


Original article

Rituximab for interstitial pneumonia with autoimmune features at two medical centres

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Abstract

Objectives Many patients with interstitial lung disease (ILD) have autoimmune manifestations but do not meet criteria for a systemic rheumatic disease. A subset meets criteria for interstitial pneumonia with autoimmune features (IPAF) and have ILD requiring therapy. We conducted a multicentre observational study to examine the use of rituximab (RTX) in IPAF.

Methods Patients from Mass General Brigham (MGB) and University of Chicago Medicine (UCM) were included if they were ≥ 18 years old, met the 2015 classification criteria for IPAF and were treated with RTX. Clinical improvement was defined as improvement in four out of four domains at 1 year after RTX initiation: documented clinician global assessment; oxygen requirement; need for respiratory-related hospitalization; and survival.

Results At MGB, 36 IPAF patients (mean age 61 years, 44% female) were treated with RTX. At 1 year, 18 (50%) were clinically improved, 12 (33%) were stable, and 6 (17%) died from progressive respiratory failure. At UCM, 14 IPAF patients (mean age 53 years, 71% female) were treated with RTX. At 1 year, eight (57%) were improved, two (14%) were stable, three (21%) died from progressive respiratory failure, and one (7%) was lost to follow-up. Two patients experienced minor infusion reactions, and two patients discontinued therapy owing to adverse events (infections).

Conclusion In patients with IPAF treated with RTX at two medical centres, the majority (40 [80%]) demonstrated improvement/stability at 1 year. These findings call for prospective studies, including randomized clinical trials, to determine the risks, benefits and cost effectiveness of RTX in IPAF.

Key words: interstitial pneumonia with autoimmune features, interstitial lung disease, lung fibrosis

Key messages

- No randomized clinical trials have assessed therapies for interstitial pneumonia with autoimmune features (IPAF).
- In a case series from two medical centres, most IPAF patients had improvement/stabilization with rituximab.
- Randomized clinical trials are needed to determine the risks and benefits of rituximab in IPAF.

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Introduction

Among patients with rheumatic diseases, interstitial lung disease (ILD) is a major cause of morbidity and mortality [1]. However, many patients with ILD have clinical, laboratory or imaging features suggestive of an autoimmune inflammatory lung disease but do not meet established classification criteria for a systemic rheumatic disease [2–8]. In 2015, the European Respiratory Society and American Thoracic Society developed consensus classification criteria for these patients, termed interstitial pneumonia with autoimmune features (IPAF) [2].

The treatment approach to ILD in the setting of IPAF remains undefined. Given the similarities between IPAF and ILD associated with systemic rheumatic diseases, it is plausible that patients with IPAF could benefit from immunosuppressive therapy [1]. To date, there are no randomized clinical trials (RCTs) examining the effectiveness or safety of immunosuppressants in IPAF [1, 9]. Small case series suggest that CYC ($n=13$) or MMF ($n=28$) can be associated with stabilization in forced vital capacity (FVC) in patients with IPAF [10, 11]. Rituximab (RTX), a chimeric monoclonal antibody that binds CD20 on pre-B and B lymphocytes, causing rapid circulating B cell depletion, has also been considered as a potential treatment for refractory ILD associated with autoimmune diseases [12, 13]. We examined the use and safety of RTX in IPAF patients at two large academic medical centres.

Methods

Study design and patient selection

At Mass General Brigham (MGB) HealthCare System, an institution-wide research patient data repository was queried for patients aged ≥ 18 years with International Classification of Diseases (ICD)-9 and ICD-10 codes for ILD (Supplementary Table S1, available at *Rheumatology Advances in Practice* online), treatment with RTX, and at least one positive autoantibody between 2000 and 2018 [14]. Charts were reviewed manually to confirm the diagnosis of IPAF according to the IPAF criteria [2]. Patients were excluded if they received RTX for a known autoimmune disease or malignancy. This study was approved by the MGB institutional review board, and informed consent was not required given the retrospective nature of the study.

At University of Chicago Medicine (UCM), patients enrolled in the prospective institutional review board-approved ILD registry from 2006 to 2019 were assessed. All new patients evaluated in the UCM ILD clinic are invited to enrol in the registry, and written informed consent is obtained at enrolment. ILD classification occurs by real-time multidisciplinary discussion using clinical, radiological, laboratory and pathological data.

