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Targeting CD20 in the treatment of interstitial lung diseases related to connective tissue diseases: a systematic review

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Running title: Rituximab in CTD-related ILD

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Highlights

- **Lung involvement is a potentially life-threating complication of CTD**
- **There is an unmet need of novel therapeutic tool, particularly for resistant cases**
- **Rituximab is able to stabilize and possibly to improve CTD-related ILD**
- **There is a need of high-quality studies testing Rituximab in CTD-related ILD**

Abstract

Introduction

The effectiveness of CD20 targeting in connective tissue diseases (CTD) with lung involvement is controversial. This paper aims to review the current evidence about rituximab (RTX) use in CTD-related interstitial lung disease (ILD).

Methods

We performed a systematic review of papers published between January 2009 and May 2019. We included clinical trials, case/control studies and cohort studies. We excluded letters, case reports, case series, reviews, and full articles when not in English. The selected studies listed as primary or secondary outcome a variation in pulmonary function tests or in the scores used to radiologically stage lung involvement, in CTD-related ILD patients after RTX.

Results

Out of 1206 potentially eligible articles, 24 papers were selected: 3 retrospectively described cohorts of patients with different CTD, 14 dealt with systemic sclerosis (SSc)-related ILD, 5 with idiopathic inflammatory myopathies (IIMs)-related ILD, and 2 with Sjögren's Syndrome-related ILD.

A direct comparison of the selected studies was hampered by their heterogeneity for outcomes, follow-up duration, the severity of lung involvement, and clinical features of study populations. However, an overall agreement existed concerning the effectiveness of RTX in the stabilization of lung disease, with some studies

reporting an improvement of functional parameters from baseline. IIM-related ILD appeared more responsive than other CTD-related ILD to CD20 targeting.

Conclusion

RTX is a promising therapeutic tool in CTD-related ILD. This systematic review remarks the unmet need of multicenter prospective studies aiming to evaluate the effectiveness of RTX with adequate sample size and study design.

Word Count = 245

Keywords: Rituximab, anti-CD20, interstitial lung diseases, connective tissue diseases, systemic sclerosis, inflammatory myositis.

1. Introduction

The definition "interstitial lung diseases" (ILD) encompasses heterogeneous diffuse parenchymal lung disorders, classified accordingly to specific clinical, radiological and histopathological features [1]. Beside idiopathic forms, ILD could be the expression of an underlying connective tissue disease (CTD), being sometimes the first and only manifestation of an occult CTD [2,3], not rarely at risk for clinical spectrum time course progression [3]. On the other hand, some CTD signs are subtle and not always easy to be identified, with an increased chance of patients' misclassification [4]. Noticeably, all CTD can associate with ILD, in particular, systemic sclerosis (SSc) and idiopathic inflammatory myopathies (IIMs), although the prevalence rates may vary accordingly to diagnostic tools applied. Non-specific interstitial pneumonia (NSIP) is the most frequent pattern of ILD involvement in CTD, followed by usual interstitial pneumonia (UIP) and by organizing pneumonia [5].

In SSc, the prevalence of clinically relevant ILD is reported to be 53% in diffuse cutaneous SSc [6], especially in the presence of anti-topoisomerase antibodies [7], and 35% in the limited cutaneous variant [6]. The presence of a parenchymal lung involvement in SSc increases the risk of death, accounting for up to 60% of SSc-related mortality [8]; the five-year survival rate is 90% in patients with an NSIP pattern and 82% in those with a UIP pattern, while the 10-year survival rate is 69% and 29%, respectively [9].

In IIMs, ILD prevalence ranges from 19.9 to 86.0%, according to the underlying subtype of myositis [10,11], and deeply influences patients' prognosis. In a cohort of 107 patients affected by IIMs-related ILD, 32.7% of

the patients had resolution of their pulmonary disorder, whereas 15.9% experienced ILD deterioration and a significantly increased mortality (47.1% vs 3.3%) [12], as also confirmed by other authors [13]. Antisynthetase antibodies are a subgroup of myositis specific antibodies, directed against the aminoacyl-tRNA synthetases, detected in 25–35 % of IIMs patients, and highly prevalent in those with lung involvement [14]. Anti-Jo-1 antibody, the most common one, can be found in 15–30 % of patients with polymyositis (PM) but in 60–70 % of those with associated ILD [15]; others antibodies, directed against OJ, EJ, PL-7, PL-12, KS, Zo and Ha antigens, account as a whole for less than 5% of seropositive IIMs. Patients positive for antisynthetase antibodies are characterized by a specific clinical phenotype (Antisynthetase Syndrome, ASSD) including myositis, ILD, and arthritis, commonly defined as the classic triad of the disease, but also other accompanying findings such as Raynaud's phenomenon, "mechanic's hands" and constitutional symptoms like fever [16-17]. Looking at the other CTD, ILD is relatively frequent in mixed connective tissue disease (MCTD), since around one-half of patients shows a certain degree of restrictive lung function [18], whereas ILD has been observed in only 3-11% of patients with primary Sjögren's Syndrome (SS) [19,20], however accounting for a significant mortality [21]. Finally, ILD might complicate the course of systemic lupus erythematosus (SLE), although it is less severe and prevalent than in other CTD [22].

