EXTENDED REPORT

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

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ABSTRACT

Objectives To compare the effectiveness of rituximab versus an alternative tumour necrosis factor (TNF) inhibitor (TNFi) in patients with rheumatoid arthritis (RA) with an inadequate response to one previous TNFi.

Methods SWITCH-RA was a prospective, global, observational, real-life study. Patients non-responsive or intolerant to a single TNFi were enrolled ≤4 weeks after starting rituximab or a second TNFi. Primary end point: change in Disease Activity Score in 28 joints excluding patient’s global health component (DAS28-3)–erythrocyte sedimentation rate (ESR) over 6 months.

Results 604 patients received rituximab, and 507 an alternative TNFi as second biological therapy. Reasons for discontinuing the first TNFi were inefficacy (n=827), intolerance (n=263) and other (n=21). A total of 728 patients were available for primary end point analysis (rituximab n=405; TNFi n=323). Baseline mean (SD) DAS28-3–ESR was higher in the rituximab than the TNFi group: 5.2 (1.2) vs 4.8 (1.3); p<0.0001. Least squares mean (SE) change in DAS28-3–ESR at 6 months was significantly greater in rituximab than TNFi patients: −1.5 (0.2) vs −1.1 (0.2); p=0.007. The difference remained significant among patients discontinuing the initial TNFi because of inefficacy (−1.7 vs −1.3; p=0.017) but not intolerance (−0.7 vs −0.7; p=0.894). Seropositive patients showed significantly greater improvements in DAS28-3–ESR with rituximab than with TNFi (−1.6 (0.3) vs −1.2 (0.3); p=0.011), particularly those switching because of inefficacy (−1.9 (0.3) vs −1.5 (0.4); p=0.021). The overall incidence of adverse events was similar between the rituximab and TNFi groups.

Conclusions These real-life data indicate that, after discontinuation of an initial TNFi, switching to rituximab is associated with significantly improved clinical effectiveness compared with switching to a second TNFi. This difference was particularly evident in seropositive patients and in those switched because of inefficacy.

INTRODUCTION

Tumour necrosis factor-α (TNF-α) inhibitors are effective treatments for patients with rheumatoid arthritis (RA), improving signs and symptoms and slowing or preventing structural damage.1 However, up to 40% of patients either fail to respond adequately to these agents (primary inefficacy) or lose responsiveness over time (secondary inefficacy).2

Options available to patients with an inadequate response to TNF inhibitors (TNF-IRs) include treatment with an alternative TNF inhibitor and switching to a biological therapy with a different mode of action. Several studies have suggested that benefits may be gained by switching to an alternative TNF inhibitor.3–7 Among biological therapies with an alternative mode of action, rituximab (an anti-CD20 B-cell-depleting therapy), abatacept (a T-cell costimulation blocking agent) and, more recently, tocilizumab (anti-interleukin (IL)6 receptor monoclonal antibody) have been demonstrated to be significantly better than placebo in TNF-IR patients.8–10

Data on the comparative effectiveness of different switching strategies are, however, limited. No head-to-head trials have been conducted, and evaluation of this question has been largely restricted to indirect meta-analyses of the randomised controlled trials noted above.11–14 Recent registry data provide evidence that switching to rituximab may be more effective than cycling to an alternative TNF inhibitor.15–17

SWITCH-RA is a prospective, global, observational study, conducted in real-life practice conditions, with the primary objective of comparing the effectiveness of rituximab with an alternative TNF inhibitor in patients with an inadequate response to one previous TNF inhibitor. This paper reports the 6-month primary effectiveness and safety data from SWITCH-RA.

METHODS

Study design and patient population

This was a prospective, global, multicentre, open-label, observational study conducted in real-life practice in adult patients with RA who were non-responsive or intolerant to a single previous TNF inhibitor. Patients were screened and enrolled up to 4 weeks after starting their second biological therapy. In patients enrolled up to 4 weeks after the...
switch to a second biological therapy, the data collected at that visit were those available at the time of the start of the second biological therapy. Missing baseline Disease Activity Score in 28 joints (DAS28) values did not preclude enrolment. Patients receiving a second biological therapy as part of a clinical trial were excluded. No additional visits or laboratory tests were required outside of routine clinical practice. Patients discontinuing the second biological therapy continued to be observed for the planned 12-month study period. Concomitant non-biological disease-modifying antirheumatic drugs (DMARDs) or other medications could be added at the investigator’s discretion.

