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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

P Emery,^{1,2} J E Gottenberg,³ A Rubbert-Roth,⁴ P Sarzi-Puttini,⁵ D Choquette,⁶ V M Martínez Taboada,⁷ L Barile-Fabris,⁸ R J Moots,⁹ A Ostor,¹⁰ A Andrianakos,¹¹ E Gemmen,¹² C Mpofo,¹³ C Chung,¹⁴ L Hinsch Gylvin,¹³ A Finckh¹⁵

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For numbered affiliations see end of article.

Correspondence to

Professor Paul Emery, Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, LMBRU LHTT, Chapel Allerton Hospital, Leeds LS7 4SA, UK; p.emery@leeds.ac.uk

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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, inefficacy or other. Inefficacy was further categorised as primary inefficacy (lack of initial clinical response to TNF inhibitor treatment) or secondary inefficacy (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 DAS28-3-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 DAS28-3-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 DAS28-3-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

Table 1 Reasons for discontinuation of previous TNF inhibitor

Reason	Rituximab	Alternative TNF inhibitor	All patients
<i>Full analysis population</i>	(n=604)	(n=507)	(n=1111)
Inefficacy	465 (77.0)	362 (71.4)	827 (74.4)
Primary*	214 (46.0)	115 (31.8)	329 (39.8)
Secondary*	244 (52.5)	233 (64.4)	477 (57.7)
Missing data	7 (1.5)	14 (3.9)	21 (2.5)
Intolerance	128 (21.2)	136 (26.6)	263 (23.7)
Other	11 (1.8)	10 (2.0)	21 (1.9)
<i>Primary effectiveness population</i>	(n=405)	(n=323)	(n=728)
Inefficacy	311 (76.8)	236 (73.1)	547 (75.1)
Primary*	130 (41.8)	74 (31.4)	204 (37.3)
Secondary*	176 (56.6)	156 (66.1)	332 (60.7)
Missing data	5 (1.6)	6 (2.5)	11 (20.1)
Intolerance	89 (22.0)	79 (24.5)	168 (23.1)
Other	6 (1.2)	8 (2.5)	13 (1.8)

Values are number (%).

*Primary inefficacy, lack of initial clinical response to TNF inhibitor treatment; secondary inefficacy, development of an inadequate response over time after an initial clinical response.

TNF, tumour necrosis factor.

(26.3) months). In addition, intolerant patients had significantly lower SJC, TJC, DAS28-3-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 DAS28-3-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), $p = 0.029$).

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 DAS28 values were made, the mean change in DAS28-3-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 DAS28-3-ESR scores were

Table 2 Patient baseline demographics and clinical characteristics (primary effectiveness population)

Characteristic	Rituximab (n=405)	Alternative TNF inhibitor (n=323)	p Value*
Age (years), mean (SD)	56.5 (12.6)	54.7 (13.3)	0.0611
Female, n (%)	310 (76.5)	259 (80.2)	0.2376
RA duration (years), mean (SD)	9.1 (7.7)	7.8 (6.8)	0.1044
No of previous DMARDs, mean (SD)	2.2 (1.1)	2.3 (1.3)	0.3853
Receiving methotrexate, n (%)	199 (49.1)	180 (55.7)	0.0769
Methotrexate dose (mg/week), mean (SD)	13.3 (4.9)	14.4 (9.4)	0.1774
Receiving corticosteroid, n (%)	293 (72.3)	229 (70.9)	0.6666
Duration of previous TNF inhibitor therapy (months), mean (SD)	27.4 (25.9)	26.3 (26.6)	0.6478
RF positive, n (%)	318 (84.1)	204 (65.6)	< 0.0001
ACPA positive, n (%)	172 (69.1)	133 (59.4)	0.0277
Seropositive (RF+ or ACPA+), n (%)	331 (81.7)	228 (70.6)	0.0004
DAS28-3-ESR, mean (SD)	5.2 (1.2)	4.8 (1.3)	< 0.0001
ESR (mm/h), mean (SD)	38.9 (26.7)	32.5 (24.7)	0.0023
CRP (mg/L), mean (SD)	26.1 (41.4)	23.8 (39.7)	0.4856
SJC (28 joints), mean (SD)	7.5 (5.5)	6.1 (5.6)	0.0024
TJC (28 joints), mean (SD)	10.2 (7.1)	8.2 (6.8)	0.0008
HAQ-DI, mean (SD)	1.5 (0.8)	1.3 (0.8)	0.0945

*Analysis of covariance or χ^2 test.

ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; DAS28-3, Disease Activity Score in 28 joints excluding patient's global health component; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor.

Table 3 Mean changes in clinical characteristics from baseline to 6 months* (primary effectiveness population)

Change over 6 months	Rituximab (n=405)	Alternative TNF inhibitor (n=323)	p Value*
DAS28-3-ESR†	-1.5 (0.2)	-1.1 (0.2)	0.007
Improved by at least 0.6, n (%)	280 (69.1)	191 (59.1)	0.005
Improved by at least 1.6, n (%)	156 (38.5)	95 (29.4)	0.010
DAS28-3-CRP	-1.4 (0.3)	-1.3 (0.3)	0.538
ESR (mm/h)	-13.2 (3.9)	-7.0 (4.2)	0.009
CRP (mg/L)	-29.1 (8.0)	-29.9 (8.4)	0.876
SJC (28 joints)	-3.3 (0.9)	-2.8 (1.0)	0.417
TJC (28 joints)	-5.7 (1.2)	-4.5 (1.2)	0.113
Physician global assessment of disease (mm)	-21.0 (6.1)	-14.8 (6.7)	0.076
Patient global assessment of disease (mm)	-17.0 (5.5)	-10.2 (5.8)	0.044
Patient VAS pain score (mm)	-15.7 (6.5)	-10.8 (7.0)	0.203
HAQ-DI	-0.6 (0.2)	-0.5 (0.2)	0.337
Duration of morning stiffness (min)	-19.0 (25.4)	-4.3 (27.4)	0.325

Values are LS mean (SE).

*LS means and p values were based on analysis of covariance (ANCOVA) models with change in outcome as the dependent variable and treatment group as the independent variable, with controls for baseline value on the outcome variable, and unbalanced baseline characteristics. p Values for counts were based on the Pearson's χ^2 test.

†Sensitivity analysis results using ANCOVA with adjustment for the propensity to receive treatment were rituximab -1.3 (0.1) and TNF inhibitor -1.0 (0.1) ($p = 0.006$). CRP, C-reactive protein; DAS28-3, Disease Activity Score in 28 joints excluding patient's global health component; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor; VAS, visual analogue scale.

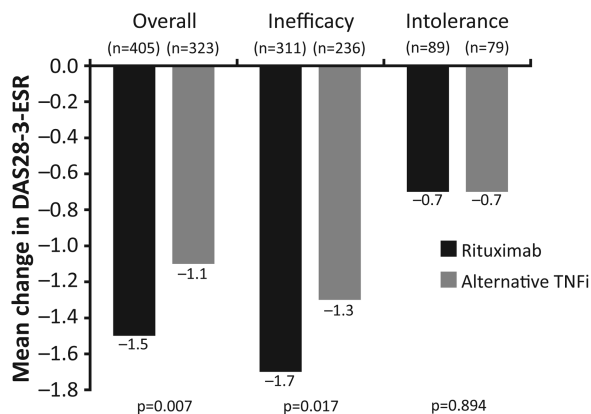


Figure 1 Mean change in Disease Activity Score in 28 joints excluding patient’s global health component—erythrocyte sedimentation rate (DAS28–3–ESR) from baseline to 6 months. Analyses were adjusted for baseline value and other covariates found to be statistically significantly different between the two groups at baseline. Values are DAS28–3–ESR least squares means. TNFi, tumour necrosis factor inhibitor.

