ORIGINAL ARTICLE

Sustainability of Rituximab Therapy in Different Treatment Strategies: Results of a 3-Year Followup of a German Biologics Register

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Objective. To compare the approved treatment of rheumatoid arthritis using rituximab + methotrexate (RTX + MTX) versus the off-label treatment variants of RTX in monotherapy or RTX in combination with leflunomide (RTX + LEF).
Methods. We included RTX-naive patients enrolled in the German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy) between 2007 and 2012 (n = 907) who started treatment with RTX. Three treatment regimens (RTX + MTX, RTX + LEF, and RTX monotherapy) were analyzed regarding therapy discontinuation, dropout, RTX retreatment, and concomitant glucocorticoid therapy. Effectiveness was evaluated with linear mixed models.
Results. Baseline patient characteristics were similar across treatment regimens, except for poorer functional status and more comorbidities in RTX monotherapy. Average doses of glucocorticoids were lower in RTX + LEF compared to the 2 other groups. The frequency and timing of RTX retreatment (*P* > 0.62) as well as improvement in the Disease Activity Score in 28 joints (DAS28) over time (*P* > 0.15) were similar in all treatment regimens. Within the first 12 months of treatment, the DAS28 decreased by 1.5 units, and between months 12 and 36, by a further 0.4 unit equally in all groups. Nevertheless, therapy discontinuation and dropout were significantly increased on RTX monotherapy (hazard ratio [HR] 1.7 [95% confidence interval (95% CI) 1.2–2.3]), and additionally when patients were rheumatoid factor negative (HR 1.5 [95% CI 1.0–2.1]).
Conclusion. In patients who continue therapy, RTX + LEF, RTX monotherapy, and RTX + MTX seem to be equally effective. However, given the lower adherence rates on monotherapy, this treatment option is not sufficient for all patients. Since many patients are intolerant to MTX, more licensed RTX treatment options are needed.

INTRODUCTION

Rituximab (RTX) is a genetically engineered monoclonal antibody targeting B cells carrying the CD20 receptor. Binding to this receptor leads to depletion of the CD20+ cell population. Several randomized clinical trials have demonstrated high efficacy of RTX in patients with rheumatoid arthritis (RA) (1–3). Since 2006, RTX is approved in combination with methotrexate (MTX) for the treatment of severe, active RA in adult patients with an inad-equate response to disease-modifying antirheumatic drugs (DMARDs), including ≥1 tumor necrosis factor (TNF) inhibitors. Administration of RTX is recommended as 2 separate infusions of 1,000 mg each at the start of treatment and after 2 weeks. Concerning retreatment with RTX, there is no published guideline; usually retreatment is considered after 6 months at the earliest (4).

Although the use of RTX in RA patients is only approved in combination with MTX therapy, a few publications report comparable efficacy and safety of unlicensed use, such as RTX administered with concomitant lefluno-

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Significance & Innovations

- The treatment of rheumatoid arthritis with rituximab (RTX) is approved with concomitant methotrexate (MTX) only. Intolerance to MTX either precludes RTX as a treatment option or leads to off-label use with leflunomide (LEF) or in monotherapy.

- To our knowledge, there are no published results from randomized controlled trials on long-term effectiveness of RTX in off-label therapy. So far, data on these clinically important treatment options were published by observational studies only, which have to deal with the problem of confounding by indication.

- This study takes into account the limitations of an observational design and incorporates therapy discontinuation, dropout processes, and concomitant glucocorticoid therapy as possible confounders of treatment effectiveness into the comparison of treatment regimens.

- We report on 907 RTX-naive patients who started RTX treatment and were observed for a mean observation time of 3 years under RTX + MTX therapy, RTX + LEF therapy, or RTX in monotherapy.

mide (LEF) or RTX in monotherapy (5–7). In fact, off-label use of RTX is concurrent in daily practice, since it is a plausible therapeutic option for certain patients, e.g., patients intolerant to MTX.