The Study Committee, a scientific board of leading international rheumatologists, designed the SWITCH-RA study and assured its proper conduct. Data collection and statistical analyses were conducted by an independent contract research organisation (Quintiles, Rockville, Maryland, USA). The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval from the institutional review boards at each study centre was received. All patients consented to data collection and review. ClinicalTrials.gov identifier NCT01557348.

Assessments
Patients were followed for 12 months from the start of the second biological therapy. Assessments included demographic and clinical variables at the time of switching to the new biological therapy and reasons for discontinuation of the first TNF inhibitor. Reasons for discontinuation were classified as intolerance, ineffectiveness or other. Ineffectiveness was further categorised as primary ineffectiveness (lack of initial clinical response to TNF inhibitor treatment) or secondary ineffectiveness (development of an inadequate response over time after an initial clinical response). Reasons classified as ‘other’ included patient choice.

Effectiveness was assessed using DAS28 excluding patient’s global health component calculated with erythrocyte sedimentation rate (DAS28-3–ESR), a validated disease activity measure.18–20 DAS28-3 was used rather than DAS28-4 because patient’s global health assessment data were disproportionately under-reported (particularly at baseline, in patients whose data were captured retrospectively). Other variables assessed included ESR, C-reactive protein (CRP), DAS28-3–CRP, swollen and tender joint counts (SJC-28, TJC-28), patient global assessment of disease, patient visual analogue scale pain score, Health Assessment Questionnaire Disability Index (HAQ-DI) and duration of morning stiffness. Adverse events (AEs) reported in the study were mapped to preferred terms in the Medical Dictionary for Drug Regulatory Activities (MedDRA). The relationship of AEs to study treatment was assessed by the investigator.

Owing to the non-interventional nature of the study, strict adherence to visit windows was not feasible. DAS28-3–ESR values at the nearest time point within a given window (±2 months for the 6-month assessment) were used. Patients were enrolled up to 4 weeks after starting their second biological therapy, resulting in a high rate of missing baseline DAS28-3–ESR values. DAS28-ESR values directly reported by the investigator were used to substitute for missing DAS28-3–ESR values. If no values were available at the start of the second biological therapy, the value at the end of the first biological therapy was used as baseline. An ‘as observed’ analysis was performed to validate the robustness of the results.

Statistical analysis
The study did not enrol up to the planned sample size (631 patients with available data in each group). The retrospective power based on the actual number of patients with a mean change value in DAS28-ESR at 6 months (n=405 for rituximab and 323 for alternative TNF inhibitor) was 70% to detect a difference of 0.3 DAS units, assuming a common SD of 1.6, using a two-group t test with a 0.05 two-sided significance level.

The primary end point was the mean change in DAS28–ESR, 6 months after the change in biological therapy (considered to be baseline). Six-month changes in clinical variables after the initiation of the new therapy in the two treatment groups were compared using analysis of covariance (ANCOVA), with adjustment for unbalanced baseline characteristics and baseline value of the outcome. Least squares (LS) means and p values were generated. As a sensitivity analysis, the end point was also analysed using an ANCOVA model with adjustment for a propensity score, calculated to determine the likelihood of selecting rituximab over an alternative TNF inhibitor as the second biological therapy driven by the patient’s baseline disease characteristics and potential confounding factors (see online supplementary text and figure S1). A subanalysis was conducted to compare switching to rituximab with an alternative TNF inhibitor in seropositive (rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) positive) and seronegative patients.

Safety results were summarised descriptively by treatment group.

RESULTS
Patient disposition
A total of 1312 patients from 11 countries (Canada, Colombia, France, Germany, Great Britain, Greece, Italy, Mexico, Norway, Portugal and Spain) were screened, of whom 1239 were enrolled in the study. Nine enrolled patients were excluded from the analysis (missing information on second biological therapy (n=3) and missing reasons for selection (n=6)). An additional 119 patients were excluded as they had received more than one previous TNF inhibitor, leaving 1111 patients valid for analysis (full analysis population). Of these, 604 (54.4%) received rituximab and 507 (45.6%) an alternative TNF inhibitor as the second biological therapy. Patients could be enrolled up to 4 weeks after starting the second biological therapy. As a result, baseline DAS28–ESR scores were missing for about a quarter of the patients (see online supplementary figure S2). Data for 728 patients (rituximab, n=405; alternative TNF inhibitor, n=323) who had baseline DAS28-3–ESR and had completed 6 months after initiation of treatment with a second biological agent were available for the primary end point analysis (primary effectiveness population).

