Effects of rituximab in connective tissue disorders related interstitial lung disease

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ABSTRACT

Objective. *Interstitial lung disease (ILD) is a key prognostic factor in connective tissue disorders (CTDs). The aim of our study was to assess the changes in pulmonary functional tests (PFTs) in various CTDs, including anti-synthetase syndrome (SYN), systemic sclerosis (SSc) and mixed connective tissue disorder (MCTD), following the use of rituximab therapy.*

Methods. *A multicentre retrospective analysis of patients with ILD secondary to SYN (n=15), MCTD (n=6) and SSc (n=23). PFTs were performed at baseline and at 1 and 2 years of follow-up. The primary outcome was the change in forced vital capacity (FVC) at 1 year.*

Results. *In the SYN population, median FVC changed from 53.0% (42.0-90.0) at baseline to 51.4% (45.6-85.0) at 1 year and 63.0 (50-88) (p=0.6) at 2 years (p=0.14). In SSc, FVC changed from 81.0% (66.0-104.0) at baseline to 89.0% (65.0-113.0) at 1 year (p=0.1) and 74.5 (50-91) at 2 years (p=0.07). In the MCTD population, FVC changed from 64.5% (63.0-68.0) at baseline to 63.0% (59.0-71.0) at 1 year (p=0.6) and 61 (59-71) after 2 years (p=0.8). DLCO showed a trend for improvement in the SYN population (p=0.06 at 1 year and 0.2 at years) while changes remain non-significant in the SSc and MCTD patients. In SYN patients, the percentage of responders at 1 year for FVC (33.3%) was greater than in SSc (9.5%) (p=0.07) and MCTD (17%) (p=0.45). RTX showed a satisfactory safety profile.*

Conclusion. *A trend of improvement of PFTs was observed in SYN patients although not reaching significance, while SSc and MCTD patients were stabilised.*

Introduction

Interstitial lung disease (ILD) is a common complication of various connective tissue diseases (CTD) including systemic sclerosis (SSc), mixed connective tissue disease (MCTD) and anti-synthetase syndrome (SYN) (1, 2). In many cases, ILD dictates the prognosis, as increased morbidity and mortality are associated with ILD (3-5). ILD is clinically mainly characterised by a progressive dyspnoea. Pulmonary function tests (PFTs) is the first line tool showing restrictive ventilation defect with a reduction of vital capacity (VC) and of forced vital capacity (FVC) but without the reduction of forced expiratory volume in the first second (FEV1) as observed in obstructive defect. In addition in patients with ILD is often observed a reduced of diffusion capacity for carbon monoxide (DLCO) (2, 6). A recent study on SSc patients suggested that a decline in PFTs represents a poor prognostic factor (7).

ILD is characterised by different histopathological subsets. In SSc, the non-specific interstitial pneumonia (NSIP) pattern may be found in up to 80% of patients (8). ILD is largely represented in MCTD by NSIP and less frequently by usual interstitial pneumonia (UIP) pattern (2). In SYN, more heterogeneous lesions may occur such as NSIP, usual interstitial pneumonia (UIP), cryptogenic organising pneumonia (COP) and diffuse alveolar damage (DAD) (2, 9).

Despite the high medical need, currently available treatments remain limited and not established. In the last years, preliminary data have suggested that anti-CD20 rituximab (RTX) may be an effective treatment option for CTD-related ILD. Indeed in SSc, preliminary studies have suggested a stabilisation of pulmonary function test (PFTs) after a follow-up of 6 months and some improvement after 1 or 2 years of follow up (10-12). In SYN, available evidence is limited on case reports or small case

Table I. Clinical characteristics of three populations.

