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Real-world experience of effectiveness of non-medical switch from originator to biosimilar rituximab in rheumatoid arthritis.

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Abstract

Objective: To evaluate the impact of non-medical switch from rituximab originator (RTX-O) to biosimilar (RTX-B) in patients with rheumatoid arthritis (RA).

Methods: Between October 2017 and October 2019, all patients on RTX-O in our centre requiring re-treatment were switched to RTX-B unless declined by patient or specified by treating clinician. Switch strategy effectiveness was assessed retrospectively using DAS28-CRP(3) and RTX retention, with patients remaining on RTX-O as a comparator group.

Results: 255/337 patients (75.6%) switched to RTX-B while 82 (24.3%) remained on RTX-O. There was no difference in DAS28-CRP(3) 4 months post-RTX-B switch versus same time-point post-RTX-O previous cycle (paired data available in 60%). Eighteen month retention estimates were 75.6% (95% CI 69.4–80.7) for RTX-B group and 82.3% (95% CI 70.4–89.8) for RTX-O [adjusted HR 1.52 (95% CI 0.85-2.73)]. 42/255 patients (16.5%) discontinued RTX-B for loss of effectiveness (LOE), 5 (2.0%) for AE. Risk of RTX-B discontinuation was associated with comorbidities and ≥2 previous bDMARDs. Risk of adverse outcome RTX cessation was associated with comorbidities, and reduced risk with number of previous RTX-O cycles and pre-switch cycle B-cell depletion. 34/255 patients (13.3%) switched back to RTX-O (LOE=30, AE=4), while 13/255 (5.1%) started other b/tsDMARDs. Of patients switched back for LOE, 28/30 remained on RTX-O at mean 7.7 months follow-up.

Conclusion: Non-medical switch to RTX-B was largely effective. Factors associated with RTX-B discontinuation, including comorbidities, previous bDMARDs, and RTX-O treatment history, may inform switch decisions. Most patients switched back to RTX-O for LOE remained on treatment at short-term follow-up.

(Abstract word count: 250)

Key Points

1. In this RA cohort, non-medical switch to RTX-B following shared decision-making was largely effective.

2. Factors predicting RTX-B discontinuation post-switch included comorbidities, previous bDMARDs, and fewer previous RTX-O cycles.

3. Where LOE occurs post-RTX-B switch, switching back to RTX-O may be a pragmatic option.

INTRODUCTION

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody (mAb), is an established treatment for rheumatoid arthritis (RA) following insufficient response to csDMARD therapy [1–7].

The patent held by Roche for the RTX originator (RTX-O), MabThera®, expired in the European Union in November 2013 and in the United States (US) in September 2016. Several manufacturers have developed biosimilar versions, which by definition must meet rigorous standards of similarity with the reference product as part of the regulatory approval process [8]. Laboratory studies and RCTs have demonstrated equivalent physicochemical and functional properties, pharmacokinetics, efficacy and safety comparing RTX-O and RTX biosimilar (RTX-B) [9–11]. At time of writing, the biosimilars Truxima®, Rixathon® and Ruxience™ have gained marketing approval for RA in Europe, while Truxima® and Ruxience™ are also approved in the US.

Given the potential cost-savings associated with biosimilar use, there has been a drive within the UK National Health Service (NHS) and other healthcare providers to switch patients established on RTX-O to RTX-B. Data from a phase III RCT in RA showed that switching to RTX-B after maximum two cycles of RTX-O was well tolerated, with no clinically meaningful differences in efficacy, safety, pharmacodynamics or immunogenicity[12]. However, the effectiveness of switching from RTX-O to RTX-B in the real-world setting, where patient populations typically differ from clinical trials, has not been reported. Furthermore, discontinuation of therapy following open-label non-medical switch to TNFi biosimilars has been observed, partly attributed to the “nocebo” effect[13–15], and there have been concerns around immunogenicity and anti-drug antibody cross-reactivity, particularly for the mAbs (with chimeric mAbs, such as rituximab, carrying higher risk in theory) [16]. In addition, when

loss of effectiveness (LOE) occurs following biosimilar switch, the optimal treatment approach (e.g. switch back to originator versus switch to alternative DMARD) is unclear.