At both institutions, criteria for classification as IPAF included the presence of interstitial pneumonia (according to high-resolution CT chest or lung biopsy), with exclusion of alternative aetiologies, incomplete features of a defined rheumatic disease, and at least one feature

from at least two IPAF domains (clinical, serological and morphological), as previously described [2]. The following classification criteria were used to exclude the presence of a defined rheumatic disease: 2017 EULAR/ACR criteria for idiopathic inflammatory myopathies [15]; 2016 ACR/EULAR criteria for primary SS [16]; 2013 ACR/EULAR criteria for SSc [17]; SLICC criteria for SLE [18]; 2010 ACR/EULAR criteria for RA [19]; and the Alarcon-Segovia criteria for MCTD [20]. A case series study design was used to avoid introducing selection bias with a comparator group because RTX was chosen at the discretion of the treating clinician.

Data collection

Clinical information was extracted from the electronic health record using a standardized data entry form at both institutions. The following baseline characteristics were collected at the time closest to RTX initiation: demographic information (age, sex and race/ethnicity), tobacco use, co-morbidities, autoantibodies, pulmonary function tests [PFTs, including FVC and diffusion capacity of the lung for carbon monoxide (DLCO)] and ILD medications.

At MGB, two thoracic radiologists (A.S. and B.P.L.), blinded to clinical data, independently reviewed all high-resolution CT images from the time closest to RTX initiation and reached a consensus pattern classification for each subject, which included non-specific interstitial pneumonia (NSIP), fibrotic NSIP, organizing pneumonia (OP), fibrotic OP, lymphocytic interstitial pneumonia (LIP), usual interstitial pneumonia (UIP) or other pattern. At UCM, a radiological consensus classification was reached at interdisciplinary meetings that included pulmonologists, rheumatologists and radiologists, as patients were enrolled in the ILD registry.

Follow-up and end point of the study

For all subjects meeting the criteria for inclusion, follow-up started at the time of RTX initiation. Assessment of RTX efficacy was performed using two co-primary outcomes.

The first outcome was a composite that incorporated four domains: clinician global assessment (improved, stable or worsened, as documented in the treating provider's clinical notes); oxygen requirement (improved, stable or worsened); need for unplanned respiratory-related hospitalization (no need for hospitalization vs need for hospitalization during the follow-up period); and 1-year survival (alive or deceased). A composite outcome was developed a priori because not all patients had baseline PFTs before RTX initiation. To be considered clinically improved or stable, patients had to have improvement or stability in clinical global assessment and oxygen requirement, have not required unplanned respiratory-related hospitalization during the follow-up period, and be alive at 1 year. All others were considered clinically worsened.

The second outcome was based on change in PFTs as determined by FVC. Only those subjects with PFTs within 3 months before or 1 month after RTX initiation and 6–18 months after RTX initiation were included in the PFT analysis, with PFT improvement defined as $\geq 10\%$ increase in the percentage predicted FVC, stability defined as the percentage predicted FVC within $\pm 10\%$ of initial measurement, and worsening defined as $\geq 10\%$ decrease in the percentage predicted FVC, as defined in prior studies [12, 13]. The minimal clinically important difference in the percentage predicted FVC has previously been estimated to be 3.0–5.3% [21]. Follow-up PFTs were assessed within a window of 6–18 months given that the timing of PFTs varied based on scheduled follow-up appointments.

Statistical analysis

Data are shown as the mean (s.d.), median with the interquartile range, or number with percentage, as appropriate. The PFT trends are expressed as the absolute change in the percentage predicted values from initiation of therapy to the end of the study period.

