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Is there a Role for Biologic Agents in the Treatment of Connective Tissue Disease-Associated Interstitial Lung Disease?

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Abstract

Except for SSc, there are no controlled clinical trial data available to guide decision making in CVD-ILD. To date, only two powered, randomized controlled trials of treatment have been conducted in scleroderma patients; with both of these assessing the benefit of cyclophosphamide compared with placebo for the treatment of scleroderma-related interstitial lung. Currently accepted initial treatments in CVD-ILD include corticosteroids, azathioprine and mycophenolate mofetil for mild disease, while cyclophosphamide has been used in severe or rapidly progressive disease. However, an optimal general approach or specific criteria for the selection of each different treatment modality, is not completely defined. During the last decade, rituximab (RTX), has been used in the treatment of a interstitial lung disease associated to connective tissue diseases (ILD-CTD) . A recent study including 50 cases of severe and refractory ILD showed that RTX therapy resulted in an an improvement of 8.9% of the FVC. Several small retrospective studies have shown at least partial benefit of RTX in refractory PM/DM, including antisynthetase syndrome (ASS) . RTX may have a role in specific subsets of CVD-ILD. Further studies are needed, but there is enough evidence to consider RTX as a suitable and safe option for the treatment of severe, relapsing or refractory patients. Several other biologic agents are now being studied in CVD, including tocilizumab that has shown a possible therapeutic benefit in patients with CVD-ILD.

Key words: interstitial lung disease, autoimmune disease, immunosuppression, biological agents, rituximab

The collagen vascular diseases (CVDs) are a heterogeneous group of autoimmune disorders withmultiple manifestations. Many of these disorders have a frequent pulmonary involvement, especially interstitial lung disease (ILD). It may estimated that no less than 15% of patients presenting for evaluation of ILD have an underlying completely defined CVD[1].

The frequency and histologic type of ILD vary with the nature of the underlying CVD. The most commonly ILD CVD-associated include rheumatoid arthritis(RA), Progressive Systemic Sclerosis(SSc), Dermatomyositis/Polymyositis(DM/PM), antisynthetasesyndrome(AS), mixed connective tissue disease (MCTD) and less frequently Sjögren syndrome (SS)[2].

Some epidemiological studies show a pulmonary involvement in 40-90% of patients with Systemic Sclerosis (SSc) and 30-70% of patients with polymyositis/dermatomyositis, but no doubt, ILD is most commonly observed in SSc and myositis patients. In those patients, the finding of ILD is as high as 90-100% of autopsy studies and the development of clinical interstitial pneumonia is common although many times often subclinical. Around 40-75% show an impaired pulmonary function and

55-85% of patients have interstitial abnormalities on high-resolution computed tomography (HRCT) of the thorax[3, 4].

The more common patterns of ILD encountered in patients with CVD include usual interstitial pneumonia (UIP),nonspecific interstitial pneumonia(NSIP)organizing pneumonia(OP), lymphoid interstitial pneumonia (LIP), and acute interstitial pneumonia(AIP)[5].

Given the high prevalence of subclinical ILD in CTDs, it is important to determine the degree of respiratory impairment in all patients with CTD-ILD. The decision to treat CTD-ILD is often based on whether the patient sows clinical impact of the ILD; whether the ILD is progressive by symptoms, pulmonary function, and/or imaging; and not less important, if therapy is required for the extrathoracic features of the disease[6].

When considering the general approach to the management of CTD-ILD, the concept commonly applied in systemic vasculitis considering a phase of induction followed by maintenance therapy, is the most common approach. Induction therapy usually includes high dosing of corticosteroids (CSs) with the addition of a short-term use of a more potent (and potentially more toxic) agent such as cyclophosphamide (CYC) followed by a maintenance regimen with a less toxic agent (such as AZA or MMF) and CS tapering. It must be reminded that because of the often-poor prognosis associated the stabilization of the disease is considered a successful outcome, and the cost-benefit of the different therapeutic approaches must be discussed in this setting not only into the multidisciplinary team (MDT) but mainly with patients.

