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PATHOLOGY REVIEW

# Interstitial lung disease in systemic sclerosis: current and future treatment

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**Abstract** Systemic sclerosis (SSc) has the highest fatality rate among connective tissue diseases and is characterized by vascular damage, inflammation and fibrosis of the skin and various internal organs. Interstitial lung disease (ILD) frequently complicates SSc and can be a debilitating disorder with a poor prognosis. ILD is the most frequent cause of death in SSc, and the management of SSc–ILD patients is a great challenge. Early detection of pulmonary involvement based on a recent decline of lung function tests and on the extent of lung involvement at high-resolution computed tomography is critical for the best management of these patients. This article summarizes classification, pathogenesis, diagnosis, prognosis, survival and finally current and future treatment options in SSc–ILD.

**Keywords** Systemic sclerosis · Scleroderma · Interstitial lung disease · Fibrosis · Treatment

## Introduction

Scleroderma is an autoimmune disease characterized by microangiopathy, excessive fibrosis of the skin and various internal organs, thus leading to organ dysfunction. Two different forms on the basis of the extent of skin involvement may be recognized: diffuse cutaneous sclerosis (dcSSc) and limited cutaneous sclerosis (lcSSc) [1]. In the last 30 years, the use of angiotensin-converting enzyme inhibitors significantly decreased the scleroderma renal crisis (SRC) associated mortality, and at present, the pulmonary involvement is considered the main cause of mortality, in these patients. In fact, the two most common types of direct pulmonary involvement: ILD and pulmonary arterial hypertension (PAH), account for 60% of SSc-related deaths [2]. Generally, epidemiological studies suggest that ILD is more common in dcSSc while PAH is more common in lcSSc. Finally, lung involvement may occur in SSc with no skin involvement (scleroderma sine scleroderma) [3].

## Classification of ILD

ILD is characterized by early pulmonary infiltration of immune competent cells followed by lung fibrosis and is classified into: (1) usual interstitial pneumonia (UIP); (2) non-specific interstitial pneumonia (NSIP); (3) diffuse alveolar damage (DAD); (4) organizing pneumonia (OP); (5) lymphoid interstitial pneumonia, on the basis of the histopathologic data. Histologically, NSIP, the most common histologic pattern seen in SSc–ILD, is characterized by varying degrees of inflammation and fibrosis; on the contrary, UIP, which is characterized by dense patchy fibrosis with honeycombing, is less frequent [4]. Some patient directly exhibit end-stage lung fibrosis, and ILD cannot be classified. Since the HRCT pattern predicts the underlying histopathology, a lung biopsy is not generally needed in SSc–ILD patients, except in the case of a discrepancy between clinical manifestations and HRCT findings [5]. However, the outcome of SSc patients is strongly associated with both the disease severity at presentation and, with the progressive DLCO decrease, more than with the histopathologic patterns [6, 7].

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## Pathophysiology

At present, the pathogenesis of SSc–ILD is still not completely understood. It has been suggested that an abnormal interaction among endothelial cells, lymphocytes, monocytes and fibroblasts results in an uncontrolled tissue fibrosis [8].

