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Original article

Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis

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Abstract

Objective. To compare the effectiveness of biologics after rituximab (RTX) treatment in RA.

Methods. The effectiveness of TNF-α inhibitors (TNFi), abatacept (ABA) or tocilizumab (TCZ) was examined in patients previously treated with RTX using clinical data collected in the Collaborative Registries for the Evaluation of Rituximab in RA Collaborative registry. Patients had stopped RTX 6 months or less prior to the new biologic and had a baseline visit within 21 days of starting the new biologic.

Results. Two hundred and sixty-five patients were analysed after 6 months of treatment. Patients on TCZ ($n = 86$) had a greater decline of DAS28-ESR and clinical disease activity index than patients on TNFi ($n = 89$) or ABA ($n = 90$). This effect was also seen after adjusting for baseline prednisone use and the number of previous biologics. The mean DAS28-ESR scores in patients on TCZ were 1.0 (95% CI: 0.2, 1.7) and 1.8 (95% CI: 1.0, 2.5) points lower than in patients on TNFi or ABA, respectively. In patients on TCZ, the clinical disease activity index was 9.4 (95% CI: 1.7, 16.1) and 8.1 (95% CI: 0.9, 15.3) points lower than on TNFi and ABA, respectively. Patients on TCZ more frequently had good EULAR responses than patients on TNFi or ABA (66 *vs* 31 *vs* 14%, $P < 0.001$). The HAQ disability index improved in all treatment groups ($P < 0.001$), but did not differ between biologics, as did drug retention rates. The reasons for discontinuation of RTX and the number of previous biologics had no influence on outcomes.

Conclusion. In this observational cohort of patients who discontinued RTX, TCZ provided a better control of RA than ABA or TNFi.

Key words: rheumatoid arthritis, biologic drugs, disease activity, rituximab, tocilizumab.

CLINICAL SCIENCE

Rheumatology key messages

- This study is the largest assessing treatment effectiveness of biologic DMARDs after rituximab in RA patients.
- After rituximab discontinuation, tocilizumab provided a better control of RA than abatacept or TNF-α inhibitors.

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Introduction

The development of biologic DMARDs (bDMARDs) has represented a major therapeutic advance in the management of RA, because bDMARDs are effective in improving the symptoms and signs of RA and in preventing structural joint damage. bDMARDs with different modes of action have become available; for example, TNF-α inhibitors (TNFi), a B-cell depleting antibody [rituximab (RTX)], an inhibitor of co-stimulatory mechanisms [abatacept (ABA)] and an IL-6 antagonist [tocilizumab (TCZ)]. One bDMARD may be switched to another with a different mode of action, particularly in cases of failure or recurrence of class-associated side effects. With the growing availability of expensive therapeutic agents in RA, it becomes increasingly important to tailor the treatment to the individual patient in order to maximize the cost–benefit and minimize time on suboptimal therapies.

Observational studies suggest that in the case of active RA despite biologic treatment, switching to a new drug class may be more effective than switching to a bDMARD with the same mode of action [1–3]. In RA patients with inadequate response to TNFi, the efficacy of other bDMARD classes, such as ABA, RTX or TCZ, has been examined in large randomized controlled trials [4–6], but data from randomized studies are not available for patients failing RTX. Furthermore, there is a lack of information about the effectiveness and safety of cycling strategies in patients who have failed second- or third-line bDMARDs. This makes it difficult for physicians to choose the most effective therapeutic strategy for patients who have been exposed to several bDMARDs. Given that most studies with regard to bDMARDs after B-cell depletion have focused on drug safety [7, 8] and there is a paucity of information on effectiveness, we aimed to analyse the effectiveness of switching to alternative modes of action after RTX discontinuation.