higher in the rituximab group than the alternative TNF inhibitor group in both seropositive (mean (SD) 5.2 (1.2) vs 4.8 (1.3); $p < 0.0001$) and seronegative (5.3 (1.1) vs 4.7 (1.3); $p = 0.0019$) patients. After adjustment for baseline differences, seropositive patients showed a significantly greater improvement in DAS28–3–ESR over 6 months with rituximab than with an alternative TNF inhibitor (table 4). The relative benefit of rituximab in seropositive patients was observed in patients who discontinued their initial TNF inhibitor because of inefficacy but not in those who discontinued because of intolerance. Although seronegative patients also showed improvements in DAS28–3–ESR at 6 months, there was no significant difference between the rituximab and alternative TNF inhibitor groups. The seronegative group was, however, much smaller than the seropositive group, and was therefore underpowered to detect small differences. A similar pattern was seen with ESR as the outcome measure. Seropositive patients receiving rituximab showed greater changes in ESR (LS mean (SE)) over 6 months than those receiving an alternative TNF inhibitor (–14.4 (4.5) vs –7.3 (4.8); $p = 0.006$); corresponding results in seronegative patients were –13.4 (8.3) vs –10.4 (9.0) ($p = 0.582$).

Safety

A summary of safety is presented in table 5. The overall incidence of AEs was similar in the rituximab and alternative TNF inhibitor groups. The most commonly reported AEs (occurring in $\geq 2\%$ of patients) in the rituximab group were urinary tract infections (4.8%), lower respiratory tract infections (2.8%), headache

(2.5%) and nausea (2.0%). In the alternative TNF inhibitor group, the most frequent AEs were urinary tract infections (3.2%), headache (3.2%), rash (3.0%), cough (2.8%), nausea (2.6%), diarrhoea (2.4%), lower respiratory tract infections (2.0%) and nasopharyngitis (2.0%). Infections were reported at a similar rate in the two groups. Serious AEs were reported by 82 (13.6%) and 56 (11.0%) patients in the rituximab and alternative TNF inhibitor groups, respectively, and most commonly occurred within the musculoskeletal and connective tissue disorders system organ class (rituximab, 21 patients (3.5%); alternative TNF inhibitor, 22 patients (4.3%)). Serious infections were reported more frequently with rituximab (25 events in 23 patients, 3.8%) than with alternative TNF inhibitor treatment (nine events in nine patients, 1.8%) with corresponding rates (95% CI) per 100 patient-years of 4.42 (2.86 to 6.52) vs 1.94 (0.89 to 3.68). Overall, the most common serious infections (rituximab vs alternative TNF inhibitor group) were pneumonia (0.5% (0.7% vs 0.2%)), urinary tract infection (0.4% (0.7% vs 0.0%)) and lower respiratory tract infection (0.3% (0.5% vs 0.0%)). There was one positive mycobacterium tuberculosis complex test (T-SPOT; Oxford Immunotec, UK) in the alternative TNF inhibitor group. The patient received antituberculosis agents (rifampicin and pyridoxine), and the event resolved without sequelae. Malignancies (neoplasms—benign, malignant and unspecified) were reported by nine rituximab patients (1.5%) and 11 alternative TNF inhibitor patients (2.2%); two of these events in each group were considered to be possibly related to study treatment (stage 0 prostate cancer and Waldenstrom’s macroglobulinaemia in the rituximab group and two patients with squamous cell carcinoma of the skin in the alternative TNF inhibitor group). Overall, seven (1.2%) and four (0.8%) patients receiving rituximab and alternative TNF inhibitor, respectively, died as a result of an AE during the study. None was considered to be related to the study treatment.

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.²¹ A common strategy for managing TNF-IR patients involves switching to a second TNF inhibitor. Although this strategy is beneficial in some patients,²² 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.²

The primary effectiveness results from this global study provide evidence from real-world practice that TNF-IR patients

Table 4 Changes in DAS28–3–ESR at 6 months according to serotype (primary effectiveness population)

	Seropositive patients (n=559)			Seronegative patients (n=169)		
	Rituximab	Alternative TNF inhibitor	p Value	Rituximab	Alternative TNF inhibitor	p Value
All patients	–1.6 (0.3)	–1.2 (0.3)	0.011	–1.3 (0.4)	–1.1 (0.4)	0.449
Inefficacy	–1.9 (0.3)	–1.5 (0.4)	0.021	–0.5 (0.6)	–0.2 (0.7)	0.472
Intolerance	–0.5 (0.5)	–0.5 (0.5)	0.997	–2.1 (1.2)	–1.9 (1.3)	0.815

Values are LS mean (SE). Patient numbers (all/inefficacy/intolerance): seropositive, rituximab 331/253/74 and TNF inhibitor 228/171/51; seronegative, rituximab 74/58/15 and TNF inhibitor 95/65/28. LS means and p values were based on analysis of covariance models with change in outcome as the dependent variable and treatment group as the independent variable, with controls for baseline value on the outcome variable, and unbalanced baseline characteristics. DAS28–3, Disease Activity Score in 28 joints excluding patient’s global health component; ESR, erythrocyte sedimentation rate; LS, least squares; TNF, tumour necrosis factor.