Many evidences suggest that the activation of the immune system, in response to one or more specific antigens, has a pivotal role during pathogenesis [9]. In SSc, a specific population of activated T cells exhibiting a pro-fibrotic type helper 2 (Th2)-polarized phenotype may be potentially relevant in mediating tissue fibrosis. Th2 T cells secrete interleukin (IL)-4 and IL-13 and participate in regulating tissue remodeling and fibrogenesis. IL-4 and IL-13 activate fibroblasts and collagen production by inducing secretion of pro-fibrotic cytokines, mainly transforming growth factor-β (TGF-β) [10]. In SSc–ILD, TGF-β plays multiple functions in cell signaling: by the canonical pathway, TGF-β causes phosphorylation of Smad2/3, which subsequently binds Smad4; Smad4 acts as a transcription activator, leading to the expression of extracellular matrix proteins. Via non-canonical pathway, TGF-β-induced cell signaling is mediated by specific regulatory proteins, including MAPK, PAR6 and RhoA [11]. Furthermore, injured tissue releases TGF-β, which recruits inflammatory cells, including macrophages, to the site of injury, which may further release TGF-β, thus exacerbating fibrosis [12]. IL-13 was found to be increased in SSc and is involved in both inflammation and fibrosis [13, 14], via the induction of TGF-β production by macrophages and/or via a TGF-β-independent mechanism [15]. Consistently, animal studies showed that overexpression of IL-13 in mice causes severe lung fibrosis [16] while IL-13 neutralization inhibits fibrosis in murine models of bleomycin (BLM)-induced lung fibrosis [17]. As far as CD8+ T cells are concerned, it is well known that these lymphocytes [9, 18] may infiltrate both the skin [19] and lung [20] of SSc patients and sharing an activated phenotype and antigen-driven oligoclonal expansion, in lung and peripheral blood [20, 21]. Moreover, it has been shown that a subset of scleroderma patients, at higher risk of progressive lung disease, show activated, long-lived CD8+ T cells in their lungs that could promote lung fibrosis, via the production of pro-fibrotic factors such as IL-4 and oncostatin M, as well as through a direct activation of TGF-β [20]. Another T cell subset regulatory T cells (Tregs) has been extensively studied during SSc. Tregs are responsible for maintaining immunologic self-tolerance and preventing potentially damaging autoimmune and protective immune responses. During SSc, although the number of Tregs is significantly increased, an impairment in their ability to suppress CD4+ effector T cells may be observed and their defective function is associated with a lower expression of surface CD69 [22]. B lymphocytes may promote fibrosis by cytokines, autoantibodies and cell–cell contact. B cells are hyper-activated in SSc. SSc patients display an increased surface expression of CD19 on B cells, associated with a lower CD19 expression, and this phenotype is generally associated with autoantibodies production. Consistently, in CD19 transgenic mice, which overexpressing CD19, elevated levels of different autoantibodies, including anti-topo I, may be observed. However, these transgenic mice do not develop fibrosis in the skin and visceral organs [23, 24]. On the contrary, in tight-skin mouse, a genetic model of SSc, which display a diffuse skin fibrosis, an increased expression of CD19, on B cells, may be observed [25]. To better understand the role that CD19 plays in modulating autoantibodies and fibrosis, BLM, which induces tissue fibrosis and inflammatory cells infiltration, is associated with autoantibodies production [26, 27], where injected in CD19-deficiency mice. Interestingly, the lack of CD19, on the surface of B cells, significantly inhibited the development of immune cells infiltration and skin and lung fibrosis, hyper-gammaglobulinemia and autoantibodies production, thus confirming that B cell activation modulates the downstream inflammatory infiltration of other immune cells [28]. Furthermore, activated B cells regulate T cell activation and differentiation, by promoting Th2 cells, shifting cytokine production toward the pro-fibrotic cytokines IL-6, IL-4 and IL-13 [29]. IL-6 expression is increased in the serum and skin of patients with early dcSSc, and high serum IL-6 levels are associated with the severity of skin sclerosis and reduced survival [30]. Blocking IL-6 in vitro decreased collagen production, and in the BLM model of lung fibrosis, IL-6 deficiency is associated with a slow progression of the pulmonary disease [31]. Since IL-6 is produced by B cells, together with TGF-β, these 2 cytokines may synergistically induce matrix synthesis without collagen degradation [32]. Finally, the CD19 overexpression is detected in both naive B cells and memory B cells in SSc patients. CD19 overexpression could be considered responsible for some abnormalities of B cell compartments characterized by expanded naïve B cells and activated memory B cells, despite a reduction in their number. Although memory B cell numbers are decreased in SSc patients, those remaining cells have an enhanced ability to produce Ig and possibly antibody [24, 33]. Finally, B cells can function as antigen-presenting cells to T cells and induce dendritic cell maturation that promotes pro-fibrotic Th2 response [34].