Methods

Study population and design

The European Collaborative Registries for the Evaluation of Rituximab in RA (CERERRA) registry is an investigator-led, industry-supported, prospective, longitudinal, multinational database with the aim of evaluating the clinical aspects of RTX use in patients with RA [9]. CERERRA also follows RA patients after treatment with RTX. The CERERRA registry was approved by the local ethics committees, and patients provided written informed consent according to national guidelines. No additional ethical approval was required for our analysis. For the purpose of this study, CERERRA patients were included if they started the new bDMARD within 6 months after the last RTX infusion and had a baseline visit within 21 days of commencement of the new bDMARD and a 6 month follow-up visit (±3 months).

We aimed to analyse the change in RA activity in patients who switched from RTX to TNFi, ABA or TCZ. The effectiveness of these treatments was assessed by the predefined disease activity scores, that is, reduction in the DAS28-ESR, the clinical disease activity index (CDAI) and the HAQ disability index (HAQ-DI) between the baseline visit and the 6 months follow-up visit (±3 months). In addition, EULAR response rates were calculated and compared at 6 months follow-up for the treatments. We also selected *a priori* the reason for switching and the number of previous bDMARDs as potential treatment effect modifiers.

Statistical analysis

Categorical variables were reported as frequencies and compared by means of Pearson's χ^2 tests or Fisher's exact tests. Continuous variables following a normal distribution were reported as means and SD. and compared by Student's *t*-test or analysis of variance. For non-normally distributed continuous variables, data were presented as medians and interquartile ranges (IQR) and compared using the Mann–Whitney *U*-test or Kruskal–Wallis test.

Multivariable linear regression was used to adjust for potential confounders across the three categories of bDMARDs. Missing data of potentially confounding variables included in the regression models were imputed using multiple imputations with chained equations [10].

Drug discontinuation rates were calculated by the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed with Stata/IC 13.1 (StataCorp, College Station, TX, USA).

Results

A total of 4356 patients (median follow-up time 13 months, IQR 5.3–30.2) were included in the CERERRA registry between January 2005 and the time of censoring in September 2013; 543 (12.5%) of these patients had started TNFi, ABA or TCZ after the administration of RTX. Of these, 161 patients had no baseline visit recorded within 21 days of the start of the new bDMARD, 79 patients had no follow-up visit and 38 patients had stopped RTX >6 months prior to the start of the bDMARD, leaving 265 patients for analysis. The CERERRA patients not included in this analysis were of a similar age and had a similar RA duration compared with the patients included; likewise, the reason for stopping RTX as well as the number of previous bDMARDs and the dose of concomitant prednisone were comparable (data not shown).

The 265 patients included were recruited by seven European registries, that is, from Denmark (101 patients), Sweden (59 patients), the Czech Republic (47 patients), Switzerland (27 patients), Finland (14 patients), Portugal (nine patients) and Slovenia (eight patients). Eighty-eight per cent of the patients included in the analysis had their baseline visit on the same day they started the new bDMARD (TNFi: 89%; ABA: 89%; TCZ: 86%) and in only 6% of the patients the baseline data were collected within 21 days after the patients were started on the new bDMARD. The majority of patients (78%) had stopped RTX owing to ineffectiveness, 14% because of an adverse event, and the remaining 8% stopped for other reasons.

Table 1 Baseline characteristics by treatment assignment in patients who had stopped rituximab and were then started with TNF-α inhibitors, tocilizumab or abatacept