Parameters	SSc (n=23)	MCTD (n=6)	SYN (n=15)
Age years (mean±sd)	58.8±10,42	50.83±6.1	50.5±15.16
Sex: Female n (%)	20 (86.9%)	5 (83.3%)	8 (67.7%)
Disease duration years (mean±sd)	7.96±7.65	8.91±8.45	6.66±6.16
Subset:			
diffuse cutaneous subset	18		
limited cutaneous subset	5		
Antibodies positivity n (%)			
ANA	23 (100%)	6 (100%)	8 (66.7%)
ACA	4 (17.4%)		
Anti-Scl70	13 (56.5%)		
Anti-RNA pol III	2 (8.7%)		
Anti-RNP		6 (100%)	
Anti-Jo1; (or other anti-tRNA synthetase)			15
Other Ab	Anticardiolipine; anti-PM/Scl; Anti-SSA;	Anti-SSA; Anti-SSB; Anti-PM/Scl; RF; Anti-CCP; Scl70	AntiCCP; AntiRo; RF; SSA; Anti-TG
Synovitis	9 (39.1%)	1 (16.7%)	6 (40%)
Myositis		1 (16.7%)	13 (86.7%)
Videocapillaroscopic pattern			
Early	7 (30.4%)		
Active	7 (30.4%)		
Late	9 (39.1%)		
Echocardiography			
sPAP>25 mmHg	16 (69.6%)		
LFEF≤40%	1 (4.4%)		
Dyspnoea n (%)			
NYHA 1	6 (26.7%)	2 (33.3)	2 (16.7%)
NYHA 2	11 (52.2%)	2 (33.3%)	2 (16.7%)
NYHA 3	3 (13%)	2 (33.3%)	2 (16.7%)
NYHA 4	1 (4.3%)	0	0
NYHA 3- NYHA 4	1 (4.3%)	0	0
DMARDs treatment during RTX therapy	15/23 (65.21%)	5/6 (83.3%)	8 (86.7%)
Previous or concomitant Cyclophosphamide	1/23 (4.3%)	1/6 (16.7%)	4/15 (26.7%)

SSc: systemic sclerosis; MCTD: mixed connective tissue disease; SYN: anti-synthetase syndrome; ANA: antinuclear antibodies; ACA: anticentromere antibodies; Anti-Scl70: antitopoisomerase I antibodies; anti-RNA pol III: anti-RNA polymerase III antibodies; anti-RNP: anti-ribonucleoprotein antibodies; anti-Jo1: anti –aminoacyl tRNA synthetase antibodies; DMARDs: disease modifying anti-rheumatic drugs.

series (5, 13). In MCTD, the potential efficacy of RTX in ILD has not yet been studied.

The objective of our study was to evaluate the mid-term effects of RTX on lung function in ILD related to SYN, SSc and MCTD.

Materials and methods

SYN patients were characterised by the presence of anti-synthethase antibodies. All SSc patients fulfilled the new ACR/EULAR classification criteria (14), MCTD patients had anti-RNP antibodies and fulfilled at least one proposed classification criteria (15). All enrolled patients presented ILD at chest high resolution computed tomography (HRCT) at baseline (ground-glass or reticular pattern or honey combing). Being a retrospective and multicentre study, lung involvement was not homogeneously followed up with HRCT according to different guidelines in these centres.

Enrolled patients were evaluated with LFTs at 1 year, and when available data concerning LFTs at 2 years of follow-up were collected.

In addition to pulmonary assessment, other baseline parameters have been collected. For all SYN patients the presence of synovitis, myositis, increased CPK levels (IU/l) and muscle weakness were recorded. In SSc population the presence of synovitis, the last systolic pulmonary artery pressure (sPAP) and left ventricular fraction injection (LVEF) at the echocardiography and the capillaroscopic pattern were recorded. MCTD patients were investigated for the presence of synovitis and myositis.

Eight centres retrospectively collected data on SYN, SSc and MCTD patients treated with RTX used in routine care (see Table I for concomitant or previous therapy). Data regarding RTX administration regimen, safety and use of methylprednisolone, DMARDs and/or immunosuppressive treatment were also collected.

The primary outcome measure was the change in FVC assessed at 1 year. The secondary outcomes were DLCO values and the percentage of responders in PTF parameters. We first defined responders as patients with a ≥10% increase in FVC and ≥15% increase of DLCO, as reported in recent randomised controlled trials evaluating treatment of idiopathic ILD (16). A second analysis was performed considering responders as patients with an increase of ≥5% of FVC and ≥10% of DLCO.

Statistical analysis

Data were analysed using the SAS System; non-parametric values are pre-

Table II. PFTs follow up.

