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Review

Where are we going in the management of interstitial lung disease in patients with systemic sclerosis?

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ABSTRACT

Interstitial lung disease (ILD) affects about 90% of patients with systemic sclerosis (SSc). It is associated with a restrictive lung disease in only 30% of patients and is progressive in an even lower percentage. A low forced vital capacity at presentation, an extent of lung fibrosis >20% as detected by lung high-resolution computed tomography, high serum interleukin-6 levels, anti-topoisomerase I antibody positivity and diffuse cutaneous SSc are each associated with SSc-ILD progression. However, no such association is absolute. Treating patients with a recent deterioration of lung function may allow to capture those with active disease. To date, cyclophosphamide (CYC) is the only drug found to stabilize or improve lung function in randomized clinical trials, but its small beneficial effect is short lived. Therefore, immunosuppressive maintenance therapy after CYC treatment is warranted. At present, however, the best therapeutical strategy after CYC therapy both in responders and in non-responders to CYC is still controversial. Based on a review of the literature, we suggest an approach to the management of SSc-ILD.

Contents

1. Introduction

Systemic sclerosis (SSc) is an autoimmune systemic disease characterized by endothelial dysfunction, immunological abnormalities and fibroblastic activation resulting in fibrosis of the skin and target internal organs [1,2]. It is associated to a shortened survival [3] most frequently related to interstitial lung disease (ILD) and pulmonary arterial hypertension [4]. Whereas the latter affects a minority of SSc patients [5,6],

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ILD is a frequent complication of SSc. The prevalence of ILD varies depending on the method used to detect the disease and reaches figures as high as 90% when detected with lung high-resolution computed tomography (HRCT) [7]. Despite its high prevalence, however, SSc-ILD is not evolutive and does not affect survival in most cases [8]. Restrictive lung disease was identified in 32% of SSc patients enrolled in the European Scleroderma Trials and Research (EUSTAR) database [9]. Moreover, in a study based on the University of Pittsburgh Scleroderma Databank, it has been reported to be severe (i.e., with a FVC < 50% of predicted value) in 16% (i.e., about 50% of patients with restrictive lung disease) [10].

Unlike pulmonary arterial hypertension, which is commonly treated according to expert-based recommendations, SSc-ILD treatment is still debated [8,11]. To date, only cyclophsphamide (CYC) was found to be effective in stabilizing or improving lung function in randomized clinical trials [12,13], but its small beneficial effect seems to be short lived [14]. Therefore, immunosuppressive maintenance therapy to be introduced after CYC seems warranted [14]. Moreover, the best therapeutical strategy to undergo after CYC therapy both in responders and in non-responders to CYC is controversial [15].

Drawing together the data available in the literature, here we suggest a therapeutical approach to SSc-ILD.

2. Which SSc-ILD patients should be treated?

The prognosis of SSc-ILD is less severe than that of idiopathic pulmonary fibrosis [16]. Actually, most SSc-ILD patients experience a stable or slowly progressive course. However, some of them undergo a rapidly progressive loss of lung function, which mainly occurs in the first years from disease onset [10].

Various factors have long been known to be associated with ILD in patients with SSc, namely, anti-topoisomerase I antibody positivity [17], African American race [18] and other genetic or environmental factors [18,19]. Table 1 lists disease features, detectable at presentation and predictive of progressive ILD. They include an extent of lung fibrosis >20% as detected by lung HRCT with an FVC <70% of predicted in undeterminate cases [20,21], high serum interleukin-6 levels [22], a low FVC, anti-topoisomerase I antibody positivity, diffuse cutaneous SSc (dcSSc) and a low DLCO, which is also known to predict pulmonary hypertension [5,23,24], while anti-centromere antibodies positivity is a protective feature [23]. Somewhat unexpectedly, the histopathologic pattern (usual interstitial pneumonia as compared to non-specific interstitial pneumonia) [25] as well as the presence of active alveolitis as detected by bronchoalveolar lavage analysis [26] do not seem to predict an unfavorable disease course in SSc-ILD patients.

Of the features listed above, an HRCT score seems the most consistent. In fact, in a recent systematic review, the extent of fibrosis on lung HRCT scan was the only variable that independently predicts at a point in time both ILD progression and mortality [27].