Biologics registers have been initiated since 2001 and focus on analyzing safety and effectiveness of biologic agents in RA patients in daily rheumatologic care. They analyze the safety of treatment strategies that have not been evaluated in randomized controlled trials. However, observational studies have to face the difficulty of confounding by indication, i.e., clinically relevant patient characteristics such as age or disease activity may systematically differ between treatment regimens. Furthermore, dropout and therapy discontinuation are inevitable in observational studies and impede comparative studies. In addition, strategies may vary concerning the frequency and timing of RTX retreatment as well as concerning the administration of concomitant glucocorticoids (GCs). All of these aspects influence effectiveness (2,6,8) and should be incorporated into the comparison of treatment variants.

Our analyses aimed to evaluate the effectiveness of 3 RTX treatment variants (RTX + MTX, RTX + LEF, and RTX monotherapy) over 3 years. To obtain valid comparisons between the treatment groups, we took differences at treatment onset, timing of retreatment with RTX, and confounding by treatment discontinuation or selective dropout into account.

SUBJECTS AND METHODS

Study design. The German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy) is an ongoing prospective cohort study initiated in 2001. Patients with RA meeting the American College of Rheumatology 1987 criteria (9) are eligible for enrollment at the start of treatment with a biologic agent or nonbiologic DMARD after failure of ≥1 nonbiologic DMARD. The registration of RA patients receiving RTX started in 2007. Substantial features of clinical status such as the Disease Activity Score in 28 joints (DAS28) (10), erythrocyte sedimentation rate, or presence of rheumatoid factor (RF) and of anti–cyclic citrullinated peptide (anti-CCP) antibodies; therapy details; the occurrence of nonserious and serious adverse events; and patient-reported outcomes (e.g., pain, function, and global health assessment) are recorded at baseline, months 3 and 6 after enrollment, and every 6 months thereafter. Functional status is captured by the Funktionsfragebogen Hannover (FFbH), a German instrument for the measurement of functional disability that is highly correlated with the Health Assessment Questionnaire (11). Further details of the study protocol are included in the studies by Strangfeld et al (2009 and 2011) (12,13). The ethics committee of the Charité-Universitätsmedizin Berlin approved the study protocol.

This investigation utilized data of 1,206 patients who started RTX at enrollment to RABBIT. Followup was censored on October 30, 2012, dropout, or death, whichever came first. We excluded 199 patients with prior exposure to RTX from these analyses as well as patients exposed to sulfasalazine, hydroxychloroquine, or gold as concomitant nonbiologic DMARDs (n = 44). A combined treatment of MTX and LEF in addition to RTX was reported in 15 patients, who were also excluded. Due to exposure to 2 biologic agents at baseline, 1 patient was excluded. In 40 patients, followup data were inaccessible and the respective patients were excluded from the subsequent analysis.

Regarding dropouts, we applied a rigorous approach and considered a patient with missing followup data ≥60 days after a missed but scheduled visit as a potential dropout. This approach overestimates the actual dropout rate. In a sensitivity analysis, we therefore calculated different intervals for the definition of a dropout: 30, 90, and 120 days after the missed visit. The results obtained with these intervals were similar to those using 60 days.

Statistical analysis. Patient baseline characteristics were compared using analysis of variance (ANOVA) or chi-square test. In case of ANOVA and the occurrence of a statistically significant difference in means (*P* value less than 0.05), we applied pairwise comparisons using the *t*-test.

Therapy discontinuation was analyzed with Kaplan-Meier survival curves and group differences were analyzed with a log rank test. We defined the switch from RTX to another biologic agent, the switch between nonbiologic DMARDs, or the start of a concomitant nonbiologic DMARD in patients receiving RTX monotherapy as changes in therapy, i.e., the switch from baseline (intent-to-treat [ITT]) therapy.

