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Rituximab for the treatment of connective tissue disease-associated interstitial lung disease

Sandra Chartrand[1], Jeffrey J. Swigris[2, 3], Lina Peykova[2], Aryeh Fischer[3]

[1] Hôpital Maisonneuve-Rosemont affiliated to Université de Montréal, Montréal, Québec, Canada; [2] Department of Medicine, National Jewish Health, Denver, Colorado, USA; [3] Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA

Abstract. *Objective:* To describe our experience with rituximab (RTX) as treatment for a diverse spectrum of chronic connective tissue disease-associated interstitial lung disease (CTD-ILD). *Methods:* Twenty-four subjects with CTD-ILD were included. All had pulmonary function testing before and after their first RTX infusion. Each subject was evaluated in a multidisciplinary autoimmune and ILD outpatient clinic. Data were extracted by retrospective review of complete medical records. *Results:* Most subjects were middle-aged white women with rheumatoid arthritis (RA) (n=15) and a nonspecific interstitial pneumonia (NSIP) pattern on high-resolution chest computed tomography scans (n=17). Sixteen subjects received a corticosteroid-sparing agent at the time of RTX initiation; mostly mycophenolate mofetil (n=8). RTX administration was not associated with corticosteroid-sparing effects: 13 subjects were on prednisone at the time of the initial RTX cycle, and 9 remained on prednisone at 6 months after (mean daily dosage 10.2±16.2 mg before vs. 5.6±11.0 mg after, p=0.27). RTX had no appreciable effect on pulmonary physiology; however, individual trajectories for percentage predicted forced vital capacity (FVC%) were highly variable. The underlying CTD (RA vs. non-RA) and ILD pattern did not appear to affect response to RTX. Among 14 subjects who received multiple RTX cycles, FVC% trajectories were variable: FVC% increased in eight and declined in six. Respiratory infections were the most common post-RTX adverse event. *Conclusion:* In this small, retrospective study of chronic CTD-ILD, RTX was not associated with changes in FVC% or corticosteroid-sparing effects. Controlled, prospective studies are needed to more confidently define the effects of RTX in CTD-ILD. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 296-304)*

Key words: interstitial lung disease, connective tissue disease, rituximab, treatment

Introduction

The interstitial lung diseases (ILD) are a group of diffuse parenchymal lung disorders associated with substantial morbidity and mortality (1, 2). ILD may arise as a result of a specific occupational or environmental exposure or as a manifestation of underlying connective tissue disease (CTD).

Immunosuppression is a commonly-used treatment strategy for CTD-associated ILD (CTD-ILD) (3, 4). Most of the data in support of immunosuppression for CTD-ILD comes from retrospective studies and small case series. Data from two well designed, controlled, prospective trials in scleroderma-associated ILD (SSc-ILD) demonstrated that cyclophosphamide (CYC) was associated with stability or only modest improvement in forced vital

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Correspondence: Aryeh Fischer, MD
Department of Medicine
University of Colorado School of Medicine
1775 Aurora Court P.O. Box 6511, Mail Stop B-115
Aurora Colorado 80045, USA
E-mail: aryeh.fischer@ucdenver.edu

capacity (FVC) (5,6). Enthusiasm for the use of CYC in SSc-ILD or other forms of CTD-ILD is blunted because CYC is not a suitable, long-term treatment option and because of its potential for causing significant acute toxicity (7).

Recent retrospective studies of patients with various types of CTD-ILD suggest that mycophenolate mofetil (MMF) may be an effective alternative to CYC (8-12). Similarly, small case series suggest that other immunosuppressive medications (e.g., azathioprine, cyclosporine, tacrolimus) may be effective for certain forms of CTD-ILD (11, 13, 14).

Rituximab (RTX), a B-cell depleting therapy initially approved in the 1990s for the management of B-cell lymphoma (15, 16), has gained popularity over the past decade for the management of a variety of systemic autoimmune diseases. RTX has proven to be as effective as CYC for the management of systemic vasculitis (17, 18), and it is an effective disease modifying therapy for rheumatoid arthritis (RA) (19, 20). Conflicting data exist regarding its role in the management of systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (21-24).