Results

MGB cohort

Thirty-six IPAF patients treated with RTX were identified (Fig. 1). At 1 year after initiation of RTX, the 36 IPAF patients had received an average of 2.4 (1.3) cycles of RTX, with each cycle containing either one or two doses of RTX 1 g. At the time of RTX initiation, the average age was 61 years, and 16 (44%) were female (Table 1). The

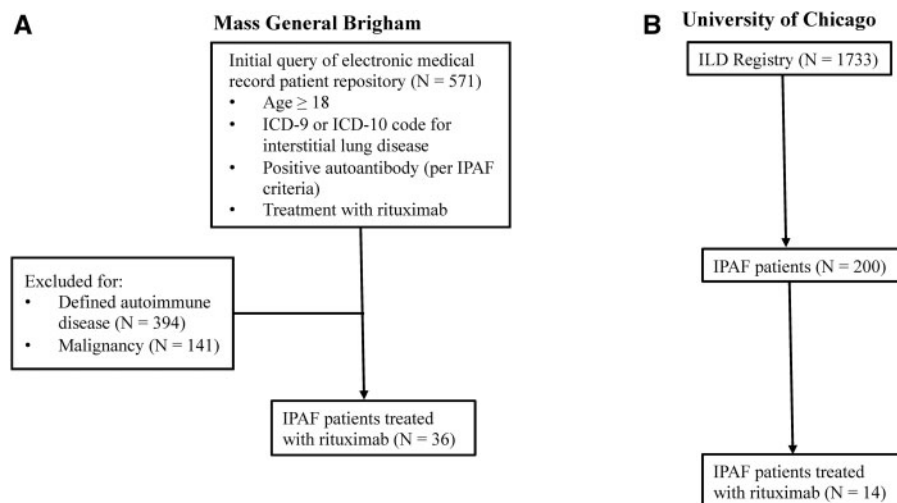
majority of patients were White (29, 81%) and had never smoked (20, 56%).

The predominant extrapulmonary clinical manifestations (Table 1) included gastro-oesophageal reflux (22, 61%), inflammatory arthritis (12, 33%), myalgias (11, 31%), RP (10, 28%) and sicca symptoms (9, 25%). The most common radiological and histological patterns included NSIP and OP (Table 2). Average creatine kinase, aldolase, ESR and CRP concentrations were elevated (Table 3). ANA (16, 44%) and SS-A/Ro-52 kDa antibody (11, 31%) were the most common positive serologies identified. Before RTX initiation, the mean FVC was 66% predicted (19%), and the mean DLCO was 45% predicted (17%).

A total of 10 (28%) patients required hospitalization for hypoxaemia, of whom 7 (19%) required intensive care unit admission, 6 (17%) required mechanical ventilation, and 2 (6%) required extracorporeal membrane oxygenation (ECMO) and were initiated on RTX as rescue therapy for their ILD. Fourteen patients (39%) had alternative NSAIDs before RTX, including MMF (4, 11%), i.v. CYC (2, 6%) and oral CYC (1, 3%). Treatments in conjunction with RTX included glucocorticoids (32, 89%), MMF (11, 31%) and IVIG (4, 11%). For 22 patients (61%), RTX was the first NSAID used for ILD treatment.

At 1 year after RTX initiation, 18 (50%) patients were improved and 12 (33%) were stable, whereas 6 (17%) had worsened and died from progressive respiratory failure from ILD (Table 4). Two of the patients who died were on ECMO at the time of RTX initiation. No patients received lung transplantation, and no patients were lost to follow-up. Of the 32 patients with follow-up PFT data available, 15 (42%) were improved and 14 (40%) were stable, whereas 3 (9%) had worsened and died from

Fig. 1 Patients selected for study inclusion



(A) Patients selected from Mass General Brigham (MGB). (B) Patients selected from University of Chicago Medicine (UCM). ICD: international classification of diseases; ILD: interstitial lung disease; IPAF: interstitial pneumonia with autoimmune features.