During SSc, many different molecules not directly linked to the immune system have been shown to be involved in SSc pathogenesis. Endothelin-1 (ET-1), which is produced by endothelial cells (ECs), is one of the best characterized molecules in these setting. It may be secreted in the skin and lungs, thus activating resident fibroblasts. ET-1 might induce fibrosis, directly by binding its specific receptors,

endothelin type A receptor (ETA) and to endothelin type B receptor (ETB) on fibroblasts, or alternatively by inducing pro-fibrotic cytokines, such as TGF-β. ET-1 levels are strongly elevated in animal models of lung fibrosis as well as in the plasma and bronchoalveolar lavage fluids (BAL) of SSc–ILD patients [28]. Specifically, transgenic mice overexpressing ET-1 spontaneously develop lung fibrosis, together with the accumulation of perivascular inflammatory cells [35, 36]. Furthermore, ET-1 levels are elevated in BLM-induced pulmonary fibrosis (PF). Epithelial cells, alveolar macrophages, ECs and mesenchymal cells are responsible for the increased levels of ET-1 in lungs of SSc patients. As far as, the ET receptors' expression in SSc–ILD lung tissue is concerned, decreased levels of the ETA associated with a slightly increase in the ETB levels have been reported [37]. ETB receptors are predominantly expressed on ECs, mediating vasodilation and removing ET-1 from the circulation. In SSc, ETB receptors are down-regulated on ECs which may diminish their vasodilatory role while are up-regulated on smooth muscle cells and can contribute to cell proliferation, hypertrophy, inflammation, fibrosis and vasoconstriction [37, 38]. Of note, ET-1 increases TGF-β expression and induces alveolar epithelial–mesenchymal transition through ETB-mediated production of TGF-β. It must be pointed out that TGF-β is able to modulate ET-1 overexpression in human lung fibroblasts. This induction occurs through a Smad-independent, activin receptor-like kinase 5 (ALK-5)/JNK-dependent mechanism and an activator protein 1 (AP-1) site in the ET-1 promoter [39]. Finally, it has been suggested that ET-1 may contribute to the TGF-β ability to promote a pro-fibrotic phenotype in human lung fibroblasts [40].

## Clinical presentation and diagnosis of SSc–ILD

The spectrum of SSc–ILD ranges from limited lung involvement, which is often non-progressive, to severe disease, which mainly occurs in the first years from disease onset and may progress to respiratory failure and death [41]. The patients may remain asymptomatic despite the presence of physical findings such as crackles on auscultation or interstitial thickening on chest radiography. The symptoms are not specific, including dyspnea on exertion and dry cough, which are frequently associated with fatigue. Chest discomfort, pain and hemoptysis are uncommon. Physical examination may show bilateral inspiratory and expiratory crackles ("Velcro" crackles) on auscultation of the lung bases. In the later stage of ILD, cyanosis and signs of right heart failure may be detected. Although ILD may develop in the course of lcSSc, it occurs more frequently in dcSSc.

Pulmonary function tests (PFTs) including spirometry and single-breath diffusion capacity for carbon monoxide (DLCO) play a major role in the investigation of lung involvement during SSc. Mild changes in function may be detected before any symptoms or changes in chest radiography. The most common change of PFTs is a reduced FVC with normal or even increased FEV1/FVC ratio that is indicative of a restrictive ventilatory pattern, similarly to ILD and PF [42]. DLCO is one of the most important functional tests, due to its ability to investigate the thickening of the interstitium, and the decrease in DLCO levels correlates with the extent of lung [4]. Severe restrictive lung disease (FVC ≤50% predicted) may occur in 10% of patients [41]. A progressive decline of DLCO is the most significant marker of poor outcome [6] while an early reduction in FVC is considered, by many authors, an important predictor for an early evolution to the end-stage lung disease [43]. In SSc, impaired DLCO may also indicate, pulmonary hypertension (PH), and/or other disease manifestations, including anemia, smoking [44]. An isolated reduction in DLCO with preservation of lung volumes (FVC/DLCO ratio >1.4–1.6) is suggestive of PAH [45]. As mentioned above, patients are asymptomatic early in the course of ILD and PH and symptoms including dyspnea, fatigue and exercise intolerance are not specific and frequently associated with other conditions (anemia, cardiovascular disease) making clinical diagnosis of both conditions challenging. Thus, early and regular screening with PFTs and DLCO should be performed at baseline and every 3–6 months during the first 4 years of disease, to detect both ILD and PH [46].