RTX is administered intravenously and typically according to either of two dosing protocols: four consecutive weekly infusions at 375 mg/m^2 (18) or two infusions separated by 14 days at 1000 mg per infusion (20). Re-dosing of RTX is often considered at six month intervals, but decision regarding the timing of repeat dosing for this agent in patients with autoimmune diseases are not yet evidence-based.

In general, RTX is well-tolerated (17, 18, 25, 26). The most common adverse effects are those associated with the infusion (27). Patients treated with RTX are at risk for post-infusion infections due to its immunosuppressive effects, yet infectious complications appear to be less common with RTX compared with other biologic therapies (e.g. anti-TNFα agents) (28).

Over the past several years, case reports and small case series have suggested that RTX may be an effective "rescue therapy" for anti-synthetase syndrome, SSc-ILD, RA-ILD, or other forms of CTD-ILD (29-39). In these series, RTX was typically given to patients with severe and refractory disease or to patients hospitalized with acute decompensation associated with their ILD (29-31).

In this study, our goal was to add to the data on using RTX for CTD-ILD by describing our center's experience with outpatient RTX treatment for a diverse spectrum of patient with chronic CTD-ILD.

Materials and methods

This study was retrospective, HIPAA-compliant, and approved by our institutional review board (protocol HS-2917).

Study cohort and data

We identified all patients in our multidisciplinary autoimmune and ILD clinic treated with RTX from January 2008 to July 2014. In total, 140 patients were identified: 83 did not have ILD, 3 did not have CTD, 20 had insufficient follow-up data, 8 had unknown RTX administration schedules, and in 2, we were unable to confirm that RTX was administered; thus, 24 CTD-ILD subjects comprised the study cohort (Figure 1). All subjects had pulmonary

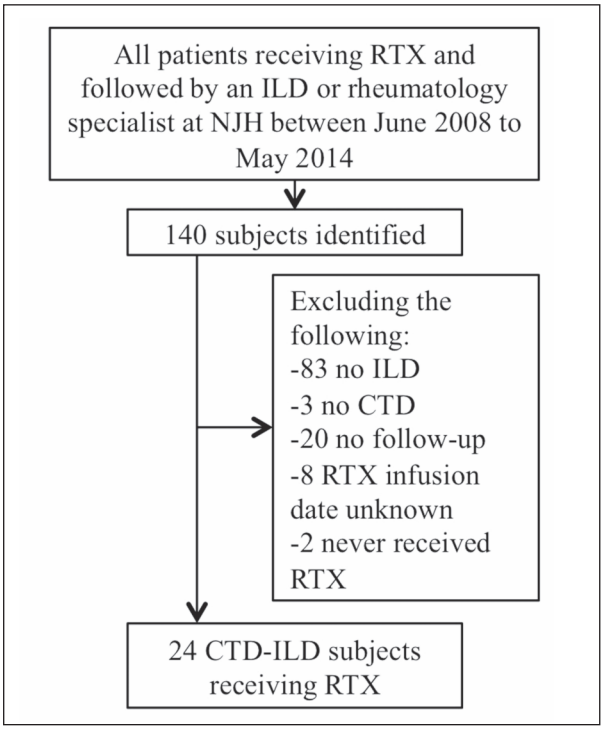


Fig. 1. Cohort formation.
CTD = connective tissue disease; ILD = interstitial lung disease; NJH = National Jewish Health, Denver, CO; RTX = rituximab.

function testing before and after their first RTX infusion cycle. Pulmonary function tests (PFT) were performed as previously described (40). Twenty-three subjects had a definite form of CTD-ILD and satisfied American College of Rheumatology (ACR) criteria for a specific CTD diagnosis as applied by board-certified rheumatologists. One subject had a suggestive form of CTD-ILD, i.e., ILD with autoimmune features, but did not meet criteria for an ACR-defined CTD. The diagnosis of ILD was made by either thoracic high-resolution computed tomography (HRCT) imaging, as interpreted by an expert thoracic radiologist, or by surgical lung biopsy, as interpreted by an expert pulmonary pathologist. All decisions regarding testing, drug administration and timing of follow-up evaluation were made by the treating physicians. All data were extracted during a retrospective review of each subject's complete medical record.