The current international guidelines for the diagnosis of idiopathic interstitial pneumonia (IIPs) recommend the exclusion of an underlying CTD in the diagnostic work-up [2,23,24], but the lack of a universally accepted approach and the paucity of some CTD findings often makes the differential diagnosis challenging [25-27]. Nevertheless, ruling out a CTD is crucial for the appropriate management of ILD, since immunosuppressive strategies are the cornerstone of CTD-related ILD treatment, but they are largely ineffective or even detrimental in other IIPs, such as idiopathic pulmonary fibrosis.

Interestingly, the use of immunosuppressive agents for the treatment of CTD-ILD relies mainly on evidence-based, retrospective studies and case series [28,29], despite being accepted worldwide. The rationale of this approach consists of switching off the inflammatory response driven by the systemic condition, in order to stabilize and possibly improve lung disease from the clinical, functional and radiological point of view, and to prevent the development of further fibrosis [1,30,31]. Several pharmacological strategies have been proposed,

with conflicting results. In past years, several authors suggested the utility of rituximab in this setting of patients.

Rituximab (RTX) is a chimeric monoclonal antibody that binds to CD20, a transmembrane antigen selectively expressed on pre-B and mature B lymphocytes but lost when B cells differentiate into plasma cells; hence, CD20 is present on healthy and most of the malignant B cells but it is not expressed on hematopoietic stem cells, pro-B cells and normal plasma cells. After the binding between the Fab domain of rituximab and CD20 antigen on B lymphocytes, the Fc domain activates immune effectors responsible for B cell lysis [32,33]. B-cell depletion is an effective strategy in different human diseases, and it has been approved for the management of lymphoproliferative disorders, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and rheumatoid arthritis (RA) [34-38]. The studies investigating its use in other autoimmune conditions, such as SLE or primary SS, were less conclusive [39-42]. Recently, the use of RTX has been proposed as rescue therapy in severe CTD-ILD [43]. This indication arises from several investigations performed in SSc and IIMs with relatively promising results. RTX had been used off-label in patients who did not respond to conventional therapy, based on a postulated pathogenetic role for B cells in SSc and IIMs, which are both characterized by positive serological tests. However, the evaluation of therapeutic efficacy may be challenging in these conditions because they are rare, have heterogeneous organ involvement, lack well-assessed disease activity scores, and display a spontaneously fluctuating clinical course [44,45].

The present paper aims at systematically reviewing the currently available evidence about the use of RTX in CTD-ILD.

2. Methods

We performed a systematic review based on PubMed. We limited our search to manuscripts published in English and dealing with CTD-ILD. We did not include RA-related ILD because this condition has important differences both from a pathogenic and a therapeutic standpoint, and the use of RTX has already been approved in RA for joint disease. We considered papers published from 2009 until our PubMed access date (May 24th, 2019). We also cross-checked with the reference list of the selected publications.

The following strings have been used for retrieving the relevant articles: "Rituximab AND interstitial lung disease", "Rituximab AND systemic sclerosis", "Rituximab AND mixed connective tissue disease", "Rituximab AND Sjogren", "Rituximab AND antisynthetase", "Rituximab AND anti-synthetase", "Rituximab AND anti synthetase", "Rituximab and anti-Jo1", "Rituximab AND idiopathic inflammatory myopathy" and "Rituximab AND myositis".

We included clinical trials, case/control studies and cohort studies with at least 10 patients enrolled for the considered CTD. We excluded letters, case reports and case series, reviews, as well as full-text articles not in English. Although not formally included, reviews have been appraised to look for potentially interesting original papers.

We included in our review only studies that evaluated the efficacy of RTX on ILD treatment, using as an outcome the variation either in pulmonary function tests (PFT) or in the scores used to stage the lung involvement based on computed tomography (CT) findings.

3. Results

3.1 Search results and study characteristics

We identified 1206 potentially eligible titles. After careful revision, 1182 titles were excluded and 24 papers eventually selected for the systematic review. Figure 1 shows the flow-chart summarizing the process of papers selection.

