Effect of rituximab or tumour necrosis factor inhibitors on lung infection and survival in rheumatoid arthritis-associated bronchiectasis

Md Yuzaiful Md Yusof[1,2], Kundan Iqbal[3], Michael Darby[4], Giovanni Lettieri[1,5], Edward M Vital[1,2], Paul Beirne[6], Shouvik Dass[1,2], Paul Emery[1,2]*, Clive Kelly[3,7]*

* P Emery and C Kelly contributed equally to this manuscript

1. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds, UK
2. NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
3. Department of Rheumatology, Queen Elizabeth Hospital, Gateshead, UK
4. Radiology Department, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
5. Radiology Department, San Carlo Hospital, Potenza, Italy
6. Respiratory Medicine, St James' University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
7. Institute of Cellular Medicine, University of Newcastle Upon Tyne, United Kingdom

Correspondence
Dr Md Yuzaiful Md Yusof,
Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds,
Chapel Allerton Hospital,
Chapeltown Road, Leeds, LS7 4SA
United Kingdom
Email: y.yusof@leeds.ac.uk

ABSTRACT

Objective: To evaluate rituximab (RTX) in patients with rheumatoid arthritis-associated bronchiectasis (RA-BR) and compare 5-year respiratory survival between those treated with RTX and tumour necrosis factor inhibitors (TNFi).

Methods: A retrospective observational cohort study of RA-BR in RTX or TNFi-treated RA patients from two UK centres over 10 years. BR was assessed using number of infective exacerbation/year. Respiratory survival was measured from therapy initiation to discontinuation either due to lung exacerbation or lung-related deaths.

Results: Of 800 RTX-treated RA patients, 68 had RA-BR (prevalence 8.5%). Post-RTX, new BR was diagnosed in 3/735 patients (incidence 0.4%). At 12 months post-Cycle 1 RTX, 21/68 (31%) patients had fewer exacerbations than the year pre-RTX, 36/68 (53%) remained stable and 11/68 (16%) had increased exacerbations. The rates of exacerbation improved after Cycle 2 and stabilised up to 5 cycles. Of patients who received ≥2 RTX cycles (n=60), increased exacerbations occurred in 7/60 (12%) and were associated with low IgG, aspergillosis and concurrent alpha-1-antitrypsin deficiency. Overall, 8/68 (11.8%) patients discontinued RTX while 15/46 (32.6%) discontinued TNFi due to respiratory causes. The adjusted 5-year respiratory survival was better in RTX-treated compared to TNFi-treated RA-BR patients; HR 0.40 (95% CI 0.17–0.96); p=0.041.

Conclusion: The majority of RTX-treated RA-BR patients had stable/improved pulmonary symptoms in this long-term follow-up. In isolated cases, worsening of exacerbation had definable causes. Rates of discontinuation due to adverse lung outcomes were better for RTX than a matched TNFi cohort. RTX is an acceptable therapeutic choice for RA-BR if a biologic is needed.

(250 words)

Keywords: B cells, Bronchiectasis, Rituximab, Rheumatoid arthritis, Tumour Necrosis Factor

Key Messages:

1. RTX showed satisfactory safety profile in rheumatoid arthritis-associated bronchiectasis.
2. Most RTX-treated RA-BR patients had either stable or improved exacerbation/year over 10-year follow-up.
3. Fewer patients with RA-BR discontinued RTX due to adverse lung outcomes than those on TNFi.

INTRODUCTION

Bronchiectasis (BR) is a chronic lung disease characterised by irreversible dilatation and thickening of the airways associated with chronic cough, increased sputum production, bacterial colonisation and recurrent infections. It is a significant pulmonary morbidity common in people with rheumatoid arthritis (RA) that is reported in up to 12% of RA patients [1]. The standardised mortality ratios of patients with co-existence of RA and bronchiectasis (RA-BR) are 7.3 times higher than the general population, 5 times that of patients with RA alone and 2.4 times that of patients with other non-cystic fibrosis BR over 5 years [2]. All deaths in the RA-BR group were due to respiratory infection and/or respiratory failure.