We compared the 3 treatment regimens regarding the rates of dropouts in a Cox proportional hazards model (14). We hypothesized that the individual course of disease

	Table 1. Baseline characteristics of patients receiving RTX*		
Parameter	RTX + MTX (n = 496)	RTX + LEF (n = 117)	RTX monotherapy (n = 294)
Women, no. (%)	385 (77.6)	89 (76.1)	233 (79.3)
Age, mean ± SD years	56.4 ± 11.7	57.2 ± 11.5	58.8 ± 12.2†
Disease duration, mean ± SD years	13.7 ± 9.9	13.8 ± 11.0	14.7 ± 10.2
No. of previous biologic agents, mean ± SD	1.5 ± 1.0	1.6 ± 0.8	1.5 ± 1.0
No. of previous DMARDs, mean ± SD	3.0 ± 1.3	3.0 ± 1.1	3.0 ± 1.2
Time to previous biologic DMARD, median (IQR) months	2.0 (1–4)	1.0 (0–3)†	2.0 (1–4)
Concomitant GCs (range 7.5–14 mg/day), no. (%)	118 (28.0)	19 (20.9)	72 (28.7)
Concomitant GCs (>15 mg/day), no. (%)	54 (12.8)	12 (13.2)	55 (21.9)†
Anti-CCP positive, no. (%)‡	202 (70.1)	55 (83.3)	130 (75.6)
RF positive, no. (%)	409 (82.5)	97 (82.9)	252 (86.0)
DAS28, mean ± SD	5.5 ± 1.2	5.3 ± 1.3	5.7 ± 1.2
FFbH, mean ± SD	55.3 ± 22.6	58.4 ± 22.3	51.4 ± 24.1†
Followup, mean ± SD years	3.2 ± 1.5	3.2 ± 1.4	3.0 ± 1.5
No. of comorbidities, no. (%)			
0	116 (23.4)	21 (17.9)	45 (15.3)
1	141 (28.5)	26 (22.2)	48 (16.3)
2	94 (19.0)	29 (24.8)	67 (22.8)
≥3	144 (29.1)	41 (35.0)	134 (45.6)†
Among comorbidities, no. (%)			
Previous malignancies	42 (8.5)	4 (3.4)	28 (9.5)
Musculoskeletal diseases	134 (27.0)	31 (26.5)	125 (42.5)†
Cardiovascular diseases	191 (38.5)	62 (53.0)†	153 (52.0)†
Smoking (ever)	257 (55.6)	62 (56.4)	156 (56.1)

* RTX = rituximab; MTX = methotrexate; LEF = leflunomide; DMARDs = disease-modifying antirheumatic drugs; IQR = interquartile range; GCs = glucocorticoids; anti-CCP = anti–cyclic citrullinated peptide antibodies; RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; FFbH = Funktionsfragebogen Hannover.
† Significant differences ($P < 0.05$) compared to patients treated with RTX + MTX.
‡ The biomarker anti-CCP is not reported by all rheumatologists and data are missing for 421 patients.

activity is associated with the risk of dropout rather than a single time-varying score value of the DAS28. Therefore, we utilized an average value of the DAS28 for each patient. These values varied over time and were calculated individually for each patient by averaging the previous scores of the DAS28 until the respective followup. Frequencies and initiation of RTX retreatment were examined using accelerated failure time models. This class of models permits the estimation of covariate effects on time to retreatment (15). Administration of concomitant GCs was analyzed in linear mixed models (16).

The overall effectiveness of each of the treatment variants over 36 months, i.e., the course of disease activity (DAS28), was analyzed in linear mixed models. We calculated 2 different models for the analysis of effectiveness. Model 1, a "completer analysis," considers only patients who did not change the initial therapy during 36 months of followup. In model 2, an ITT approach was applied. The clinical status after switching of therapies or after dropout from the observation was considered by multiple imputations, taking confounding by selective discontinuation or dropout into account. The imputation model included age, sex, number of previous nonbiologic DMARDs, and the previous courses of disease activity, as well as functional capacity. Multiple imputations were generated by the application of sequential regression models (17). Within the mixed model, the following co-variables assessed at baseline were included for adjustment: DAS28, functional status (FFbH), treatment, RF serologic status, number of

comorbidities, and the number of previous anti-TNFα failures. Random effects were defined as the random intercept and slope for each patient. This assumption reflects the individual level and course of disease activity for each patient. The issue of collinearity concerning the DAS28 and the FFbH was considered to be marginal due to a Pearson's correlation coefficient of $\rho = -0.39$. Alterations in doses of concomitant nonbiologic DMARDs were not considered.

