Pharmacological treatment of systemic sclerosis-associated interstitial lung disease: an updated review and current approach to patient care

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ABSTRACT

Interstitial lung disease (ILD) has a high prevalence among patients with systemic sclerosis (SSc), carrying high mortality and morbidity. During the last decade, the emergence of new pharmacological therapies for SSc-associated ILD (SSc-ILD) and improved tools for its diagnosis and monitoring have changed the prevailing clinical approach, highlighting the need for early recognition and prompt treatment for SSc-ILD. Furthermore, the recent approval of multiple therapies for SSc-ILD poses challenges for the rheumatologist and pulmonologist in choosing the appropriate therapy for individual clinical scenarios. We review the pathophysiology of SSc-ILD, and the mechanisms of action and rationale behind current therapies. We also review the evidence of the efficacy and safety of immunosuppressive drugs, antifibrotic agents, and immunomodulators from cyclophosphamide and mycophenolate to novel agents such as nintedanib and tocilizumab. We also emphasise the importance of early diagnosis and monitoring and describe our approach to pharmacological therapy for SSc-ILD patients.

Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterised by three pathophysiological processes: 1. excessive accumulation of extracellular matrix molecules (ECM) causing fibrosis of the skin and internal organs (1), 2. fibro-proliferative vasculopathy (2, 3), and 3. innate, cellular, and humoral immune dysregulation (4, 5). SSc carries a high mortality rate (4). However, the cause of death among patients with SSc has changed over the last decades, most likely owing to progress in the prompt recognition and successful treatment of severe complications, such as SSc-renal crisis (6). It is currently accepted that the main cause of death in SSc is due to progressive cardiopulmonary involvement (7), with SSc-associated interstitial lung disease (SSc-ILD) accounting for up to 33–35% of all SSc deaths (6, 7).

Whereas patients with diffuse cutaneous involvement and those harbouring anti-topoisomerase antibodies or anti-nuclear antibodies displaying a nucleolar pattern on immunofluorescence are more prone to develop SSc-ILD (8), the high prevalence of ILD in SSc and its profound clinical significance for all SSc patients, require active early screening for prompt recognition and treatment.

Pathogenesis of SSc-ILD

The pathogenesis of SSc-ILD is still not well understood. Clinical heterogenicity is manifested not only as a different speed in the progression of lung disease but is also reflected in the different radiographical and histological patterns showing various degrees of inflammatory, fibrotic and vascular involvement, adding complexity to the understanding of its pathogenesis. However, it is widely accepted that an initial epithelial (alveolar) and endothelial insult caused by an unknown aetiologic agent (viral, environmental factors, or autoimmune causes have been proposed), results in local inflammation, as well as the activation of quiescent tissue fibroblasts and the recruitment of activated fibroblasts and myofibroblasts from many different sources including migration and change of phenotype of bone marrow-derived circulating fibrocytes, epithelial cells (EMT), endothelial cells

(EndoMT) or pericytes, into mesenchymal cells (9, 10). The molecular events caused by persistent activation of myofibroblasts result in permanent changes in the architecture of lung parenchyma. In contrast, mild and transient inflammation usually resolves without substantial permanent tissue damage.

Immune response

Following the initial injury, an innate immune response is followed by T cell differentiation. In the case of SSc-ILD, naïve T cells are stimulated by IL-4 and through intracellular activation of GATA-3 and STAT-6 polarise into T2 cells that secrete high amounts of IL-13, IL-4, and IL-5 (11, 12). These cytokines subsequently recruit and activate eosinophils and M2 macrophages, inducing TGF-β, PDGF, and FGF production in lung tissues (13, 14).