Patient demographics and disease characteristics
In the full analysis population, the majority of patients were female (79.1%); mean age was ~55.5 years and mean disease duration was ~8.3 years. Patients in the two groups had received a similar number of prior non-biological DMARDs and had been on their first TNF inhibitor for a similar length of time, ~25 months (see online supplementary table S1). Baseline disease characteristics were generally similar between the two treatment groups, although patients who received rituximab appeared to have higher disease activity in terms of SJC, TJC, ESR and DAS28–ESR. Patients receiving rituximab were more likely to be seropositive (RF+). Reasons for discontinuing initial TNF inhibitor are given in table 1. Compared with patients discontinuing because of inefficacy, patients discontinuing because of intolerance had longer disease duration (mean (SD) 10.7 (8.7) vs 7.7 (6.6) years), and had been receiving their first TNF inhibitor for a shorter period of time (20.4 (24.0) vs 28.4
In a robustness analysis, in which no imputations of missing disease activity (mm) values were made, the mean change in DAS28-3 from baseline to 6 months remained significant.

Changes in clinical characteristics over 6 months are summarised in Table 3. The mean change in DAS28-3–ESR from baseline to 6 months was significantly greater in the rituximab group than in those who switched to an alternative TNF inhibitor: 5.2 (1.2) vs 4.8 (1.3), p < 0.0001 (Table 3). This difference was also observed in patients who discontinued their initial TNF inhibitor because of inefficacy (n=547) (5.3 (1.2) vs 4.9 (1.2), p < 0.0001) and in those who discontinued because of intolerance (n=168) (5.0 (1.3) vs 4.5 (1.4), p = 0.029).

**Effectiveness**

Changes in clinical characteristics over 6 months are summarised in Table 3. The mean change in DAS28-3–ESR from baseline to 6 months was significantly greater in the rituximab group than in the alternative anti-TNF group (p = 0.007) (Table 3 and Figure 1). This difference remained statistically significant among the cohort of patients who discontinued initial TNF inhibitor because of inefficacy. However, among patients who discontinued because of intolerance, there was no significant difference between rituximab and an alternative TNF inhibitor (Figure 1).

A greater decrease in ESR was also observed in the rituximab versus the alternative TNF inhibitor group, both overall and in the inefficacy cohort (−13.2 vs −7.0; p = 0.009 and −10.0 vs −4.3; p = 0.038). SJC and TJC showed numerically greater improvements with rituximab, although the differences were not statistically significant.

In a robustness analysis, in which no imputations of missing DS28 values were made, the mean change in DS28–ESR from baseline to 6 months remained significantly greater in the rituximab group versus the alternative TNF inhibitor group (LS means −1.2 vs −0.9; p = 0.033).

**Subanalysis by serotype**

Overall, 559 (77%) patients in the primary effectiveness population were seropositive. Baseline DS28–ESR scores were (26.3) months. In addition, intolerant patients had significantly lower SJC, TJC, DS28–ESR and HAQ-DI scores at the end of their first TNF inhibitor treatment (data not shown).

In this fully adjusted analysis, mean (SD) baseline DS28–ESR in the primary effectiveness population was significantly higher in patients who switched to rituximab than in those who switched to an alternative TNF inhibitor: 5.2 (1.2) vs 4.8 (1.3), p < 0.0001 (Table 2). This difference was also observed in patients who discontinued their initial TNF inhibitor because of inefficacy (n=547) (5.3 (1.2) vs 4.9 (1.2), p < 0.0001) and in those who discontinued because of intolerance (n=168) (5.0 (1.3) vs 4.5 (1.4), p = 0.029).
DISCUSSION
Currently, there are no clear guidelines for managing patients with RA with an inadequate response to initial TNF inhibitor therapy. Consequently, decisions regarding further treatment generally depend on factors such as patient choice and how comfortable physicians are with the available alternatives. A common strategy for managing TNF-IR patients involves switching to a second TNF inhibitor. Although this strategy is beneficial in some patients, a number of studies have reported reduced efficacy with the second TNF inhibitor compared with the first and high rates of early discontinuation among patients who switch.