Statistical analysis

Descriptive statistics were generated for baseline data. We analyzed longitudinal changes in FVC% with mixed-effects, piecewise linear regression models (Proc Mixed procedure in SAS) that considered time as a continuous factor. These models used least-squares to fit curves to the data to generate estimates for the mean FVC% as a function of time in relation to initiation of RTX. In each model, an unstructured variance-covariance matrix was used to model the covariance structure among the repeated measures by subject. Other structures were tested but yielded worse fits. In our final model, we inserted knots, thus allowing for changes in slope of FVC%, at week 0 (i.e., at the time of RTX initiation) and week 26; we selected these time points, because they create a window during which we would expect to see the effects of RTX on FVC%.

We chose to analyze the data with longitudinal models rather than an analysis of FVC% before-and-after-RTX-initiation because of the variability in timing and number of outcome assessments both within and between subjects. We used the same model structure to compare FVC% changes between subjects stratified on type of underlying CTD (RA vs. non-RA). We conducted similar analyses with the cohort stratified on lung injury pattern as defined by surgical lung biopsy or thoracic HRCT pattern. All statistical analyses were performed using SAS software (version 9.2; SAS Institute). We considered $p<0.05$ to represent statistical significance and did not adjust for multiple comparisons.

Results

Clinical characteristics of the cohort

The cohort was composed of 24 subjects. Their clinical characteristics are displayed in Table 1. The majority were white women in their sixth decade. The majority of subjects had RA (n=15), and their mean CTD duration was nearly 10 years.

RTX dosing and concomitant therapies

For the first RTX cycle, 22 subjects received two 1000 mg infusions of RTX separated by 14 days, and two subjects received four, weekly RTX infusions at a dose of 375 mg/m^2 per infusion. Fourteen subjects received more than one cycle of RTX. Most subjects were on a corticosteroid-sparing agent at the time of RTX initiation (n=16); most frequently MMF (n=8). RTX replaced CYC in two, MMF in two and tacrolimus in one subject. RTX administration was not associated with a corticosteroid-sparing effect: 13 subjects were on prednisone at the time of the initial RTX cycle, and 9 remained on prednisone at 6 months after the initial RTX cycle (mean daily dosage 10.2±16.2 mg before vs. 5.6±11.0 mg after, p=0.27).

Longitudinal pulmonary physiology

Individual FVC% trajectories were highly variable (Figure 2, Panel A); however, modeled values suggest that RTX administration had no appreciable effect on FVC% over time (Figure 2, Panel B). Figure 3 shows spaghetti plots for subjects stratified by the presence or absence of RA. There was no difference in slope from week 0 to week 26, i.e., from the time of RTX initiation to six months later, for subjects with or without RA (with RA: slope=0.1751±0.1781 vs. without RA: slope=-0.05410±0.2239; difference=0.2291±0.2861, p=0.44). In a similar analysis of subjects with HRCT patterns suggestive of usual interstitial pneumonia (UIP) or NSIP, there was no difference in slope from