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.

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 completer 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.²³ Data from a Swiss registry also indicated that rituximab treatment led to better clinical outcomes in TNF-IR patients than an alternative TNF inhibitor.^{16 17} The latter registry also recently reported that rituximab and alternative TNF inhibitors were as effective in preventing radiographical joint damage.²⁴

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.^{25 26} Enhancement of clinical response to rituximab in patients who discontinued their first TNF inhibitor because of inefficacy was observed in the Swiss registry.¹⁶ 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.^{27–30} 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.^{31–34}

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.

Author affiliations

- ¹Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK
- ²NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK
- ³Department of Rheumatology, CHU Strasbourg, Strasbourg, France
- ⁴University of Cologne, Cologne, Germany
- ⁵L Sacco University Hospital, Milan, Italy
- ⁶University of Montreal, Montreal, Canada
- ⁷Facultad de Medicina, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain
- ⁸Hospital de Especialidades Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, México City, México
- ⁹Department of Rheumatology, University of Liverpool, Liverpool, UK
- ¹⁰Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
- ¹¹Hellenic Foundation for Rheumatological Research, Athens, Greece
- ¹²Quintiles, Rockville, Maryland, USA
- ¹³F Hoffmann-La Roche Ltd, Basel, Switzerland
- ¹⁴Genentech Inc, San Francisco, California, USA
- ¹⁵University Hospital of Geneva, Geneva, Switzerland

Contributors The study was designed by PE, AF, VMMT, LB-F, JEG, AR-R, RJM, CM, and conducted by PE, AO, EG, JEG, RJM, 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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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. VMMT has received research funding from Schering-Plough, Wyeth-Pharma and Roche, has participated on advisory boards for UCB-Pharma, Bristol-Myers Squibb, Roche, Cellierix, 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, MSD, 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.

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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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Supplemental Text

As with any observational study, there is always a concern of differences in baseline characteristics that are associated with disease activity, which may substantially influence response to therapy. Given the observational nature of this study, there is a possibility of selection bias resulting due to non-random assignment of treatment. The following baseline variables were available for analysis:

- Patient age
- Gender
- Country
- Years of initial RA diagnosis
- RF status
- Presence of anti-CCP
- Evidence of structural joint damage
- Number of surgical procedures related to RA
- Extra-articular manifestation of RA
- Number of comorbid conditions at baseline
- Type of first TNF inhibitor (antibody/receptor)
- Number of ongoing medications at baseline
- Factors related to selection of the particular second biologic
- Reason for discontinuation of first TNF inhibitor treatment (reason for change)
- Baseline outcome variables (e.g., HAQ score, physician's global assessment of disease activity, DAS28 score, etc.)
- Concurrent NSAID user anytime during the first 6 months of the study
- Concurrent corticosteroid user anytime during the first 6 months of the study
- Concurrent disease-modifying anti-rheumatic drugs (DMARD) use anytime during the first 6 months of the study

Factors clearly associated with selecting rituximab or an alternative TNF inhibitor (identified by a stepwise variable selection and multivariate logistic regression model) are illustrated in Figure S2.

