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REVIEW

Efficacy and safety of rituximab in the treatment of connective tissue disease-related interstitial lung disease

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Abstract

Interstitial lung disease (ILD) represents a severe pulmonary complication of connective tissue diseases, rheumatoid arthritis (RA), and antineutrophil cytoplasmic antibody-associated vasculitis. Treatment of ILD, mainly based on immunosuppression, remains challenging. Rituximab (RTX), a monoclonal antibody binding to CD20, is considered a valuable therapeutic choice in cases of refractory ILD. Here, we review the available efficacy and safety data on the use of RTX in the treatment of rheumatic disease-related ILD. Despite controversial efficacy data, RTX seems to be able to stabilize or improve ILD related to RA and antisynthetase syndrome and in established and severe ILD complicating systemic sclerosis. Fewer data are available regarding ILD related to Sjögren syndrome, systemic lupus erythematosus, and antineutrophil cytoplasmic antibody-associated vasculitis. To date, few prospective studies are available and randomized trials are still ongoing with the purpose of exploring the role of RTX in this condition, including the supposed relationship between efficacy and ILD radiologic patterns and safety data, up to now derived mainly from RA studies. Despite an overall acceptable safety profile, concerns remain regarding an increased infectious disease risk in patients with ILD as well as possible lung toxicity and the increased rate of immune-mediated reactions in patients with connective tissue diseases. In conclusion, RTX is a relevant therapeutic option for rheumatic disease-related ILD despite the existing uncertainties; ongoing trials are expected to clarify its use.

Keywords: connective tissue diseases, efficacy, interstitial lung disease, lung fibrosis, rheumatic diseases, rituximab, safety.

Citation

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Introduction

Interstitial lung disease (ILD) represents a severe pulmonary complication of connective tissue diseases (CTDs), rheumatoid arthritis (RA), and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). ILD often results in progressive chronic disability, decreased quality of life, increased utilization of healthcare resources, and high mortality. ILD is more common in patients affected by RA, systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIMs), although its prevalence is variable according to different classification modalities.[1–3] Therapy for ILD related to rheumatic diseases remains challenging, mainly due to the limitation in treatment effectiveness and the level of the scientific evidence available.

The available therapeutic strategies are mainly based on glucocorticoids (GCs) and immunosuppressive drugs such as mycophenolate mofetil (MMF) and cyclophosphamide (CYC).[4] Rituximab (RTX), a chimeric monoclonal antibody binding to CD20, selectively expressed on pre-B and mature B lymphocytes, is considered a valuable therapeutic choice in patients that have failed a previous immunosuppressive drug.[5] The depletion of B cells is a central strategy in the treatment of various haematological, neurological, and rheumatic diseases, including RA, AAV, and some CTDs.[6–8] Indeed, the role of B cells in autoimmune processes seems to be crucial in these diseases.[6] In the pathogenesis of ILD, B cells directly interact with fibroblasts and stimulate collagen production through tumour growth factor-β signalling.[9] However, RTX has been associated with a higher risk of infection and acute lung toxicity as well as with

infusion-related adverse events,[10,11] albeit with good tolerance, comparable to traditional immunosuppressive schemes.[12]

The aim of this review is to assess the efficacy and safety data available in literature regarding the use of RTX in CTD-related ILDs. Of note, although not classified as CTDs, we also discuss the role of RTX in the treatment of ILD in the context of RA and AAV given the growing evidence available on the use of this drug in the treatment of such challenging conditions.

Methods

A systematic literature review was conducted by two authors (GC and CV) using PubMed, Web of Science, Scopus, Latin American and Caribbean health Sciences Literature (LILACS), Cochrane Central, and Embase. The search string was ((Rituximab*) AND (interstitial lung disease* OR interstitial pneumonia* OR lung fibrosis*) AND (rheumatoid arthritis* OR connective tissue diseases* OR systemic sclerosis* OR primary Sjögren syndrome* OR systemic lupus erythematosus* OR idiopathic inflammatory myopathies* OR undifferentiated CTD* OR interstitial pneumonia with autoimmune features* OR ANCA-associated vasculitis* OR small vessel vasculitis*)) in the text, title, and abstract sections. We considered randomized clinical trials, systematic reviews, observational studies, case series, and case reports. We did not consider abstract or grey literature. The snowballing strategy was used, searching the bibliographies for relevant references from the reference list or moving forward to the citing articles. No language restriction was considered, no years of publication restriction were applied, and only published articles were considered. Due to the low quality of included studies, only a narrative review was conducted and no quantitative synthesis was performed.