Table 1. Characteristics of subjects at time of initiation of rituximab

	All patients n=24	RA patients n=15
Age, years (mean±SD)	61.3±10.4	62.9±10.3
Female, n (%)	15 (62.5)	10 (66.7)
Race, n (%)		
White	21 (87.5)	14 (93.3)
Afro-American	2 (8.3)	1 (6.7)
Asian	1 (4.2)	0 (0.0)
Past smokers, n (%)	8 (33.3)	5 (33.3)
Current smokers, n (%)	1 (4.2)	1 (6.7)
Pack-year (mean±SD)	27.1±9.5	29.7±6.8
Expired, n (%)	1 (4.2)	0 (0.0)
Diagnosis, n (%)		
Rheumatoid arthritis (RA)	15 (62.5)	15 (100.0)
Idiopathic inflammatory myositis (IIM)	3 (12.5)	
IIM+RA	2 (8.3)	
Systemic sclerosis	3 (12.5)	
Suggestive CTD-ILD	1 (4.2)	
Rheumatic disease duration, years (mean±SD)	9.5±9.1	11.6±10.0
ILD duration, years (mean±SD)	3.0±2.8	2.5±2.1
RTX regimen		
RA protocol	22	14
Vasculitis protocol	2	1
Concurrent corticosteroid-sparing agent, n (%)		
Mycophenolate mofetil	8 (33.3)	3 (20.0)
Methotrexate	4 (16.7)	4 (26.7)
Leflunomide	1 (4.2)	1 (6.7)
Azathioprine	1 (4.2)	1 (6.7)
Intravenous immunoglobulin	1 (4.2)	0 (0.0)
Cyclophosphamide	1 (4.2)	0 (0.0)
Thoracic HRCT patterns, n (%)		
NSIP	11 (45.8)	7 (46.7)
NSIP+OP	5 (20.8)	1 (6.7)
NSIP+UIP	1 (4.1)	1 (6.7)
UIP	4 (16.7)	4 (26.7)
LIP	1 (4.1)	1 (6.7)
Undefined diffuse lung disease	2 (8.3)	1 (6.7)

Legend: CTD = connective tissue disease; HRCT = high-resolution computed tomography scan; ILD = interstitial lung disease; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RTX = rituximab; SD = standard deviation; UIP = usual interstitial pneumonia

week 0 to week 26 between subjects with UIP-pattern vs. NSIP-pattern (difference=0.2769±0.2111, p=0.19) (data not shown).

The longitudinal FVC% trajectories in the 14 subjects who received multiple cycles of RTX can be found in the Supplement. Over the observation period, a greater than 10% improvement in FVC% was identified in 4 subjects (subjects 7, 14, 15, and 39; all had RA) and an improvement of less than 10% was identified in 4 (subjects 9, 21, 24 and 44; three had RA and one had idiopathic inflammatory myopathy (IIM)). A decline in longitudinal FVC% of less than 10% was identified in four subjects,s (1, 34, 36 and 45: all with diverse CTDs and ILD patterns) and a greater than 10% decline in two subjects (5, 13: both with RA, one with LIP and one with NSIP+ organizing pneumonia).

Adverse effects associated with RTX

Five infectious episodes (four uncomplicated respiratory tract infections and one disseminated *Herpes Zoster* infection) occurred in five different subjects within six months post-initial RTX cycle.