	PFTs parameters	Prior-RTX	Baseline	1 Year	*p*-value (baseline-1 year)	2 Years	*p*-value (baseline-2 years)
SYN	FVC median (IQR) % (n)	58 (48-82) 11	53 (42-90) 15	51.4 (45,6-85) 15	0.59	63.05 (50-88) 6	0.14
	TLC median (IQR) % (n)	74 (53-88) 6	60.8 (49-84) 11	66 (55.6-88) 9	0.48	58 (54-81) 4	0.1
	DLCO median (IQR) % (n)	52 (33-79) 7	41.7 (31.10-61) 12	52 (34.9-65) 11	**0.059**	51.85 (34-63.4) 5	0.20
	DLCO/AVmedian (IQR) % (n)	72.7 (51-95) 6	76 (69-83) 11	73 (64-93.3) 10	0.83	82.5 (33-86) 5	0.89
SSc	FVCmedian (IQR)% (n)	88 (79–102) 18	81 (66-104) 23	89 (65-113) 21	0.98	74.5 (50–91) 10	**0.066**
	TLC median (IQR) %(n)	94 (82-109.5) 16	85 (77-99) 21	90,5 (72.5-103.45) 20	0.51	77 (59-105) 7	0.40
	DLCO median (IQR)% (n)	62.5 (55-68) 18	54 (39-67.8) 23	61 (47-64) 19	0.62	57.5 (38.5-70.5) 8	0.89
	DLCO/AV median (IQR)% (n)	73 (69.5-92) 15	79.1 (61-87) 21	76 (64.2-82) 15	0.53	74.5 (66-88) 6	0.75
MCTD	FVC median (IQR) % (n)	59 (50-75) 3	64.5 (63-68) 6	63 (59-71) 5	0.58	61 (59-71) 5	0.78
	TLC median (IQR) % (n)	74 (59-80) 3	69 (68-72) 5	68 (68-91) 4	1.00	72 (69-73) 5	0.58
	DLCO median (IQR) % (n)	53 (40-61) 3	41 (30-46) 6	38 (34-49) 5	0.88	47 (46-51) 5	0.36
	DLCO/AVmedian (IQR) % (n)	94 (84-96) 3	75 (59-88) 6	67 (64-69) 5	1.00	82 (55-94) 5	0.58

FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; TLC: total lung capacity; DLCO/AV: DLCO corrected for alveolar volume; Prior-RTX: evaluation about 12 months before the baseline; Baseline: time 0= beginning of RTX therapy; 1 year: evaluation 1 year after the baseline; 2 years: evaluation 2 years after the baseline; SSc: Systemic sclerosis; MCTD: Mixed connective tissue disease; SYN: Anti-synthetase syndrome; N.R.: Wilcox test non realisable for the small population. In the graph, FVC and DLCO values are expressed as median for each disease.

sented as median±interquartile range (IQR) and normally distributed data as mean±standard deviation (SD). Changes in PFTs parameters were analysed using the Wilcoxon Signed Rank Sum Test. The Fisher test was used to compare percentage of responders (a *p*-value <0.05 was considered statistically significant).

Results

Forty-four patients from 8 centres were enrolled: 15 with SYN, 23 with SSc and 6 with MCTD. Table I reports baseline characteristics. The detailed results for the change from baseline to 1 or 2 years are shown in Table II and Figure 1.

For all the patients co-treatment with DMARDs or immunosuppressant was recorded. In SYN population, 8 patients received concomitant treatment with azathioprine (out of these subjects, two received prednisone, one methotrexate (MTX) and intravenous immunoglobulin (IVIg), one cyclosporine and one IVIg). One patient was treated with prednisone and IVIg, one with prednisone only and another one received concomitant treatment with MTX and cyclosporine. Still in SYN population, three patients were treated with cyclophosphamide during the first and third RTX infusions. In SSc population, 9 patients were treated with MTX (out of these 9 subjects, one also received mycophenolate mofetil (MMF)). One patient was treated with cyclophosphamide and oral prednisone, two patients with MMF and two with azathioprine. One patient received oral prednisone. In MCTD, two patients received concomitant treatment with cyclophosphamide (one only during the first year, during the second year he received MMF); two patients received MTX and one azathioprine.

The cumulative mean dose of RTX did not significantly differ between patients with SYN (2.170 gr at 1 year, 1.910 gr at 2 years), SSc (2.800 gr at 1 year, 1.750 gr at 2 years) and MCTD (1.900 gr at 1 year, 1.400 gr at 2 years). All patients received premedication with steroid; in Table I, DMARDs and immunosuppressive co-treatment are shown.

