a non-TNFi bDMARD used as first bDMARD. Some observations regarding baseline (start of the second bDMARD) characteristics, such as the higher percentage of female patients and the low percentage of patients receiving concomitant csDMARDs, suggests that our study population is not a typical RA cohort, but rather a selection of patients (e.g., for some of whom a TNFi was contraindicated).

Our results indicate that approximately 50% of patients remained on the second bDMARD at 1 year after switching to this treatment. With respect to individual drugs, none of the different modes of action was associated with superior drug survival in the multivariable Cox regression analysis. On the other hand, lack of power should be acknowledged as a possible reason for lack of statistical significance. Interestingly, concomitant treatment with a csDMARD was the only factor linked with superior drug survival. There was a trend of better drug survival with RTX. However, patients on RTX were often seropositive, and it has been shown that seropositivity, and mainly anti-CCP positivity, is associated with better response to RTX.[10] In addition, interpretation of drug survival for RTX is challenging due to the difficulty in defining discontinuation. Our source of information on treatment discontinuation was the physician's recorded decision to stop treatment. There is a risk that a patient would remain registered on RTX treatment, even though no additional treatment courses would be administered, if that patient would not start on a new bDMARD.

With respect to response, the overall response was moderate to poor, with at most one-third of patients achieving CDAI LDA or remission while remaining on therapy, whereas the percentage of patients remaining on drug and achieving EULAR good response ranged from 6% to 22%. It has previously been shown that the effectiveness of bDMARDs and drug survival diminish parallel to the line of treatment.[11,12] In a study from the national Swedish register assessing the effectiveness of a second TNFi after the failure of 1 TNFi as first-line bDMARD, almost 40% of patients with RA achieved LDA or remission, and the drug survival was slightly better, with approximately 60% of patients remaining on treatment at 12 months.[13] In another study from the national Swedish register ARTIS comparing non-TNFi bDMARDs to TNFi, both as first-line bDMARDs and as second line after the failure of a TNFi, drug survival at 1 year for TNFi and non-TNFi was approximately 70% and 80%, respectively.[4] After switch from a first TNFi, RTX and TCZ, but not ABA, were consistently associated with significantly better drug survival and response. Although it is hard to indirectly compare results across studies, slightly worse results were observed in the present study. This could potentially be explained by differences in patient population, representing a more difficult-to-treat population of patients with RA. Indeed, in the Frisell, *et al* study,[4] patients starting TNFi compared with non-TNFi were younger, more

well educated, had lower disease activity, and had fewer comorbidities, all of which would contribute to a superior (observed) drug survival.

A somewhat unexpected observation in the current study was that after the failure of a non-TNFi as first bDMARD, the most commonly used second bDMARD (69%) was a TNFi. In many cases, a non-TNFi would be chosen as first-line bDMARD due to presence of contraindications, such as malignancy or intolerance to concomitant csDMARDs (in the case of TCZ[14]). The finding of the present study implies that many such contraindications are relative rather than absolute (e.g., based on absence of evidence), and that in some cases it might be other, nonmedical reasons, such as the cost of a particular bDMARD, that drives treatment choices; local treatment protocols can change and put a particular bDMARD as first-line bDMARD if it is appreciably less expensive.[15] Both local treatment protocols and costs vary from country to country and even within each country and across years.

To our knowledge, this is the first study addressing the important clinical question of how TNFi and non-TNFi perform after failure of a non-TNFi as first bDMARD. Studies on rare treatment exposures require collaborative efforts, such as in this 5-country collaboration. The similar register structure, underlying healthcare systems, and homogeneity of data collection and the way they are collected, are significant strengths of this study. The results of our study provide information on the outcome of bDMARDs following a failed attempt with a non-TNFi as first bDMARD. We demonstrate that—across all drugs—the effectiveness and retention of this second bDMARD is modest.

One limitation is the observational cohort study design, as patients were not randomly allocated to a specific bDMARD agent, which might cause confounding by indication. Although all patients were equally selected in terms of not having used a TNFi as their first bDMARD, we cannot exclude the risk of selection bias regarding the choice of the second bDMARD. The treatment groups under comparison were not entirely balanced for baseline characteristics and some differences were observed that might introduce the risk for confounding, such as seropositivity for RTX. Other unknown baseline factors may also differ between the drugs. In our study, missingness regarding the DAS28 was limited to approximately 20%, but a higher missingness was observed regarding the CDAI, due to the lack of physician global assessment scores in some of the data sources. Missingness, however, did not differ between drugs. Since the vast majority of patients with RA who start a first-ever bDMARD start a TNFi, the number of patients eligible for our assessment was inherently limited. Thus, despite a collaborative effort across registers, it is difficult to reach a study population size that permitted more sophisticated modeling. For all of the above reasons, we therefore focused on a simple, descriptive analysis and did not embark on a full comparative effectiveness analysis, nor do we claim to provide such results. Instead, we present absolute proportions and effectiveness scores for each of the drugs. In the almost complete absence of data from this treatment setting, we consider these results of clinical interest.

To conclude, the 6- and 12-month drug survival and the effectiveness at 6 months of a second bDMARD in patients with RA switching due to failure of a non-TNFi bDMARD as first-ever bDMARD was modest. Concomitant csDMARD treatment was associated with longer drug survival. Further, TNFi was associated with the better point estimate (although not statistically significant).

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DATA SHARING POLICY

All data relevant to the study are included in the article or in the supplementary information (available from the authors on request).

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