The primary effectiveness results from this global study provide evidence from real-world practice that TNF-IR patients...
achieve significantly better clinical responses over 6 months if they receive rituximab rather than an alternative TNF inhibitor as their second biological therapy. Similar to most non-interventional studies, this open-label, observational study had the limitation of substantial missing data, especially due to enrolment of patients up to 4 weeks of starting the second biological therapy, which resulted in many with a missing baseline. Because the number and timing of visits were left to investigators’ discretion, limited data were available to implement most of the imputation methods appropriate to handle the withdrawal. However, the complete results are broadly in agreement with recent reports from national European registry studies. In a study of patients with a single TNF inhibitor failure from the British Society for Rheumatology Biologics Register, patients who received rituximab as their second biological therapy were significantly more likely to achieve a European League Against Rheumatism response and improvements in HAQ at 6 months than those who received a second TNF inhibitor. Data from a Swiss registry also indicated that rituximab treatment led to better clinical outcomes in TNF-IR patients than an alternative TNF inhibitor. The latter registry also recently reported that rituximab and alternative TNF inhibitors were as effective in preventing radiographical joint damage.

The difference in clinical response at 6 months between rituximab and alternative TNF inhibitor therapy in the present study was observed in the primary effectiveness population, with differences greatest among patients who discontinued their first TNF inhibitor because of inefficacy. Patients who discontinued because of intolerance showed no statistically significant difference between rituximab and TNF inhibitor treatment. These results are also consistent with previous studies, in which TNF-IR patients who stopped because of primary inefficacy experienced lesser clinical responses with subsequent TNF therapy than those who stopped because of secondary inefficacy or intolerance. Enhancement of clinical response to rituximab in patients who discontinued their first TNF inhibitor because of inefficacy was observed in the Swiss registry. Patients exhibiting primary non-responsiveness to TNF inhibitors are likely to have non-TNF-α-mediated disease and consequently would be predicted to respond better to subsequent therapy with an alternative mode of action. In contrast, patients with secondary inefficacy to TNF inhibitors may have lost response because of the development of drug antibodies; these patients would therefore be expected to exhibit a response to an antigenically distinct treatment, whether within or distinct from the previous class. The presence of drug antibodies was not measured in this study. Finally, as most toxicity is independent of a class effect, this explains the similarities between outcomes with rituximab and TNF inhibitors in patients discontinuing their initial TNF inhibitor because of intolerance.

A subanalysis according to serological status revealed that the difference between rituximab and an alternative inhibitor was further enhanced among the ~80% of patients who were seropositive at baseline. In addition, as observed with the entire primary effectiveness population, the improvement with rituximab versus TNF inhibitor treatment was significantly greater in seropositive patients with a previous TNF inhibitor failure due to inefficacy. Assessing the relative effectiveness of rituximab and TNF inhibitor therapy in seronegative patients was limited by the lower patient numbers in this subgroup. Interestingly, of patients discontinuing a TNF inhibitor because of intolerance, seronegative patients in both the rituximab and TNF inhibitor groups exhibited numerically greater responses than those observed in seropositive patients. In general, responses to rituximab in seronegative patients were numerically, but not statistically significantly, superior to those achieved with TNF inhibitors. Overall, the results of the subanalysis by serological status concur with recent studies reporting enhancement of clinical responsiveness to rituximab in seropositive over seronegative patients. In addition, serological status did not appear to influence responsiveness to TNF inhibitors in our study. Previous studies examining the influence of serological status on responsiveness to TNF inhibitors yielded inconsistent results.

The incidence and type of AEs observed with the two treatments evaluated in this study were broadly similar and as expected on the basis of the known safety profiles of these therapies. Rituximab was associated with a slightly higher incidence of serious AEs and serious infections, while there was one positive mycobacterium tuberculosis test in the TNF inhibitor group.

In conclusion, these results from the SWITCH-RA study, conducted in real-life conditions reflective of current clinical practice, indicate that, after discontinuation of a first TNF inhibitor, patients switching to rituximab achieved greater clinical effectiveness on average over 6 months compared with patients switching to an alternative TNF inhibitor. This difference was particularly evident among seropositive patients who discontinued their initial TNF inhibitor because of inefficacy.

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### Contributors

The study was designed by PE, AF, VMMT, LB-F, JEG, AR-R, RJM, CM, and conducted by PE, AO, EG, JEG, RUM, CM, CC and LHG. Data analysis and interpretation were carried out by PE, AF, VMMT, LB-F, AO, EG, JEG, AR-R, RJM, CM, CC and LHG. The manuscript was developed and approved by all authors.