The aims of this study were to report our real-world single-centre observational experience of non-medical switch from RTX-O to RTX-B in RA, including disease activity, B-cell depletion and drug retention as measures of effectiveness, RTX-B discontinuation reasons, and treatment strategies following LOE or adverse effects (AEs) to RTX-B. Patients remaining on RTX-O for medical reasons or patient choice were included as a comparator group. Factors associated with discontinuation of RTX-B were also explored, with the aim of informing patient selection for non-medical switch.

METHODS

Study design

We conducted a retrospective observational cohort study of RTX-treated RA patients in Leeds, United Kingdom, from May 2002–January 2020 (including off-label use prior to licensing). All patients requiring re-treatment from October 2017 (when RTX-B was made available in the Leeds Medicines Formulary, Leeds Teaching Hospitals NHS Trust) were included. According to NHS Research Ethics Committee guidelines, this study was considered as service evaluation and formal ethical approval was not required[17].

Patients

Patents included in this study were age >16 years; fulfilled the 1987 American College of Rheumatology classification criteria for RA[18]; had a history of at least one previous cycle of RTX-O; and had undergone clinical review following switch to RTX-B.

Treatment decisions

From October 2017, all patients requiring re-treatment with RTX were considered for non-medical switch from RTX-O (Mabthera®) to RTX-B (Truxima®). Switch decisions were

made by the treating clinicians on a case-by-case basis after counselling and obtaining informed consent in accordance with shared decision-making. Retreatment with RTX was mostly 'on demand' following emergence of disease flare (relapse) and consisted of 100mg of methylprednisolone and either 1000mg (standard dose) or 500mg (lower dose, where indicated e.g. for hypogammaglobulinaemia, recurrent infections) of Truxima® (i.e. RTX-B switch group; those who consented to non-medical switch) or Mabthera® (i.e. RTX-O group; those who remained on originator for medical reasons or patient choice), given intravenously on days 1 and 14. Management decisions post-switch were again at the discretion of treating clinicians; for example, patients with LOE or AEs to RTX-B could be switched back to RTX-O or switched to alternative b/tsDMARDs as appropriate.

Data collection

Baseline clinical data were obtained from patient records and included age, sex, number of comorbidities (of hypertension, diabetes, ischaemic heart disease, stroke or transient ischaemic attacks, previous cancer, asthma, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis, chronic kidney or liver disease, epilepsy, multiple sclerosis, dementia, depression)[19], seropositivity, disease duration, concomitant csDMARD and oral prednisolone use, number of previous bDMARDs, and number of previous cycles of RTX-O. Standard clinical assessment with disease activity measurement was carried out 4 months post-RTX-B, and approximately 4-6 monthly thereafter. Follow-up data (for drug retention +/- subsequent treatment) were collected up to 31 January 2020. For those who discontinued RTX, reason for discontinuation [LOE (according to clinician judgement accompanied by disease activity assessment), AEs, death, or other (new contraindication, no longer indicated, patient choice)], date of discontinuation (date started new targeted therapy, date of death, or date of decision to stop RTX for other reason), and (where applicable) subsequent treatment were recorded.

Laboratory assessment

Peripheral blood B-cell subsets (naïve, memory, and plasmablast) were measured at the accredited Leeds Haematological Diagnostic Service using highly sensitive flow cytometry, as previously described[20], at 0 and 2 weeks post-RTX, without knowledge of clinical status other than time since RTX. Complete B-cell depletion at 2 weeks was defined as total B-cell counts < 0.0001×10^9 cells per litre.

Clinical outcomes

Disease activity: The disease activity score in 28 joints (DAS28-CRP) with 3 variables [DAS28-CRP(3)][21] was used in order to maximise the number of patients that could be included in analyses (data for patient global assessment were missing in 33%). Maintenance of response was assessed by comparing DAS28-CRP(3) at 4-month clinical review post-RTX-B to DAS28-CRP(3) at the same timepoint following previous cycle of RTX-O.

RTX-B / RTX-O retention: RTX retention time was measured in months and defined as follows: i) RTX-B retention time – date of first RTX-B infusion to date of RTX-B discontinuation (for any reason); and ii) RTX-O retention time – date of first infusion following decision to remain on RTX-O (hereby referred to as the index infusion) to date of RTX-O discontinuation (for any reason).