Except for SSc, there are no controlled clinical trial data available to guide decision making in CTD-ILD. Being a heterogeneous group of patients, it is hard to generate evidence based data and, being realistic, recruitment to trials is challenging and will be difficult to have powered studies that provide such evidence in the short term. Most available information come from registries, case series or individual case reports. To date, only two powered, randomized controlled trials of treatment have been conducted in scleroderma patients; with both of these assessing the benefit of cyclophosphamide compared with placebo for the treatment of scleroderma-related interstitial lung disease (ILD)[7,8]. Thus, there is much that is unknown regarding optimal treatment of other CTD-related pulmonary disease and even in scleroderma patients, the magnitude of the effect of the studied treatments, the optimal dose and length of therapy and the potentially different groups of patients with different rate of responses is a non-answered challenge.

In the absence of evidence supporting disease modifying effects of aggressive treatment of CTD-ILD and taking into account the potential toxic effects of immunosuppressant treatment, the majority of clinicians tend to base their therapeutic decisions on disease severity and the level of functional impairment experienced by the affected patient. The underlying histological pattern, may preduct prognosis, and, only to a certain extent, predicts response to treatment. Organizing pneumonia and cellular NSIP can be expected to improve or even regress with therapy, and, on the other hand, the presence of UIP, characterized by marked architectural destruction predicts no hope of regression with treatment making stabilization of disease and slowing of further decline the best potential outcome.

Currently accepted initial treatments in CTD-ILD include corticosteroids, azathioprine and mycophenolate mofetil for mild disease, while cyclophosphamide has been used in severe or rapidly progressive disease. However, an optimal general approach or specific criteria for the selection of each different treatment modality, is not completely defined.

Although, corticosteroids are very widely used in the management of CTD-associated pulmonary disease, there are few evidence-based data about their usefulness or to define their use. The dose and route of corticosteroid administration is guided mainly by expert opinion, and by reference to data generated from nonpulmonary disease.

Azathioprine shows an immunosuppressant effect through inhibition of T- and B-lymphocyte proliferation. Although, commonly used in combination with oral corticosteroids in the treatment of CTD-ILD, azathioprine has not been studied as monotherapy in any prospective randomized trials. On the other hand, the information available based on RCT is only about scleroderma. In the study by Hoyles et al of intravenous cyclophosphamide, azathioprine (at a dose of 2.5 mg/kg/d) was used as maintenance therapy for 6 months following initial treatment with intravenous cyclophosphamide[7].

Cyclophospamide is the drug of choice for induction therapy in patients with severe or progressing disease. In the placebo-controlled trial of oral cyclophosphamide in SSc-ILD, beneficial effects at 1 year on FVC levels, dyspnea, skin thickening, and quality of life were statistically better in the treatment group[8]. In a subsequent placebo-controlled study of intravenous cyclophosphamide (once a month for 6 months), followed by oral azathioprine, the the magnitude of the benefit on FVC was similar to those seen in the Taskin trial. HOwever, because of the small size of the sample (n = 45), those results were nor definetely significant (p = 0.08)[7]. Based on these two studies, it was concluded in a EULAR statement that cyclophosphamidewas an appropriate therapy in SSc-ILD[9]. It must be remarked that no treatment effect was observed in the SLS trial in those patients with mild disease on HRCT, but the treatment effect on FVC was more significant when the disease was extensive and fibrotic[8].

MMF is also a quite well established option for patients with mild disease, maintenance therapy or contraindication for corticosteroids. MMF has been shown to be well tolerated in systemic sclerosis with retrospective studies suggesting that the drug has favorable effects on systemic manifestations of disease[10, 11, 12]. The scleroderma lung study (SLS) II is currently evaluating the effect of MMF as first-line therapy compared with cyclophosphamide in scleroderma ILD in a 2- year randomized controlled trial (NCT00883129). Recent advances presented as an abstract at the CHEST meeting 2015 showed at 24 months the improvement in %FVC was comparable in the two treatment groups but leukopenia/thrombocytopenia were noted significantly less frequently in the MMF arm[13].

Given the scarcity of evidence-based data to select any treatment and the only partially successful reported results, new therapies have been explored in the last years. Initially investigated for refractory or very severe disease, those new options are being considered for a wider population and even as first line therapies and not only following the failure of the more conventional treatment. The scenario of CVD-ILD is that of a group of potentially life-threatening diseases whose available treatments are associated with serious adverse effects and heterogeneous responses to treatment. New options with better rates of response and fewer side effects are an urgent need in CVD-ILD patients.