While the treatment of RA has greatly improved over the last 15 years with the introduction of biologic disease modifying anti-rheumatic drugs (bDMARDs), the use of these therapies has often been restricted in RA-BR due to concerns of infectious complications. Indeed, in a retrospective study of 40 patients with RA-BR, the authors reported that both the use of bDMARDs i.e. tumour-necrosis factor inhibitors (TNFi) or rituximab (RTX) and sputum colonisation by any bacteria increased the odds of infection compared to those treated with conventional synthetic DMARDs (csDMARDs) [3]. In addition, the long-term safety profile of TNFi in RA from randomised controlled trials and observational studies showed increased rates of severe infection in TNFi-treated compared to csDMARDs-treated patients [4, 5]. Therefore, a non-TNFi such as RTX is often preferentially used to treat RA-BR patients with moderate to severely arthritis.

The rationale for B-cell targeted therapy in RA-BR is supported by the multiple pathogenic roles of B-cells including their antibody-dependent function since B-cells are the source of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPAs). A previous study also reported that ACPA response to citrullination was more specific in patients with RA-BR than those with BR alone [6]. Nevertheless, clinical evidence for the efficacy and safety of RTX in the context of BR is scarce. Furthermore, patients with RA-BR are normally excluded from formal clinical trials due to comorbidity. Therefore, data from larger longitudinal studies are needed.

In order to address the gaps in knowledge and in the absence of a head-to-head trial of RTX against TNFi for the treatment of RA-BR, the objectives of this study were to evaluate effect of RTX in patients with RA-BR as assessed by number of infective exacerbations, imaging,

mortality and compare 5-year respiratory survival between patients with RA-BR who were treated with RTX and TNFi.

METHODS

Patients and Design

All patients with moderate to severe RA who were treated with RTX or TNFi at two different centres in the UK; Leeds Teaching Hospitals NHS Trust and Gateshead Hospital NHS Foundation Trust between January 2002 and May 2017 were evaluated retrospectively from the biologics databases of each institution. From this, a longitudinal cohort study of consecutive patients with RA-BR was conducted. Inclusion criteria were adults (≥18 years old), fulfilling the revised 1987 American College of Rheumatology for RA [7] and detection of BR by high resolution computed tomography (HRCT) [8]. Leeds (West) Research Ethics Committee and Gateshead Hospitals Ethical Committee confirmed that ethical approval was not required in accordance with the UK National Health Service Research Ethics Committee guidelines because all treatment decisions were made prior to evaluation of data.

Treatment Protocol

For the RTX group, all patients received a first cycle of therapy of 100 mg of methylprednisolone and 1000 mg of RTX (MabThera) given intravenously on days 1 and 14. Further treatment cycles consisted of the same regimen were repeated on clinical relapse. For the TNFi group, all patients were treated with either infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira) or certolizumab (Cimzia) as per summary of product characteristics for each drug.

Demographics

Identical data collection methodology were undertaken between the two centres. Age, gender, disease duration for RA and BR, seropositivity status i.e. RF and/or ACPA, previous treatment with bDMARDs, concomitant csDMARDs, daily corticosteroid dose and smoking history were recorded.

Arthritis

Disease activity was assessed using the Disease Activity Score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline and every 3 months. Articular response at 6 months was assigned according to the criteria of the European League Against Rheumatism (EULAR) [9].

Infective exacerbation of bronchiectasis

Medical case notes, rheumatology and respiratory clinic letters, hospital discharge letters and electronic health records for all patients with RA-BR treated with RTX or TNFi who attended the rheumatology and/or respiratory clinics at both centres were inspected thoroughly for infective exacerbation episodes and sputum culture results. Infective exacerbation was defined as acute deterioration (usually over several days), with worsening of cough, increased sputum volume, viscosity, or purulence and/or systemic upset and requiring new prescriptions for antibiotics, which was in line with the British Thoracic Society guideline [8]. These episodes were then summarised as number of infective exacerbations/year. Clinical lung response was defined as stable or improvement in number of infective exacerbation/year.

HRCT Scoring for Bronchiectasis

HRCT scans were acquired (when clinically indicated) in RTX-treated patients with worsening dyspnoea and/or deterioration in the rate of infective exacerbation using a standardised method at the two centres. The scans were scored independently by two radiologists; MD, a chest radiologist and GL, a general radiologist; both who had over 10 years' experience in reporting BR and blinded to clinical information, treatment and the sequence of scans.