Adverse outcome RTX cessation following RTX-B switch: An alternative drug retention definition focussing on adverse clinical outcomes leading to cessation of B-cell depleting therapy (i.e. either RTX-B or RTX-O) was also used in exploratory analyses and defined as follows: date of first RTX-B infusion to date started new b/tsDMARD for LOE or AEs, or date of death.

Statistical analyses

Associations between variables were assessed using Chi^2 test for categorical variables and Student's *t*-test (paired *t*-test for disease activity pre- and post-switch) or Mann-Whitney U test for continuous variables, depending on data type and distribution.

Drug retention for RTX-B and RTX-O groups was described using Kaplan-Meier survival analyses with estimates at 12 and 18 months. Cases were censored at end of follow-up period if the outcome (RTX discontinuation) was not experienced. Cox proportional hazards method was used to estimate the hazard ratio (HR) for discontinuation comparing RTX-B and RTX-O groups (unadjusted and adjusted for relevant confounders).

Factors associated with RTX-B discontinuation post-switch were tested using multivariable logistic regression. Multiple imputation by chained equations was used to estimate missing data for baseline disease activity and B-cell subsets; twenty multiple imputation sets were used to provide stability of results. Stepwise backward elimination was used for model building, with p values <0.25 associated with the deviance used for model exclusion. For factors associated with adverse outcome RTX cessation (defined above), since the overall event rate was low, multivariable penalised logistic regression by least absolute shrinkage and selection operator (LASSO) method was used to minimise overfitting of results[22]. The Stata package *plogit* was used to identify the largest penalty coefficient lambda within 1 standard error of the value that minimised deviance in each imputed dataset; average coefficients from the best models were calculated. Statistical analyses were performed using Stata software version 16 (StataCorp, College Station, Texas, US) and IBM SPSS Statistics v.21.0 (IBM Corp, Armonk, New York, US).

RESULTS

Study population

803 patients with RA had received ≥1 cycle of RTX since May 2002. Of these, 346 required re-treatment during the study period and were considered for switch from RTX-O to RTX-B. Of 337/346 patients with evaluable data, 255/337 (75.6%) were switched to RTX-B (i.e. RTX-B switch group) and 82/337 (24.4%) remained on RTX-O (i.e. RTX-O group). Reasons for RTX-O continuation comprised patient choice=42, medical decision=37, unknown=3, detailed in the (**Supplementary Table S1**).

Mean follow-up was 18.1 months (SD 5.6) with total follow-up of 507 patient-years. A flow chart of participants is illustrated in **Figure 1.**

Clinical characteristics

Baseline characteristics of all 337 patients included are described in **Table 1**. Mean (SD) age was 63.7 (12.3) years, 264 (78.2%) were female, 331 (98.1%) were seropositive, 184 (54.6%) had at least one comorbidity, 203 (60.2%) had previous bDMARD therapy exposure (with 28.8% having failed ≥ 2), and median (IQR) number of previous cycles of RTX-O was 6 (3 - 9). Patients in the RTX-B switch group had fewer previous bDMARDs and fewer previous cycles of RTX-O compared to the RTX-O group, with no significant differences in other salient characteristics.

Clinical response

In the RTX-B switch group [complete paired data available for N=154/255; 60%], there was no difference between the DAS28-CRP(3) following last RTX-O cycle and following RTX-B switch; mean (SD) of 2.77 (1.04) and 2.86 (1.14) respectively; mean difference -0.09 (95% CI -0.29 to 0.11, p=0.367).

Similarly, in the RTX-O group [complete paired data available for N=51/82; 62%], there was no difference between the DAS28-CRP(3) following last RTX-O cycle and following index infusion of RTX-O; mean (SD) of 2.72 (1.21) and 2.95 (1.17) respectively; mean difference -0.23 (95% CI -0.55 to 0.09, p=0.160) (see **Supplementary Tables S2 and S3**).

B-cell depletion

In the RTX-B switch group, the proportion of patients achieving complete B-cell depletion was 217/248 (87.5%) following last RTX-O cycle and 199/247 (80.6%) following RTX-B switch. In the RTX-O group, complete depletion was achieved in 64/81 (79.0%) following last RTX-O cycle and 65/78 (83.3%) post-index infusion of RTX-O.