Three of the selected papers included retrospective cohorts of patients with different underlying CTD. We identified 14 studies about SSc-related ILD (table 1), of which 2 were based on retrospective cohorts, 1 was a retrospective case-control study, 1 was a nested case-control study, and 1 was a multicenter prospective cohort. We included 9 additional clinical trials: 5 open-label, 2 randomized (RTX vs standard of care), 1 randomized placebo-controlled, and one head-to-head non-inferiority trial vs cyclophosphamide (CYC). All the studies reported a functional endpoint; conversely, only 5 listed a radiological endpoint.

Concerning IIMs-related ILD, we identified 4 retrospective cohort studies and 1 open-label trial, the results of which are summarized in table 2. All the studies reported a functional endpoint, while 4 also included a radiological endpoint. Finally, we considered 1 registry study and 1 retrospective cohort, which describe the effects of RTX on lung involvement in patients affected by SS.

In the following two paragraphs, we will outline the current knowledge deriving from the selected studies about SSc and IIM, respectively. The last paragraph of this section of results contains the available evidence concerning the use of RTX in the management of ILD associated with other CTD, namely SS, SLE and MCTD.

3.2 Rituximab use in systemic sclerosis-related ILD

In the last decade, different groups have investigated the effectiveness of CD20 targeting in patients with SSc and lung involvement, with conflicting results.

Daoussis et al., in 2010, randomly assigned 14 SSc patients to receive either standard treatment (various combinations of prednisone, mycophenolate mofetil – MMF - and/or CYC) or RTX (association with MMF and/or prednisone allowed). All patients had a clinically relevant ILD. The authors reported a significant improvement of forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) in the RTX arm compared to baseline, while PFT remained unchanged after 1 year in the control group. The authors also described the stabilization of high-resolution CT (HRCT) findings in the RTX group [46]. After

24 months from inclusion, the 8 patients randomized to receive RTX, re-treated at 12 and 18 months, showed a significant linear improvement of PFT, being both FVC and DLCO significantly higher at 2-years compared to 1-year follow-up visit [47]. Moreover, 5/8 patients showed a modest decrease (5-10%) in their ground glass lung lesions at 18 months, while reticular lesions remained unchanged.

Consistently, a further multicenter study from the same Authors and other centres in Greece enrolled 51 SSc-ILD patients: all of them were offered to receive either RTX as a single therapy or as an add-on to ongoing treatment; 33 accepted, while 18 declined and were therefore considered controls. The median follow-up period was 4 years and all the RTX-treated patients received at least two RTX cycles, 375 mg/m^2 weekly for 4 weeks, every six months. The RTX arm showed a significant increase of FVC at two years and an almost significant upward trend for DLCO. Although no differences were reported after direct comparison between groups at 2 years, the FVC in the 5 subjects who were still on RTX at 7 years was significantly increased from baseline and was higher than the one observed in the 9 patients of the control group still on follow-up at this time point. Finally, DLCO remained stable in the RTX group, while declined in the control group [48].

Similarly, another randomized controlled trial comparing RTX to intravenous CYC in the treatment of diffuse scleroderma showed that RTX is more effective in improving PFT, significantly increasing FVC [49]. Hopefully, this issue will be soon further clarified by a large ongoing prospective study (RECITAL trial), which compares the efficacy of RTX vs CYC in patients with SSc-ILD to improve FVC at 24 weeks; the completion of the study is estimated in November 2019 [50].

Other prospective clinical trials proved the stabilization but not the improvement of PFT parameters. In an open-label single-arm trial, a subset of severe SSc patients refractory to CYC were investigated; a single cycle of 2 RTX infusions was able to stabilize DLCO and FVC at 3-years [51]. Later on, the same group confirmed these findings in about 20 patients prospectively enrolled and treated with RTX [52]. More recently, similar results were also obtained by Melsens et al., who reported a stable FVC and DLCO after 2 years of follow up of 16 patients treated with two cycles of RTX [53].

Looking at early systemic sclerosis with mild pulmonary involvement, Lafyatis et al. observed an unchanged FVC and DLCO after RTX in this subset of patients in a small open-label single-arm clinical trial in 2010 [54]. A recent small randomized placebo-controlled trial including a comparable group of patients with early SSc showed that RTX was not superior to the placebo in terms of FVC and DLCO improvement at 1 and 2 years

from enrollment [55]. Overall, these results suggest that, early in the disease, RTX is effective in stabilizing lung involvement, however, its superiority to other regimens should be demonstrated in head-to-head trials. The benefits of RTX, instead, seem to be more explicit in patients with a severe baseline lung involvement.

The results of studies on this topic including prospective cohorts have been published in two papers from the EUSTAR initiative. In the first article, the clinical records of 63 RTX-treated patients were analyzed [56]. FVC remained stable, and DLCO significantly increased in the 9 patients with a clinically relevant ILD, defined for FVC<70% with consistent HRCT findings, 6 months after RTX treatment. The authors also performed a nested case-control study matching these patients with non-RTX treated subjects from the same EUSTAR database; in sharp contrast to RTX-treated patients, matched controls showed a decline in FVC at 6 months.