The modified Bhalla score [10, 11] was used to evaluate the fourteen HRCT parameters in the six lung zones, as detailed in **the online supplementary file.** The total score for each patient was obtained by summing the scores for each morphological change, which were attributed on the basis of the severity/extent of the abnormalities; with a maximum total score possible of 37. Each paired scan (pre- and post-treatment) was then rated as 0 = worsening, 1 = same and 2 = improving. Any discrepancy was resolved by consensus.

Respiratory Survival

All causes of deaths and cessation of RTX or TNFi were recorded. Respiratory survival was defined as the time from therapy initiation to discontinuation either due to lung exacerbation or deaths from respiratory causes.

Laboratory Assessment

Total serum immunoglobulin titres were measured by nephelometry (in accredited diagnostic laboratories) at baseline and at 4-6 months after each cycle of RTX (normal range for IgM: 0.5-2.0 g/L; IgA: 0.8-4.0 g/L and IgG: 6.0-16.0 g/L). An automated Fluorescent Immuno Enzyme Assay (FIEA) ImmunoCAP was used to detect IgG antibodies to Aspergillus.

Peripheral blood B-cell subsets were analysed using highly sensitive flow cytometry (HSFC) as previously described in Leeds [12] and conventional flow cytometry at Gateshead at week 0, 2 and 26 without knowledge of clinical status other than time since RTX. In order to standardise B-cells reporting between centres, complete B-cell depletion was defined as counts $<0.0001 \times 10^6$ cells/L.

Statistical Analysis

Associations between categorical variables were tested by Fisher's exact. Continuous variables were compared using either Student's T-tests or Mann-Whitney U test depending on data type and distribution. For prediction of the initial lung exacerbation, multiple imputation by chained equations was used to estimate missing data and twenty multiple imputation sets were used to provide stability of results. For multivariable logistic regression analyses, backward elimination was used with a p-value of <0.25 associated with the deviance used for exclusion from the model.

Survival (measured in weeks and years) was calculated from the date of first RTX infusion or TNFi administration to either the date of death, cessation of therapy or the date of data last updated (May 2017). The 5-year respiratory survival between the two treatment groups was analysed using Cox-regression proportional hazard and adjusted for the relevant confounders. All statistical analysis was performed using IBM SPSS Statistics v21.0 (IBM Corp, Armonk, New York, USA) and Stata v.13 (StataCorp College Station, Texas, USA) for Windows.

RESULTS

Patient Characteristics

Of 800 patients with RA treated with RTX in both centres, 68 patients had RA-BR (i.e. prevalence 8.5%) and were included in the analysis. Of these, 48 (71%) were female, mean age 63 years (standard deviation (SD) 10), median RA duration 7 years (interquartile range (IQR) 4-12), median BR duration 6 years (range 1-67) at RTX initiation. Total follow-up: 298.5 patient-years (PY). Post-RTX, new BR was diagnosed in only 3/735 patients (i.e. incidence 0.4%). Of these 3 patients, BR was diagnosed after 1.7 years of exposure and at least two RTX cycles.

Baseline characteristics of RTX-treated and TNFi-treated patients are compared in **Table 1.** Most characteristics were matched between these two cohorts. However, median number of infective exacerbations/year in the previous 12 months pre-bDMARDs was higher in those treated with RTX than TNFi.

Treatment Characteristics

213 cycles of RTX were administered to the 68 patients studied. Median (IQR) duration of response for cycles 1–3 (C1–3) were 54 (46–68), 50 (40–64) and 52 (46–60) weeks respectively. Prior to C1, 22/68 had either inadequate response or intolerance to TNFi (TNF-IR), of which their first TNFi were infliximab=13, etanercept=6 and adalimumab=3. Of these, the reasons for TNF-IR were primary non-response=3, secondary non-response=9, lung exacerbation=7 and other adverse events=3. In C1 of RTX, 43/68 (63%) of the patients were on concomitant csDMARDs. Of 46 patients in the TNFi-treated group, their first TNFi therapies were etanercept=20, infliximab=18, adalimumab=7 and certolizumab=1. Total follow-up for this group was 222.2 PY.