This important role of T lymphocytes in SSc is highlighted by several observations including the presence of lymphoid follicles in lung tissues of patients with SSc-ILD (15), the presence of alveolar CD8+ lymphocytes (16) secreting IL-4 associated with the severity of the lung disease, and the strong correlation between the presence of serum Th2 polarising cytokines and the severity of lung restrictive pattern in SSc patients (12)

The Th2 cytokine response stimulates M2 macrophages that express a mannose receptor (CD206) and scavenger receptors (CD163 and CD204). The M2 macrophage population consists of different subtypes: M2a, M2b, M2c, and M2d (13) which are activated by specific Th2 cytokines such as IL-4, IL-13, IL-1, and IL-10 (13). M2 cells can promote further polarisation of Th2 lymphocytes through secretion of IL-13, C-C motif chemokine ligand 17 (CCL17) (13, 17), CCL18 (18), and CCL22; but also, secrete high amounts of TGF-β, favouring the mesenchymal trans-differentiation and activation of fibroblasts, and myofibroblasts as described below (19).

Myofibroblasts

Myofibroblasts are highly specialised mesenchymal cells with contractile and secretory properties. Phenotypically they are characterised by the expression of α-smooth muscle actin forming abundant stress fibers and are able to produce and secrete large amounts of collagen and other ECM proteins. Consequently, myofibroblasts are key players in initiating and sustaining normal and pathological fibrotic responses. These cells also exert mechanical interaction with the tridimensional architecture of the ECM surrounding the alveoli. This interaction causes stretching of their cytoplasmic stress fibers inducing slow mechano-stimulation through ROCK pathways that increase the synthesis and secretion of collagen and other ECM proteins (20). Physiologically, myofibroblasts are a central part of the normal injury repair process, but in SSc, myofibroblast contraction is increased and their collagen production and secretion are highly upregulated. In normal homeostatic conditions, fibroblasts and myofibroblasts are cleared by apoptosis, however, in lung fibrosis, TGFβ1 interaction with its receptor activates downstream proteins such as focal adhesion kinase (FAK), conferring fibroblasts apoptosis resistance through the PI3K-Akt pathway (22). At the same time, TGFβ through ABL signalling, stimulates the expression of BCL-2 and BCL-XL, pro-survival proteins, whereas the FAK–PI3K–AKT signalling pathway inhibits the pro-apoptotic protein BCL-2-associated death promoter (BAD) (21).

The origin of tissue myofibroblasts is a key subject of continued research interest although notable progress has been accomplished by the identification of Epithelial-Mesenchymal transdifferentiation (EMT), Endothelial-Mesenchymal transdifferentiation (EndoMT), as well as through the recruitment and activation of bone marrow-derived fibrocytes, monocyte-derived progenitor cells that in addition to displaying immune functions such as cytokine production, also synthetise extracellular matrix proteins (22).

EMT, or epithelial-mesenchymal transdifferentiation

It has been postulated that recurrent alveolar epithelial cell injury, in a predisposed host can trigger an aberrant response causing alveolar cell apoptosis and their transdifferentiation into myofibroblasts (23, 24). In this process the epithelial cells change their phenotype, losing their epithelial receptors, and acquiring new surface markers as well as initiating the expression of α-smooth muscle actin. At the same time, they develop a robust reticulum-endoplasmic system and become able to synthesise high amounts of collagen and other ECM proteins, contributing to the lung fibrotic process (25, 26). Alveolar epithelial cell injury also causes leakage of specific glycoproteins into the blood stream. Serum levels of those proteins including Krebs von den Lungen-6 (KL-6) and surfactant protein -D (SPD) are elevated in patients with SSc-ILD and are strong candidates to become SSc-ILD biomarkers (27-30).

EndoMT, or endothelial mesenchymal transdifferentiation

Myofibroblasts in SSc can also result from the phenotypic conversion of endothelial cells into activated myofibroblasts, a process known as endothelial to mesenchymal transition (End-MT or Endo-MT). Recently, it has been postulated that EndoMT may play a role in the development of SSc-ILD and evidence of this phenotype change has been found in lungs from patients with advanced SSc-ILD (31, 32), and pulmonary hypertension (SSc-PAH) (33, 34). This process can potentially explain not only the origin of activated myofibroblasts but also can contribute to explain the link between vasculopathy and interstitial lung disease. The EndoMT phenomenon is postulated to start very early in SSc and to persist through the disease progression, contributing to the establishment and worsening of SSc vasculopathy and lung fibrosis.