In general, to prevent model overfitting and to select appropriate covariance structures in random-effects models, we performed model selection by utilizing the Bayesian information criterion (BIC) (18). Covariate effects in the linear mixed-effects model were evaluated according to the change in BIC in each of the multiple imputed data sets. We used statistical software from SAS Institute, version 9.3, and R, version 2.15 (19).

RESULTS

Patient characteristics. The data of 907 patients with ≥1 followup were included in the analyses. The recommended dose of 1,000 mg RTX infusion, to be administered at the start and after 2 weeks, was administered in at least 94.2% of the patients in all treatment variants. The mean observation time in all therapies was ~3 years (Table 1). Concerning the number of previous nonbiologic DMARDs or biologic agents or the proportion of RF-
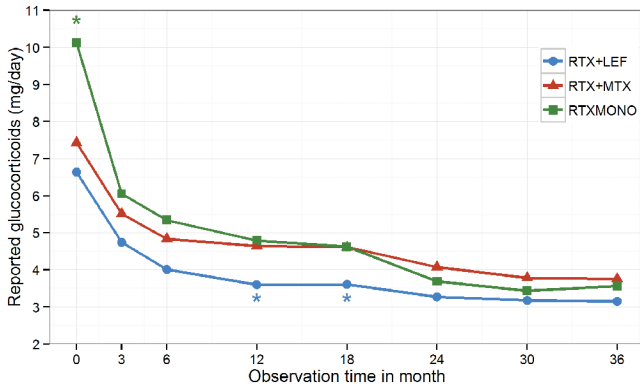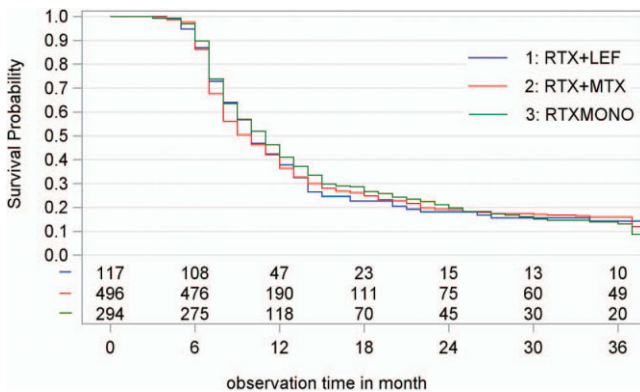
Figure 1. Reported glucocorticoid (GC) doses over time. The asterisks (∗) indicate statistically significant differences in GC doses. Reference is rituximab plus methotrexate (RTX+MTX) therapy. RTX+LEF = RTX plus leflunomide therapy; RTXMONO = RTX monotherapy.

positive patients, no statistically significant differences between the treatment groups were found. Patients receiving RTX monotherapy had significantly more comorbidities compared to patients receiving RTX + MTX therapy ($P < 0.01$), and lower scores for functional status ($P < 0.03$) and higher DAS28 ($P < 0.02$) compared to those receiving RTX + LEF therapy.

Application of GCs. At baseline, patients who started RTX monotherapy received significantly higher doses of concomitant GCs ($P < 0.01$) (Table 1). In all treatment groups, the mean dose of GCs decreased significantly within the first 3 months of treatment ($P < 0.01$) (Figure 1). Between months 6 and 36, there were no differences in the mean doses of GCs between RTX monotherapy and RTX + MTX. However, patients receiving RTX + LEF therapy received on average 1.6 mg/day fewer GCs ($P \leq 0.01$).