TABLE 1 Baseline characteristics of patients with interstitial pneumonia with autoimmune features treated with rituximab at two academic medical centres

Characteristic	Mass General Brigham (<i>n</i> = 36)	University of Chicago (<i>n</i> = 14)
Age at rituximab initiation, years, mean (s.d.)	61 (11)	53 (11)
Female sex, <i>n</i> (%)	16 (44)	10 (71)
Race/ethnicity, <i>n</i> (%)		
White	29 (81)	6 (43)
Black	4 (11)	8 (57)
Asian	3 (8)	0
Latinx	1 (3)	2 (14)
Smoking status, <i>n</i> (%)		
Current	1 (3)	0
Past	15 (42)	4 (29)
Never	20 (56)	10 (71)
Prior diagnosis, <i>n</i> (%)		
Chronic obstructive pulmonary disease	2 (6)	4 (29)
Pulmonary hypertension	2 (6)	7 (50)
Obstructive sleep apnoea	6 (17)	4 (29)
Coronary artery disease	2 (6)	4 (29)
Heart failure	3 (8)	7 (50)
Clinical manifestations, <i>n</i> (%) ^a		
Gastro-oesophageal reflux	22 (61)	13 (93)
Dysphagia	4 (11)	4 (29)
Inflammatory arthritis	12 (33)	6 (43)
Myalgia	11 (31)	5 (36)
RP	10 (28)	9 (64)
Sicca symptoms	9 (25)	6 (43)
Proximal muscle weakness	3 (8)	1 (7)
Mechanic's hands	2 (6)	6 (43)
Oral/nasal ulcers	2 (6)	0
Serositis	2 (6)	1 (7)
Abnormal nailfold capillaroscopy	2 (6)	4 (29)
Telangiectasias	1 (3)	2 (14)
Puffy hands	1 (3)	4 (29)
Gottron's sign	1 (3)	4 (29)
Photosensitive rash	0	2 (14)
Digital ulcers	0	2 (14)
Required hospital admission for hypoxaemia, <i>n</i> (%)	10 (28)	1 (7)
Required intensive care unit admission, <i>n</i> (%)	7 (19)	1 (7)
Required mechanical ventilation, <i>n</i> (%)	6 (17)	1 (7)
Required extracorporeal membrane oxygenation, <i>n</i> (%)	2 (6)	0
Treatments before rituximab, <i>n</i> (%)		
Glucocorticoids	32 (89)	12 (86)
Oral CYC	1 (3)	0
i.v. CYC	2 (6)	2 (14)
MMF	4 (11)	9 (64)
AZA	1 (3)	6 (43)
LEF	1 (3)	0
Tacrolimus	0	9 (64)
Treatments in conjunction with rituximab, <i>n</i> (%)		
Glucocorticoids	32 (89)	14 (100)
MMF	11 (31)	2 (14)
IVIG	4 (11)	2 (14)

^aNo patients in either cohort had sclerodactyly or heliotrope rash.

TABLE 2 Radiological and histopathological patterns observed in patients with interstitial pneumonia with autoimmune features treated with rituximab at two academic medical centres

Pattern	Mass General Brigham (<i>n</i> = 36 for radiological pattern, <i>n</i> = 13 for histopathology)	University of Chicago (<i>n</i> = 14 for radiological pattern, <i>n</i> = 6 for histopathology)
Radiographic pattern, <i>n</i> (%)		
NSIP	5 (14)	4 (29)
Fibrotic NSIP	4 (11)	4 (29)
OP	10 (28)	0
Fibrotic OP	4 (11)	0
NSIP + OP	8 (22)	3 (21)
Other ^a	5 (14)	3 (21)
Histopathological pattern, <i>n</i> (%)		
NSIP	2 (15)	0
OP	6 (46)	4 (66)
NSIP + OP	1 (8)	1 (17)
Lymphoid germinal centres	2 (15)	1 (17)
Lymphoplasmacytic infiltrate	2 (15)	0

^aOther patterns include non-classifiable, desquamating interstitial pneumonia, hypersensitivity pneumonitis and diffuse lung injury. No patients had a usual interstitial pneumonia pattern. NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia.

progressive respiratory failure. Fourteen (39%) patients were able to taper off glucocorticoids completely. Over the course of 1 year of treatment, no patients had infusion reactions, and seven patients had infections (cholangitis, urinary tract infection, septic arthritis of prosthetic joint, and four cases of pneumonia). Of the seven patients with infections, five patients had severe infections requiring hospitalization, and two patients discontinued RTX therapy owing to infections (septic arthritis of a prosthetic joint in one patient and recurrent pneumonia in one patient). Among the 30 patients with improvement or stability at 1 year, 21 (70%) patients continued RTX, 3 (10%) patients transitioned to MMF, 1 (3%) patient transitioned to tocilizumab (owing to a new diagnosis of GCA), and 5 (17%) patients were monitored off therapy.