Conversely, a further study from the same European network reporting data about 146 SSc patients treated with RTX raised doubts about the effectiveness of RTX in SSc-ILD. After treatment, FVC and DLCO were comparable in RTX-treated and untreated patients (n=497). Although this result might suggest the inefficacy of RTX on lung disease, it should be kept in mind that RTX-treated patients were twice as likely to stop or decrease steroids. Therefore, similar effects on lung involvement were obtained by sparing steroids.

Moreover, it is plausible that the decision of prescribing RTX was largely influenced by the presence of a severe lung disease; therefore, the trajectory of lung involvement and respiratory function decline is expected to be more detrimental in RTX-treated patients. Thus, the stabilization of lung disease might be considered a desirable outcome in these patients [57].

Other retrospective cohorts replicated these findings, confirming the stabilization rather than the improvement of lung function after RTX [45,58-60].

3.3 ILDs in idiopathic inflammatory myopathies and antisynthetase syndrome

The vast majority of published studies about the efficacy of RTX in the treatment of IIMs-related ILD are case reports and case series.

The only prospective data come from a French open-label, prospective, multicenter, single-arm pilot study published in 2015, which analyzed the effect of RTX on 12 patients affected by refractory ASSD. Patients were included upon failing alternative therapeutic regimens and received two infusions of RTX 1 g 2 weeks apart, followed by a single 1 g administration 6 months later. Concomitant corticosteroids were allowed

according to clinical indication. At 1 year, median FVC did not change significantly from baseline, but ameliorated in 4/10 patients and remained stable in 5/10. More generally, PFT documented improvement of ILD in 5 patients, suggesting a potential beneficial effect, the magnitude of which might have been underscored by the small sample size [61].

Several retrospective cohorts evaluated the effectiveness of CD20 targeting in ASSD. In a paper published in 2009, Sem et al. reported data from a Norwegian retrospective cohort of 11 patients with severe ILD. Out of 8 patients who deteriorated the PFT before RTX, 6 showed an improvement in FVC > 10% after treatment, and 3 improved the DLCO (> 15%) significantly; this was paralleled by an improvement of CT findings in the majority of patients [62]. Later on, the same group published results from a larger retrospective cohort study on 34 ASS patients who received RTX, aiming to investigate the long-term effectiveness of this drug. In the 24 subjects with ILD who completed a follow-up period of at least 12 months, the administration of RTX significantly improved the FVC, FEV1 (forced expiratory volume in 1 second), DLCO and the HRCT findings [63]. Consistently, in another retrospective cohort including 18 anti-Jo1 positive ASSD patients treated with RTX, the 10 patients with ILD showed a statistically significant improvement of DLCO and FVC at last follow-up visit [64]. Lately, a US multicentric retrospective cohort demonstrated the efficacy of RTX in the maintenance of a stable or improved HRCT scan score, FVC and DLCO, suggesting a potential benefit from retreatment [65]. IIMs-related ILD seems to respond to RTX better than ILD associated to other CTD, as shown in a retrospective cohort [66] in which the 13 patients affected by IIMs-related ILD underwent a significantly larger improvement of FVC and DLCO. Consistently, in a further retrospective cohort study published by Lepri et al., 33% of ASSD patients responded to RTX, defining the responders in case of ≥ 10% increase in FVC and ≥ 15% increase of DLCO. This percentage was higher than the one observed in SSc (9.5%) and MCTD (16.7%) [59]. This is in line with the report of Keir et al. [67], although this study was not included in our systematic review because the authors considered CTD-ILD as a whole, thus preventing sub-analyses according to rheumatologic diagnosis. Nevertheless, it is worth remarking that the proportion of responders was higher in IIMs-related ILD (50%) than in the other CTD (18.2%).

Finally, in a recent meta-analysis, RTX in association with steroids was moderately effective as a second-line strategy, similarly to cyclosporine A, azathioprine and tacrolimus; however, the number of patients treated with RTX was very limited [68].

3.4 ILDs in other connective tissue diseases

Despite the prevalence of lung involvement is generally lower, ILD can also complicate SS, MCTD and SLE. In 2016, Chen et al. retrospectively investigated the effect of RTX on 10 patients affected by SS-related ILD; at 6 months after RTX treatment, the authors observed a significant increase of DLCO (49.3 ± 12.6 to 56.9 ± 11.4%, p=0.02) which was paralleled by a subjective improvement [69]. Consistent with these findings, in a registry study on 78 primary SS patients treated with RTX, 7 out of 9 with pulmonary involvement responded to RTX treatment and were further re-treated two to nine times [70]. The currently available guidelines by the British Society of Rheumatology and Sjögren's Syndrome Foundation suggest considering the use of RTX in patients with primary SS and systemic manifestations, herein including ILD [71,72].