Figure S1 Factors associated with selection of rituximab versus an alternative TNF inhibitor

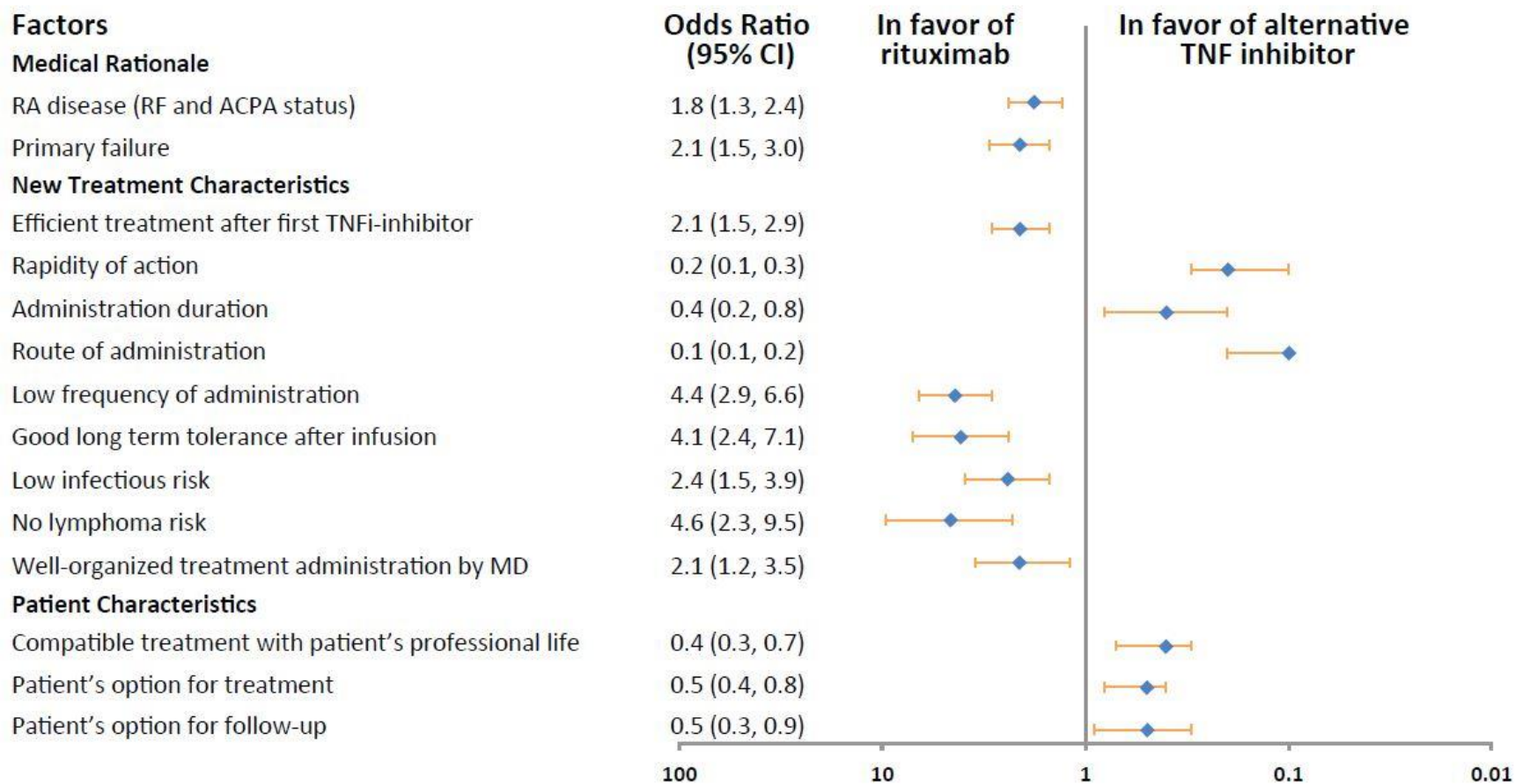


Figure S2 Patient disposition

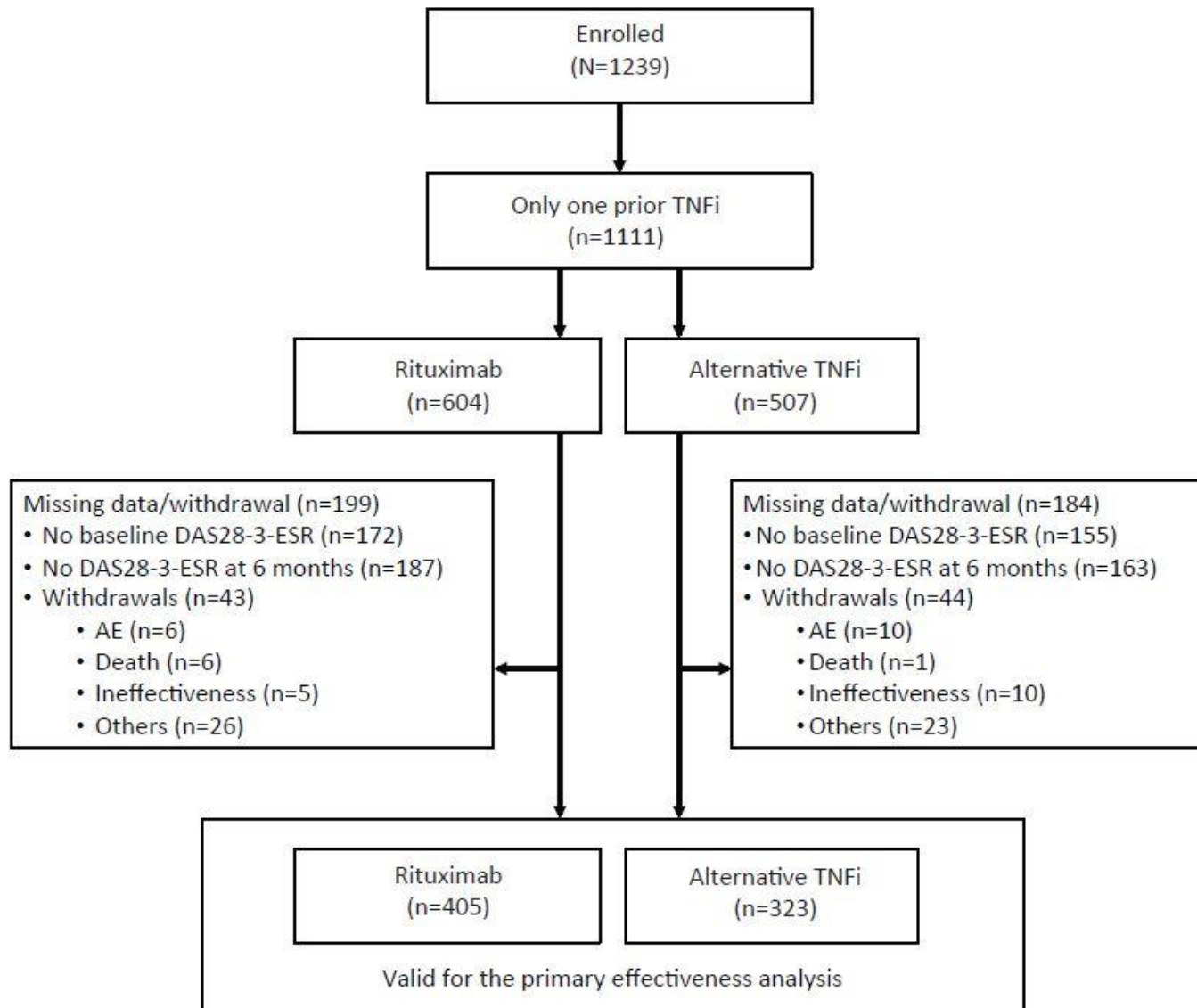


Table S1 Type of the first (failed) and the second (alternative) TNF inhibitors

n (%)	Rituximab	Alternative TNF Inhibitor	
Full Analysis Population	(n=604)	(n=507)	
	1 st TNF Inhibitor	1 st TNF Inhibitor	2 nd TNF Inhibitor
Adalimumab	205 (33.9)	182 (35.9)	224 (44.2)
Etanercept	257 (42.5)	255 (50.3)	190 (37.5)
Infliximab	136 (22.5)	66 (13.0)	36 (7.1)
Other (Certolizumab, Golimummab, etc.)	6 (1.0)	4 (0.8)	57 (11.2)
Primary Effectiveness Population	(n=405)	(n=323)	
Adalimumab	131 (32.3)	116 (35.9)	151 (46.7)
Etanercept	176 (43.5)	162 (50.2)	117 (36.2)
Infliximab	95 (23.5)	42 (13.0)	23 (7.1)
Other (Certolizumab, Golimummab, etc.)	3 (0.7)	3 (0.9)	32 (9.9)