Characteristic	*n*	All patients (*n* = 265)	TNFi (*n* = 89)	ABA (*n* = 90)	TCZ (*n* = 86)	*P*-value
Female, %	265	57.0	61.8	57.8	51.2	0.36
Age, mean (S.D.), years	264	55.0 (12.2)	56.3 (12.3)	55.6 (12.0)	53.2 (12.2)	0.26
RA duration, median (IQR), years	257	12.0 (7.0–17.2)	12.7 (5.0–19.0)	11.7 (8.0–17.5)	12.0 (7.0–17.0)	0.91
RF positive, %	252	72.6	70.2	72.4	75.3	0.77
Anti-CCP positive, %	106	73.6	68.4	78.8	74.3	0.61
Number of bDMARDs prior to RTX, %						
0	219	11.4	13.5	17.6	2.8	0.08
1		25.6	29.7	21.6	25.4	
2		32.9	32.4	29.7	36.6	
⩾3		30.1	24.3	31.1	35.2	
Prednisone use, %	264	65.5	68.5	71.9	55.8	0.06
Prednisone dose, median (IQR), mg	264	7.0 (5.0–10.0)	6.3 (5.0–10.0)	7.5 (5.0–10.0)	5.0 (5.0–10.0)	0.50
MTX use, %	264	63.3	62.9	64.0	62.8	0.98
LEF use, %	264	11.0	12.4	12.4	8.1	0.59
Other sDMARD use, %	264	17.4	22.5	13.5	16.3	0.27
No concomitant sDMARD use, %	264	22.4	19.1	20.2	27.9	0.32
RTX stopped due to ineffectiveness, %	239	78.2	80.0	80.0	74.7	0.65

ABA: abatacept; bDMARD: biologic DMARD; *n*: number of patients with available information for each variable; IQR: interquartile range; RTX, rituximab; sDMARD: synthetic DMARD; TCZ: tocilizumab; TNFi: TNF-α inhibitors.

Of the 265 patients, 90 patients were prescribed ABA, 86 were started on TCZ and the remaining 89 patients on TNFi [38 (42.7%) on etanercept, 23 (25.8%) on adalimumab, 18 (20.2%) on infliximab, six (6.7%) on certolizumab and four (4.5%) on golimumab]. The demographics and baseline disease characteristics as well as the use of concomitant MTX, LEF or other synthetic DMARD (sDMARD) were similar between the treatment groups (Table 1). However, patients in the TCZ group tended to be slightly younger and more often male, although there was no statistical difference between the groups. Patients on TCZ also tended to have a higher number of previous bDMARDs and a lower frequency of prednisone use than patients who were subsequently administered other bDMARDs.

The median time between the baseline and the follow-up visit was 24.6 weeks (IQR 20.1–28.1). The follow-up period was similar between the treatment groups, ranging from 24.4 weeks in the TNFi and ABA groups to 24.6 weeks in the TCZ group.

At the follow-up visit, 59.0% of patients received MTX (TNFi: 58.6%; ABA: 59.5%; TCZ: 58.8%; $P = 0.99$) and 9.4% received LEF (TNFi: 7.1%; ABA: 13.5%; TCZ: 7.4%; $P = 0.33$). Overall, 14.6% of patients received another sDMARD at the follow-up visit (TNFi: 17.1; ABA: 16.2; TCZ: 10.3; $P = 0.47$). Of the patients, 29.7% did not take any concomitant sDMARD at the follow-up visit (TNFi: 28.6%; ABA: 25.72%; TCZ: 35.3%; $P = 0.47$).