Key studies on RTX for the treatment of ILD related to rheumatic diseases are summarized in Table 1.

Table 1. Key studies on rituximab for the treatment of interstitial lung disease related to rheumatic diseases.

Author	Year	Study design	Population	Results
RA				
Yusof et al.[19]	2017	Observational, retrospective	44 patients with RA-ILD	Stability in 52%, improvement in 16%, worsening in 32%
Becerra[20]	2013	Observational, retrospective	38 patients with RA-ILD	Clinical and radiological stability in most patients
SS				
Daoussis et al.[24]	2010	Randomized controlled, prospective	14 patients with SSc (8 RTX *versus* 6 controls)	Improvement of FVC and DLCO and stability of HRCT scores in RTX group
Jordan et al.[27]	2015	Nested case–control	9 patients with SSc-ILD	Stability of FVC and improvement of DLCO after 6 months
Elhai et al.[28]	2019	Prospective cohort study	147 patients with SSc-ILD	No variations in decrease of FVC and DLCO but reduction in steroid dose
Sircar et al.[29]	2018	Randomized controlled, prospective	60 patients with SSc-ILD (30 RTX *versus* 30 CYC)	Improvement of FVC in RTX group
Idiopathic inflammatory myopathy				
Allenbach et al.[49]	2015	Open label, phase II trial	10 patients with ASS-ILD and anti-Jo1 positive	Improvement of lung function in 5 patients, stability in 4, and worsening in 1
pSS				
Chen et al.[69]	2016	Observational, retrospective	10 patients with pSS-ILD	Improvement of lung function, dyspnoea and cough; stability of HRCT scores

ASS, antisynthetase syndrome; CYC, cyclosporin; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; pSS, primary Sjögren syndrome; RA, rheumatoid arthritis; RTX, rituximab; SSc, systemic sclerosis.

Rheumatoid arthritis

Symptomatic ILD affects about 7% of patients affected with RA and is responsible for 10–20% of mortality.[3] Usual interstitial pneumonia (UIP) is the predominant histological/radiological pattern in about 44–66% of cases, while non-specific interstitial pneumonia (NSIP) and organizing pneumonia (OP) are less frequent.[3] RTX has been largely used in RA-ILD, including in severe refractory forms.[13]

In 2012, Hartung et al.[14] first described the case of a 66-year-old patient with severe RA-ILD successfully treated with RTX after failure of prednisolone and CYC. In 68 patients with RA-ILD in the pNEumology RhEumatology Autoimmune diseases (NEREA) Spanish registry, exposure to RTX resulted in a lower risk of functional impairment after 1.75 years; GC, disease activity, and disease duration also influenced the outcome.[15] Similarly, in 151 patients with RA-ILD in the British Rheumatoid InterstitiaL Lung (BRILL) registry, a significantly better survival was observed in 51 patients firstly treated with RTX compared to that in 100 patients treated with tumour necrosis factor inhibitors; the difference was already evident by 3 years and was preserved at 5 and 7 years.[16]

However, these results were not confirmed in another study from the British Society for Rheumatology Biologics Register on 43 patients with RA-ILD treated with RTX and in 309 patients treated with tumour necrosis factor inhibitors;[17] despite the adjusted mortality risk being reduced in the RTX cohort for all-cause mortality, the difference in the risk of mortality due to ILD was not statistically significant between the two groups. Unsatisfactory results were also observed by Matteson et al.[18] in an open-label pilot study, where only 1 out of 10 patients with progressive RA-ILD improved, whereas four worsened and three withdrew from the study due to adverse events; 1 patient died because of pneumonia and respiratory distress syndrome. Yusof et al.[19] noted a worsening of ILD in 32% of 44 patients with RA-ILD; moreover, a high number of patients recorded severe infectious adverse events, in particular involving the lower respiratory tract. Furthermore, Becerra et al.[20] described a high rate of respiratory infections: 19 patients with RA-ILD showed clinical and radiological stability after RTX, but 15/19 (66%) had respiratory tract infections.