Fibroblasts are also being recruited from resident lung fibroblasts and from circulating fibrocytes, a bone marrow-derived precursor, which converts to myofibroblasts through the effects of numerous cytokines and inflammatory factors displayed in Figure 1.

Clinical aspects of SSc-ILD

The incidence and time of presentation of ILD in SSc patients are mainly driven by the SSc clinical phenotype.

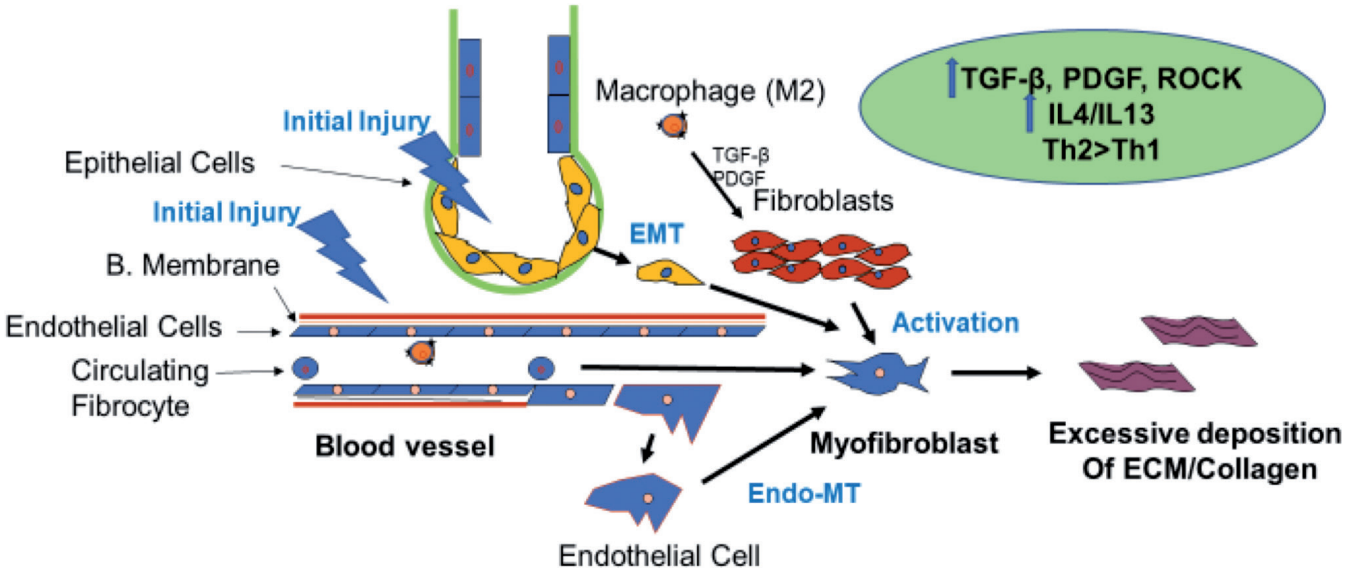

Fig. 1. SSc-ILD pathophysiology of lung fibrosis. After an initial injury in a predisposed host, innate and adaptive immune response deregulation favours the differentiation of naive T cells to Th2 (not shown), secreting high amounts of IL-13, IL-4, and IL-5. These cytokines subsequently activate eosinophils and M2 macrophages, inducing TGF-β, PDGF, and FGF production. This local cytokine and growth factor environment, triggers the differentiation and activation of resident fibroblasts as well as transdifferentiation of endothelial and epithelial cells into myofibroblasts. Myofibroblasts synthetise large amounts of collagen and extracellular matrix proteins causing an accumulation of these fibrotic products in the pulmonary parenchyma, restricting lung function.

SSc-ILD presents within 1–3 years following SSc diagnosis in patients with SSc diffuse phenotype, and 3–5 years after diagnosis in patients with limited SSc phenotype. However, these time intervals may under-represent how early SSc-ILD presents in the course of the disease as those estimates were obtained employing screenings consisting of chest x-rays (CxR) and serial yearly pulmonary function tests (PFTs). Other factors affecting the incidence of ILD are the presence of anti-topoisomerase antibodies, and antibodies characterised by anti-nucleolar pattern including RNA polymerase III, PM/Scl, and Th/To.