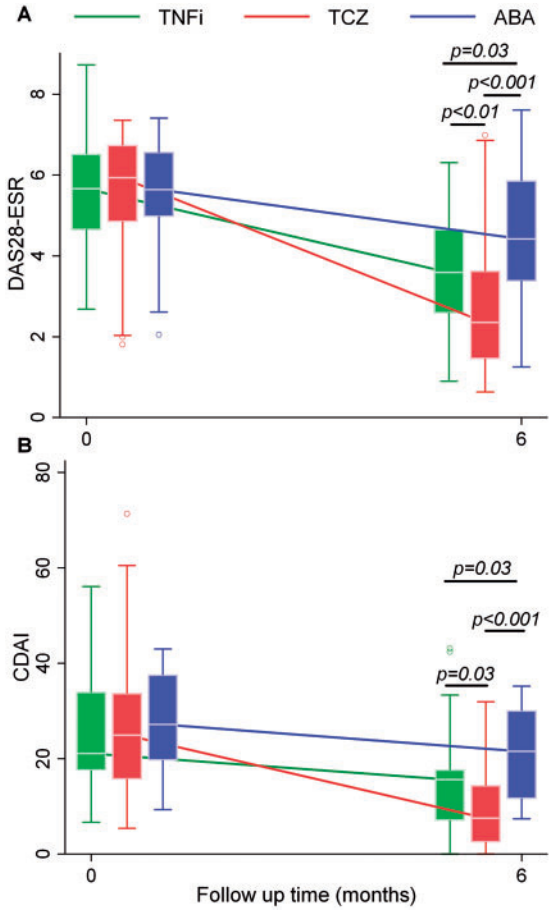
At follow-up, 66.0% of patients used prednisone (median dose 5 mg, IQR 5–10); 71.4% of patients in the TNFi group, 68.9% in the ABA group and 57.4% in the TCZ group ($P = 0.18$). The median dosage was 5 mg (IQR 5–7.5), 7.5 mg (IQR 5–10) and 5 mg (IQR 5–7.5), respectively ($P = 0.01$).

Improvement of DAS28-ESR

At baseline, the median DAS28-ESR was 5.7 (IQR 4.8–6.6) among all patients and was similar across treatment groups ($P = 0.97$; Fig. 1). Numerically, patients in the TCZ group had the highest baseline DAS28-ESR (5.9, IQR 4.9–6.7) and patients on ABA the lowest baseline DAS28-ESR (5.6, IQR 5.0–6.6). After 6 months of treatment, the DAS28-ESR in all groups had declined significantly ($P < 0.001$ in each treatment group). At follow-up, the DAS28-ESR of patients treated with TCZ was lower than that of patients exposed to the other bDMARDs; furthermore, in patients on TNFi the DAS28-ESR decline was greater than in those treated with ABA. The average decrease of the DAS28-ESR in all patients was 1.9 (S.D. 1.6). Among the different bDMARDs, the greatest decline of the DAS28-ESR was observed in the TCZ group (2.9, S.D. 1.8), followed by 2.0 (S.D. 1.3) in the TNFi group and 1.1 (S.D. 1.4) in the ABA group. The difference in the DAS28-ESR scores between the treatment groups was not driven solely by the rapid decrease of ESR in the TCZ group, because the median decline of the swollen joint count and the decrease in the tender joint count were greatest and significant in the TCZ group (data not shown).

The overall decline as well as the differences in the treatment groups were also seen after adjusting for age, sex, baseline prednisone use and the number of previous bDMARDs; compared with patients on TCZ, the average decline in DAS28-ESR was 1.0 (95% CI: 0.2, 1.7) units

Fig. 1 Decline of DAS28-ESR and clinical disease activity index after 6 months of treatment with TNF-α inhibitors, tocilizumab or abatacept



Boxes represent the 25th, 50th and 75th percentiles; whiskers define the lowest and highest data point within 1.5 interquartile range. ABA: abatacept; CDAI: clinical disease activity index; TCZ: tocilizumab; TNFi: TNF-α inhibitors.

smaller in patients on TNFi and 1.8 (95% CI: 1.0, 2.5) units smaller in patients on ABA.

At baseline, only ~5% of all patients were either in DAS28-ESR remission, defined as a DAS28-ESR of <2.6, or had a low disease activity (2.6 to ⩽3.2; Table 2) [11]. Thus, the vast majority of subjects had either a moderate (3.2 to ⩽5.1) or a high baseline disease activity (>5.1), and the distribution of disease activity was similar across all treatment groups at baseline ($P = 0.71$). Six months after the new bDMARD had been started, however, the distribution of disease activity varied significantly between the treatment groups ($P < 0.001$), because <20% of patients in the ABA group and 36% in the TNFi group were either in DAS remission or had low disease activity, compared with >70% of patients on TCZ.