The role of ILD pattern in predicting the response to RTX in patients affected with RA is still unclear. Yusof et al.[19] described UIP pattern as a negative prognostic factor associated with ILD progression. In fact, 9 out of 14 patients with disease progression showed a UIP pattern; among them, 7 died because of progression of ILD and 3 presented with infectious pneumonia. A previous history of lung progression and a low value of lung diffusing capacity for carbon monoxide (DLCO) before RTX administration were also associated with ILD progression. In a retrospective Portuguese cohort, 13 patients with RA-ILD and OP, NSIP or unclassifiable pattern showed an improvement or stability in lung function and chest high-resolution computed tomography (HRCT) after 1 year of follow-up. Among 5 patients with UIP, 2 showed a decline in forced vital capacity (FVC) and only 1 achieved radiological stability. Nevertheless, 2 patients with UIP who withdrew RTX due to an arthritis flare showed progressive functional worsening, suggesting an effect in reducing lung disease progression, even if less evident in other patterns than in UIP.[21]

Finally, in 2019, Fui et al.[13] retrospectively explored the possible effect of RTX on lung function after 6 and 12 months on 14 patients with RA-ILD. Among them, 9 patients presented with UIP, 3 with NSIP, and 2 with nodular ILD patterns. Patients with RA-UIP showed a significant greater deterioration in FVC when compared to patients without UIP-RA. Similarly, no differences according to the ILD pattern were reported by Chartrand et al.[22] in 15 patients with RA-ILD who were retrospectively evaluated.

Systemic sclerosis

Among CTDs, SSc has the highest prevalence of ILD, reaching 70–90% according to HRCT and representing the leading cause of death.[1] NSIP is the most common ILD pattern, while UIP is reported in about 25–40% of patients with SSc.[1]

The first encouraging results on the use of RTX in SSc-ILD were derived by some open-label prospective experiences. In 20 patients with ILD-SSc treated with RTX, at 1 year of follow-up, there was a significant increase in FVC and total lung capacity compared to baseline (p=0.024 and p=0.005, respectively), while mean DLCO remained stable.[23] Considering the last available follow-up in 6 patients with restrictive lung disease at baseline, 2 (33.3%) patients experienced a significant increase in FVC, one (16.7%) patient exhibited a significant decrease, while 3 (50%) patients had a stable FVC. After a mean follow-up of 48.5±20.4 months, among patients with normal lung function at baseline, FVC remained stable in 12 (85.7%) and increased in 1 (14.3%). The majority of patients presented radiological stability regardless of the presence of restrictive lung disease at baseline.

The first randomized controlled study evaluating RTX in SSc-ILD was conducted in 2010 and compared standard treatment with GC, MMF, and/or CYC (6 patients) and 4-weekly pulses of RTX 375 mg/m^2 (8 patients) every 6 months. The study allowed the association with MMF and/or GC in 14 patients with clinically relevant ILD-SSc. The authors described a significant improvement in lung function, both FVC and DLCO, and radiological stability after 1 year in the RTX treatment arm, while FVC and DLCO remained unchanged in the control group.[24] Eight patients were retreated at 12 and 18 months, showing a significant linear improvement of both FVC and DLCO after 24 months of follow-up. Five patients showed a modest decrease (5–10%) in ground-glass lung lesions at 18 months, with stable reticular lesions. Interestingly, lung function deteriorated in all patients after RTX cessation.[25]

After this preliminary study, Daoussis et al.[26] conducted a controlled open-label multicentre study in Greece, involving 51 patients with SSc-ILD followed-up for a median of 4 years.