Articular Response to RTX

In C1, there was a significant reduction in DAS-28(CRP); mean (SD) pre-RTX 5.81 (0.76) versus 3.50 (1.09) post-RTX, mean difference (SD) at 6 months -2.31 (-1.12) [95% confidence interval (CI) -2.68 to -1.94]; $p<0.001$. EULAR response rates; Good, Moderate and Poor at 6 months post-RTX were 26/68 (38.2%), 35/68 (51.5%) and 7/68 (10.3%) respectively. 58/68 (85.3%) had complete B-cell depletion post-RTX.

Of the 7 patients who were C1 non-responders, 4/7 had incomplete B-cell depletion post-RTX. 6/7 were re-treated at 6 months with subsequent complete B-cell depletion and response in only 2/6 patients in C2.

EULAR response rates (Good and Moderate) for C2, C3, C4 and C5 were 43/60 (71.7%), 20/24 (83.3%), 19/21 (90.5%) and 11/12 (91.7%) respectively **(Figure 1A)**. At the last follow-up, 5/68 (7.4%) had secondary non-response to RTX and were switched to different bDMARDs; tocilizumab (n=3) and abatacept (n=2).

Clinical lung response to RTX in the initial follow-up

The number of infection episodes reduced from 216 events in 58 RTX-treated RA-BR patients (3.18 PY) in the year pre-RTX to 190 in 48 patients (2.79 PY) at 12 months post-C1 RTX.
At 12 months post-C1 RTX, there was no significant difference in median number of infective exacerbations/year versus the year pre-RTX; p=0.105. Median (IQR) number of infective exacerbations/year 12 months pre-RTX and 12 months post-C1 RTX were 3 (1-4) and 3 (0-4) respectively. At 12 months post-C1 RTX, 21/68 (31%) patients had fewer exacerbations compared to the year pre-RTX; 36/68 (53%) remained stable and 11/68 (16%) had increased exacerbations.

Timing of infective exacerbation since first cycle RTX

The cumulative proportions of patients who had their first infective exacerbation within 6 weeks, 12 weeks, 26 weeks and 52 weeks from C1 RTX were 15/48 (31.3%), 24/48 (50%), 46/48 (95.8%) and 48/48 (100%) respectively. This is illustrated in **Figure 1B.**

Factors predicting increased lung exacerbation at 12 months post-RTX

In imputed multivariable analysis, the presence of pseudomonas colonisation in sputum was associated with increased risk of lung exacerbation at 12 months post-RTX, OR 7.23 (95% CI 1.28-40.80), p=0.025. Older age was associated with reduced risk, OR 0.44 (95% CI 0.21-0.90) per 10 years of age, p=0.025 **(Table 2).**

Clinical lung response to RTX in long-term follow-up

Overall, median number of infective exacerbations/year improved after C2 RTX and remained stable up to 5 cycles **(Figure 1C)**. At the end of the follow-up, 17/68 (25%) patients discontinued RTX. Reasons for discontinuation were i) deaths = 9, of which 5/68 (7%) were

from respiratory causes; ii) lung exacerbation or safety issues = 3 and iii) secondary inefficacy = 5.

Factors associated with lung worsening following initial stability to RTX

60/68 patients received at least two RTX cycles. Of these, 7/60 (12%) had worsening number of infective exacerbations/year following C2 RTX. The median (range) RTX cycles where lung worsening occurred was 4 (3-8).

The causes contributing to lung worsening were investigated and identified. These were secondary hypogammaglobulinaemia (IgG<6 g/L) = 5 (of which, one required immunoglobulin replacement), aspergillosis = 3 and concurrent alpha-1-anti-trypsin deficiency = 1. Aspergillosis was diagnosed based on a combination of typical characteristics on HRCT, positive ELISA test for *Aspergillus* antibody from broncho-alveolar lavage and strongly positive IgG antibody to *Aspergillus* (>39.9 mg/L) [13]. **Figure 2** depicted HRCT scans of a patient who developed aspergillosis at 5 years post-RTX. Of 3 patients with concurrent aspergillosis, 1 discontinued RTX despite treatment with voriconazole and subsequently underwent lobectomy.