Because SSc–ILD may develop in the absence of dyspnea, HRCT should be performed at the time of diagnosis of SSc, together with PFT with DLCO. The extent of PF is considered a powerful predictor of both decline and mortality [47]. Goh et al. proposed a simple staging system for SSc–ILD as limited or extensive disease, based on simplified HRCT evaluation and FVC estimation that provides more powerful prognostic information than each single component. In particular, extensive disease (>20% HRCT involvement) would warrant immunosuppressive treatment, whereas limited disease (<20% HRCT involvement) would not. In those patients with an indeterminate extent of PF on HRCT, the use of an FVC threshold of 70% FVC would drive the decision to treat (<70% predicted) or not to treat (>70% predicted) [48]. Later, Moore et al. [47] reported that extensive disease on HRCT at baseline, evaluated using a semiquantitative grading system, is predictive of decline or mortality in SSc–ILD, when compared with limited disease, and that during follow-up, both increased HRCT grade and decreased PFT parameters are predictive of poor outcome. Furthermore, it has been reported that the extent of fibrosis on lung HRCT was the only variable that independently predicts both ILD progression and mortality [49]. Finally, the extent of changes on HRCT appears to be

more important than pattern of abnormality (ground glass) in predicting outcome. Findings of ground-glass pattern of the lung bases on HRCT are suggestive for active alveolitis, which may progress toward lung fibrosis. When the disease progresses, fibrosis becomes prominent and the "honeycombing" pattern of lung parenchyma may be observed. Generally, HRCT, due to the excessive radiation risk, should be performed routinely to confirm or exclude SSc–ILD only in a higher risk group of patients (SSc patients positive for anti-topoisomerase I autoantibodies) or when clinically significant progression of SSc–ILD is suspected and other serial variables are inconclusive. Therefore, PFTs and HRCT, when used in combination, may be a powerful tool for predicting disease progression and mortality in SSc–ILD.

During ILD, BAL may be used to detect inflammation and to confirm active alveolitis. Although, previous studies on SSc patients suggested that BAL neutrophilia was associated with subsequent declines in PFTs in untreated patients [50, 51] and with extensive fibrotic disease on HRCT in SSc, the current use of BAL cellular analysis for SSc–ILD is limited to exclude infection. In fact, in more recent studies, BAL did not show any predictive value for evaluating the rate of response to cyclophosphamide (CYC) in the Scleroderma Lung Study (SLS) [52], and only one retrospective study suggested that >5% eosinophils in BAL represented an unfavorable prognostic factor, associated with reduced survival [6].

## Prognosis and survival in patients with SSc–ILD

A recent meta-analysis of 27 studies was conducted to identify variables that predict mortality and ILD progression in SSc–ILD. A total of 1616 SSc–ILD patients were included. Male sex, extent of disease on HRCT scan, presence of honeycombing, elevated Krebs von den Lungen values and increased alveolar epithelial permeability were identified as predictors of both mortality and ILD progression on unadjusted analysis. The extent of disease on HRCT scan was the only variable that predicts, independently, both mortality and ILD progression. DLCO was the most consistent predictor of mortality and may help to identify patients with a poor prognosis; however, more rigorous studies are needed to confirm and expand these findings [49]. Other several risk factors that are associated with the risk to develop ILD in SSc patients, including African-American race, extent of skin involvement, anti-topoisomerase I antibodies, selected biomarkers such as serum IL-6, CXCL4, chitinase 1, tenascin-C, lysyl oxidase and IL-33 [53–56].

As far as the survival in SSc is concerned, a recent meta-analysis that included a total of 43 studies reporting data from 13,529 patients was conducted. SSc presents a larger mortality than general population (survival mortality rate = 2.72) [57]. SSc–ILD is responsible for up to 30% of the mortality of SSc patients [58], and the median survival is 5–8 years for SSc–ILD [48]. The overall survival rate of SSc–ILD patients, at 5 years, is more than 90% [59], but significantly lower (38% at 9 years) if the patient is affected by the diffuse form.

## Candidate patients for treatment

A very important challenge for Rheumatologists is to identify the patients who should be treated for their SSc–ILD and the ideal timing to start the treatment. Many papers have been published in the last years, suggesting [47, 48, 60] that the SSc–ILD patients showing the following criteria would warrant an immunosuppressive treatment : (1) either an extent of lung disease >20% on HRCT or an indeterminate extent (disease extent not readily classifiable as minimal or severe; HRCT extent 10–30%) [48] of disease plus an FVC <70%, (2) patients experiencing a significant decrease in pulmonary functional assessment during the follow-up (FVC >10% or DLCO >15% or both, whatever the extent of lung involvement for 12 months [46, 61].