Thirty-three patients received RTX monotherapy or as add-on to ongoing treatment, while a control group of 18 patients continued prior treatment. All patients treated with RTX received at least two RTX cycles (375 mg/m^2 4-weekly pulses of RTX, every 6 months) and showed an increase in FVC compared to baseline. Although there was no difference at 1 year, the increase in FVC became significant at 24 months (p=0.041). Furthermore, DLCO also showed a trend in improvement in the RTX group. The differences in terms of FVC and DLCO between the treatment and control group were not significant, but the authors reported a trend in favour of the RTX group. At 7 years of follow-up, the RTX group presented higher FVC compared to baseline and to the control group (p=0.001). DLCO remained stable while it declined in the control group; however, no differences were identified in the direct comparison between the two groups. In six patients treated with RTX, treatment was temporarily discontinued, observing a decline in FVC following treatment cessation. All these patients were rechallenged with RTX, but a subsequent increase in FVC was observed in only half of them. In consideration of the long-term data provided by this study, the authors reported a good safety profile. Treatment with RTX was indeed generally well tolerated, even in cases of comorbidities and/or advanced disease.

The European Scleroderma Trials and Research group conducted a multicentre, nested case–control study, including 63 patients of whom 9 had clinically relevant ILD. Six months after RTX treatment, FVC remained stable and DLCO significantly increased in all 9 patients. Furthermore, comparing patients with matched controls not treated with RTX, patients treated with RTX showed a significant prevention in further decline of FVC (p=0.02). RTX presented an acceptable safety profile, including the risk of infections.[27]

Nevertheless, no significant effects were recorded in a prospective study on 643 patients (146 treated and 497 untreated) with ILD-SSc from the EUSTAR cohort.[28] After a median follow-up of 24.3 months, FVC and DLCO remained stable in both the treated and untreated groups. However, patients treated with RTX were twice as likely to stop or decrease steroid dosages compared to the control arm; moreover, patients in the RTX group showed lower baseline FVC values, suggesting that these patients could present with more severe lung disease.

Sircar et al.[29] randomly assigned 60 patients with ILD-SSc to monthly pulses of CYC 500 mg/m^2 or RTX 1000 mg, two infusions separated by 2 weeks. FVC improved in the RTX arm while it declined in the CYC arm (p=0.003).

Ebata et al.[30] also observed a better performance of RTX when compared to CYC in a retrospective study of 39 Japanese patients with SSc-ILD presenting anti-Scl70. At the 24-month evaluation, the improvement rates of FVC and DLCO in the RTX group (nine patients) were significantly higher than those in the CYC group (30 patients) (p<0.01).

These studies suggest that the use of RTX in severe ILD may be beneficial when compared to the current standard of care[31–33] and could represent a safe and effective alternative to CYC.[29]

Differences in the effectiveness of RTX in the above-reported studies could be influenced by the different severity and progression of lung disease of the enrolled patients. In fact, the benefits of RTX seem to be more explicit in patients with severe ILD, rather than in patients with mild lung involvement and/or with early SSc. As demonstrated by the INBUILD study, the inclusion of patients with progressive ILD allows assessment of the effect of therapy, while in non-severe non-progressive disease, the effect of the drug could be less evident and the disease could be itself non-evolutive. This hypothesis should be confirmed in specifically designed randomized trials.[34]

In this regard, in a randomized, double-blind, placebo-controlled, single-centre trial on 16 patients with early SSc (disease duration <2 years) and mild lung involvement, FVC and lung disease extension slightly improved in the RTX arm but without reaching statistical significance.[35] Similar results were obtained in some observational or retrospective studies in patients with mild ILD.[36–38] A network meta-analysis including 9 randomized clinical trials comparing 8 interventions *versus* placebo for an average follow-up of 1 year demonstrated that only RTX significantly reduced FVC decline.[39]