Although lung involvement is common in MCTD, there is a paucity of data about the use of RTX for the management of pulmonary manifestations in this condition. More specifically, we were unable to identify a single study satisfying the sample size criteria adopted for the present systematic review; however, it is worth mentioning that in the above-cited paper by Lepri et al., 6 patients were identified [59] and a stabilization of FVC and DLCO was observed after 2 years from RTX treatment.

We also failed to recognize any study fulfilling the inclusion criteria for this review about the effect of RTX on the lung of SLE patients. The effectiveness of RTX in the management of SLE is still an ongoing matter of debate because the general perceived efficacy conflicts with the results of controlled and observational studies, which are far less convincing, possibly reflecting the heterogeneity of SLE clinical picture [73]. Consistently, the recently published update of the EULAR recommendations for the management of SLE [74] suggests considering the use of RTX only after the failure of more than one immunosuppressive drug.

4. Discussion

ILD early diagnosis and effective treatment are crucial in the management of CTD because lung involvement is burdened by a high degree of morbidity and mortality [22]. Mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus are all reasonable options in CTD-ILD [75-80]; generally, CYC is considered the treatment of choice for more aggressive and evolutive forms of ILD being associated with stabilization of FVC, although its impact on DLCO is less remarkable [81,82]. This outlines the need for novel therapeutic options, particularly for patients with more severe lung involvement. Our review aimed to evaluate the potential role for RTX in this context.

We classified the different studies according to the CTD considered. Based on the papers we reviewed, it is not possible to draw definitive conclusions about the use of RTX in SS, MCTD and SLE patients for lung involvement. There is relevant literature about the use of RTX in SS and SLE, but a paucity of data about the specific effects on ILD; the available knowledge on the use of RTX in MCTD is instead almost exclusively anecdotic.

Despite a decent number of papers about the RTX effectiveness in SSc and ASSD-related ILD, to date, properly designed clinical trials are still missing and a large amount of evidence is based on retrospective studies. When prospective data are available, the lack of placebo-controlled trials, the differences of the used regimens and number of RTX administrations, the variability of ongoing immunosuppressive strategies, and the different time-points selected make the results of these studies difficult to be compared. The largest amount of studies is focused on SSc-related ILD and, to a lesser extent, on IIMs-related ILD, hence emphasizing the importance of planning new prospective studies on other CTDs. Regarding SSc-related ILD, all the papers included in the present review support the effectiveness of RTX in ILD stabilization over time; moreover, there is weaker evidence deriving from few clinical trials that RTX might ameliorate PFT and DLCO. These data are evident in subjects with established pulmonary disease, while the advantage of RTX use in patients with mild lung involvement is not determined. Re-challenging patients with multiple cycles of RTX might offer additional benefit on ILD, possibly contributing to a progressive and linear improvement of PFT over time. Of note, all the prospective studies included in this systematic review had a small sample size, which might have affected the power of their findings, potentially underestimating the effectiveness of RTX. Furthermore, since the stabilization of lung disease in CTD can be considered a desirable outcome in this clinical context, these

results support the use of RTX in established, severe ILD. In particular, RTX seems promising in those patients with progressive SSc, unresponsive to CYC, being able to stabilize lung function tests [51]. Compared to other treatments, RTX was shown to be superior to CYC in a single trial [49], once again suggesting that the use of RTX in severe ILD may be beneficial when matched to the current standard of care. Of course, this hypothesis must be confirmed in larger randomized clinical studies; hopefully, the results of the ongoing RECITAL trial will be soon available to help elucidating this issue.

When considering IIMs-related ILD, the pieces of evidence seem to be more consistent, particularly in the context of ASSD, pointing out an effect of RTX in PFT and DLCO improvement over time. Though, it should be acknowledged that these results derive from a single prospective uncontrolled trial and a few, small retrospective cohorts, even in the absence of established classification criteria for ASSD [83]. Nonetheless, the lack of guidelines about the management of ILD and severe manifestations in IIMs is a perceived unmet need [84].

In conclusion, according to the studies here presented, RTX can stabilize and, possibly, improve ILD complicating SSc and ASSD. Our review also underpins the absolute need for further investigation in this context, in particular in ASSD, since RTX is a promising therapeutic tool, the availability of which would be quintessential, particularly for patients with more severe and refractory disease.

Tables and figures

Figure 1. Flow-chart of study selection. For abbreviation: N., number; ILD, interstitial lung disease; CTD, connective tissue disease; SSc, Systemic sclerosis.