When available, PFT values prior to RTX treatment were also recorded. SYN patients had already a reduced FVC value as compared to expected values, and they also exhibited a recent decline before starting RTX therapy (58 (48-82) to 53 (42-90)). In SSc population, although there was a prior decline in FVC values (from 88 (79-102) to 81 (66-104)), it is of note that the median value remained weakly altered. In the MCTD group of patients, no prior decline in FVC values was observed although the decision of the clinicians was driven by a recent decrease in DLCO (23 (40- 61) to 41 (30-46)).

Primary outcome measure

In the SYN population, median FVC changed from 53.0% (42.0-90.0) at baseline to 51.4% (45.6- 85.0) at 1 year (*p*=0.59) and a trend of improvement was observed at 2 years (63.0 (50-88), *p*=0.1).

In SSc population an increase of FVC from baseline to 1 year value was observed (81.0% (66.0-104.0) to 89.0% (65.0-113.0); *p*=0.1), on the contrary it showed a decrease at 2 years of follow-up (74.5 (50-91); *p*=0.07).

In the MCTD population, FVC was stable from the baseline to the 1 year of follow-up (from 64.5% (63.0-68.0) to 63.0% (59.0-71.0), *p*=0.6) and a minimal decrease was stable after 2 years (61 (59-71), *p*=0.8).

Secondary outcome measures

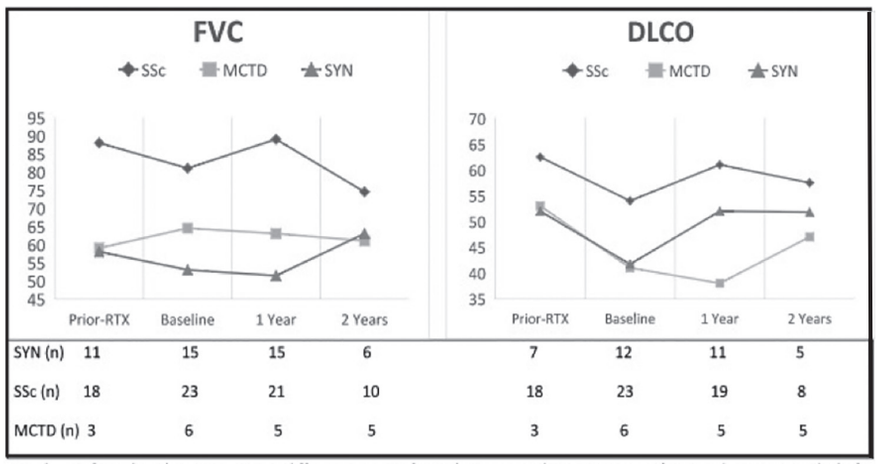
In SYN, an increase of DLCO close to significance was observed from baseline to 1 year (41.7 (31.1-61) to 52 (34.9-65), *p*=0.06) and a stabilisation of this value was observed at 2 years of follow up (51.8 (34-63.4), *p*=0.2.

In patients with SSc, DLCO was stable from baseline to 2 years of follow-up (54 (39-67.8 to 57.5 (38.5-70.5) and a trend of improvement at 1 year (61 (47-64), *p*=0.6).

In MCTD group, a stabilisation of DLCO was observed from baseline to 1 year (41 (30-46) to 38 (34- 49), *p*= 0.8) and it showed a trend in improve-

ment at 2 years of follow-up (82 (55-94), *p*=6).

As specified, the secondary outcome was also the percentage of responders in PFT parameters comparing the baseline value to the last available one. The percentage in FVC responders was greater in the SYN population than SSc (33.3% *vs*. 9.5%, *p*=0.071) and MCTD patients (33.3% *vs*. 16.7%, *p*=0.454). Conversely, the percentage of responders in DLCO, was similar in SYN and SSc populations (27.3% *vs*. 23.8%, *p*=0.830). Defining responders as patients with an increase in FVC≥5%, the SYN population confirmed to have a higher percentage of responders compared to SSc patients (53.3% *vs*. 21.7%) (*p*=0.051).