In addition, the shorter the time span was between discontinuation of the last therapy with a biologic agent and the start of RTX, the lower the doses of GCs were at baseline. This applied to all treatment regimens. In the RTX + LEF group, the proportion of patients who had

Table 2. Cox proportional hazards of dropouts*

Parameter	Hazard ratio	95% CI
DAS28 (average)	1.5	1.3–1.7
RTX + MTX	Reference	NA
RTX + LEF	1.1	0.7–1.7
RTX monotherapy	1.7	1.2–2.3
RF positive	Reference	NA
RF negative	1.5	1.0–2.1

* 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; RTX = rituximab; MTX = methotrexate; NA = not applicable; LEF = leflunomide; RF = rheumatoid factor.

switched from anti-TNFα therapy to RTX within the last 30 days was significantly larger than in the other groups (31.6% versus 19.0% in RTX + MTX and 21.1% in RTX monotherapy), which explained, at least in part, the lower doses of GCs at enrollment.

Retreatment with RTX. There were no significant differences between treatment groups in time to first, second, or third retreatment with RTX (P min > 0.62). The time span between RTX start and the first retreatment with RTX is shown in Figure 2. The second retreatment with RTX was initiated in 55.6% of patients receiving RTX + MTX therapy, 62.4% receiving RTX + LEF therapy, and 56.5% receiving RTX monotherapy.

Dropout. Analysis of dropout was conducted to find predictors of attrition and to examine whether selective dropout was present in one of the treatment variants. Over 3 years of observation, we classified 179 patients (19.7%) as potential dropouts, including 83 (16.7%) receiving RTX + MTX, 20 (17.1%) receiving RTX + LEF, and 76 (25.9%) receiving RTX monotherapy, which corresponded to 6–7% dropout annually. Patients with an elevated average DAS28, those treated with RTX monotherapy, and RF-negative patients had significantly higher risks to drop out (Table 2).

Figure 2. Survival plot of the time to first retreatment with rituximab (RTX). The numbers of subjects at risk, at the top of the x-axis, represent the number of patients who did not receive a second course of RTX at the specific month of observation. RTX+LEF = RTX plus leflunomide therapy; RTX+MTX = RTX plus methotrexate therapy; RTXMONO = RTX monotherapy.
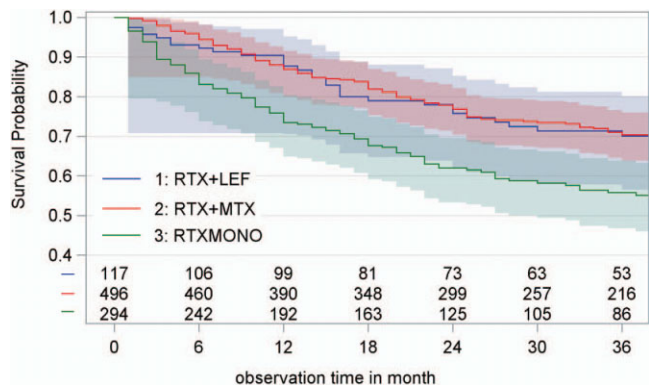
Figure 3. Survival estimates for continuation on therapy. At the top of the x-axis, the respective number of patients under risk is noted, i.e., the number of observed patients at the respective month who did not change the treatment. Hall-Wellner bands represent 95% confidence intervals. RTX+LEF = RTX plus leflunomide therapy; RTX+MTX = rituximab plus methotrexate therapy; RTXMONO = RTX monotherapy.

	N	DAS28 at baseline	DAS28 at month 12 (95% CI)	DAS28 at month 24 (95% CI)	DAS28 at month 36 (95% CI)
Table 3. Adjusted mean estimates of the DAS28 for treatment regimens*					
Completer analysis (approach 1)					
RTX + MTX	216	5.6	3.9 (3.7–4.1)	3.8 (3.6–4.0)	3.6 (3.4–3.9)
RTX + LEF	53	5.6	4.2 (3.8–4.6)	4.1 (3.7–4.6)	3.7 (3.2–4.1)
RTX monotherapy	86	5.6	3.7 (3.5–4.0)	3.5 (3.2–3.7)	3.4 (3.1–3.7)
ITT analysis (approach 2)					
RTX + MTX	496	5.5	4.1 (4.0–4.2)	3.8 (3.7–4.0)	3.7 (3.6–3.8)
RTX + LEF	117	5.5	4.1 (3.9–4.3)	3.9 (3.7–4.2)	3.6 (3.3–3.9)
RTX monotherapy	294	5.5	4.0 (3.8–4.1)	3.7 (3.5–3.8)	3.6 (3.4–3.8)