## Treatment approaches for SSc–ILD

Currently, the management of SSc–ILD is largely confined to immunomodulation. Non-selective immunosuppressants such as CYC followed by mycophenolate mofetil (MMF) and azathioprine (AZA) are still the most widely used medications in SSc–ILD. Several alternative approaches may be considered, including B cell depletion therapies (rituximab; RTX), bosentan, anti-TGF-β antibody, tyrosine kinase inhibitors (imatinib, dasatinib), anti-IL-6 antibody, anti-IL-13 antibody, pirfenidone and haematopoietic stem cell transplantation (HSCT). Finally, lung transplantation may be limited to those patients, with severe SSc–ILD, unresponsive to pharmacologic interventions.

## Cyclophosphamide

Although conflicting results are reported in the available literature, CYC is recommended as first-line therapy in SSc–ILD patients. The efficacy and safety of oral or pulse CYC in the treatment of SSc–ILD disease were shown in two randomized clinical trials (RCTs): the Scleroderma Lung Study (SLS) [52] and the Fibrosing Alveolitis in Scleroderma Trials (FAST), respectively [62]. The SLS study showed that 1 year of oral CYC (≤2 mg/kg/day for 12 months followed for an additional 1 year) improved

lung function, skin scores, dyspnea and health status/disability, and these effects might persist or increase, for several months after CYC discontinuation. However, except for a sustained impact on dyspnea, all of these effects waned and were no longer apparent at 24 months. Moreover, treatment with CYC was associated with severe toxicity than the placebo group. The FAST study did not show an improvement in the primary (FVC or DLCO) or secondary endpoints in the CYC group. However, for FVC, there was a trend toward statistical significance between the 2 groups. It must be pointed out that, despite of several studies support the effectiveness of CYC therapy in preventing a decline in lung function and premature death in SSc–ILD patients, recent systematic review and meta-analysis of RCTs and observational prospective cohort studies fail to confirm any clinically significant improvement in pulmonary function in SSc patients treated with CYC [63, 64].

### Mycophenolate mofetil

MMF, an inhibitor of lymphocyte proliferation, is a safer and less toxic alternative to CYC for the treatment of SSc–ILD. Several case series, uncontrolled studies and more recently 2 meta-analyses [65, 66] reported the safety and efficacy of MMF in SSc–ILD patients [67, 68]. Recently, SLS II, a study in which SSc–ILD patients were treated with MMF for 2 years or CYC for 1 year, showed that both the treatment resulted in a significant improvement in the pre-specified measures of lung function over the 2-year course of the study. Although MMF was better tolerated and associated with less toxicity, the hypothesis that it would have greater efficacy at 24 months than CYC was not confirmed. These findings support the potential clinical effectiveness of both CYC and MMF for progressive SSc–ILD, and a possible preference for MMF because of its better tolerability and toxicity profile [69]. Finally, Owen et al. [70] showed that in SSc–ILD patients and decline of pulmonary function, MMF therapy was associated with clinical stability for up to 36 months and lower frequency of early adverse events when compared with AZA treated patients.

### Azathioprine

A randomized unblended clinical trial, comparing CYC and AZA (a purine analog), as first-line treatment, did not provide any evidence of efficacy for AZA in the treatment of SSc–ILD [71], although small case series and retrospective studies suggested the use of AZA as maintenance immunosuppressive treatment for SSc–ILD [72–74]. Importantly, the very recent study showed the efficacy and tolerability of MMF and AZA in the management of SSc–ILD [70].

### Pirfenidone

Pirfenidone is a pyridone showing both anti-inflammatory and anti-fibrotic effects and has been approved for the management of patients with idiopathic pulmonary fibrosis (IPF). Pirfenidone was administered as a compassionate treatment in 8 patients with IPF and 2 patients with SSc–ILD. The drug was overall well tolerated, and although it did not improve survival, it stabilized the effects on progressive PF [75]. Further studies reported that pirfenidone has a stabilizing effect on ILD in SSc patients although the efficacy of pirfenidone for SSc remains unclear [76, 77]. Recently, the LOTUSS study, a phase II, open-label, randomized, 16-week study was designed to assess the safety and tolerability of pirfenidone in patients with SSc–ILD. The drug showed an acceptable tolerability profile that was not affected by concomitant treatment with MMF, but result about efficacy is still not available [78].