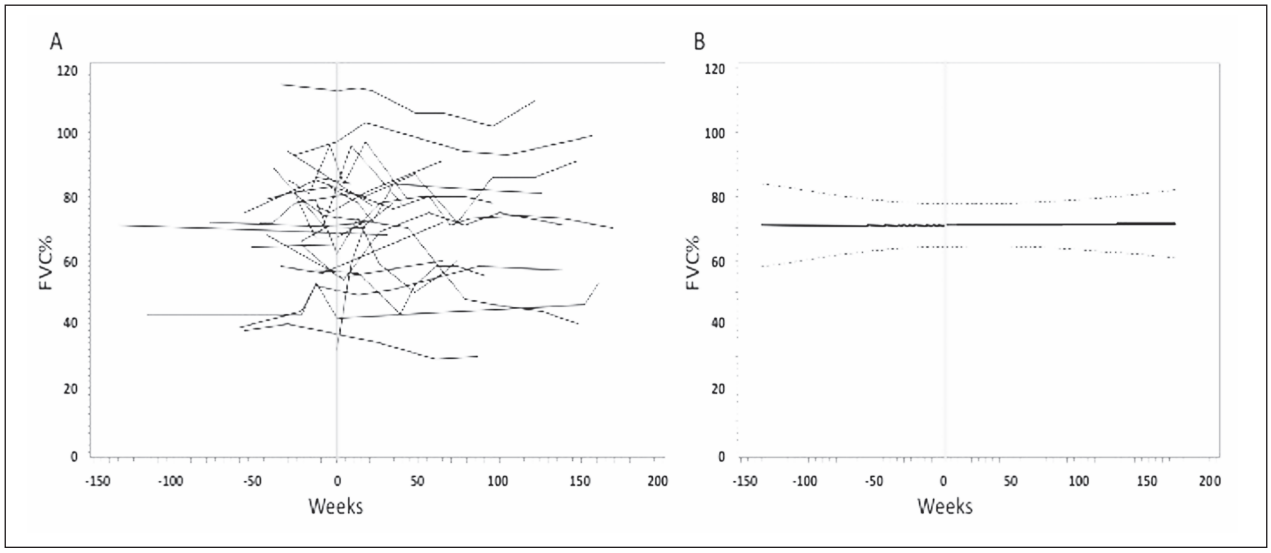


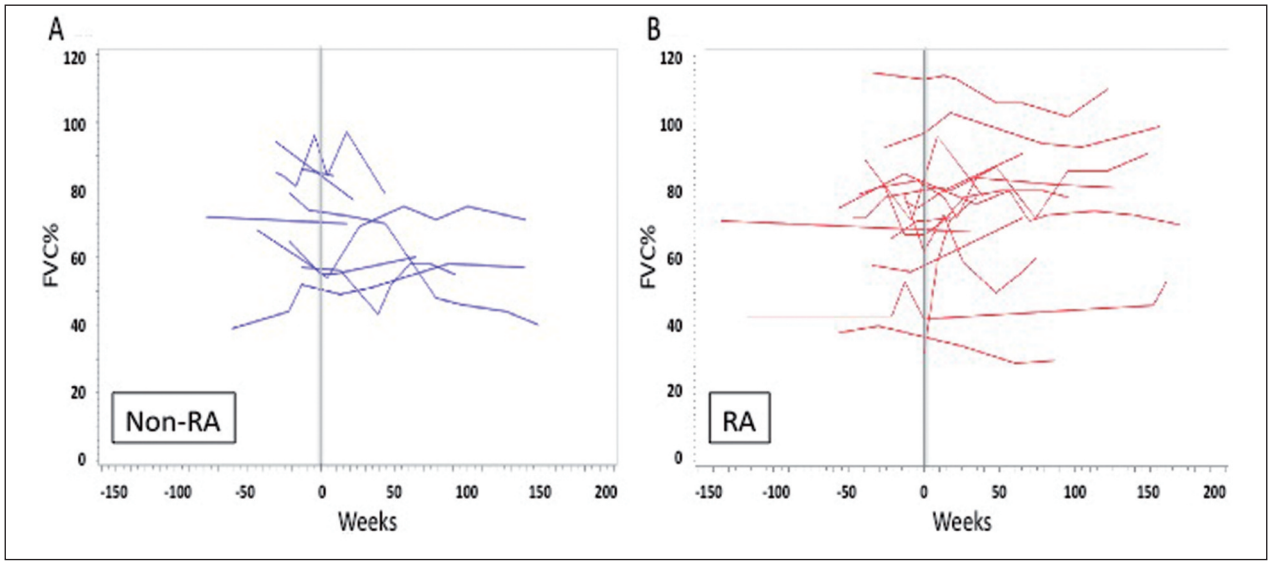
Fig. 2. Spaghetti plot **(Panel A)** showing trajectories for percentage of predicted forced vital capacity (FVC%) over time for each subject (n=24) and mixed-effects model estimates **(Panel B)** for percentage of predicted forced vital capacity (FVC%) over time for the entire cohort. Vertical line at time 0 denotes timing of first rituximab infusion.
Solid line = mean FVC%; broken lines show 95% confidence bands.

An additional 11 infectious episodes (nine respiratory tract infections, one gastro-enteritis, one *Herpes Zoster* infection) occurred in five subjects who received more than one RTX cycle (mean observation period of 35.6±19.3 months and a total of 66 RTX cycles). Only a single cycle of RTX was administered to six subjects: in three subjects because their ILD remained stable; in one subject because there were infectious complications; and in two subjects, for unclear reasons, but based on the discretion of their provider. Only one mild infusion reaction was noted in over 66 RTX cycles.