During the last decade, rituximab (Rtx), an anti-CD 20+ mAb, has been used in the treatment of a several rheumatic inflammatory diseases. Rituximab, a chimeric (human/mouse) monoclonal antibody with a high affinity for the CD20 surface antigen expressed on pre-B and B-lymphocytes, produces a rapid depletion of B cells from the peripheral circulation. Rituximab acts via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and apoptosis to effectively deplete B cells for 6-9 months in over 80% of patients.The mechanism of B-cell killing by rituximab is believed to depend on its antibodydependent cell-mediated cytotoxicity. The rationale for its use in immune-mediated diseases is based on that mechanism of action[14]. It was originally approved for the treatment of non-Hodgkin's lymphoma and for the treatment of ANCA-associated vasculitis and rheumatoid arthritis. Evidence for potential benefits of RTX in other autoimmune diseases has been published in the last decade[15]. The shared immune dysfunction underlying these conditions has promoted the research of its use in CTD-ILD.

The first report of successful treatment of scleroderma- associated ILD with Rtx was in 2008, in a cohort of eight patients, showing significant improvement of FVC and diffusing capacity of carbon monoxide (DLCO) compared to a matched group who received standard treatment[16]. Keir and colleagues[17] reported 8 cases of CTD-ILD (5 IIM-ILD; median FVC, 45% of predicted; median DLCO, 25% of predicted) with refractory ILD and used RTX as rescue therapy. Before RTX infusion, all patients had decline in FVC and DLCO, and after RTX infusion, DLCO improved of 22% (P 5 .04) and FVC 18% (P 5 .03). The same Bromptom's group reported later a larger experience with RTX infusions in 50 cases of severe and refractory ILD. Amongst those patients, 33 suffered CTD-ILD (10 IIM, 8 SSc, 9 undifferentiated CTD), DLCO was 24.5% of predicted, and FVC was 44.0% of predicted. In 85% of the patients with CTD-ILD the response was considered positive. In the 6 to 12 months previous to the treatment with RTX, a median decline in FVC of 13.3% and in DLCO of 18.8% had been shown and in the 6 to 12 months post-treatment with RTX therapy an improvement of 8.9% of the FVC (P<.01) and a stabilization of

the DLCO (P<.01) were noted[18]. In contrast to this data, Dodds et al showed in 20 patients with CTD-ILDs treated with rituximab no improvement in FVC, DLCO or total lung capacity, but interestingly, those patients remained stable. A subgroup analysis of nine patients with myositis demonstrated an improvement in FVC (P = 0.011)[19]. In the study of the European Scleroderma Trial and Research (EUSTAR) group (n = 63)[20] that analysed scleroderma patients that received RTX in routine clinical practice upon the decision of their physicians, the effects of RTX treatment on lung function was studied in SSc patients with FVC <70% predicted, and evidence for ILD on HRCT (n = 9). The DLCO was significantly improved in patients treated with RTX compared with baseline (41.1 ± 2.8 vs 44.8 ± 2.7%; p = 0.03). In contrast to RTX-treated patients, patients in the control group showed a decline in FVC at follow-up. This resulted in significant differences between RTX treated and matched controls in change of FVC% predicted in both the percentage (0.4 ± 4.4 vs −7.7 ± 3.6; p = 0.02) and the absolute change (0.8 ± 2.2 vs −4.8 ± 1.7; p = 0.01). Those studies suggest that in individuals with SSc-ILD for whom cyclophosphamide is not a convenient option or fails to induce a therapeutic response, rituximab may be an effective alternative.

However, the most attractive use of RTX is the treatment of inflammatory myopathies (IIM). The pulmonary involvement in this group of patients is particularly severe and clinical experience shows that those are the patients who fail more frequently with the use of conventional approaches, including cyclophosphamide and high doses of corticosteroids.