Imaging lung response to RTX

Pre- and post-HRCT scans were performed in 12 RA-BR patients with worsening dyspnoea and/or deterioration in the rate of infective exacerbation. The median (IQR) duration between the two scan time-points was 5 (1.4-6.5) years. There was no statistical difference in the modified Bhalla score between pre-RTX and post-RTX scans, median (IQR) 14 (8-17) and 15 (11-17) respectively; p=0.064. Overall, 7/12 (58%) had unchanged images while 5/12 (42%) had worsening imaging changes post-RTX.

Comparison of 5-year respiratory survival between RTX and TNFi-treated RA-BR

In the RTX-treated RA-BR group, 8/68 (11.8%) patients discontinued RTX due to respiratory causes (lung infection-related deaths = 5; lung exacerbation = 3). While in the TNFi-treated RA-BR group, 15/46 (32.6%) patients discontinued TNFi due to respiratory causes (lung infection-related deaths = 2; lung exacerbation = 13 including one patient treated with etanercept who later developed aspergillosis) **(Table 3).** The death rates due respiratory causes were nearly similar in the RTX-treated than the TNFi-treated groups; (5/68) 7.4% and (2/46)

4.3% respectively. Distribution of TNFi in those who discontinued therapy due to respiratory causes was etanercept = 6, infliximab = 6, adalimumab = 2 and certolizumab = 1.

After inspecting for various demographic variables including BR disease duration and number of exacerbation/per year, only centre effect emerged as a confounder. There was a significantly better 5-year respiratory survival in the RTX-treated RA-BR compared to TNFi-treated RA-BR patients; hazard ratio (HR) 0.40 (95% CI 0.17 – 0.96); p=0.041 after adjusting for age, gender and centre effect **(Figure 1D).**

Discussion

This is the first reported experience to date of patients with RA-BR treated with RTX or TNFi from a multicentre cohort study. The majority of patients with RA-BR (as assessed by number of infective exacerbation/year and survival) remained stable or improved during RTX therapy over 10 years follow-up.

A handful of case series have reported on the development or worsening of BR following treatment with RTX [14, 15]. These data need to be interpreted with caution due to publication bias, lack of generalisation and inability to establish cause-effect relationship. By reviewing records of every patient who received RTX to capture every BR patient in a systematic way, our data ameliorate the difficulties in the interpretation of these case reports. The data show that RTX appears to be generally safe and the incidence of BR after RTX therapy was low i.e. 0.4%.

In the 12 months post-RTX, 84% of patients had either stable or improved number of exacerbations compared to the year prior to RTX initiation. This rate is better than the 68% reported on the use of RTX in another lung comorbidity i.e. RA-related interstitial lung disease [16]. However, 16% of the patients experienced temporary worsening of infective exacerbation of their BR. A factor predicting this exacerbation was pseudomonas colonisation in sputum. This was despite 7/8 of patients with pseudomonas colonisation being treated with either prophylactic macrolide antibiotics or inhaled colomycin at RTX baseline. This highlighted the need to improve on strategies to eradicate *pseudomonas aeruginosa* in the management of BR. Pseudomonas colonisation was also identified as a risk factor of exacerbation in cystic fibrosis [17] and non-autoimmune related BR [18]. In contrast to other studies of non-cystic fibrosis

BR [19, 20], older age reduced the risk of initial exacerbation following RTX in this study. One explanation could be that this group of patients had slower progressive disease compared to younger patients.

The long-term clinical lung response to RTX was also supported by the unchanged HRCT scores in over half of the symptomatic patients, in whom a deterioration in HRCT scores would have been expected. Nevertheless, isolated cases of worsening of exacerbations following initial stability were observed. These had definable causes including secondary hypogammaglobulinaemia, aspergillosis and concurrent alpha-1-antitrypsin deficiency. Low IgG level is an independent predictor of infection during RTX therapy [21, 22]. Thus, immunoglobulin should be monitored at RTX initiation and before each retreatment and RA-BR patients with low IgG should be considered for other therapies than RTX from the perspective of safety. In line with the British Thoracic guidelines, RA patients being treated with immunosuppressive therapies who present with increasing productive cough and breathlessness should be investigated using HRCT and other secondary causes of BR including aspergillosis and alpha-1-antitrypsin deficiency [23] sought. It is unclear whether repeated treatment with RTX increase the risk of aspergillosis in RA-BR since previous case series only reported in RTX-treated haematological malignancy patients who also underwent haematopoietic stem cell transplant [24] or combination therapy with other chemotherapies [25].