RTX-B / RTX-O discontinuation

In the RTX-B switch group, 62/255 (24.3%) patients discontinued RTX-B by end of study period [LOE = 42/62, of which 30/42 (11.8% of total) switched back to RTX-O and 12/42 (4.7% of total) started new b/tsDMARD; AEs = 5/62, of which 4/5 switched back to RTX-O (palpitations, headaches, widespread itching, blistering rash) and 1/5 started new b/tsDMARD (suspected infusion reaction secondary to anti-drug antibodies); deaths = 7/42 (2.7% of total); stopped treatment for other reasons = 8/42 (patient choice = 3, no longer indicated = 3, new contraindication = 2)].

In the RTX-O group, 14/82 (17.1%) discontinued RTX-O by end of study period [LOE = 3/14, of which all started new b/tsDMARD (3.7% of total); AEs = 2/14; deaths = 5/14 (6.1% of total); other reasons = 4/14] (**Table 2**).

Anti-drug antibodies were not formally measured in this study. However, of all patients who discontinued treatment for AEs, only 1/7 (from the RTX-B switch group) met criteria for secondary non-depletion non-response (i.e. severe infusion reaction lasting >24 hours and failure to deplete CD20+ naïve / memory B-cells), which was defined and associated with presence of anti-drug antibodies in a previous publication[23] (see **Supplementary Table S4**).

RTX-B / RTX-O retention

Drug retention estimates for the RTX-B switch group were 83.0% (95% CI 77.6 – 87.1) at 12 months and 75.6% (95% CI 69.4 – 80.7) at 18 months; for RTX-O these values were 91.3% (95% CI 82.6 – 95.8) and 82.3% (95% CI 70.4 – 89.8) respectively (**Figure 2**).

There was no significant difference in discontinuation risk (for any reason) between the RTX-B and RTX-O groups; unadjusted HR 1.47 (95% CI 0.82 to 2.63), p=0.194 **;** adjusted HR 1.52 (95% CI 0.85 to 2.73), p=0.157, adjusted for age, sex, concomitant csDMARD use and previous bDMARD exposure.

Factors associated with RTX-B discontinuation

In imputed multivariable logistic regression analysis, greater number of comorbidities [OR 2.03 (95% CI 1.39 to 2.95); p<0.001] and ≥2 previous bDMARDs [OR 5.23 (2.19 to 12.48); p<0.001] were associated with increased risk of RTX-B discontinuation, and shorter RA disease duration was associated with marginal reduced risk [OR 0.96 (95% CI 0.93 to 0.99; p=0.040] **(Supplementary Table S5).**

Factors associated with adverse outcome RTX cessation following RTX-B switch

In imputed multivariable penalized logistic regression analysis, greater number of comorbidities [OR 1.88 (95% CI 1.21 to 2.93; p=0.005)] was associated with increased risk of adverse outcome RTX cessation (as defined above) following RTX-B switch. Greater number of previous RTX-O cycles [OR 0.73 (95% CI 0.61 to 0.89; p=0.002) and complete B cell depletion in the RTX-O cycle pre-RTX-B switch [OR 0.28 (95% CI 0.09 to 0.89; p=0.032] were associated with reduced risk **(Table 3)**.

Outcomes following switch back to RTX-O

Of 30 patients switched back from RTX-B to RTX-O for LOE, 26/30 switched back after 1 cycle of RTX-B only, 3/30 after 2 cycles, and 1/30 after 3 cycles. There was a significant reduction in DAS28-CRP(3) following switch back to RTX-O for LOE on RTX-B [complete paired data available for N=17/30; 56.7%]; mean (SD) of 3.98 (1.39) post RTX-B and 2.94 (1.25) post-switch back to RTX-O; mean difference -1.04 (95% CI -1.92 to -0.16, p=0.023) [**Supplementary Table S6** for DAS28-CRP(4) and individual component data]. 28/30 patients remained on RTX-O at end of study period, but follow-up time was limited [mean (SD) follow-

up post-switch back 7.7 (5.2) months; 20/30 have received 1 cycle RTX-O only, 2 cycles = 9/30, 3 cycles = 1/30]. Of the remaining 2/30 patients, one died and one was started on a tsDMARD.