Despite the statistical significance of each of the above listed associations, none of them fully discriminated between patients with a stable or slowly progressive course and those with a rapidly progressive loss of lung function. This holds true also for putative "protective" disease features. Indeed, the limited cutaneous subset [28] as well as "protective" marker autoantibodies can be associated with clinically significant and evolutive ILD [29]. These evidence have so far hampered the development of an algorithm for the treatment of ILD in the single SSc patient [8], in particular in the early stages of the disease when the extent of fibrosis, as detectable by lung HRCT, may be limited.

A study of idiopathic ILD showed that, at presentation, the histologic pattern (i.e., usual interstitial pneumonia as opposed to non-specific interstitial pneumonia) is the most important prognostic marker, while changes in FVC together with initial lung diffusion for carbon monoxide (DLCO) and gender are the only independent prognostic factors during follow-up, and the morphological pattern provide no additional prognostic information [30]. Regarding SSc-ILD, Moore et al. [22] reported that the extent of fibrosis on lung HRCT at baseline independently predicts outcome, and that during follow-up the diffusing capacity for carbon monoxide divided by the alveolar volume (DLCO/VA) and FVC strongly predict outcome.

These data suggest the following patients be treated: (i) all patients presenting at first observation with either an extent of lung disease >20% on HRCT or an indeterminate extent of disease plus an FVC <70%, and (ii) during follow-up, all patients experiencing a significant decrease of DLCO (>15%) or FVC (>10%) or both, whatever the extent of lung involvement. Treating SSc-ILD patients who have only a decrease in DLCO is not at present warranted because DLCO is not considered a primary endpoint in ILD treatment due to both pathophysiological and variability reasons [31]. Nevertheless, it has been recently demonstrated that DLCO provides the best overall estimate of HRCT-measured SSc-ILD disease in the absence of pulmonary hypertension [32]. Therefore, the approach we propose is to treat patients with early disease in whom extensive damage has not yet occurred. This holds true also for patients with a disease duration >4 years given the finding of similar rates of progression of lung disease, irrespective of disease duration in patients enrolled in the placebo arm of the Scleroderma Lung Study [33].

3. Which drug should be used first?

A few years ago, experts from EUSTAR performed a systematic review of the literature ensuing in 14 evidence-based recommendations [34] and recommended treating patients affected by SSc-ILD with CYC. The recommendation was based on the data of two high quality randomized controlled trials on the efficacy of oral (the Scleroderma Lung Study) [12] or pulse (Fibrosing Alveolitis in Scleroderma Trials) [13] CYC compared to placebo. A further unblinded, randomized trial versus azathioprine and a number of observational studies also supported the effectiveness of CYC with or without oral or pulse methylprednisolone in the treatment of SSc-ILD. However, Nannini et al. [35] did not find any significant change in FVC or DLCO in a systematic review of 3 randomized trials and 6 observational studies. Similarly, Poormoghin et al. [36] did not detect a significant improvement, as defined by an increase >10% in FVC and/or DLCO, in CYC-treated SSc-ILD patients.

These results do not rule out that CYC is able to stabilize the progression of SSc-ILD as we previously suggested [37]. They also could induce to hypothesize that CYC is more effective in patients with clinically active disease such as in those with a recent decline in lung function [38]. After the pivotal study by Silver et al. [39], we also detected a significant improvement of lung physiology in 60% of patients enrolled for a significant decline of FVC and/or DLCO during the previous 6 months [40].

Mycophenolate mophetil (MMF), rituximab and Imatinib have also been investigated as first-line therapy in SSc-ILD patients. MMF has been investigated only in case-series and uncontrolled studies and has been found to be safe and effective in stabilizing lung function in patients with SSc-ILD [41]. These data suggest that MMF could be used as the first drug in active SSc-ILD patients. However, a recent case–control study comparing lung function changes in SSc-ILD patients treated either with MMF or CYC [42] pointed out in both groups a stabilization

Table 1
Clinical, serological, physiologic and radiologic features, detected at presentation and predictive of disease progression in SSc-ILD.

Feature	HR (95%CI)	Reference
FVC < 65%	3.18(1.76–5.72)	23
DLCO ≤ 55%	3.027(1.75–5.23)	23
HRCT fibrosis extent > 20%	3.0 (1.2–7.5)	21
Serum IL-6 > 7.67 pg/ml	2.58 (1.6–3.56)	22
Anti-Scl70 +	1.76 (1.22–2.52)	23
FVC 65–80%	1.71 (1.0–2.93)	23
dcSSc	1.69 (1.05–2.72)	23