### Bosentan

Despite of the potential pathogenic role of ET1 in SSc–ILD, bosentan, a non-selective endothelin receptor antagonist, failed to show any positive effect on SSc–ILD, in a prospective, double-blind, randomized, placebo-controlled trial (BUILD-2, Bosentan in Interstitial Lung Disease in Systemic Sclerosis-2) enrolling 163 patients: 77, randomized to receive bosentan, and 86, randomized to receive placebo. Although many outcome variables were stable, bosentan did not reduce the frequency of clinically important worsening and these data do not support the use of endothelin receptor antagonists as therapy for SSc–ILD [79].

### Anti-tyrosine kinases

#### *Imatinib*

Imatinib, a tyrosine kinase inhibitor, may be a therapeutic option for SSc patients. The first two open-label studies conducted to assess the safety and effectiveness of imatinib mesylate in the treatment of dcSSc showed a statistically significant improvement in skin thickening and FVC [80, 81]. However, the feasibility and efficacy to use imatinib to treat skin fibrosis in dcSSc were further evaluated in two randomized, double-blind, placebo-controlled studies. In the first study, although imatinib was poorly tolerated, and the number of patients enrolled was too small for definite conclusions. The second study failed to demonstrate the efficacy of imatinib in skin fibrosis. To better explain the potential role of tyrosine kinase inhibition, a phase II pilot study was conducted on 30 SSc patients with active pulmonary involvement, unresponsive to CYC, and treated

with a lower dose of imatinib 200 mg/day for 6 months followed by a 6-month follow-up. The drug was well tolerated and stabilized the FVC in a large proportion of patients, improving the HRCT lung scans, thus suggesting the need of more extensive studies in SSc–ILD [82]. More recently, dasatinib, another tyrosine kinase inhibitor, with a better safety profile, has been suggested for the treatment of patients who cannot tolerate imatinib. An open-label study was concluded on 2012, but no results were published until now (NCT00764309; Table 1).

*Transforming growth factor-β*

The role of CAT-192, a recombinant human antibody neutralizing TGF-1β, in the treatment of early-stage dcSSc was evaluated in a phase I/II randomized, placebo-controlled study. A total of 45 patients were enrolled (treatment groups: 10, 5, 0.5 mg/kg, infusions: day 0 and weeks 6, 12, and 18). Unfortunately, the results of this study did not show any evidence of clinical efficacy for CAT-192. Furthermore, a higher mortality rate was observed in this study [83]. Lastly, in an open–label trial, the effect of fresolimumab, a high-affinity neutralizing antibody that targets all 3 TGF-β isoforms, on skin fibrosis was evaluated. A significant improvement in the MRSS was observed, showing that fresolimumab may rapidly reverse skin fibrosis [84]. However, further studies are needed to better evaluate the role of this molecule for the treatment of SSc–ILD.

*Rituximab*

An improvement in SSc–ILD with RTX was reported in a few case reports and open-label, uncontrolled studies [85, 86]. The largest study, assessing the efficacy of RTX on skin and lung fibrosis, was conducted in 63 patients, 9 out of them with SSc–ILD. The primary objective of this study was to measure the change of MRSS from baseline to follow-up between the RTX and control groups. Secondary objectives were to measure the change of the FVC from baseline to follow-up between the two groups and safety measures. The most frequent application was 2 infusions of 1000 mg in 2 weeks (75% of patients), but there were also other application schemes. In these 9 patients, RTX significantly prevented the decline of FVC ($0.4 \pm 4.4$ vs $-7.7 \pm 3.6\%$; $p = 0.02$). An improvement in skin fibrosis was also reported. Furthermore, the safety profile of RTX was acceptable and no serious adverse events were reported [87].