UCM cohort

Among 200 patients classified as IPAF within the UCM registry, 14 patients were treated with RTX (Fig. 1). At 1 year after initiation of RTX, the 14 IPAF patients had received an average of 2.9 (2.1) cycles of RTX, with each cycle containing an average of 2.0 (0) doses per cycle. Compared with the MGB cohort, the UCM cohort was slightly younger (mean age 53 years), predominantly female (10, 71%) and had higher proportions of Black (8, 57%) and Latinx (2, 14%) patients. The UCM cohort also had a higher prevalence of co-morbidities, such as heart failure (7, 50%) and pulmonary hypertension (7, 50%).

Patients in the UCM cohort more frequently had gastroesophageal reflux (13, 93%), RP (9, 64%), sicca symptoms (6, 43%) and mechanic's hands (6, 43%) compared with the MGB cohort. The most common radiological and histological patterns included NSIP and a combination of OP and

NSIP (Table 2). Similar to the MGB cohort, average aldolase, ESR and CRP concentrations were elevated, although creatine kinase concentrations were normal (Table 3). Before RTX initiation, the mean FVC was 49% predicted (15%), and the mean DLCO was 35% predicted (14%). At the time of RTX initiation, only one patient (7%) in the UCM cohort required hospital admission, intensive care unit admission and mechanical ventilation, and RTX was given as rescue therapy for ILD; no patients required ECMO. All patients in the UCM cohort had other NSAIDs tried before RTX, including MMF (9, 64%) and tacrolimus (9, 64%), in contrast to the MGB cohort. The distribution of treatments administered simultaneously with RTX was similar [glucocorticoids (14, 100%), MMF (2, 14%) and IVIG (2, 14%)].

At 1 year after RTX treatment initiation, eight (57%) patients were improved and two (14%) were stable, whereas three (21%) had worsened and died from progressive respiratory failure from ILD, and one patient was lost to follow-up (Table 4). No patients received lung transplantation. Of the 12 patients with PFT data available, 7 (58%) were improved and 5 (42%) were stable. Seven (50%) were able to taper off glucocorticoids completely. Over the course of 1 year, two patients had minor infusion reactions, and two patients had infections (colitis, pneumonia) requiring hospitalization. No patients discontinued therapy owing to adverse events. At UCM, among the 10 patients with improvement or stability at 1 year, nine (90%) continued RTX and one (10%) was transitioned to MMF.

Discussion

RTX treatment was associated with clinical improvement or stability in the majority of patients with IPAF at two academic medical centres. Despite baseline differences

TABLE 3 Baseline laboratory values of patients with interstitial pneumonia with autoimmune features before treatment with rituximab at two academic medical centres

Parameter	Mass General Brigham (n = 36)	University of Chicago (n = 14)
Creatine kinase, units/l (normal 40–150)	169 (208)	95 (62)
Aldolase, units/l (normal <7.7)	10 (4)	9 (5)
ESR, mm/h (normal <13)	45 (35)	27 (22)
CRP, mg/l (normal <8)	33 (45)	8 (6)
ANA, n (%) ^a	16 (44)	5 (36)
Homogeneous pattern ^b	9 (25)	1 (7)
Speckled pattern ^b	5 (14)	3 (21)
Centromere pattern ^b	1 (3)	0
Nucleolar pattern ^b	1 (3)	1 (7)
dsDNA antibody, n (%)	3 (8)	1 (7)
SS-A/Ro 60 kDa antibody, n (%)	3 (8)	6 (43)
SS-A/Ro 52 kDa antibody, n (%)	11 (31)	5 (36)
SS-B/La antibody, n (%)	2 (6)	2 (14)
Smith antibody, n (%)	1 (3)	0
RNP antibody, n (%)	3 (8)	3 (21)
Scl-70 antibody, n (%)	1 (3)	0
RF, n (%) ^c	9 (25)	5 (36)
EJ antibody, n (%)	1 (3)	0
Jo-1 antibody, n (%)	1 (3)	0
PL-7 antibody, n (%)	0	3 (21)
PL-12 antibody, n (%)	0	1 (7)
PM-Scl antibody, n (%)	2 (6)	0
Ku antibody, n (%)	2 (6)	0
NXP-2 antibody, n (%)	1 (3)	0
MDA-5 antibody, n (%)	0	1 (7)
p155/140 antibody, n (%) ^d	1 (3)	0
ACPA, n (%)	0	0
ANCA, n (%)	0	0
Anti-RNA polymerase III antibody, n (%)	0	0