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### Table 5  Safety summary (full analysis population)

| Adverse event          | Rituximab (n=604) | Alternative TNF inhibitor (n=507) |
|------------------------|-------------------|---------------------------------|
| All adverse events     | 291 (48.2)        | 241 (47.5)                      |
| Serious adverse events | 82 (13.6)         | 56 (11.0)                       |
| Infusion reactions     | 66 (10.9)         | 20 (3.9)                        |
| Infections             | 112 (18.5)        | 99 (19.5)                       |
| Serious infections     | 23 (3.8)          | 9 (1.8)                         |
| Number of events (rate*)| 25 (4.42)        | 9 (1.94)                       |
| 95% CI of rate         | 2.86 to 6.52      | 0.89 to 2.68                    |

*Values are number (%). *Per 100 patient-years. TNF, tumour necrosis factor.
Health Interactions drafted the manuscript based on consultation with senior authors and revised the manuscript based on the involvement and input of all authors. All authors read and approved the final content of the manuscript.

Competing interests PE has undertaken clinical trials and provided expert advice for Pfizer, MSD, Abbvie, Novartis, Roche and Bristol Myers Squibb. AF has received consulting and speaker fees from Roche, Abbott, Pfizer, Bristol Myers Squibb and MSD. AR-R has received consulting and speaker fees from Roche, Chugai, Abbott, Pfizer, Bristol Myers Squibb, UCB and MSD. PS-P has received consulting and speaker fees from Roche Products, Bristol Myers Squibb, Johnson & Johnson, Pfizer and Merck. DC has received consulting and speaker fees from Abbvie, Amgen, Astra-Zeneca, Janssen, Bristol Myers Squibb, GlaxoSmithKline, Pfizer, UCB and F Hoffmann La Roche. VMM has received research funding from Schering-Plough, Wyeth-Pharma and Roche, has participated on advisory boards for UCB-Pharma, Bristol-Myers Squibb, Roche, Cellerix, Pfizer, Sobi and Boehringer Ingelheim, and has been involved in clinical trials for Novartis, Schering-Plough, Centocor, Wyeth-Pharma, Abbott, Bristol Myers Squibb, Roche, Serono, Amgen, GlaxoSmithKline and Pfizer. LB-F has received consulting and speaker fees from Roche, UCB, GlaxoSmithKline, Jansen, MSD and Bristol Myers Squibb. AO has received support from (including attendance at conferences), undertakes clinical trials for, and acts as a consultant to Roche, Chugai, Abbott, Pfizer and Bristol Myers Squibb. AA has received speaker fees from Roche and MSD. EG is an employee of Quintiles. CM and LHG are employees of F Hoffmann-La Roche Ltd. CC is an employee of Genentech Inc.

Patient consent Obtained.

Ethics approval Institutional review boards at each study centre.

Provenance and peer review
Institutional review boards at each study centre.

Conflicts of interest
PE has undertaken clinical trials and provided expert advice for Pfizer, MSD, Abbvie, Novartis, Roche and Bristol Myers Squibb. AF has received consulting and speaker fees from Roche, Abbott, Pfizer, Bristol Myers Squibb and MSD. AR-R has received consulting and speaker fees from Roche, Chugai, Abbott, Pfizer, Bristol Myers Squibb, UCB and MSD. PS-P has received consulting and speaker fees from Roche Products, Bristol Myers Squibb, Johnson & Johnson, Pfizer and Merck. DC has received consulting and speaker fees from Abbvie, Amgen, Astra-Zeneca, Janssen, Bristol Myers Squibb, GlaxoSmithKline, Pfizer, UCB and F Hoffmann La Roche. VMM has received research funding from Schering-Plough, Wyeth-Pharma and Roche, has participated on advisory boards for UCB-Pharma, Bristol-Myers Squibb, Roche, Cellerix, Pfizer, Sobi and Boehringer Ingelheim, and has been involved in clinical trials for Novartis, Schering-Plough, Centocor, Wyeth-Pharma, Abbott, Bristol Myers Squibb, Roche, Serono, Amgen, GlaxoSmithKline and Pfizer. LB-F has received consulting and speaker fees from Roche, UCB, GlaxoSmithKline, Jansen, MSD and Bristol Myers Squibb. AO has received support from (including attendance at conferences), undertakes clinical trials for, and acts as a consultant to Roche, Chugai, Abbott, Pfizer and Bristol Myers Squibb. AA has received speaker fees from Roche and MSD. EG is an employee of Quintiles. CM and LHG are employees of F Hoffmann-La Roche Ltd. CC is an employee of Genentech Inc.

Patient consent Obtained.

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Data sharing statement All authors had full access to all the data in the study and contributed to data interpretation.

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