*Anti-IL-6*

Tocilizumab (TCZ), an anti-IL-6 soluble receptor monoclonal antibody, was administered in 2 patients with dcSSc over 6 months. After TCZ treatment, both patients showed an improvement in skin fibrosis, without any effect on SSc–ILD [88]. Furthermore, a study was conducted in patients with a longstanding lung involvement, but results were inconclusive [89]. More recently, the results of a phase II, randomized, controlled trial, conducted on 87 patients with early SSc, to assess the safety and efficacy of subcutaneous TCZ (162 mg weekly) did not produce definitive data about skin and lung effectiveness [90]. These results need to be tested in an adequately powered phase 3 study. Such a study is currently recruiting patients (NCT02453256; Table 1).

*Anti-IL-13 antibody*

Currently, a randomized, double-blind, placebo-controlled, multiple-dose, multicenter pilot study, to assess safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous doses of QAX576 (fully human antibody against human IL-13) in patients with PF secondary to SSc is ongoing. The study has been completed, and results are awaited in the next year (NCT00581997; Table 1).

*TNF-alpha inhibitors*

As far as the role of TNF-alpha inhibitors in SSc is concerned, an EUSTAR expert consensus statement, by using Delphi technique, does not recommend the routine use of these biologic drugs in SSc [91].

*Abatacept*

Abatacept is a recombinant fusion protein inhibiting T cell activation. A randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of abatacept in patients with diffuse SSc has been completed, and results are awaited with interest (NCT00442611; Table 1). The primary endpoint was the change in MRSS, whereas the secondary endpoints were change in oral aperture and hand extension, in PFTs (FVC and DLCO), digital ulcerations and Scleroderma Health Assessment Questionnaire. Recently, an observational study to evaluate the safety and effectiveness of TCZ and abatacept in SSc-polyarthritis or SSc-myopathy was conducted on 20 patients, but, despite of a good safety profile, no change in lung fibrosis was reported in patients treated with abatacept [92].

## Cell-based therapies

*Haematopoietic stem cell transplantation*

HSCT emerged as a novel rescue therapy for a variety of refractory autoimmune diseases. The therapeutic strategy

**Table 1** Ongoing clinical trials in SSc–ILD

| Number of CT | Title | Phase | Drug | Primary outcome measure | Secondary outcome measure | Enrollment | Status |
|---|---|---|---|---|---|---|---|
| NCT00764309 | Safety evaluation of dasatinib in subjects with scleroderma pulmonary fibrosis | 1, 2 | Dasatinib | | | 31 | Completed, unpublished |
| NCT00581997 | QAX576 in patients with pulmonary fibrosis secondary to systemic sclerosis | 2 | QAX576 | Vital signs, ECG's, echocardiograms and blood draws. | PFTs,<br>Biomarkers of PF and SSc, MRSS | 8 | Completed<br>No results |
| NCT02453256 | A study of the efficacy and safety of tocilizumab in participants with systemic sclerosis (SSc) [focuSSced] | 3 | TCZ | MRSS | FVC<br>Laboratory findings | 210(estimated) | Recruiting |
| NCT01445821 | Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial | 3 | Cytoxan rATG/fludarabine/HSCT | FVC, MRSS, GI and renal failure | Survival | 160 (estimated) | Recruiting |
| NCT01413100 | Scleroderma Treatment with Autologous Transplant (STAT) Study | 2 | HSCT/MMF | Event-free survival | PFTs, cardiac and renal function | 30 (estimated) | Recruiting |
| NCT00442611 | A Study to evaluate the safety and efficacy of abatacept in patients with diffuse systemic sclerosis (scleroderma) | 1, 2 | Abatacept | MRSS | PFTs, HAQ-DI | 10 | Completed<br>No results |

*MMF* mycophenolate mofetil, *CYC* cyclophosphamide, *FVC* forced vital capacity, *DLCO* diffusing capacity of carbon monoxide, *TLCO* total lung capacity, *HRCT* high-resolution computed tomography, *SAE* serious adverse events, *AE* adverse events, *PFTs* pulmonary function tests, *PF* pulmonary fibrosis, *MRSS* modified Rodnan skin score, *TCZ* tocilizumab, *GI* gastrointestinal involvement, *HSCT* hematopoietic stem cell transplantation, *HAQ-DI* health assessment questionnaire

involves the ablation of the aberrant self-reactive immune cells by chemotherapy and the regeneration of a new self-tolerant immune system formed by the transplanted stem cells.