In the absence of head-to-head trials of RTX and TNFi, the 5-year respiratory survival and mortality of the patients in these two cohorts were compared. It is worth noting that median number of exacerbations/year in the RTX was higher than the TNFi groups. This was due to channelling bias and tendency of the clinicians to treat patients with the most severe lung morbidity with RTX, thus resulting in an increase in reports of adverse events in the RTX-treated RA-BR cohort. Despite this, our data showed that the 5-year respiratory survival was significantly better in the RTX compared to the TNFi groups. In the TNFi group, there was no difference between the use of monoclonal antibodies and receptor protein with regards to respiratory survival.

This study has some limitations. First, the design was retrospective, hence could lead to recall bias by the patients. However, a standard proforma was used in the clinics to document the number of exacerbations/year as well as infection episodes were thoroughly searched for

during data collection. Second, pulmonary function testing was not routinely undertaken at both centres and there was a varied availability of pre- and post-RTX HRCT scans for every patient. Nevertheless, number of exacerbation/year is a valid measure to assess clinical efficacy in BR and has been widely used as a primary endpoint in clinical trials [26, 27]. Lastly, only 12/68 (18%) of the patients in this cohort were treated with prophylactic antibiotics during RTX therapy despite over half i.e. 35/68 (59%) having ≥3 exacerbations/year as advocated by the European [28] and British Thoracic Society [23] guidelines. Thus, this could contribute to higher rate of infection episodes in this RTX-treated RA-BR cohort.

To conclude, since most patients with RA-BR had stable or improved lung exacerbations during RTX therapy as well as better 5-year respiratory survival against a matched TNFi cohort, our findings offer reassurance that RTX is an acceptable treatment choice for RA-BR patients with severe arthritis, who require treatment with a biologic. These data also support a definitive study of RTX for the management RA-BR from both an articular and a respiratory perspective.

(3205 words)

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Table 1: Baseline characteristics of the 114 patients with RA-BR included in this study

	All patients (n=114)	RTX-treated RA-BR (n=68)	TNFi-treated RA-BR (n=46)
Age, years: mean (SD)	62.9 (9.9)	63.3 (10.1)	62.4 (9.8)
Female: n (%)	81 (71.1)	48 (70.6)	33 (71.7)
Sero-positivity [RF and/or anti-CCP antibody positive]: n (%)	110 (96.5)	68 (100)	42 (91.3)
RA Disease duration, years: median (IQR)	6.5 (3.3-11.5)	7.2 (4.2-12.0)	4.7 (2.2-9.0)
*BR Disease duration: median (IQR)	5.0 (1.4-10.7)	6.4 (2.1-12.0)	4.8 (0.9-8.5)
No. of infective exacerbation/year in the previous 12 months pre-bDMARDs: median (IQR)	2.0 (0-3)	3.0 (1-4)	0 (0-2)
Biologic naïve: n (%)	92 (81)	46 (68)	46 (100)
No. of previous TNFi: median (range)	0 (0-1)	0 (0-3)	0 (0)
Concomitant anti-malarial only: n (%)	6 (5.3)	6 (8.8)	0 (0)
Concomitant csDMARDs: n (%)	72 (63.2)	43 (63.2)	30 (65.2)
Methotrexate	60 (52.6)	31 (45.5)	29 (63.0)
Leflunomide	9 (7.9)	9 (13.2)	0 (0)
Sulfasalazine	2 (1.8)	1 (1.5)	1 (2)
Azathioprine	1 (0.9)	1 (1.5)	0 (0)
Mycophenolate Mofetil	1 (0.9)	1 (1.5)	0 (0)
Concomitant prednisolone: n (%)	38 (33.3)	23 (33.8)	15 (32.6)
Daily prednisolone dose, mg: median (IQR)	0 (0-5)	0 (0-5)	0 (0-5)
Ever smoked: n (%)	54 (47.4)	29 (42.6)	25 (54.3)
DAS-28(CRP) score: mean (SD)	5.9 (0.7)	5.9 (0.8)	5.6 (0.6)