Patients switched back to RTX-O for LOE on RTX-B had more previous cycles of RTX-O than patients switched to alternative b/tsDMARDs [median (IQR) number of previous cycles 6.5 (4-10) versus 2 (1-3), p<0.0001], lower swollen joint counts following RTX-B switch [median (IQR) 1 (0-3) versus 4 (2-9); p=0.037], and were older [mean (SD) age 66.4 (9.9) versus 58.8 (11.4); p=0.037] **(Table 4).**

Of 4 patients with AEs on RTX-B who switched back to RTX-O, all were switched back after 1 RTX-B cycle only. Three out of 4 patients (with palpitations, headaches, widespread itching respectively) have been successfully retreated with RTX-O [mean (SD) follow-up post switch back 5.3 (5.0) months; all have received 1 cycle RTX-O only], with treatment pending in 1/4 (with blistering rash).

DISCUSSION

This is the first report of real-world effectiveness of non-medical switch from RTX-O to RTX-B in RA and offers insights into the pragmatic use of RTX-B in this context as well as having implications in guiding patient selection for non-medical switch.

In a tertiary referral centre cohort comprising patients with multiple prior bDMARD exposure, concurrent comorbidities and variable RTX-O history, RTX-B was observed to be largely effective. No significant deterioration in disease activity post-switch was detected, B cell depletion data were comparable to the previous RTX-O cycle, and the majority (approximately 75%) of patients switched to RTX-B remained on treatment at the end of the study period.

Drug retention was compared with patients remaining on RTX-O for medical reasons or patient choice. Whilst retention was slightly lower in the RTX-B group in absolute terms, no

statistically significant difference was detected (although this may be explained by lower numbers and event rate in the RTX-O group, which is a limitation of the data and study type). The RTX-O group should not be considered a strict control group, as it was a selected population with important differences in baseline characteristics; patients remaining on RTX-O had more previous bDMARD failures and longer RTX-O treatment history, which likely influenced retention. Nevertheless, this group formed a natural comparator and the broadly similar retention estimates provide reassurance as to the overall effectiveness of switching to RTX-B when considered in the context of data as a whole. Notably more RTX-B switch patients discontinued treatment for LOE, however most of these were successfully switched back to RTX-O, particularly those with longer time on RTX-O pre-switch and lower swollen joint counts following RTX-B switch (suggesting less objective evidence of disease flare). The proportions requiring a change in b/tsDMARD therapy (indicating clear failure of B-cell depletion as a treatment strategy) were similar between RTX-B switch and RTX-O groups.

Given data from RCTs have demonstrated equivalent efficacy of RTX-O and RTX-B[10–12], the discrepancy in discontinuation for LOE in our dataset, and the apparent effectiveness of switching back to RTX-O, could be interpreted as evidence of the nocebo effect in action. These findings mirror some of the published data following open-label switch to TNFi biosimilars[13,14]. Ideally pre-switch counselling and shared decision-making would nullify the impact of the nocebo effect, but these measures do not appear sufficient in all cases.

The observational nature of our data and non-protocolised treatment decisions mean we are unable to draw definite conclusions about optimal management for lack of effectiveness following biosimilar switch. However, switching back to the originator may be the least disruptive, pragmatic option for individuals who have irrevocably lost confidence in the biosimilar. In our study, a significant overall reduction in disease activity was detected following switch back to RTX-O (albeit based on limited numbers), and most patients who

switched back remained on treatment at short-term follow-up; only one patient required a change in b/tsDMARD therapy after failure to recapture response with B-cell depletion.

Some degree of patient selection may be appropriate when implementing a non-medical switch strategy in RA in order to minimise treatment disruption on B-cell depleting therapy. In our exploratory analyses, RTX-B discontinuation (for any reason) was associated with number of comorbidities (which are often exclusion criteria for patient selection into RCTs) and number of previous bDMARDs. With regards the alternative retention analysis (adverse outcome RTX cessation i.e. LOE or AEs post RTX-B switch leading to change in b/tsDMARD, or death), this risk was also associated with number of comorbidities, as well as fewer previous RTX-O cycles and incomplete peripheral B-cell depletion in the last cycle pre-switch (although these may have been driven by patients with poor or partial response to initial cycle(s) of RTX-O, who may have been more appropriately changed to a different b/tsDMARD, rather than RTX-B switch). Overall our data suggest that an individualised approach may be warranted, with patients who are "RTX-experienced" and with absent or lower number of comorbidities and previous bDMARDs most suitable for non-medical RTX-B switch.