In conclusion, RTX might be suggested in progressive and severe forms of SSc-ILD.[40–43] However, as the stability of lung disease in CTD can be considered a desirable outcome, these results support the use of RTX in SSc-ILD, which may also represent a better-tolerated alternative to CYC. Moreover, rechallenging patients with multiple cycles of RTX might offer additional benefit on ILD, possibly contributing to a progressive and linear improvement in lung function over time.[26] The ongoing trial might contribute to clarify the role of RTX in SSc-ILD treatment.[44]

Idiopathic inflammatory myositis

IIMs are a heterogeneous group of CTDs including dermatomyositis, polymyositis, amyopathic dermatomyositis, and antisynthetase syndrome (ASS). Skeletal muscle inflammation and multiple organ involvement are the main manifestations in IIM with ILD representing the most common extra-musculoskeletal manifestation and it is characterized by variable prognosis.[1,45] Among ASS, ILDs can reach a prevalence of 70–100% (according to case series) and show a better treatment responsiveness and a lower risk of recurrence in comparison with other IIM-ILDs.[46] Even if the majority of published studies on the efficacy of RTX in the treatment of IIM-related ILD are case reports and case series, favourable responses to RTX have been reported, in particular regarding ASS-ILD.[47–50]

In a recent meta-analysis on IIM-ILD treatment in a total of 533 patients (with only 20 treated with RTX), the authors described a moderate effectiveness of RTX plus steroids as a second-line strategy[51]; similar results were observed for

cyclosporine A, azathioprine (AZA), and tacrolimus. Many observations have been reported on the use of RTX in ASS. Of note, considering the possible pathogenetic role of autoantibodies in ASS, RTX may have a good indication in this disease.[52]

A US multicentric retrospective cohort, evaluating lung function and radiological features during a 3-year follow-up included 25 patients with ILD-ASS (16 anti-Jo1, 6 anti-PL-12, 3 anti-PL-7).[53] The most common imaging pattern on HRCT was NSIP (13 cases), followed by UIP or fibrotic NSIP with or without concurrent elements of OP. In most cases (84%), the main indication for RTX use was recurrent or progressive and refractory ILD. At the 12-month follow-up, the authors observed a stability or improvement in radiological score and FVC in 88% and 79% of patients, respectively. Moreover, RTX allowed a GC decalage from 18±9 to 12±12 mg/day. DLCO slightly declined after 1 year but significantly increased at 3 years of follow-up, suggesting a potential benefit of retreatment. Furthermore, the majority of patients tolerated RTX treatment well.

Consistently, median FVC/DLCO significantly improved and HRCT remained stable at 1 year in 7 patients who were anti-Jo1 positive with ILD refractory to steroids and/or cytotoxic drugs[48]; moreover, respiratory symptoms decreased or resolved in all patients and a decrease in associated GC dosage was recorded. Opportunistic or severe pyogenic infections did not occur during the follow-up period.

In a retrospective study,[54] a significant improvement in DLCO and FVC was observed in 10 patients with anti-Jo1-positive ASS and ILD treated with RTX. Conversely, a fatal infection 3 months after the last infusion with RTX was described in 11 patients with refractory ASS-ILD, 10 of whom were positive for anti-Jo1. Subsequently, the same authors retrospectively described 24 patients with ILD (19 of whom were anti-Jo1 positive).[50] After at least 12 months of follow-up, FVC, forced expiratory volume in 1 second, DLCO, and HRCT findings significantly improved. The authors reported 12 infectious adverse events with 6 deaths due to *Pneumocystis jirovecii* pneumonia. However, in this cohort, a large proportion of patients received concurrent immunosuppressive therapies other than RTX, including CYC, explaining the high rate of severe infections.

Only one small prospective study has been published including 10 patients treated with RTX affected by refractory anti-Jo1 ASS-ILD or intolerant to steroids and at least two other immunomodulatory or immunosuppressive drugs.[49] Although median FVC did not significantly change from baseline, authors reported improvement in or stability of lung function (FVC and DLCO) in 9 out of 10 patients at the 1-year follow-up; moreover, the steroid dose was decreased in 6 patients or they were discontinued from other immunomodulatory/immunosuppressive drugs. In only one case, the authors described a reduction in interstitial infiltrates on HRCT. Regarding safety, the authors reported six infectious adverse events of various origin and no infusion-related adverse events.