	Prior-RTX	Baseline	1 Year	2 Years	Prior-RTX	Baseline	1 Year	2 Years
SYN (n)	11	15	15	6	7	12	11	5
SSc (n)	18	23	21	10	18	23	19	8
MCTD (n)	3	6	5	5	3	6	5	5

Fig. 1. FVC and DLCO follow-up.
FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; Ante-RTX: evaluation about 12 months before the baseline; Baseline: time 0= beginning of RTX therapy; 1 year: evaluation 1 year after the baseline; 2 years: evaluation 2 years after the baseline; SSc: Systemic sclerosis; MCTD: Mixed connective tissue disease; SYN: Anti-synthetase syndrome. In the graph, FVC and DLCO values are expressed as median for each disease.

RTX safety

In RTX-treated patients, the following serious adverse events were reported: cardiac involvement with arrhythmia (n=1), fatigue (n=3), infections requiring antibiotic therapy in 6 patients (without hospitalisation) (n=6), serum sickness requiring hospitalisation (n=2).

Discussion

Few preliminary studies suggested RTX efficacy on ILD in SSc and SYN at least in the short term (10-13). As far as we know, we herein report the first retrospective study investigating three CTDs and providing 1 or 2 years of follow-up. The effects of RTX in the SYN population were indeed encouraging in the present study showing a trend of improvement from baseline to 2 years of follow-up and an improvement of DLCO close to significance; in addition in SYN patients the highest percentage of FVC responders was observed.

Our preliminary data are consistent with the results of previous studies (13) showing a possible role of rituximab in patients with ILD-related to SYN and with the data indicating PFTs improvement after a median follow-up of 52 months (17). However, in our study, the trend of improvement of FVC and DLCO does not reach significance and a study with a larger population is requested in order to confirm our data. In addition, RTX in SYN population could improve also the muscle involvement leading to a greater expansion of the thoracic cage and contributing to the improvement in PFTs. For this reason, other studies focusing on the broader RTX effects in SYN population are mandatory.

In SSc and in MCTD, our data are partially in line to those of previous studies (12, 13). In SSc, FVC showed a stable value at 1 year and 2 years and can be interpreted as a "non-progression" of the disease and these data seem very similar with what has been obtained in SSc-ILD with cyclophosphamide with a stability of lung functions (18, 19). In the study of Jordan *et al*. (10), showing a stability of FVC and a significant improvement of DLCO, the SSc population presented evidence of ILD at HRCT and a mean disease duration similar to our patients. However, in this EUSTAR analysis (10), patients seemed to have a more severe ILD involvement with baseline DLCO and FVC values <70%. These parameters may influence the response to RTX therapy: more severe patients may be more likely to respond. These observations might suggest the need of more homogenous population for future studies. In addition, in our study, SSc patients had a higher baseline FVC value when compared to the SYN population which may partially explain the higher percentage of responders in SYN compared to SSc. Indeed, SYN patients presenting with a lower FVC value may have a greater margin for improvement. To our knowledge, this is the first study on the role of RTX in ILD MCTD patients where a potential role for RTX in stabilisation of lung involvement is suggested.

RTX was well tolerated with an acceptable safety profile, consistent with the safety data reported in other rheumatic autoimmune diseases (10).

Our retrospective study presents some limitations, including, a limited sample size (although reflecting the rarity of these diseases) and the different administration scheme of RTX among centres. However, in previous studies demonstrating the efficacy of RTX in pulmonary disease, different schemes of administration have been used (11, 18) without significant differences in the clinical outcomes. This evidence highlight the need to analyse the better dosing of RTX in controlled study in order to confirm its potential role to control SSc lung involvement and to verify with a meta-analysis the possible different outcomes based on the administration regimen.

Another limitation of our study was the fact that some patients received DMARDs and/or immunosuppressive treatment concurrently to RTX and they may have influenced the effects of RTX.

In conclusion, this study indicates that RTX in CTDs may help to control the course of ILD, representing a promising treatment of SYN-related ILD and producing a stabilisation of lung involvement in SSc and MCTD. Indeed, immunosuppression, despite not being able to reverse fibrotic changes, may help in slowing disease progression. In the future, randomised controlled trials should clarify whether RTX treatment may help to counteract the evolution of ILD, a critical prognostic factors in these diseases.

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