Given the high mortality associated with SSc-ILD progression, close follow-up and monitoring of ILD progression is of uttermost importance for the patient and treating physician and is a key variable in clinical trials. Classically, the progression or appearance of a restrictive pattern in serial PFTs is considered clinically meaningful when a forced vital capacity (FVC) decline of 10% or greater compared to prior absolute values is observed. The consensus is less clear when an isolated decline of diffusion lung capacity (DLCO) is observed, but a DLCO reduction of 15-20% without evidence of new-onset or worsening pulmonary hypertension, should be considered clinically relevant. It should be emphasised, however that in order to minimise variability, serial PFTs should be performed at the same facility testing.

An observed decline of PFT values beyond the above-mentioned threshold should be corroborated either by a repeated PFT performed within 3 months of the abnormal initial test or by demonstration of radiological progression of parenchymal changes in high resolution CT scan of the chest (HRCT). Other measurements of progression such as a six-minute walking test have not shown enough sensitivity to change owing to other factors affecting mobility and tolerance to exercise in SSc patients. However, quantification of dyspnoea (*i.e.* Mahler dyspnoea index) has shown to be useful in disease monitoring. Radiological changes have been well recognised to occur during the course of the disease. Changes in CxRs are not sensitive enough to constitute a proper tool for follow up, but HRCTs have shown to be useful as a qualitative measurement of progression (35) and, whereas HRCT is used in the clinical practice to assess progression and rule out overlapping lung disease, lack of well-validated quantitative tools, and risk of radiation exposure, limits their use as a periodical follow up measurement. In our clinical practice, we found it useful to perform HRCTs every 1-2 years in patients with SSc-ILD, providing valuable information in conjunction with PFT values over time and patient symptomatology.

When the progression of SSc-ILD is clinically recognised, prompt treatment should be considered. This recommendation is based on the cumulative evidence of multiple studies showing that different therapeutic alternatives are effective in halting the progression of SSc-ILD, as opposed to reversing the already established damage. Consequently, we advocate for early treatment of any patient with progressive SSc-ILD, regardless of the absolute value of their lung volumes.

Early diagnosis

The vast variation in prevalence in SSc-ILD is driven by the method used for its assessment. CxR and PFTs were considered to be the standard of care for ILD screening in SSc patients, how-

ever, recent evidence has shown that HRCT is superior to PFTs alone to perform early diagnosis of ILD in SSc patients. Given the high mortality associated with the development and presence of ILD in SSc, it is crucial to perform HRCT in this population, in addition to PFTs. Typically, SSc-ILD tomographic early pattern includes reticulonodular or ground glass parenchymal changes with subpleural sparing and peribronchial extension in both lung bases. The presence of traction bronchiectasis is a radiological feature that correlates with tissue fibrosis (36, 37). On the other hand, it is important to emphasise that a PFT value obtained during the first evaluation and reported to be within the "normal range", may underestimate the presence of ILD (progressive or not), since a patient's baseline pre-disease PFTs may be in the higher limits of normal for the age-adjusted population. Consequently, follow-up PFTs within 6 months of the initial one is needed for early identification of progressive ILD. It must be taken into consideration that in early stages of SSc-ILD, non-typical patterns can be observed: For example, isolated low DLCO values with normal pulmonary pressures at echocardiography may represent early ILD (38, 39) in more than 22% of the cases (38); and ground-glass opacity in early stages may also represent early fibrosis as seen in other immune mediated ILDs (40).

Exploratory approaches

It is important to mention that early evidence points toward using a personalised medicine approach for identifying SSc and SSc-ILD subsets in the future: There is evidence that inflammatory gene expression signature in the skin of patients with diffuse cutaneous forms (dcSSc) is associated with mRSS improvement during treatment with mycophenolate mofetil (MMF) (41). Furthermore, pre-and post-treatment gene expression change in the skin occurred almost exclusively in clinical responders in a study on dcSSc patients employing MMF plus belimumab (42).
However, there is not yet enough data at this moment to extrapolate these findings from studies with skin or compounded scores as primary outcomes to SSc-ILD. Furthermore, since SSc-ILD can occur in patients with limited skin involvement (lcSSc) or without skin involvement (scleroderma sine scleroderma) skin findings may be less valuable. Other exploratory approaches includes examining RNA from PBMC samples showed that SSc-ILD with higher baseline lymphoid module scores were associated with a better PFT course, while worsening PFTs were seen in patients with higher myeloid cell lineage activation score and treated with MMF (43). We hope these efforts will extrapolate into practical clinical approaches in the near future.