A better response to RTX has been described in patients with IIM and ASS in comparison to other forms of CTDs. In 33 patients with CTD-ILD, including 10 with IIM, the proportion of responders was higher in IIM-ILD (50%) than in the other CTDs (18.2%).[55] Of note, patients with IIM were most likely to show improved lung function following B cell depletion, with a trend bordering on statistical significance, maybe due to the key pathogenic role played by T cells in IIM-ILD.[55,56]

Sharp et al.[57] described a better response in patients with myositis, including ASS, among patients with CTDs. Comparing patients with IIM (3/24) or ASS (10/24) and 14 other CTDs, the authors observed a greater improvement in FVC (p=0.002) and DLCO (p=0.009) in the IIM subgroup. They did not report treatment-related complications, but 1 patient died 4 months after treatment due to disease progression.

In a multicentre retrospective analysis of patients with ILD related to ASS (15 patients), mixed CTD (MCTD) (6 patients) and SSc (23 cases), lung function was tested at baseline and at 1 and 2 years of follow-up. Even if the results did not reach statistical significance, 33% of patients with ASS responded to RTX compared to 9.5% in SSc and 16.7% in MCTD; RTX presented an acceptable safety profile.[38]

Among myositis-specific antibodies, antimelanoma differentiation-associated gene 5 antibody (anti-MDA5) is significantly associated with ILD. Studies mainly from eastern Asia have suggested that anti-MDA5 is specifically expressed in patients with amyopathic dermatomyositis who develop rapidly progressive ILD, associated with a high mortality and poor prognosis.[58,59]

Recently, successful treatment of ILD related to anti-MDA5 IIM with RTX in addition to other immunosuppressive drugs was reported in some case reports.[60,61] In particular, RTX allowed the improvement of respiratory symptoms, HRCT findings, and lung function tests in 4 patients with anti-MDA5-related ILD refractory to GCs and immunosuppressants; of note, 2 patients developed infective adverse events within 6 months after RTX infusion.[62] On the other hand, in another case series, two elderly patients died despite aggressive immunosuppressive treatments including RTX.[63]

In conclusion, RTX seems to be able to stabilize or improve ILD in patients with IIM and ASS. However, further investigation is necessary, in particular for patients with more severe and refractory disease.[34]

Sjögren syndrome

Primary Sjögren syndrome (pSS) is a CTD characterized by sicca syndrome, in particular xerostomia and xerophthalmia, due to lymphocytic infiltration into salivary and lacrimal glands. pSS-related ILD represents the most frequent lung involvement and it is associated with a reduced physical capacity, quality of life, and premature mortality.[64,65] NSIP is the most frequent ILD pattern, while UIP and OP are less frequently observed. Of note,

lymphocytic interstitial pneumonia is typically associated with pSS, although rarely detected.[1,65]

Observational studies and clinical trials have yielded conflicting results on the use of RTX in sicca syndrome related to pSS.[66,67] Nevertheless, clinical guidelines and expert opinion support a potential role of RTX for extra-glandular manifestations such as purpura, vasculitic neuropathy, cryoglobulinaemia, and pSS-related non-Hodgkin's lymphoma.[67,68] However, data regarding pSS-ILD treatment are still lacking.[1]

In 2016, Chen et al.[69] retrospectively investigated the effect of RTX in 10 patients affected by pSS-ILD; after 6 months, DLCO and clinical symptoms (namely dyspnoea and cough) improved, and the HRCT score was stable; non-fatal pneumonia 4 months after RTX infusion was observed in only 1 patient.