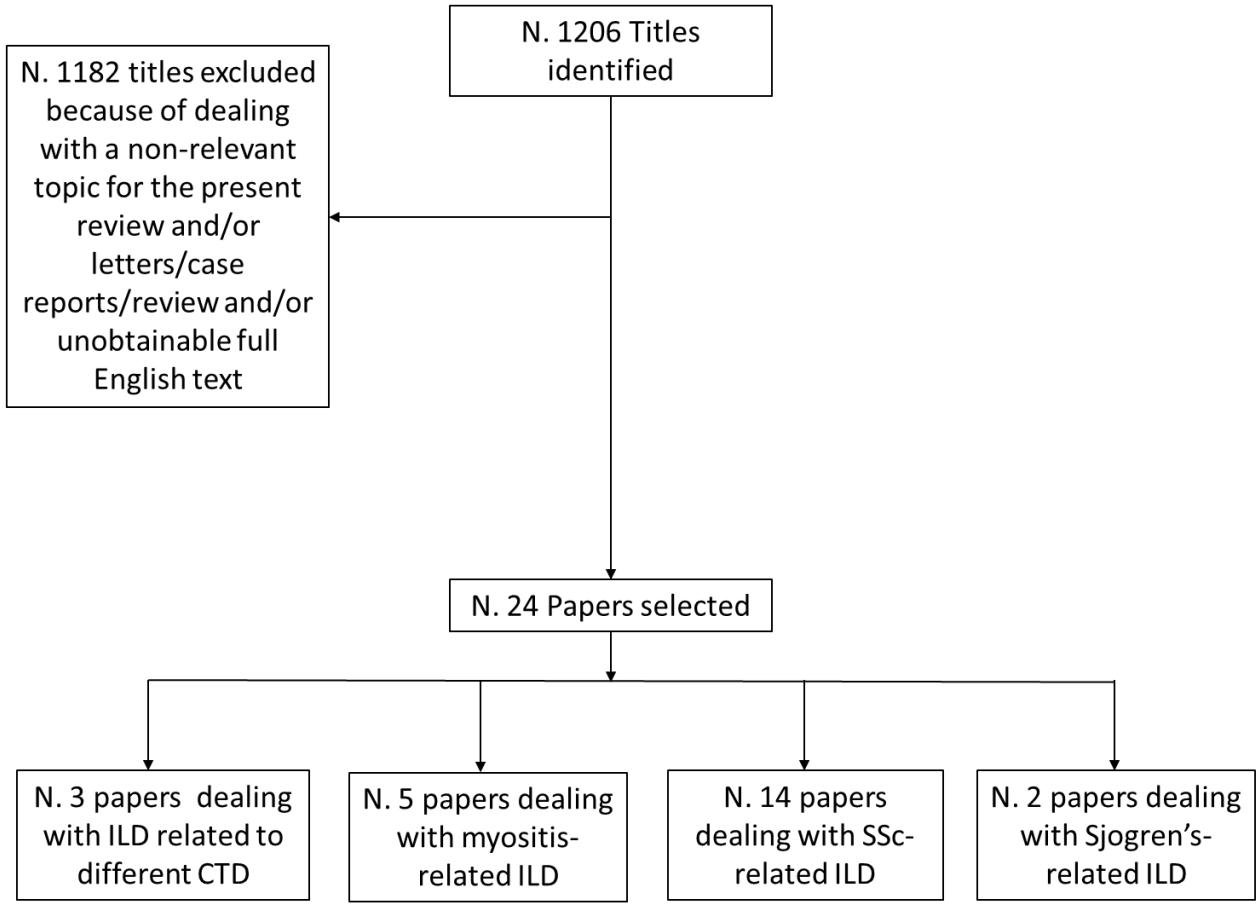

Table 1. Studies on the use of rituximab in Systemic Sclerosis related ILD. For abbreviation: dcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; f-u, follow-up; RTX, rituximab; CYC,

cyclophosphamide; MTX, methotrexate; PDN, prednisone; Bos, Bosentan; MMF, mycophenolate mofetil; pt, patients; ILD, interstitial lung disease; N/A, not applicable.