Table 2 Proportions of patients in DAS28-ESR and clinical disease activity index categories before and 6 months after switching to new biologic DMARDs

Category	All patients	TNFi	ABA	TCZ	*P*-value
DAS28-ESR at baseline, %					
Remission	2.7	0	2.4	6.9	0.71
Low activity	2.7	5.1	2.4	0	
Moderate activity	26.4	28.2	26.1	24.1	
High activity	68.2	66.7	69.1	69.0	
DAS28-ESR at 6 months, %					
Remission	30.9	25.5	14.3	62.1	<0.001
Low activity	7.3	10.3	2.4	10.3	
Moderate activity	39.1	46.2	45.2	20.7	
High activity	22.7	18.0	38.1	6.9	
CDAI at baseline, %					
Remission	0	0	0	0	0.28
Low activity	8.1	4.0	9.1	10.0	
Moderate activity	33.3	48.0	18.2	32.5	
High activity	58.6	48.0	72.7	57.5	
CDAI at 6 months, %					
Remission	16.1	8.0	0	30.0	0.001
Low activity	28.7	36.0	18.2	30.0	
Moderate activity	34.5	40.0	31.8	32.5	
High activity	20.7	16.0	50.0	7.5	

DAS28-ESR categories: remission <2.6; low disease activity 2.6 to ⩽3.2; moderate disease activity 3.2 to ⩽5.1; and high disease activity >5.1. CDAI categories: remission ⩽2.8; low disease activity 2.8 to ⩽10; moderate disease activity 10 to ⩽22; and high disease activity >22 [11, 13]. ABA: abatacept; bDMARD: biologic DMARD; CDAI: clinical disease activity index; TCZ: tocilizumab; TNFi: TNF-α inhibitors.

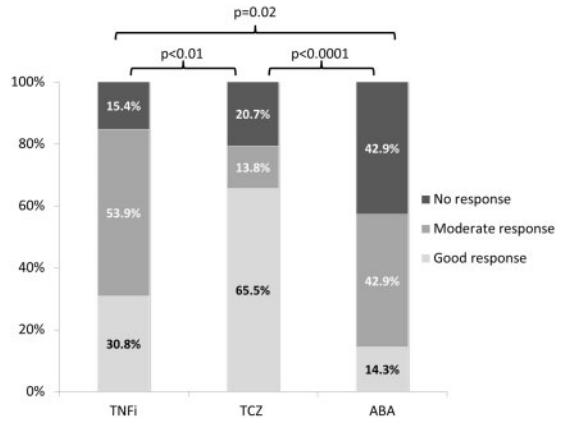
EULAR response

Six months after the commencement of the new bDMARD, 34% of all subjects had a good EULAR response [12], 39% had a moderate response and 27% no response (Fig. 2). The rates of EULAR responses varied significantly between treatment groups ($P < 0.001$). Only 14% of the patients receiving ABA and only 31% of the patients receiving TNFi had a good EULAR response, whereas 65% of the patients receiving TCZ met this criterion. More than 40% of patients treated with ABA showed no EULAR response. EULAR response was not predicted by any of the baseline demographics and disease characteristics.

Improvement of CDAI

At baseline, the median CDAI in all patients was 25.1 (IQR 17.6–34.9). The CDAI was similar across the three treatment groups ($P = 0.41$), ranging from a median CDAI of 21.1 (IQR 17.6–33.9) in the TNFi group to 27.2 (IQR 19.7–37.5) in the ABA group (Fig. 1B). After 6 months of treatment, the CDAI in all treatment groups declined significantly ($P < 0.01$ in each group), with a mean decrease of 12.2 units (S.D. 14.1). The greatest decline of 16.2 units (S.D. 13.8) was present in the TCZ group, followed by the

FIG. 2 EULAR responses at month 6 in the three treatment groups



P-values refer to pairwise comparisons of bDMARDs by means of Pearson's χ^2 tests. ABA: abatacept; bDMARD: biologic DMARD; TCZ: tocilizumab; TNFi: TNF-α inhibitors.