There are three prospective, multicenter studies aimed to evaluate the safety and efficacy of HSCT in SSc: the Autologous Stem cell Transplantation International Scleroderma Trial (ASTIS), the American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) and the Scleroderma: Cyclophpsphamide or Transplantation (SCOT).

The ASTIS was the first phase III HSCT trial in a rheumatic autoimmune disease, targeted patients with early dcSSc at high risk of mortality, and a better event-free survival and overall survival rate in the HSCT group were observed. Other key observations included improvements in skin thickness (which correlates with a better survival) and lung function, expressed as improvement in vital capacity. However, this approach may be still considered in selected, severe SSc–ILD cases [93].

The ASSIST trial was a North American phase II trial, launched in 2006 and designed to assess the efficacy and safety of autologous non-myeloablative HSCT versus the standard of care, CYC. All patients randomly allocated to receive HSCT show an improvement in skin score, pulmonary function test when compared to controls [94].

A randomized study of different non-myeloablative conditioning regimens with Hematopoietic Stem Cell Support in patients with Scleroderma (Autologous Systemic Sclerosis Immune Suppression Trial—II ASSIST IIb) is currently recruiting patients, in order to compare the ASSIST I conditioning regimen of CYC and Rabbit Anti-thymocyte Globulin (rATG) with a less intense regimen of rATG/CYC/fludarabine, in order to determine whether a lesser cardiotoxic regimen might be safer than the standard regimens (NCT01445821; Table 1).

The SCOT is a North American randomized controlled phase III trial, designed to compare high-dose immunosuppressive therapy and HSCT to monthly pulse CYC. Until now, no data are available about the results of this trial, except of the mortality rate, that was approximately 10% [95]. This datum seems to be related to the cardiac toxicity associated with high-dose CYC therapy and to higher cardiovascular risk associated with altered cardiopulmonary function related to SSc. Finally, the Scleroderma Treatment with Autologous Transplant (STAT) trial, a multicenter, non-comparative study which is still recruiting patients, is aimed at evaluating the event-free survival when maintenance MMF therapy for up to 2 years is used after autologous HSCT (NCT01413100; Table 1).

At present, due to the limited number of patients enrolled in these studies, the results of larger randomized, double-blind clinical trials are a strong unmet need, in order to improve the clinical use of stem cell therapies in SSc patients.

*Lung transplantation*

Lung transplantation is a life-saving option for SSc–ILD patients who are unresponsive to pharmacologic interventions. Carefully selected SSc patients, without multi-organs involvement, undergoing lung transplantation have acceptable morbidity and mortality comparable to patients undergoing lung transplantation for IPF [96].

## Conclusions

SSc–ILD represents the main cause of death during SSc, and so far, a gold standard treatment for this complication is still lacking. Despite of, in the last decade, many different novel therapies, targeting different molecules or cell-based therapies has been used trying to improve the therapeutic possibilities and the outcome of these patients, the therapeutic choice is still a major challenge for rheumatologists. Until now, studies conducted on the SSc–ILD have favored the use of CYC as first-line therapy. However, the benefit of CYC for this disease is tempered by its complex adverse event profile. The results of the very recent SLS II study showed that the effectiveness and the tolerability of MMF may be comparable to CYC with lower side effect rate. Finally, HSCT may be considered a rescue therapy for selected SSc–ILD patients, while lung transplantation remains a life-saving option for SSc–ILD patients who are not responsive to any pharmacologic interventions.

In the next future, the improvement of our knowledge regarding the genetic background of the disease and the molecular pathways, involved in the susceptibility and pathophysiology of SSc–ILD, will allow us to better identify/classify patients, that are potentially good-responder to specific targeted therapies, in order to improve our skill in SSc–ILD treatment, a complication in which an effective treatment is still an unmet need.

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**Compliance with ethical standards**

**Conflict of interest** RG, VL, OB, PR, PDB, FCa, GG, SDB, FCi, GT and PC declare that they have no conflict of interest for this work.

**Ethical approval** This article does not contain any studies with animals or human participants performed directly by any of its authors. Authors of the included studies have declared in their published articles that their protocols were approved by institutional review boards or ethics committee at each participating site.

**Informed consent** The authors of this article did not directly involve any human subjects; however, the individual studies have declared obtaining informed consent from the patients.

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