* Means of the Disease Activity Score in 28 joints (DAS28) by treatment group adjusted for an averaged, common baseline DAS28 and functional status (Funktionsfragebogen Hannover), treatment, rheumatoid factor, time, number of comorbidities, and the number of previous anti–tumor necrosis factor α failures are shown. The completer analysis considered patients who continued the initial treatment over 36 months. In the intent-to-treat (ITT) analysis, additional adjustments for therapy discontinuation and dropout were made. 95% CI = 95% confidence interval; RTX = rituximab; MTX = methotrexate; LEF = leflunomide.

Discontinuation of baseline (ITT) therapy. Within 3 years of observation, 161 patients switched to treatment with another biologic agent; this applied significantly more often ($P = 0.03$) to patients treated with RTX + MTX (103 [20.8%]) than to those treated with RTX + LEF (16 [13.7%]) or RTX monotherapy (42 [14.3%]). The nonbiologic DMARD was switched (or a new one was added in RTX monotherapy) in 150 patients: 46 (9.3%) were receiving RTX + MTX therapy, 18 (15.4%) were receiving RTX + LEF therapy, and most frequently ($P < 0.01$), 86 patients (29.3%) were receiving RTX monotherapy. The discontinuation of baseline (ITT) treatment by a switch of the biologic agent, the nonbiologic DMARD treatment, or both was significantly higher ($P < 0.01$) in patients treated with RTX monotherapy (RTX + MTX: 124 [25.0%], RTX + LEF: 31 [26.5%], and RTX monotherapy: 113 [38.4%]). The Kaplan-Meier estimates for receiving ITT treatment after 36 months of observation were 70.4% of patients receiving RTX + MTX therapy, 70.0% receiving RTX + LEF therapy, and 55.8% receiving RTX monotherapy (Figure 3).

Effectiveness. In the completer analysis (approach 1), we restricted the number of patients to those who were still observed at month 36 on ITT therapy, which is equivalent to the number of patients at risk after 36 months in Figure 3. We found a significant benefit for patients treated with RTX monotherapy ($P = 0.04$) compared to patients treated with RTX and a concomitant nonbiologic DMARD. This gain in effectiveness was constant over time (Table 3) and varied between 0.3 and 0.6 unit of the DAS28. We adjusted for patient characteristics assessed at baseline (DAS28, FFbH, number of comorbidities, previous anti-TNF failures, and RF). In approach 2, we additionally adjusted for the effects of treatment changes and dropout processes by multiple imputations. Consequently, no significant differences between the 3 treatment regimens were found concerning the outcome in DAS28 at months 12, 24, or 36 (Table 3).

In all treatment groups, the improvement in DAS28 was lower for RF-negative patients (on average, 0.3 unit [95% confidence interval 0.07–0.53] over time). Further significant predictors of response were baseline DAS28, number of comorbidities (>2 versus ≤2), or previous anti-TNF failures (>1 versus ≤1), whereas there was no association with age, sex, or weight. The mixed-model analysis showed a significant decrease of the DAS28 over time ($P < 0.01$), but no significant interaction between time and treatment group, which supported the assumption of equal effectiveness of the 3 treatment regimens.

DISCUSSION

We compared 3 treatment regimens of RTX that are common in daily rheumatologic practice. Although RTX is approved in combination with MTX only, a substantial number of patients do not tolerate MTX in this combination. With lacking evidence from randomized trials, there is a need for clinicians and payers to know whether RTX is safe and efficient in monotherapy or in combination with LEF, and whether there are clinical situations in which certain treatment variants should be avoided.