TNFi group (9.9 units, S.D. 15.5). The least CDAI improvement was observed in patients treated with ABA (7.5 units, S.D. 11.5). The decline in CDAI and the differences in this decline between the treatment groups were also seen in the multivariable regression analysis. Taking account of the distributions of age, sex, baseline prednisone use and the number of previous bDMARDs, the CDAI decline in patients on TNFi or ABA was on average 9.4 (95% CI: 1.7, 16.1) and 8.1 (95% CI: 0.9, 15.3) units smaller than in patients on TCZ.

At the baseline visit, no patient was in CDAI remission (CDAI $\leqslant$ 2.8) [13]. In all treatment groups (Table 2), no more than 10% of patients had a low CDAI activity (2.8 to $\leqslant$10); hence, the vast majority had a moderate (10 to $\leqslant$22) or high CDAI activity (>22) [13]. The disease activity in all treatment groups was similar at baseline ($P = 0.28$; Table 2). After 6 months on the new bDMARD, however, the disease activity distribution differed between the treatment groups ($P = 0.001$); 60% of patients in the TCZ group were in remission or had a low disease activity, compared with only 18 and 44% in the ABA and TNFi groups, respectively.

Patient-reported outcomes

At baseline, the patient-reported outcome, as assessed by the HAQ-DI score, was similar among all treatment groups ($P = 0.77$). However, the median HAQ-DI in the ABA group was slightly higher (1.56, IQR 1.1–2.0) compared with the median HAQ-DI in the group of patients on TNFi and TCZ groups (1.38, IQR 1.1–2.0 and 1.38, IQR 1.1–1.9, respectively).

After 6 months of treatment, the HAQ-DI decreased significantly among all patients ($P < 0.0001$). Numerically, the greatest decline in HAQ-DI was observed in the TCZ (0.29, S.D. 0.53) and the TNFi groups (0.28, S.D. 0.62) and the lowest in the patients on ABA (0.20, S.D. 0.48). There was, however, no statistically significant difference in the HAQ-DI decline between treatment groups ($P = 0.63$). In 45.8% of patients, the decline in HAQ-DI was $\geqslant$0.22, which is regarded as the minimal clinically important improvement [14, 15]. In the TCZ group, 54.2% of patients reported a HAQ-DI improvement greater than the minimal clinically important improvement compared with 48.7% in the TNFi group and 40.4% in the ABA group ($P = 0.38$).

Effects of the causes of RTX discontinuation and of the number of previous bDMARDs

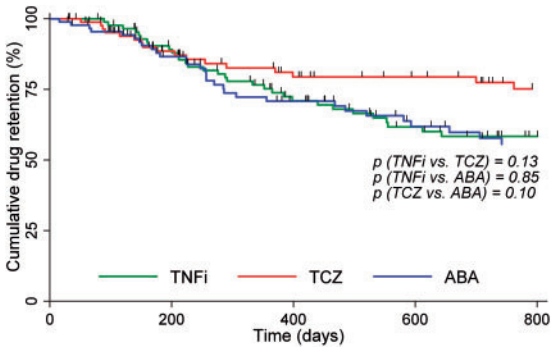
There was no difference between the DAS28-ESR at baseline as well as the percentage of patients in the DAS28-ESR activity categories (remission, low, moderate or high activity) among patients who had stopped RTX owing to ineffectiveness and those who discontinued RTX for other reasons ($P = 0.20$ and $P = 0.51$, respectively). Likewise, with regard to CDAI, the median baseline score did not differ between the groups of RTX discontinuation ($P = 0.60$); additionally, a high/moderate/low CDAI activity was found in 59%/35%/6% of patients who had stopped RTX because of ineffectiveness, compared with 64%/18%/18% in the group who had discontinued RTX for other reasons ($P = 0.21$). Furthermore, no difference was seen when comparing the two groups of RTX discontinuation with respect to the decline of DAS28-ESR and CDAI after 6 months of new treatment ($P = 0.58$ for DAS28-ESR and $P = 0.48$ for CDAI decline). Finally, the EULAR response rates were similar in patients who discontinued RTX owing to ineffectiveness and those who did so for other reasons; in the former category, 37% of subjects showed a good EULAR response compared with 33% in the latter category ($P = 0.64$). The lack of effect of the reason of the RTX discontinuation on RA control was also replicated when we analysed the individual bDMARD assignments (data not shown).