Author and year	Study design[1]	N patients on RTX (treatment arm)	RTX scheme	N of patients treated with other agents (comparator arm)[2]	Other agents administration scheme	Length of study (maximum)	Main findings
Lafyatis 2009[54]	Open label trial	15	1 g days 0-14 (PDN < 10 mg/d allowed; 1 pt on MTX)	N/A	N/A	6 months	1. Unchanged FVC (89.2% vs. 92.7%; p=n.s.) and DLCO (79.7% vs 77.8%; p=n.s.) from baseline to end of f-u, respectively; 2. No patients showed HRCT progression
Daoussis 2010[46]	Randomized open label trial	8	375 mg/m^2 weekly, 4 weeks at baseline and after 6 months (concomitant treatment with PDN, MMF, Bos allowed)	6	Various associations of PDN, Bos, CYC, MMF	12 months	1. RTX increases FVC (68.1% vs. 75.6%; p=0.0018) and DLCO (52.2% vs 62.0%; p=0.017) from baseline to end of f-u, respectively; 2. RTX add-on improves FVC (p=0.002) and DLCO (p=0.02) with respect to controls 3. HRCT score in RTX group, no differences with controls
Bosello 2010[51]	Open label trial	9	1 gr days 0-14, 3 pts retreated (MTX allowed)	N/A	N/A	36 months	1. Unchanged FVC (91.6% vs. 96.8%; p=n.s.) and DLCO (58.0% vs 58.4%; p=n.s.) from baseline to end of f-u, respectively
Daoussis 2012[47]	Open label trial	8	4 courses; 375 mg/m^2 weekly, 4 weeks, every 6 months (concomitant treatment with PDN, MMF, Bos allowed)	N/A	N/A	24 months	1. RTX increases FVC (68.1% vs. 77.1%; p<0.0001) and DLCO (52.2% vs 63.3%; p<0.01) from baseline to end of f-u, respectively; 2. Modest decrease (5-10%) of ground glass opacities in 5 pts
Jordan 2014[56]	Multicentre nested case control observational study	63 25 matched	Different schemes (1 g days 0-14, 75% of pts); Different underlying ongoing immunosuppressants allowed	25 matched	Different underlying immunosuppressants	Median f-u: 7 [4-9] years	1. Stable FVC (60.6% vs. 61.3%; p=n.s.) and increased DLCO (41.1% vs 44.8%; p=0.03) from baseline to end of f-u, respectively; 2. RTX improves FVC (p=0.02) and DLCO (p=0.01) with respect to controls
Bosello 2015[52]	Open label trial	20	1 gr days 0-14; 8 patients retreated	N/A	N/A	Mean f-u: 48.5 ± 20.4 months	1. Stable FVC (87.4% vs. 88.0%; p=n.s.) and DLCO (55.0% vs 59.8%; p=n.s.) from baseline to end of f-u, respectively

Giuggioli 2015[58]	Retrospective cohort	10	375 mg/m^2 weekly, 4 weeks; from 1 to 5 cycles/pt (PDN allowed)	N/A	N/A	Mean f-u: 37 ± 21 months	1. 8 patients with lung involvement: out of them 6 showed a stable lung disease at the end of follow-up, while 2 showed a worsening lung involvement
Lepri 2016[59]	Retrospective cohort	23	Different schemes; Different underlying ongoing immunosuppressants allowed	N/A	N/A	24 months	1. Stable FVC (81.0% vs. 74.5%; p=n.s.) and DLCO (54.0% vs 57.5%; p=n.s.) from baseline to end of f-u, respectively
Daoussis 2017[48]	Open label multicentre trial	33	375 mg/m^2 weekly, 4 weeks every 6 months; Different underlying ongoing immunosuppressants allowed	18	Different immunosuppressants	7 years	1. RTX increases FVC (80.6% vs. 86.9%; p=0.041) and DLCO (59.2% vs 61.5%; p=0.053) from baseline to 2-years f-u, respectively; 2. No differences between RTX group and controls in FVC (p=0.063) and DLCO (p=0.384) variation 3. In those patients with a 7-year f-u (5 RTX and 9 controls) the RTX group had a significant advantage in term of FVC (p=0.001)
Sari 2017[60]	Retrospective cohort	14	Different schemes; Concomitant PDN (median dose 11.2 mg [7.5-20])	N/A	N/A	30 months	1. Stable FVC (52.5% vs. 58.0%; p=0.06) from baseline to end of f-u, respectively 2. FVC improvement > 10% in 4/14 patients, stable FVC in 10/14 patients 3. HRCT available in 10 patients, stable in 7/10, worsened in 3/10
Thiebaut 2017[45]	Retrospective case control study	13 + 40 derived from literature data	Different schemes	26 matched controls receiving other immunosuppressants	Different immunosuppressants	Median f-u: 24 months [12-46]	1. Stable FVC (72.0% vs. 85.0%; p=n.s.) and DLCO (40.0% vs. 49.0%; p=n.s.) from baseline to end of f-u, respectively 2. RTX superior in dSSc with respect to untreated controls (ΔFVC 12 vs -1.5, p=0.003; ΔDLCO 4 vs -4.5, p=0.03) 3. No differences between RTX group and controls treated with other immunosuppressants in FVC (ΔFVC 4 vs -1.5, p=n.s.); RTX advantage in DLCO (ΔDLCO 0 vs -7, p=0.05)