Treatment of SSc-ILD with immunosuppressive agents

Cyclophosphamide

Cyclophosphamide (CyC) is a cytotoxic alkylating agent that has been used extensively for the treatment of malignancy and autoimmune diseases. It was the first agent used extensively to treat SSc-ILD, supported by multiple retrospective and open-label prospective studies in small cohorts (44-49). Furthermore, in 2009 and 2017, the European League Against Rheumatism (EULAR) recommended considering the use of CyC for the treatment of SSc-ILD (50, 51). These recommendations were made based on two prospective, randomised placebo-controlled trials, the Scleroderma Lung Study 1-trial (SLS-1) (35) and the UK Lung Study (52) (also termed FAST). The SLS-1 evaluated patients with SSc-ILD with either inflammatory bronchoalveolar lavage (BAL) findings or a HRCT showing ground-glass opacities. These patients were randomised into two groups, one was treated with oral CyC (≤2 mg per kilogram of body weight per day), whereas the second group was maintained on a matching placebo for one year. The patients were then followed for an additional year (35, 53). This study found that at 12 months, there was a modest treatment effect of CyC on FVC changes (adjusted mean absolute difference in FVC of 2.53 percent, favouring CyC) as well as on total lung capacity (absolute difference of 4.09 percent, favouring CyC). There was also an improvement in several health-related quality of life indicators. A follow-up longitudinal study performed assessing the effects following discontinuation of treatment found that the benefits of CyC persisted for several additional months but subsequently waned, and by 24 months, were absent (53). This observation suggested the need for continued immunosuppressive therapy. However, oral CyC use was associated with a higher average frequency of adverse effects, namely leukopenia and neutropenia, which are well known to be associated with CyC and responded to dose adjustments. The FAST study investigated the use of monthly IV CyC for 6 months, in addition to oral prednisone on alternate days, followed by azathioprine for 6 months compared to placebo for 12 months in patients with SSc-ILD. The primary endpoint of FVC was found not to be statistically significant in the treatment group but with a favourable trend (absolute difference of 4.19 percent, favouring CyC), similar to the differences shown in the SLS-1 study (52). Overall, these 2 prospective studies suggested that CyC may benefit lung function over 1 year in patients with SSc-ILD. However, given the observed wearing-off effect and the increased toxicity noted in the CyC group, the need for a better long-term tolerated therapy was evident.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) depletes guanosine nucleotides through the inhibition of inosine-5'-monophosphate dehydrogenase (IMPDH), essentially impairing lymphocyte proliferation and migration (54). MMF has been shown in various retrospective and prospective cohorts to be useful to treat progressive SSc cutaneous manifestations as well as SSc-ILD (15, 55-61). Given the findings that the effects of CyC waned after discontinuation, the high frequency of CyC adverse effects, and the risk for development of treatment-related malignancies with long-term use (35, 53, 62); the use of MMF was assessed in patients with SSc-ILD using a double-blind, parallel-group, randomized trial. The Scleroderma Lung Study 2 (SLS-2) evaluated patients given oral MMF (3 g/d) over 2 years *vs*. oral CyC (titrated

to 2 mg/kg/day) for one year followed by placebo the following year. The primary endpoint, the adjusted difference in FVC percentage over 2 years, was found to improve from baseline to 24 months by 2.17 in the MMF group (95% CI, 0.53–3.84) and 2.86 in the CyC group (95% confidence interval 1·19–4·58) with no statistical significance between treatment groups (63). A *post-hoc* analysis performed subsequently noted significant improvement from baseline in FVC percentages not only at 12 months but also at 21 and 24 months in the MMF group (63).