We did not identify an association between the number of previous bDMARDs and the improvement of RA activity, namely the overall decline of DAS28-ESR ($P = 0.35$), CDAI ($P = 0.48$) and EULAR response ($P = 0.63$). This lack of association of the number of previous bDMARDs with outcome measures was also seen in the individual treatment groups (all $P > 0.1$).

Drug retention

Given that drug discontinuation rates can be regarded a measure of effectiveness, we also analysed the retention rates of the bDMARDs in the different treatment arms. The 265 CERERRA patients were followed on average for 1.7 years after being switched from RTX to the new bDMARD. Drug retention rates were not significantly different between TNFi, ABA and TCZ (Fig. 3). Finally, the cause of RTX discontinuation (ineffectiveness *vs* other reasons) had no influence on the survival of subsequent bDMARDs ($P = 0.60$).

FIG. 3 Kaplan–Meier curves for the time to discontinuation of TNF-α inhibitors, tocilizumab or abatacept



ABA: abatacept; TCZ: tocilizumab; TNFi: TNF-α inhibitors.

Discussion

The objective of this study was to compare the effectiveness of different bDMARDs in RA patients following discontinuation of RTX. By analysing different predefined outcome parameters, we found differences in the relative benefit of the new bDMARDs. TCZ, in particular, was more effective than the alternative bDMARDs in our cohort. Interestingly, a large randomized trial in patients for whom MTX was deemed inappropriate had compared bDMARDs in the setting of monotherapy. That trial also suggested that the efficacy of TCZ was superior to that of a TNFi [16]. Previous data from small cohorts suggest that the efficacy of ABA and TNFi as a third-line bDMARD after RTX is limited [17, 18]. Our new data suggest that patients who fail RTX do have a better perspective to enter remission or low disease activity in clinical practice when they are switched to TCZ. Likewise, a better clinical response with TCZ compared with ABA has recently been suggested in a small cohort of 51 patients [18]. Rituximab depletes B cells, which operate as antigen-presenting cells in RA. As demonstrated previously [18], rituximab non-responders are characterized by low numbers of B cells, but high serum and synovial concentrations of IL-6. In this situation, the effect of co-stimulation blockade may be more limited than that of IL-6 inhibition, providing a mechanistic explanation for the difference in our findings [18]. We also found that the effectiveness of the new bDMARD was not modified by the reason for interrupting prior RTX (ineffectiveness *vs* other reasons). While the question of the effectiveness of bDMARDs following B-cell depletion has not been addressed before, other observational studies have investigated the influence of the reason for the switch away from TNFi [1–3]. Those studies suggest that RA disease activity is more favourably controlled if the reason for switching is ineffectiveness, rather than other reasons. Furthermore, we found that the number of bDMARDs prior to the switch had no influence on the outcome. The results of this study contrast with those of other small observational studies, which suggest that the responsiveness to a new bDMARD is reduced with intensive pre-treatment [2, 19]. Although our results are not directly comparable with the studies addressing the switch away from TNFi, the fact that RA activity was influenced neither by the reason for switching nor by the intensity of prior bDMARD exposure must not be over-emphasized, because our study may lack statistical power. Similar reasoning may also apply with regard to the failure of HAQ-DI improvement [20].