Several small retrospective studies have shown at least partial benefit of Rtx in refractory PM/DM, including antisynthetase syndrome (ASS)[21-23]. A small retrospective series of 11 patients with antisynthetase syndrome–ILD studied RTX as a rescue therapy[24]. Compared to the 8 months'pretreatment data 6 patients had an FVC improvement of greater than 10% and 3 had a DLCO increase of greater than 15% during the 7 months of follow-up after RTX infusion and the thoracic HRCT scan showed a regression of the ground-glass opacities in 4 patients. However, the controlled randomized study of 195 Rtx treated patients with refractory myositis did not show any statistical difference between the two treatment arms for primary and secondary endpoints, but the authors found that patients with anti-aaRS antibody had a shorter time to improvement compared with patients without myositis-specific antibodies[25]. Recently, a retrospective analyses of 24 Rtx-treated ASS patients with ILD was performed with a median follow-up time of 52 months. Significant improvements, both in PFT and ILD extent in HRCT images were observed. Thirty four of 112 ASS patients showed ILD and received Rtx; 24 of those 34 had severe ILD. In these 24 patients, the median percentage of predicted forced vital capacity, forced expiratory volume in 1 s (FEV1) and DLCO increased by 24%, 22% and 17%, respectively after the infusion of Rtx. The most pronounced effects on lung function were observed in patients with a longer disease (duration <12 months at the first Rtx cycle). In this group, seven patients increased > 30% in FVC, FEV1 and DLCO during the observation period[25]. Twenty one percent (7/34) of the patients died during the follow-up, most of the deaths were related to infections. The mortality rate for the total cohort was 32% (25 of 78) suggesting that the mortality rate was not higher in the Rtx-treated group than in non-Rtx-treated ASS patients.

Concerning RA-ILD, the results of 10 patients (4 UIP, 6 NSIP, baseline FVC 68%, baseline DLCO, 48%) treated with RTX were reported initially by Matteson[27] showing that measures of lung disease remained stable in the majority of study completers. Later, a multicentre study in 188 patients with RA-ILD during a 25-year period (65% UIP), analysed 57 patients that were treated with a biologic agent. No difference in all-cause or respiratory mortality was reported in patients treated with biologics versus other agents. However, there was a statistically significant difference in respiratory mortality between patients treated with anti-TNF (n 5 30) versus RTX (n 5 27) (15% vs 4%; P 5 .04) and in all-cause mortality in 31% of patients treated with anti-TNF versus 8% of patients treated with RTX (P 5 .03) in the UIP subgroup[28].

Over half a million people worldwide have received rituximab therapy during the last 15 years. The drug appears to be safe and well tolerated[29]. Frequently reported adverse effects include infusion reactions manifested by fever, chills, headache, nausea, bronchospasm, hypotension and angioedema[30]. Most of these reactions are mild, and take place only during the first infusion. Infectious

complications are fequent, although reported in 50% of patients in the early post-treatment period, they are usually mild, mainly upper respiratory tract infections and less frequently herpes zoster and influenza. More serious infections hjave been occasionally reported. Progressive multifocal leukoencephalopathy (PML) is the most serious complication associated to infection or reactivation of JC virus, but has been reported in few patients, usually with risk factors for PML development, mainly lymphoproliferative diseases.

A systematic literature review conducted using PubMed, the Cochrane Library and EMBASE for reviews, meta-analyses, clinical studies and randomized controlled trials, case studies and series, showed that in 65 studies of RTX an association with non-infectious pulmonary toxicity was demonstrated in 121 cases; however, only 6 of these cases had an underlying rheumatological condition[31].

Clinical trials studying RTX in ANCA-related vasculitis have allowed to compare the rate of side effects of cyclophosphamide and RTX. The Rituximab in ANCA-Associated Vasculitis (RAVE) trial[32] randomly assigned 197 patients with newly diagnosed or relapsed AAV to intravenous rituximab (375 mg/m^2 weekly for 4 weeks) or control (oral daily CYC, 2.0 mg/kg per day, followed by azathioprine once remission was achieved). The second trial was the Rituximab Versus Cyclophosphamide in ANCA-associated Vasculitis (RITUXVAS) study[33], that randomly assigned 44 patients with AAV and renal involvement to standard therapy (intravenous CYC, 15 mg/kg every 2 weeks for three doses, then every 3 weeks thereafter until remission, followed by azathioprine, 2 mg/kg per day, when in remission) or the addition of rituximab (375 mg/m^2 weekly for four doses) to a CYC-containing regimen (intravenous CYC, 15 mg/kg, with first and third rituximab doses). In the RAVE trial, the number of total or severe adverse events were similar in both groups. Fourteen percent of patients in the rituximab group and 17% of patients in the CYC group had treatment- or disease-related events leading to discontinuation of therapy. During 18-month follow-up of these patients, the number or rates of total adverse events, serious adverse events, and non-disease-related adverse events did not significantly differ. Leukopenia was more common in the CYC group (23% versus 5%), but serious infections were similar in both groups (12% with rituximab versus 11% with control).