Nintedanib

Nintedanib (NTD) is a small intracellular competitive inhibitor of tyrosine kinases including fibroblast growth factor receptor (FGF), platelet-derived growth factor receptor (PDGF), vascular endothelial growth factor (VEGF) receptor, and intracellular tyrosine kinases of the Src family (64, 65). It was initially designed to inhibit cancer-related angiogenesis, but given the growing evidence that FGF, PDGF, and VEGF play a role in the pathophysiology of interstitial lung fibrosis, the clinical development of NTD was directed to evaluate its effects on idiopathic pulmonary fibrosis (IPF): The TOMORROW study was a Phase II randomised placebo-control clinical trial (66). The study was conducted for 52 weeks followed by an open-label extension comparing NTD *versus* placebo. The results showed a reduced rate of decline in FVC (-125.4mL/year) in the NTD group along with a clinical reduction in exacerbations. Following this initial study, two replicate phase III trials (INPULSIS-1 and INPULSIS-2) (67, 68), which included more than 1000 patients with IPF were conducted. The results found that treatment with NTD significantly reduced the annual rate of decline in FVC by 50% after 52 weeks when compared to patients in the placebo arm. As these trials demonstrated the efficacy of NTD in halting the progression of IPF, it was approved by the FDA for the treatment of IPF in 2014.

Although the pathophysiology for IPF and SSc-ILD differ, it is generally accepted that in both diseases, the transformation of fibroblasts to a myofibroblastic phenotype is a key step for the up-regulation and accumulation of extracellular matrix components. Given the successful results of the use of NTD in Phase II-III clinical trials for IPF, a large Phase III clinical trial (SENSCIS) was conducted in patients with SSc-ILD. The SENSCIS trial was a randomised double-blinded phase III placebo-controlled study that investigated the annual rate of decline in FVC over a 52-week period in SSc-ILD patients treated with NTD 150mg twice daily *versus* placebo. This study included 576 patients meeting 2013 ACR/EULAR classification criteria for SSc with an onset of first non-Raynaud's symptoms within 7 years before the screening, 51.9% of whom had diffuse cutaneous SSc and 48.4% of whom were receiving MMF as concomitant therapy at baseline. The results of the primary endpoint of this study showed that the rate of decline in FVC over a 52-week period in SSc-ILD patients was lower in the NTD group -52.4ml per year *versus* -93.3ml per year in the placebo group, a reduction of 44% (69).

It is important to note that the decline in FVC in the placebo arm showed a slower rate of decline in those receiving MMF when compared with patients not taking MMF (-66.5ml per year *vs.* -119.3ml per year) which suggests a potential benefit of MMF on lung function. The MMF benefit persisted among patients on the NTD arm, in whom the annual rate of change in FVC among patients receiving MMF at baseline was -40.2ml in patients in MMF and -63.9ml in patients not on MMF (69).

The safety and adverse events frequency in the SENSCIS trial were similar to those observed in the INPULSIS trials, with the most common adverse event being diarrhoea although this side effect was observed in a higher percentage in both active drug and placebo groups (75.7% of patients on NTD *vs.* 31.6% of patients on placebo) (69). Despite the magnitude of the effect of NTD on lung function, no effect on skin fibrosis in either limited or diffuse cutaneous SSc, assessed using the modified Rodnan skin score (mRSS), was observed (69). As this study demonstrated the beneficial effects of NTD on lung fibrosis in patients with ILD-SSc, an uncontrolled open-label extension study is ongoing, further providing long-term data regarding its use.

Tocilizumab

IL-6 is a proinflammatory cytokine produced by lymphocytes, fibroblasts, and monocytes that has pleiotropic effects on T cell activation, production of acute-phase reactants, and haematopoiesis. Patients with SSc were found to have increased IL-6 levels in dermal fibroblasts, mononuclear and endothelial cells, particularly in those with diffuse cutaneous involvement (70). Studies have also revealed a correlation between IL-6 expression and more severe disease progression, in terms of both severe skin involvement as well as lung function in SSc (71, 72).