All values are the mean (s.d.) for continuous variables or number (percentage) for categorical variables. Of note, only the serologies listed in the interstitial pneumonia with autoimmune features criteria were used to determine cohort eligibility.

^aANA was considered positive if titre $\geq 1:320$. ^bPercentage of patients with a given pattern out of the total patients with positive ANA. ^cRF was counted as positive if ≥ 2 times the upper limit of normal. ^dNo patients had other myositis-associated or myositis-specific antibodies except as noted in the table. MDA-5: melanoma differentiation-associated protein 5.

between the MGB and UCM cohorts, including age, race/ethnicity, co-morbidities, prior treatments and clinical manifestations, the majority of patients in both cohorts had improved or stable ILD. Although the data presented here are observational, this is the first multi-centre study to evaluate the use and safety of RTX in IPAF.

There were several differences between the MGB and UCM cohorts, which relate to the underlying heterogeneity of the disease. For example, the MGB cohort had higher rates of hypoxaemia, intensive care unit admission and mechanical ventilation compared with the UCM cohort. RTX was often the first DMARD used in the MGB cohort, whereas most patients in the UCM cohort had previously tried other DMARDs, such as MMF or tacrolimus. It is possible that earlier initiation of RTX might have led to different outcomes; a question that

would be important to explore in future RCTs. Notably, no patients from MGB or UCM had a UIP radiological pattern, which has previously been associated with higher mortality among IPAF cohorts [1, 6]. Despite underlying differences between cohorts, a similar percentage of patients had stabilization or improvement clinically and by PFT after RTX initiation.

To date, there are no RCTs regarding treatment of IPAF. A single-centre case series that included 19 patients with IPAF showed a trend toward improvement in FVC with MMF [9]. In a single-centre case series that included nine patients with IPAF treated with RTX, eight patients survived, and four out of five patients with follow-up PFTs had stable or improved FVC [13]. Our study with a larger sample size extends evidence that RTX might be effective for IPAF. RTX use has previously been examined in SSc and inflammatory myopathy,

TABLE 4 Outcomes after treatment with rituximab in patients with interstitial pneumonia with autoimmune features at two academic medical centres

Outcome	Mass General Brigham (<i>n</i> = 36 total; <i>n</i> = 32 for PFTs)	University of Chicago (<i>n</i> = 14 total; <i>n</i> = 12 for PFTs)
Clinically improved, <i>n</i> (%) ^a	18 (50)	8 (57)
Clinically stable, <i>n</i> (%) ^a	12 (33)	2 (14)
Clinically worsened, <i>n</i> (%) ^a	6 (17)	3 (21)
Deaths, <i>n</i> (%)	6 (17)	3 (21)
Lost to follow-up, <i>n</i> (%)	0	1 (7)
Absolute change in percentage predicted FVC, mean percentage (s.d.)	9.3 (16.4)	1.3 (6.3)
Absolute change in percentage predicted DLCO, mean percentage (s.d.)	2.0 (13.5)	7.0 (8.8)
PFT improved, <i>n</i> (%) ^b	15 (42)	7 (58)
PFT stable, <i>n</i> (%) ^b	14 (40)	5 (42)
PFT worsened, <i>n</i> (%) ^b	3 (9)	0
Tapered off glucocorticoids completely, <i>n</i> (%)	14 (39)	7 (50)