Discussion

In this retrospective study, we describe our center's experience with using RTX in the outpatient setting to treat patients with a heterogeneous spectrum of chronic CTD-ILD. Nearly two-thirds of the cohort received multiple cycles of RTX, three-quarters were on a concomitant corticosteroid-sparing agent, and approximately half were on concomitant prednisone. As a group, no meaningful changes in longitudinal FVC% trajectories were identified. However, individual subjects had variable responses. Neither the presence of RA, nor a specific HRCT pattern appeared to impact response to RTX. After the first RTX cycle, RTX was not associated with any corticosteroid-sparing effects. Respiratory infectious were the most common post-RTX adverse events after the first cycle and with multiple cycles, but only in a subgroup of patients.

A number of retrospective cohort studies describe the use of RTX in CTD-ILD. Keir et al. (29) first reported 8 cases of CTD-ILD (5 with IIM; median FVC 45% of predicted and median DLco 25% of predicted) in which RTX 1000 mg IV twice at 2-week interval was used as rescue therapy. Six of these patients had serial PFT: prior to RTX infusion, all had a decline in FVC%, and post-RTX infusions, a median FVC% improvement of 18% (p=0.03) was noted. In a follow-up study, some of these same investigators reported their experience with RTX infusions in 50 cases of severe and refractory ILD; 33 of these cases had CTD-ILD (10 IIM, 8 SSc, 15 other forms of CTD-ILD [SLE, SjS, MCTD, UCTD]) (30). Subjects in that cohort had severe disease: 49 out of 50 had received prior immunosuppression with cytotoxic medications, 4 required mechanical ventilation, mean DLco was 24.5% of predicted and mean FVC% was 44.0%. In the CTD-ILD sub-group, 85% (most with IIM) were classified as responders. In the 6-12 month period prior to



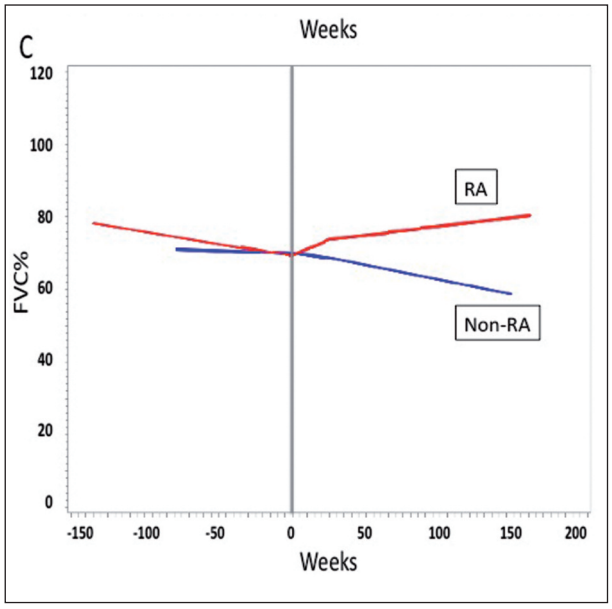


Fig. 3. Panels A and **B.** Spaghetti plot showing trajectories for percentage of predicted forced vital capacity (FVC%) over time for subjects without RA (Panel A) or with RA (Panel B). Vertical line at time 0 denotes timing of first rituximab infusion.
Panel C. Spaghetti plot showing trajectories for percentage of predicted forced vital capacity (FVC%) over time for subjects without RA (Panel A) or with RA (Panel B). Vertical line at time 0 denotes timing of first rituximab infusion.
FVC% = percent predicted forced vital ca

RTX, there was a median decline in FVC% of 13.3% compared to an improvement of 8.9% ($p<0.01$) in the 6-12 month period post-RTX therapy. Dodds et al. reported their experience with RTX as rescue therapy in 22 patients with severe refractory CTD-ILD. The cohort was composed of 5 patients with RA, 7 with IIM, 2 with SLE, 2 with SSc and 3 with other forms CTD. Nine patients showed definitive, radiographic evidence of stability or improvement, and four patients showed continued evidence of deterioration despite having been treated with RTX. In those patients where RTX prevented disease progression (n=8), there was improvement in FVC% (median 2.5%, range 0-7%; p=0.08) (31).