Consistent with these findings, 6 out of 9 patients with ILD from a registry study showed a good response to RTX with a lower rate of serious infections than RA or SLE patients from the same registry.[70,71] However, 4 out of 9 serious infusion-related adverse events occurred as well as 1 case of delayed serum sickness-like disease.[72,73]

The currently available guidelines by the British Society of Rheumatology and Sjögren's Syndrome Foundation suggest the use of RTX in patients with pSS presenting with systemic manifestations, including ILD.[65,74–76]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune systemic disorder involving multiple organs, including the lung. The most common ILD pattern is NSIP, although lymphocytic interstitial pneumonia and OP have also been described in the context of SLE, while UIP seems to be very uncommon.[1]

Controlled and observational studies have yielded conflicting results on the effectiveness of RTX in the management of SLE, likely related to the heterogeneity of the SLE clinical picture.[77] Consequently, many experts suggest RTX only as third-line treatment for some SLE manifestations.[78–80]

The preferred treatment for active symptomatic SLE-ILD might be based on both clinical experience and evidence from other CTD-ILDs.[31,81] Experts suggest induction therapy with GC and MMF or CYC and maintenance therapy with AZA or MMF, while RTX or intravenous immunoglobulins are proposed in refractory cases.[82]

ANCA-associated vasculitis

AAVs are a group of systemic necrotizing vasculitides involving small-sized vessels. AAVs comprise granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic GPA.[83] The prevalence of ILD is variable among AAVs, ranging from ~23% in GPA to up to 45% in microscopic polyangiitis. ILD is rarely described in eosinophilic GPA.[2]

No recommendations are currently available for the treatment of AAV-ILD. Pharmacological treatment mainly relies on corticosteroids frequently associated to immunosuppressants such as CYC, methotrexate, MMF, or AZA, with a therapeutic scheme composed by an induction and maintenance regimen.[84] Although RTX plays an increasing role in the treatment of AAV, evidence on AAV-ILD is still lacking and only retrospective studies and case series are available to date.[84–87]

In this regard, a study on 49 patients with AAV-ILD suggested a longer survival for patients treated with a combination therapy of GC and CYC or RTX compared to GC alone.[88] On the other hand, immunosuppressants did not improve the prognosis of AAV-ILD in a recent study including 62 patients.[89]

Ongoing trials

The Rituximab vs Cyclophosphamide in Connective Tissue Disease-ILD trial (RECITAL trial, NCT01862926) is a multicentre, randomized, prospective, double-blind, controlled study of patients with ILD related to IIM (including ASS), SSc, or MCTD. The trial aims to compare RTX (1000 mg, two infusions separated by 2 weeks) *versus* intravenous CYC (600 mg/m^2 administered monthly). The FVC change at 24 weeks is the primary endpoint of the trial, while secondary endpoints include change in FVC at 48 weeks, survival, and change in oxygen requirements.[44]

Evaluation of Efficacy and Safety of Rituximab with Mycophenolate Mofetil in Patients with Interstitial Lung Diseases (EvER-ILD, NCT02990286) is a randomized 24-week trial recruiting patients with ILD related to idiopathic interstitial pneumonia, CTD, or interstitial pneumonia with autoimmune features. The trial aims to compare MMF (1 g twice daily) plus RTX (1000 mg, two infusions separated by 2 weeks) or placebo. The primary outcome is the change in FVC(%), while secondary outcomes include progression-free survival, changes in the quality of life and dyspnoea, and changes in chest HRCT, DLCO, and the 6-minute walking test.[90]

Rituximab in Interstitial Pneumonitis (RITUX-IP, NCT02251964) is a phase II–III study aiming to explore the effects of RTX (1000 mg, two infusions separated by 2 weeks) as a rescue therapy for progressive and steroid-refractory ILD related to immune-mediated inflammatory diseases. The primary outcome is the pulmonary function at 6 and 12 months. The study was completed on February 2018 but the results are awaited.[91]

Safety

In patients affected by ILD related to rheumatic diseases, RTX is considered overall a safe treatment despite its association with a higher risk of infection and acute lung toxicity,[10,11] other than infusion-related adverse events. The lung toxicity of RTX has been described in patients with malignancy, RA,[92] and CTDs.[3,18] The most common presentation of lung toxicity is acute/subacute hypoxaemic OP presenting after 2 weeks with RTX

treatment. Acute respiratory distress syndrome has also been reported, usually within hours after the first infusion.[93]