From the perspective of safety, discontinuation for adverse effects on RTX-B was rare. Some patients with adverse effects were successfully switched back to RTX-O, but in these cases the adverse effects were either mild or tenuously linked mechanistically to RTX itself. We did not routinely measure anti-drug antibodies, but only one patient had a serious infusion-related adverse event meeting the definition of secondary non-depletion non-response, which was associated with presence of anti-drug antibodies in a previous publication [23]. This patient was switched to another b/tsDMARD, as recurrence would have been expected with either RTX-B or RTX-O given their chemical similarity.

This study has some further limitations. First, the study design was retrospective and treatment decisions were non-protocolised. Nevertheless, treatment decisions were made in a tertiary

referral centre with multidisciplinary approach to ensure consensus and uniformity. Second, the single-centre nature of our data may limit the generalisability of findings. As discussed above, our shared decision-making approach involved clinician discretion and patient selection for appropriateness of switch. However, treatment outcomes for all patients from the inception of the study were captured, and the use of a comparator group (patients who remained on RTX-O) enhances the internal validity of our RTX-B switch effectiveness findings. Third, just over one third of data were missing for DAS28-CRP calculation, however drug retention was used as an additional measure of strategy effectiveness and indeed may be a more appropriate surrogate for effectiveness in the real-world setting. Defining RTX discontinuation can be challenging due to episodic dosing and variable treatment intervals, and some registry-based drug retention studies have imposed arbitrary stop dates based on B-cell repopulation time[19]. In our study, patients were considered to remain on treatment until a clear decision was made to stop, which may better reflect clinical response times. Lastly, more follow-up data post-RTX-B switch would serve to confirm the effectiveness of switching over the longer term.

In conclusion, our data support the overall effectiveness and safety of a shared decision-making biosimilar switch strategy approach, and highlights that certain patient characteristics (particularly multiple comorbidities and multiple previous bDMARDs) may have utility in guiding patient selection in order to minimise treatment disruption.

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Table 1. Baseline characteristics for all RTX-treated patients included in the study

	All patients (n=337)	RTX-B switch (n=255)	RTX-O group (n=82)	p value[a] (RTX-B vs RTX-O group)
Age, mean (SD), years	63.7 (12.3)	63.2 (12.3)	65.3 (12.2)	0.181[b]
Female, n (%)	264 (78.3)	199 (78.0)	65 (79.3)	0.878
Comorbidities, n (%)				0.869[c]
0	153 (45.4)	116 (45.5)	37 (45.1)	
1	103 (30.6)	77 (30.2)	26 (31.7)	
2	59 (17.5)	49 (19.2)	10 (12.2)	
3+	22 (6.5)	13 (5.1)	9 (10.9)	
CCP positive, n (%)	302 (91.0)	226 (90.4)	76 (92.7)	0.660
RF positive, n (%)	284 (84.3)	218 (85.5)	66 (80.5)	0.297
CCP or RF positive, n (%)	331 (98.2)	249 (97.6)	82 (100)	0.342
Disease duration, median (IQR), years	15 (10,23)	14 (9,23)	16.5 (11,24)	0.239[c]
csDMARD, n (%)				
Any	267 (79.2)	206 (80.8)	61 (74.4)	0.215
Methotrexate	214 (63.5)	159 (62.4)	55 (67.1)	
Sulfasalazine	3 (0.9)	3 (1.2)	0 (0)	
Leflunomide	8 (2.4)	6 (2.4)	2 (2.4)	
Hydroxychloroquine	40 (11.9)	36 (14.1)	4 (4.9)	
Azathioprine	2 (0.6)	2 (0.8)	0 (0)	
None	70 (20.8)	49 (19.2)	21 (25.6)	
Oral steroid, n (%)	52 (15.4)	38 (14.9)	14 (17.1)	0.603
Previous biologics, n (%)				0.030
Any	203 (60.2)	149 (58.4)	54 (65.9)	
0	134 (39.8)	106 (41.6)	28 (34.1)	
1	106 (31.5)	85 (33.3)	21 (25.6)	
2	67 (19.9)	46 (18.0)	21 (25.6)	
3+	30 (8.9)	18 (7.1)	12 (14.6)	
Previous TNFi, n (%)	198 (58.8)	145 (56.9)	53 (64.6)	0.083
Number of previous RTX-O cycles, median (IQR)	6 (3,9)	5 (3,9)	7.5 (5,11)	0.002[c]
Time since 1st cycle RTX-O, median (IQR), years	5 (3,9)	5 (3,8)	7 (4,10)	0.010[c]

[a] Chi^2 test unless stated.
[b] Unpaired Student's *t*-test.
[c] Mann-Whitney test.