There are several small studies of RTX in SSc-ILD. In one, 15 patients with diffuse cutaneous SSc and mild-moderate ILD (patients with a FVC or DLco <50% of predicted were excluded) received one cycle of RTX (1000 mg infusions two weeks apart). At six months, the FVC%, DLco and the HRCT remained stable (32). Daoussis et al. used RTX in 14 SSc-ILD patients: eight subjects treated with the

vasculitis protocol and then again six months later were compared with six subjects in the "control group" that received standard treatment (including prednisone, MMF, CYC and bosentan) (33). At 1 year, the FVC% in the RTX group increased from 68.1±19.7 to 75.6±19.7% of predicted (p=0.0018), an improvement of 10.3% compared to the control group which lost 5.0% of predicted (p=0.23). The DLco also improved significantly in those that were treated with RTX (from 52.3±20.7 to 62.0±23.2% of predicted [p=0.017]) compared to the control group in whom DLco decreased 7.5%. At two years from the first infusion (34) both FVC% and DLco remained improved over baseline (p<0.0001 for both values). In another prospective series of five SSc-ILD patients refractory to CYC were treated with RTX at a lower but more frequent dosing schedule (500 mg at days 0 and 14 every three months for a year), RTX treatment was associated with a significant increase in both FVC% (48.5±6.7 to 66.0±4.0 % of predicted [p<0.001]) and DLco (72.0±5.2 to 89.0±3.2% of predicted [p<0.004]) (35).

A number of case reports support the use of RTX in severe, refractory IIM-ILD (41). A small retrospective series of 11 patients with anti-synthetase syndrome (36) were treated with RTX as a rescue therapy after failure of CYC and/or other immunosuppressive therapies. Comparing the PFT data obtained in the eight months preceding treatment with PFT data obtained in the seven months following treatment, six patients had in improvement of >10% of their FVC%. Three to six months following infusion, the thoracic HRCT scan showed a regression of the ground glass opacities in four patients and progression in one patient. In another study, eight patients with IIM-ILD were treated with RTX (37). The baseline FVC% of 74±19% increased to 83±21% at 7 months, 91±21% at 12 months and 108±15% at 21 months following the initial cycle (4 of these patients received more than one RTX cycle). The DLCO did not significantly improve at 6 months from the initial RTX cycle. In another study, 10 patients with RA-ILD (four with UIP and six with NSIP) were treated with RTX (38). Of the seven subjects with data at baseline and 48 weeks (one had an infusion reaction at baseline, one died after hip fracture and one died of pneumonia), the FVC% worsened in one subject, stabilized in four and improved by >10% in two.

Our study has a number of limitations. As with any retrospective study, it is limited by a lack of prospectively defined, systematic methods for data collection, drug initiation and dosing, and surveillance for adverse effects. Because of the retrospective design, we cannot reliably determine the motives that drove treatment-oriented decisions. However, all subjects were confirmed to have CTD-ILD, and the use of RTX was explicitly for this clinical scenario. The heterogeneity and the small cohort size preclude the ability to draw definitive conclusions. It is also possible that no dramatic response was associated with RTX because of the nature of the cohort studied. We highlight that because our cohort was comprised of patients managed outside the hospital setting and with chronic ILD, the indolent nature of their illness may have blunted the treatment response.

Conclusion

In this relatively small cohort of subjects with a diverse spectrum of chronic CTD-ILD, outpatient treatment with RTX was not associated with changes in longitudinal FVC% or effective corticosteroid dose reduction. Although past series suggest that RTX may have a role as a rescue therapy for CTD-ILD, it may not be as effective in those with more chronic CTD-ILD. Controlled, prospective studies are needed to better define the role of RTX for the management of the spectrum of CTD-ILD.

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