*BR disease duration was analysed in patients who BR were diagnosed prior to therapy with bDMARDs

bDMARDs: Biologic disease modifying agent anti-rheumatic drugs, BR: Bronchiectasis, CCP: Cyclic citrullinated peptide, csDMARDs: Conventional synthetic disease modifying agent anti-rheumatic drugs, DAS-28 (CRP): Disease activity score in 28 joints based on C-reactive protein, IQR: interquartile range, RA: rheumatoid arthritis, RF: Rheumatoid factor, RTX: Rituximab, SD: standard deviation, TNFi: Tumour necrosis factor inhibitor

Table 2: Predictors of lung exacerbation at 12 months post-RTX

	Stable or Improving Lung Disease N = 57	**Lung Exacerbation N = 11**	**Univariable OR (95% CI), P-value (with multiple imputation)**	**Multivariable OR (95% CI), P-value (with multiple imputation)**
Age, years: mean (SD)	64.2 (9.3)	58.4 (12.7)	**0.58 (0.31-1.08) Per 10 years of age, P = 0.085**	**0.44 (0.21-0.90) Per 10 years of age, P = 0.025**
BR Disease duration, years: median (IQR)	2.9 (0.7-8.7)	2.8 (0.6-5.4)	0.96 (0.88-1.06) Per year, P = 0.454	-
No. of infective exacerbation/year in the previous 12 months pre-RTX: median (IQR)	2 (1-4)	4 (2-6)	1.16 (0.93-1.44), P = 0.186	1.17 (0.92-1.49), P = 0.197
Ever smoked: n (%)	23 (40.4)	6 (54.6)	1.78 (0.48-6.51), P = 0.387	2.71 (0.59-12.35), P = 0.198
Pseudomonas colonisation in sputum: n (%)	4 (7.0)	4 (36.4)	**7.57 (1.54-37.29), P = 0.013**	**7.23 (1.28-40.80), P = 0.025**
Concomitant prednisolone, n (%)	19 (33.3)	4 (36.4)	1.14 (0.30-4.39) P = 0.846	-
Concomitant csDMARDs: n (%)	37 (64.9)	5 (45.5)	0.45 (0.12-1.66) P = 0.231	-

BR: Bronchiectasis, csDMARDs: Conventional synthetic disease modifying anti-rheumatic drugs, IQR: interquartile range, RTX: Rituximab, SD: standard deviation, TNFi: Tumour necrosis factor inhibitor

Table 3: Reasons for bDMARDs discontinuation in RA-BR patients

Causes	Rituximab (N = 68)	TNF-inhibitor (N = 46)
Deaths, n (%)	9 (13.2)	2 (4.3)
Lung infection-related, n (%)	5 (7.4)	2 (4.3)
Cerebrovascular accident, n (%)	2 (2.9)	0
Myocardial infarction, n (%)	2 (2.9)	0
Lung exacerbation, n (%)	3 (4.4)	13 (28.3)
Patients who stopped therapy due to mortality/respiratory causes, n (%)	8 (11.8)	15 (32.6)
Primary inefficacy, n (%)	0	3 (6.5)
Secondary inefficacy, n (%)	5 (7.4)	9 (19.6)
Other adverse events, n (%)	0	3 (6.5)
Total patients who discontinued bDMARDs therapies, n (%)	17 (25)	30 (65)

bDMARDs: Biologic disease modifying agent anti-rheumatic drugs

Figure 1: Efficacy and safety of RTX in RA-BR. A) High EULAR (Good and moderate) response rates were observed over 5 RTX cycles. B) There was no difference in the number of infective exacerbation/year in the year pre-RTX versus 12 months post-RTX. These rates had improved and were stable up to 5 RTX cycles. The bars represent median and the error bars denote 95% confidence interval. C) Survival graph of timing of the first infection episode following RTX therapy. D) Comparison of 5-year respiratory survival between RTX-treated and TNFi-treated RA-BR patients. Grey line in the graph represents RTX while black line denotes TNFi.

Figure 2: HRCT image of a RTX-treated RA-BR patient who developed aspergillosis after RTX therapy. A and B) Orange arrows denote bronchial wall thickening and signet-ring signs. Blue arrows denote cystic formation towards the lung peripheries. Red arrow denotes progression of the cysts containing air fluid crescents suggestive of pulmonary mycetoma formation.