Although, to our knowledge, our data set represents the largest to date analysing RA treatment effectiveness of bDMARDs after RTX, observational studies do have limitations. Selection bias may occur because treatment assignment is not random. At baseline, however, we failed to identify significant differences in important factors known to be associated with a favourable or adverse influence on disease activity [21]. Another concern with observational studies is missing data. Our inclusion criteria permitted the analysis of about half of all patients included in the CERERRA registry. The patients excluded from the analyses, however, had similar demographic, disease and treatment characteristics compared with the patients included. This suggests that we acquired a representative sample of the CERERRA population. Selecting patients with follow-ups also tends to over-sample patients with good tolerability and adequate response to therapy, thereby potentially inducing a bias of completers. By comparing outcomes at 6 months of treatment, we were trying to minimize this effect, but at the same time were unable to compare secondary treatment failure. The fact that drug retention rates were similar between different bDMARDs, however, makes it unlikely that the bias of completers was the main driver of the outcome of this study.

Although our findings need to be confirmed in other studies, the results from this multinational cohort suggest that in clinical practice IL-6 blockade may be superior to alternative bDMARD classes following RTX discontinuation and represents a feasible strategy in the attainment of remission or low disease activity using a treat-to-target approach.

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References

1 Finckh A, Ciurea A, Brulhart L *et al*. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69:387–93.

2 Emery P, Gottenberg JE, Rubbert-Roth A *et al*. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis 2015;74:979–84.

3 Finckh A, Möller B, Dudler J *et al*. Evolution of radiographic joint damage in rituximab-treated versus TNF-treated rheumatoid arthritis cases with inadequate response to TNF antagonists. Ann Rheum Dis 2012;71:1680–5.

4 Genovese MC, Becker JC, Schiff M *et al*. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. N Engl J Med 2005;353:1114–23.

5 Cohen SB, Emery P, Greenwald MW *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793–806.

6 Emery P, Keystone E, Tony HP *et al*. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67:1516–23.

7 Genovese MC, Breedveld FC, Emery P *et al*. Safety of biologic therapies following rituximab treatment in rheumatoid arthritis patients. Ann Rheum Dis 2009;68:1894–7.

8 Mishra R, Singh V, Pritchard CH. Safety of biologic agents after rituximab therapy in patients with rheumatoid arthritis. Rheumatol Int 2011;31:481–4.

9 Chatzidionysiou K, Lie E, Nasonov E *et al*. Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and leflunomide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. Ann Rheum Dis 2012;71:374–7.

10 Carpenter JR, Kenward MG. Multiple Imputation and its Application. Chichester: John Wiley & Sons, 2013.

11 van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.

12 Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am 2009;35:745–57.

13 Aletaha D, Smolen JS. The Simplified Disease Activity Index and Clinical Disease Activity Index to monitor patients in standard clinical care. Rheum Dis Clin North Am 2009;35:759–72.

14 Wells GA, Tugwell P, Kraag GR *et al*. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20:557–60.

15 Kosinski M, Zhao SZ, Dedhiya S *et al*. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43:1478–87.

16 Gabay C, Emery P, van Vollenhoven R *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541–50.

17 Walker UA, Courvoisier DS, Dudler J *et al*. Do new biologics meet the unmet medical need in rheumatoid arthritis? Safety and efficacy of abatacept following B-cell depletion. Rheumatology 2011;20:243–4.

18 Das S, Vital EM, Horton S *et al*. Abatacept or tocilizumab after rituximab in rheumatoid arthritis? An exploratory study suggests non-response to rituximab is associated with persistently high IL-6 and better clinical response to IL-6 blocking therapy. Ann Rheum Dis 2014;73:909–12.

19 Finckh A, Ciurea A, Brulhart L *et al*. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56:1417–23.

20 Strand V, Rentz AM, Cifaldi MA *et al*. Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. J Rheumatol 2012;39:63–72.

21 Hyrich KL, Watson KD, Silman AJ, Symmons DPM. Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45:1558–65.