We therefore analyzed 3-year followup data of 907 patients enrolled in the German biologics register RABBIT with a start of 1 of 3 different RTX treatment variants. We found similar effectiveness of RTX used in monotherapy or with concomitant LEF compared to the licensed treatment variant of RTX in combination with MTX. Taking treatment discontinuation and dropout processes in an ITT approach into account, a significant reduction in disease activity within the first 12 months of observation by 1.5 units of the DAS28 was found in all 3 treatment variants. Between month 12 and month 36, we found an additional and significant improvement in DAS28 by on average 0.4 unit for all treatment variants. We could preclude the time to retreatment and GC doses as potential confounders of the outcome.

By this approach, we confirmed the findings of others (5–7) in a more robust manner and added information on the longer-term effectiveness over a mean of 3 years. A lower DAS28 at baseline, fewer comorbid conditions, and fewer previous anti-TNF treatment failures were significantly associated with lower disease activity at followup. RF positivity remained as a highly predictive factor for the success of treatment with RTX.

Regarding the effectiveness of the combination RTX + LEF, our results are different from those of Chatzidionysiou et al (7), who found higher effectiveness compared with RTX + MTX or RTX alone. The mean ± SD doses of nonbiologic DMARDs in their study were 14.4 ± 5.4 mg a week for MTX and 17.6 ± 3.4 mg daily for LEF, thus being similar to those of our cohort (14.2 ± 5.0 for MTX and 17.4 ± 4.7 for LEF). We attribute the difference of the results to an overrepresentation of biologic agent–naive patients in the study by Chatzidionysiou et al, who are known to respond better to initial treatment with a biologic agent in their RTX + LEF group (20,21).

Similarly, we could not confirm the results of Solau-Gervais et al (6), who found no significant difference in European League Against Rheumatism response between patients naive to TNF inhibitors (78.6%) and those with prior exposure (74.1%). In our study, a higher number of previous anti-TNF failures was a significant predictor of a poorer response. Of note, in their data, the interval of retreatment that was given after relapse only differed significantly between patients with and without previous anti-TNF failures (35 and 60 weeks), which could be an indicator for better effectiveness without previous TNF failures.

In addition to the ITT approach, we performed a completer analysis. We found that patients who stayed on RTX monotherapy had a significantly greater reduction of the DAS28 compared to the other treatment variants. However, this result has to be interpreted against the background that treatment discontinuation and dropout were significantly increased in patients receiving RTX monotherapy. Therefore, a considerably lower portion of RTX monotherapy patients completed the 3-year period, i.e., those who responded well and tolerated this treatment.

This study has strengths and weaknesses. We have to keep in mind that all analyses in this comparison utilized data from an observational study, which implies the possibility of residual confounding. We could not analyze the predictive value of anti-CCP antibodies, as recently discussed by Isaacs et al (22), since a considerable proportion of rheumatologists did not measure this parameter in the early enrollment period of patients treated with RTX.

Strengths of the study are that patients under all treatment regimens were observed in the same manner and intensity. Further, different from pooled analyses of data from several countries, all patients stemmed from the same population and were treated under the same health care conditions. Information related to the investigated off-label RTX treatment variants almost exclusively came from real-life data, and no long-term data were available from randomized controlled trials. Furthermore, the high completeness of our data allowed us to look at the change of patient case mix and clinical variables over time. To our knowledge, this is the first study on the effectiveness of RTX in which confounding by dropout, differences in retreatment intervals, and the individual courses and doses of concomitant GC treatment were considered in the analysis. Our findings have implications for the use of RTX in daily rheumatologic practice. However, RTX monotherapy or RTX + LEF are still off-label treatment variants. Evaluation of the results in the more rigorous

setting of a randomized clinical trial is therefore highly needed.

We conclude that for patients intolerant to MTX, the combination of RTX + LEF is an effective option even in the long term, as well as using RTX in monotherapy, if the patient is RF positive.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Mr. Richter had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data. Richter, Strangfeld, Listing, Zink.

ROLE OF THE STUDY SPONSORS

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