Boonstra 2017[55]	Randomized placebo controlled trial	8	1 gr days 0-14; Different underlying ongoing immunosuppressants allowed	8	Placebo + other immunosuppressants	24 months	1. No differences between groups with respect to ΔFVC (placebo -1.4%, RTX +4%; p=n.s.) and ΔDLCO (placebo -0.3%, RTX +0.7%; p=n.s.) from baseline to the end of f-u 2. No differences in HRCT finding between groups
Sircar 2018[49]	Randomized clinical trial	30	1 gr days 0-14	30	CYC: 500 mg/m^2 iv every 4 weeks	6 months	1. RTX increases FVC (61.3% vs. 67.5%; p=0.002) from baseline to end of f-u, respectively; 2. RTX superior to CYC in term of FVC variation (p=0.003)
Melsens 2017[53]	Open label multicentre trial	17	1 gr days 0-14, repeated after 6 months; Different underlying ongoing immunosuppressants allowed	N/A	N/A	24 months	1. Stable FVC (92.0% vs. 88.5%; p=n.s.) and DLCO (64.0% vs. 64.5%; p=n.s.) from baseline to end of f-u, respectively
Elhai 2019[57]	Multicentric prospective cohort	146	Different schemes; Different underlying ongoing immunosuppressants allowed	497	Different immunosuppressants	Median f-u: 24.3 months	1. Stable FVC (76.3% vs. 77.7%; p=n.s.) and DLCO (54.4% vs. 55.5%; p=n.s.) from baseline to end of f-u, respectively 2. No differences between RTX group and controls in FVC and DLCO decrease 3. RTX group more likely to decrease or stop steroids (p<0.0001)

1. For clinical trials, the study is intended as single center based enrollment if not otherwise stated

2. N/A apply to single arm clinical trials where a comparator arm was not planned

Table 2. Studies on the use of rituximab in Inflammatory myopathies. For abbreviation: DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; f-u, follow-up; RTX, rituximab; pts, patients; ILD, interstitial lung disease; ASS, anti-synthetase syndrome; CTDs, connective tissue diseases.

Author and year	Study design	N patients	Treatment and follow-up	Main findings
Sem 2009[62]	Retrospective cohort	11	Different schemes; f-u: 6 months	1. Improvement > 10% FVC in 6 pts and improvement > 15% DLCO in 3 pts; 2. Radiologic improvement in 5 pts out of 9 with an available HRCT pre-treatment
Andersson 2015[63]	Retrospective cohort	24	1gr days 0-14, Median number of 2.7 cycles/pt; Median f-u: 84 months	1. RTX increases FVC (58% vs. 72%; p<0.018) and DLCO (41% vs 48%; p<0.025) from baseline to end of f-u, respectively; 2. Median volume of total lung parenchyma with ILD decreased from 50% to 33%
Allenbach 2015[61]	Open label multicentre clinical trial	12	1gr days 0-14 and after 6 months; f-u: 12 months	1. Not significant improvement in FVC (Δ FVC +5% p=n.s.) and DLCO 2. No differences in HRCT finding from baseline to the end of f-u
Bauhammer 2016[64]	Retrospective cohort	10	1gr days 0-14 every 6 months; mean f-u: 35 months	1. RTX increases FVC (61% vs. 86%; p<0.05) and DLCO (33.1% vs 55.7%; p<0.05) from baseline to end of f-u, respectively
Lepri 2016[59]	Retrospective cohort	15	Different schemes; f-u: 24 months	1. Stable FVC (53% vs. 63%; p=n.s.) and DLCO (41.7% vs. 61.8%; p=n.s.) from baseline to end of f-u, respectively 2. ASS more responsive to RTX than other CTDs (higher percentage of FVC responders 53.3 vs. 21.7%)
Sharp 2016[66]	**Retrospective cohort**	13	**1 gr d 0-14;** Mean f-u: 29.6 months	1. RTX increases FVC (p<0.01) and DLCO (p<0.01) from baseline to end of f-u, respectively 2. ASS more responsive to RTX than other CTDs (p=0.002 for FVC, p=0.009 for DLCO)
Doyle 2018[65]	Multicenter retrospective cohort	25	Different schemes; Mean f-u: 36 months	1. Stable FVC (57% vs 62%, p=n.s.) and DLCO (42% vs. 53% p=n.s.) from baseline to 2 years f-u, respectively 2. Improved FVC at 3 years f-u (57% vs. 82%, p=0.016) 3. Stable HRCT score (p=n.s.)

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The authors have no conflict of interest to declare.

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