All values are reported as the mean (s.d.) for continuous variables or number (percentage) for categorical variables. ^aDefinition was based on composite of clinician global assessment, change in oxygen requirements, need for unexpected respiratory-related hospitalization, and survival. All patients with clinical worsening died during the follow-up period. ^bPFT was recorded for subjects with PFTs within 3 months before or 1 month after rituximab initiation and 6–18 months after rituximab initiation. Improvement was defined as $\geq 10\%$ improvement in FVC. Stable was defined as FVC $\leq 10\%$ of prior measurement. Worsening was defined as $\geq 10\%$ decline in FVC. DLCO: diffusion capacity of the lung for carbon monoxide; FVC: forced vital capacity; PFT: pulmonary function testing.

disease processes that commonly have concomitant ILD, with mixed results. An open-label proof-of-concept RCT of RTX vs placebo showed a median of 10% improvement in FVC among patients with SSc treated with RTX (*n* = 8), compared with 5% worsening in FVC in patients receiving placebo (*n* = 6, *P* = 0.002) [22]. However, a large prospective cohort study comparing 254 patients with SSc treated with RTX to propensity score-matched comparators showed no improvement or stabilization in lung function [23]. In an RCT of RTX in refractory inflammatory myopathy, 83% of patients improved based on the international myositis definition of improvement, although the trial contained few patients with ILD and did not specifically report pulmonary outcomes [24, 25]. Smaller case series in myositis-related ILD (*n* = 2–24) and CTD-associated ILD (*n* = 24) have suggested effectiveness and safety of RTX [26, 27]. Lastly, retrospective studies of patients with ILD associated with RA have shown that RTX treatment is associated with lower risk of functional respiratory impairment and death compared with other therapies [28, 29]. The patients in our cohorts had predominantly NSIP or OP patterns on high-resolution CT, whereas RA patients generally have a UIP pattern, which raises the possibility that an autoimmune-associated UIP pattern might respond to RTX in a similar manner [28, 29].

Twenty-one (42%) patients in our study were tapered off glucocorticoids successfully. Long-term glucocorticoids carry many risks, including increased susceptibility to infections, fractures and metabolic syndrome [30]. CYC, which was previously used commonly in refractory

autoimmune ILD, is associated with serious side effects, including infections, bone marrow suppression, infertility and long-term risk of malignancy [31]. In comparison, RTX has a favourable safety profile in multiple longitudinal studies [32–34]. In our study, few adverse events were noted, except for two minor infusion reactions and nine infections, similar to prior reports; only two patients discontinued therapy owing to adverse events (infections) [35]. Given that the majority of patients who received RTX were also receiving glucocorticoids during some portion of the RTX therapy time period, we are unable to determine the proportion of infections resulting from increased susceptibility to infection attributable to RTX alone.

The limitations of our study deserve comment. First, given the observational nature of the study, inherent differences in patient characteristics could have prompted the selection of RTX as a treatment choice. For this reason, a comparator group was not used, owing to concerns for selection bias. Severity of illness and refractoriness of disease could have influenced the decision to use RTX. For many patients in the MGB cohort, RTX was chosen owing to severe and rapidly progressive illness despite aggressive therapy (including two patients who received RTX while on ECMO), and for others we do not have information on why RTX was chosen as the first-line treatment. Second, the IPAF criteria were applied retrospectively at MGB, and certain characteristics of autoimmune diseases, especially subtle clinical manifestations, might not have been documented in the electronic health record. The denominator

of the number of IPAF patients at MGB is not known. Differences in cohort selection could account for the lower baseline rates of symptoms and co-morbidities in the MGB cohort compared with the UCM cohort, although rates of stability and improvement were similar in both cohorts. There was heterogeneity in terms of the histopathological and radiological patterns of ILD among subjects, and these might influence the degree of response to RTX therapy. Lastly, not all subjects had baseline PFTs within the prespecified time range, and therefore change in FVC, the currently preferred measurement for ILD treatment response, could not be determined for all subjects. We therefore developed a composite outcome to assess treatment response; however, this composite has not been validated in other studies.

This is the largest study to date examining the use and safety of RTX treatment for patients with IPAF, and the first study to show similar positive results at two large academic medical centres. Future prospective studies and RCTs are needed to determine whether RTX is safe and effective in IPAF and to determine which clinical, serological and radiological phenotypes of IPAF might respond best to RTX therapy.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Supplementary data

[Supplementary data](#) are available at *Rheumatology Advances in Practice* online.

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