Table 2. Treatment outcomes for patients switched to RTX-B and patients remaining on RTX-O

Outcome	Switch to RTX-B, n = 255	Remain on RTX-O, n = 82
Follow up, mean (SD), months	18.2 (5.7)	17.6 (5.1)
Discontinued treatment, n (%)	62 (24.3)	14 (17.1)
Discontinuation reason / treatment outcome, n (% of discontinued, % of total):		
Loss of effectiveness	42 (67.7, 16.5)	3 (21.4, 3.7)
- Switch back	30 (48.4, 11.8)	N/A
- Other biologic[a]	12 (19.4, 4.7)	3 (21.4, 3.7)
Adverse effects[b]	5 (8.1, 2.0)	2 (14.3, 2.4)
- Switch back	4 (6.5, 1.6)	N/A
- Other biologic[c]	1 (1.6, 0.4)	2 (14.3, 2.4)
Death[d]	7 (11.3, 2.7)	5 (35.7, 6.1)
Other	8 (12.9, 3.2)	4 (28.6, 4.9)
- Contraindication[e]	2 (3.2, 0.8)	3 (21.4, 3.7)
- Patient choice	3 (4.8, 1.2)	0 (0, 0)
- No longer indicated[f]	3 (4.8, 1.2)	1 (0.1, 1.2)
Total cycles during study period, n (%)		
- 1	105 (41.2)	28 (34.1)
- 2	105 (41.2)	39 (47.6)
- 3	37 (14.5)	14 (17.1)
- 4	8 (3.1)	1 (1.2)

[a] RTX-B group: abatacept (4), baricitinib (4), tocilizumab (4); RTX-O group: abatacept (1), tocilizumab (2).
[b] RTX-B group: palpitations (1), headaches (1), widespread itching (1), blistering rash (1), suspected infusion reaction suspected secondary to human anti-chimeric antibodies (1); RTX-O group: shortness of breath (1), hypogammaglobulinaemia (1).
[c] RTX-B group: tocilizumab; RTX-O group: abatacept (1), tofacitinib (1).
[d] RTX-B group: cancer (2), myocardial infarction (1), other thrombotic event (1), pneumonia (1), unknown (1); RTX-O group: cancer (1), myocardial infarction (1), unknown (3).
[e] RTX-B group: cancer (1), pregnancy (1); RTX-O group: liver failure (1), neurodegenerative disease (1), pregnancy (1).
[f] Absence of active disease and clear decision not to re-treat despite > 18 months since last cycle.

Table 3. Factors associated with adverse outcome RTX cessation following RTX-B switch