In the RITUXVAS trial, at 12 months, the percentage of patients experiencing severe adverse events (42% with rituximab versus 36% with control), the incidence of severe adverse events, and the incidence of infections (0.66 per patient-year in the rituximab group versus 0.60 in the control group) were similar between the two treatment groups. At last follow-up, death rates were identical in both groups (18%). Taken together, these data suggest that rituximab is not a more dangerous alternative to CYC as first-line therapy in AAV, and it should be the case in CTD-ILD patients.

All the published evidence suggest that RTX may have a role in specific subsets of CTD-ILD, such as the antisynthetase syndrome (even as first line therapy) and those cases in which conventional treatment with CYC is contraindicated or has not been successful. Further studies are needed to more precisely define its role in CTD-ILD, but there is enough evidence to consider RTX as a suitable and safe option for the treatment of severe, relapsing or refractory patients. It is important to remark that in many patients CTD-ILD is a life-threatening condition or result in severe morbidity and disability and that all the established treatments have limited results or are completely useless in a certain subgroup pf patients.

Several other biologic agents are now being studied in CTD, especially in RA, however the role of these in related ILD remains unclear. Tocilizumab (an anti-interleukin-6 receptor antibody), has been reported to produce pneumonitis and exacerbation of pre-existing ILD related to RA[34]. But also several case reports have shown a possible therapeutic benefit in patients with CTD-ILD[35, 36, 37]. Although there is no experience for the use of this agent as a primary treatment in ILD, it might be considered in the failure of better studied treatments in refractory severe disease[34].

The IL1 receptor antagonist, Anakinra, has not reported non-infective pulmonary toxicity. There is, however, little to suggest therapeutic benefit[36], although it may have promising potential benefits in the treatment of silicosis[38].

A different category category of biologic agent, of particular interest in the field of interstitial lung disease, is the tyrosine kinase inhibitors. The results of the INPULSIS clinical trials showing benefit of nintedanib in Idiopathic Pulmonary Fibrosis (IPF)[39] have raised enthusiasm about the potential benefit of nintedanib in fibrotic forms of CTD-ILD

(UIP or fibrotic NSIP. However those results cannot be extrapolated to the treatment of CTD-ILD yet and there is currently no literature to support a possible therapeutic role. However, it is possible that these agents may have a benefit, especially in RA-ILD, the CTD-ILD with closer similarities to idiopathic pulmonary fibrosis. Initial evidence of benefitial effect in preclinical models of pulmonary fibrosis in scleroderma[40]. The drug is currently only approved for IPF treatment but clinical trials including other "fibrotic" conditions are expected in the next future.

Today, pharmacologic intervention with immunosuppression is the mainstay of therapy for all forms of CTD-ILD, but should be reserved only for those that show clinically significant and/or progressive disease. However, it is crucial to remark that once a patient has received a diagnosis of mild ILD in the context of a CTD, he or she must be meticulously followed in the search of a progressing disease. That is the most common course of the disease and taking into account that treatment rarely reverses the disease and most of the times only get an stabilisation, the delay of the initiation of treatment may have considerable consequences.

The management of CTD-ILD is not yet evidence based and there is an urgent need for controlled trials across the spectrum of CTD-ILD. Robust clinical trials are urgently needed to improve the decision making in these conditions. An ongoing clinical trial, the RECITAL study (NCT01862926), is assessing, in a double dummy, randomized controlled trial, the efficacy of rituximab compared with intravenous cyclophosphamide when given as first-line therapy in progressive CTD-ILD (including scleroderma, IIM, and MCTD). Until the publication of those results, the available evidence permit to select RTX as the treatment of choice following the clinical judgement of a MDT.

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