Franzen et al.[92] prospectively evaluated 33 patients with RA treated with RTX to investigate the incidence and risk factors of RTX-induced lung toxicity. None of the patients reported new respiratory symptoms, but DLCO progressively declined over 26 weeks. In particular, 6 (22%) patients showed a decline in DLCO >15% from baseline. By contrast, the course of FVC was unchanged over follow-up. The risk factors for pulmonary function changes were cigarette smoking and previous administrations of RTX prior to study inclusion. A worsening of DLCO could indeed represent an early signal of subclinical RTX lung toxicity.[94–97]

Regarding infections, ILD itself carries an increased infectious disease exposure, and immunosuppressive therapy, including RTX, might increase the risk.[50,98] Therefore, it is mandatory to consider the infectious disease risk in patients with ILD treated with RTX and to evaluate prophylaxis with vaccinations, trimethoprim/sulfamethoxazole, or immunoglobulin-replacement therapy. Flu and antipneumococcal vaccinations are recommended and should be administered, whenever possible, before RTX is started. Live vaccines are contraindicated for patients treated with RTX in the previous 6 months.[99]

Low IgG levels at RTX onset and IgG decline after treatment are associated with an increased rate of infection.[11] Immunoglobulin replacement therapy should be mandatory in cases of hypogammaglobulinaemia and recurrent symptomatic bacterial infections.[11,73]

Finally, prophylaxis with trimethoprim/sulfamethoxazole or pentamidine aerosol could be evaluated to prevent *P. jirovecii* pneumonia[100] while antivirals could be proposed for the prophylaxis of herpesvirus infections.[101] In addition, hepatitis B virus prophylaxis, associated with repeated HBV-DNA monitoring, is recommended to prevent hepatitis reactivation in HBV carriers treated with RTX.[98]

RTX biosimilars

Recently, RTX biosimilars have been approved and are currently used in the treatment of RA. At present, only limited data about the use of RTX biosimilars in ILD related to rheumatic diseases are available. In particular, trials on RA did not include pulmonary outcomes. A retrospective multicentre analysis on 33 patients with SSc suggested that the RTX biosimilar CT-P10 could reduce skin thickness, inflammatory arthritis, and stabilize lung function after 6 months of treatment, in both patients naive to treatment or in those who switched, with a satisfactory safety profile.[102] In a retrospective study on pSS, 9 patients received an RTX originator and 8 the RTX biosimilar CT-P10, showing similar efficacy and safety profiles at 48 weeks of follow-up, but no data were reported about outcomes on pulmonary involvement.[103]

Discussion

RTX represents an option for the treatment of ILD in the context of CTDs, RA, and AAV. Data regarding efficacy are still controversial and are burdened by several biases. Furthermore, the supposed relationship between efficacy and ILD radiologic patterns has not yet been investigated.[18,21] To date, indeed few prospective studies are available and randomized trials are still ongoing with the purpose of exploring the role of RTX in this condition. Safety data derive mainly from trials and real-life analyses in patients with RA, in whom RTX administration has been previously approved and widely used as a disease-modifying antirheumatic drug. Despite an overall acceptable safety profile, concerns still regard an increased infectious disease risk in patients with ILD, the possible lung toxicity, and the increased rate of immune-mediated reactions in patients with CTD.

Conclusion

In conclusion, RTX is increasingly involved in the choice of treatment for ILD related to rheumatic disease. Results from ongoing randomized trials are expected to better assess the efficacy and safety of RTX in this challenging condition.

Highlights and future perspectives

- RTX represents a possible treatment option for ILD related to rheumatic diseases.
- Efficacy data are still controversial and are burdened by several biases.
- The safety profile derives mainly from studies on RA, and there are concerns regarding infectious risk, possible lung toxicity, and immune-mediated reactions.
- Future large prospective studies and randomized trials are expected to better assess efficacy, in particular in relation to the radiologic patterns of ILD and to progressive refractory ILD as well as on the safety of RTX treatment in patients with ILD related to CTDs, RA, and AAV.

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