Characteristic	Remains on RTX (n = 233)	Stopped RTX (n = 22)	Imputed Univariable analysis OR (95% CI), P value	Imputed Multivariable analysis OR (95% CI), P value
Age, mean (SD), years	63.2 (12.3)	63.6 (12.1)	1.03 (0.72 – 1.47) per 10 years, P=0.882	-
Female sex, (%)	79.4	63.6	0.45 (0.18 – 1.14), P=0.094	-
RF positive, (%)	84.5	95.5	3.84 (0.5 – 29.43), P=0.196	-
Disease duration, mean (SD), years	17.3 (10.3)	14.2 (11.4)	0.97 (0.92 – 1.07), P=0.188	-
No. of comorbidities, median (IQR)	1 (0 - 1)	2 (0 - 2)	1.74 (1.17 – 2.60), P=0.007	1.88 (1.21 – 2.93), P=0.005
Concomitant csDMARD, (%)	81.6	72.7	0.60 (0.22 – 1.63), P=0.332	-
Baseline DAS28CRP(3), mean (SD)	2.77 (1.01)	3.22 (1.16)	1.48 (0.97 – 2.24), P=0.068	1.36 (1.84 – 2.20), P=0.214
Complete B cell depletion last cycle, (%)	89.5	64.8	0.22 (0.08 – 0.60), P=0.003	0.28 (0.09 – 0.89), P=0.032
Prior No. of bDMARDs, (%): 0 1 2+	 42.1 33.9 24.0	 36.4 27.3 36.3	 - 0.93 (0.31 – 2.79), P=0.898 1.75 (0.62 – 4.92), P=0.289	 -
No. of previous RTX cycles, median (IQR)	6 (3 - 9)	2 (2 - 4)	0.71 (0.58 – 0.87), P=0.001	0.73 (0.61 – 0.89), P=0.002
Naïve B cells (x 1000), 10^9 cells per litre, median (IQR)	34 (9.8 – 85.3)	43 (9.2 – 99.8)	1.00 (0.99 – 1.01), P=0.799	-
Memory B cells (x 1000), 10^9 cells per litre, median (IQR)	1.5 (0.5 – 3.4)	1.8 (1.1 - 4.8)	1.00 (0.97 – 1.03), P=0.999	-
Plasmablasts (x 1000), 10^9 cells per litre, median (IQR)	0.6 (0 – 1.6)	0.9 (0.5 – 3.7)	1.07 (0.98 – 1.17), P=0.141	1.08 (0.97 – 1.20), P=0.138

Table 4. Comparing patients switched back to RTX-O versus other b/tsDMARDs following loss of effectiveness on RTX-B

Characteristic	Switch back RTX-O (n=30)	Other targeted therapy (n=12)	p value[a]
Age, mean (SD), years	66.4 (9.9)	58.8 (11.4)	0.037[b]
Female, n (%)	27 (90.0)	9 (75.0)	0.209
Co-morbidities, n (%) 0 1 2 3+	 7 (23.3) 13 (43.3) 9 (30.0) 1 (3.3)	 6 (50.0) 4 (33.3) 2 (16.7) 0 (0)	0.098[c]
CCP positive, n (%)	26 (86.7)	12 (100)	0.184
RF positive, n (%)	25 (83.3)	12 (100)	0.132
CCP or RF positive, n (%)	29 (96.7)	12 (100)	0.522
Disease duration, median (IQR), years	12 (11)	10 (10)	0.417[c]
csDMARD, n (%) Any Methotrexate Sulfasalazine Leflunomide Hydroxychloroquine Azathioprine None	 22 (73.3) 25 (50.0) 0 (0) 2 (6.7) 4 (13.3) 1 (3.3) 8 (26.7)	 8 (66.7) 6 (50.0) 0 (0) 0 (0) 2 (16.7) 0 (0) 4 (33.3)	0.666
Oral steroid, n (%)	5 (16.7)	3 (25.0)	0.534
Previous biologics, n (%) Any 0 1 2 3+	 20 (66.6) 10 (33.3) 9 (30.0) 9 (30.0) 2 (6.6)	 10 (83.3) 2 (16.7) 4 (33.3) 3 (25.0) 3 (25.0)	0.538[c]
Previous TNFi, n (%)	19 (63.3)	10 (83.3)	0.205
Number of previous RTX-O cycles, median (IQR)	5 (5)	2 (3)	< 0.001[c]
Time since 1st RTX-O cycle, median (IQR), years	5 (5.5)	1 (3.5)	< 0.001[c]
No. of swollen joint count post-RTX-B switch, median (IQR)	1 (0 – 3)	4 (2 – 9)	0.037[c]
No. of tender joint count post-RTX-B switch, median (IQR)	4 (1 – 12)	10 (6 – 13)	0.108[c]
CRP post-RTX-B switch, median (IQR)	2 (2 – 14)	7 (2 – 11)	0.976[c]
DAS28-CRP(3) post-RTX-B switch, median (IQR)	3.35 (2.89 – 4.38)	4.33 (3.87 – 5.08)	0.272[c]

[a] Chi^2 test unless indicated.
[b] Unpaired Student's *t*-test.
[c] Mann-Whitney test.

Figure legends.

Figure 1. Flow diagram to show identification of study participants from total cohort of RTX-treated patients.

Figure 2. Kaplan-Meier survival estimates following switch / consideration of switch to RTX-B.