Although the exact cellular mechanisms driving the pro-fibrotic effects of IL-6 are unknown, they seem to be mediated by the activation of M2-macrophages, which play an important role through the release of profibrotic factors (70). Indeed, it has been described that mRNA expression of a cluster of macrophage genes, including CD14 in the skin, whose expression is prognostic for progressive skin disease, was elevated, correlating strongly with the mRSS (73).

Tocilizumab (TCZ) is a humanised monoclonal antibody targeting both, soluble and membrane-associated IL-6 receptors, thus, preventing IL-6 binding and inhibiting IL-6 signalling pathways. Initial case reports from patients with SSc suggested that treatment with TCZ improved skin sclerosis and systemic sclerosis-associated polyarthritis (72, 74), encouraging TCZ clinical development including the faSScinate trial, a randomised, double-blind, placebo-controlled phase II study that investigated the efficacy and safety of subcutaneous TCZ in patients with SSc of 5 or fewer years of disease duration from first non-Raynaud's event. Patients were randomly assigned (1:1) to weekly subcutaneous TCZ (162mg) or placebo and the mean change from baseline in mRSS was evaluated at 24 and 48 weeks. This clinical trial demonstrated that the use of TCZ when

compared with placebo, had a clinically meaningful but not statistically significant effect on the decline in mRSS with the mean change of -6.33 *versus* -2.77 (95% CI -7·23 to 0·12; *p*=0·0579). In an exploratory analysis performed, it was noted that fewer patients in the TCZ group, when compared to placebo, had a decline in the percentage of predicted FVC at 48 weeks (*p*=0·0373) (74). In this study, 83% of patients receiving placebo and 54% of patients receiving TCZ declined their FVC values from weeks 0 to 48. Interestingly, during the open-label follow-up of this study (all patients were switched to TCZ), only 42% of patients in the placebo-TCZ group and 46% of patients in the continuous-TCZ group had absolute decreases in % FVC. Moreover, during the open-label period, no patients in either treatment group who completed week 96 or withdrew experienced >10% absolute decline in % of predicted FVC after receiving TCZ (75).

Following the phase 2 trial, a randomised, double-blind, placebo-controlled phase 3 trial, known as the focuSSced trial, was conducted to investigate the use of TCZ for skin fibrosis and interstitial lung disease in SSc patients. Patients were randomly assigned (1:1) to receive subcutaneous TCZ 162 mg or placebo weekly for 48 weeks with a primary endpoint of change from baseline in mRSS. In addition to the assessment of effectiveness on skin fibrosis, the percent predicted FVC was also analysed. Regarding the primary endpoint of skin fibrosis, the least-squares mean (LSM) change from baseline to week 48 in mRSS was -6.14 for TCZ and -4.41 for placebo (adjusted difference -1·73 [95% CI -3·78 to 0·32]; *p*=0.10). Analysis of lung function showed, that change from baseline in FVC% predicted at week 48 was favourable to the TCZ group with a difference of 4.2% (95% CI 2·0-6·4; *p*=0.0002), supporting the use of TCZ in this patient cohort for prevention of SSc-ILD progression (76).

Other agents under clinical development

Pirfenidone

Pirfenidone (PFD) is a pyridine with substituted phenyl and methyl groups at positions 1 and 5. Although its mechanism of action is not totally elucidated, PFD appears to exert its main antifibrotic effect by inhibition of TGF-β, but can also inhibit fibroblast, epidermal, platelet-derived growth factors along with inhibition of tissue inhibitor of metalloproteinases (TIMP) (77). It has demonstrated efficacy in halting the progression of IPF (78) and was recently approved for this indication by the FDA and other regulatory agencies. Two studies have explored the safety and efficacy of PFD in SSc: one open-label study evaluated the tolerance and safety of PFD in patients receiving PFD with either a 2- or 4-week titration regimen for 16 weeks in 63 patients and found an acceptable tolerability profile in SSc-ILD, and this tolerability was not affected by concomitant use of MMF (79). A more recent randomised placebo-controlled trial study recruited patients with SSc-ILD with FVC between 50 and 80% receiving either PFD (2400 mg/day) or placebo for 6 months (80). This study did not reach statistical significance in its primary outcome (proportion of patients with either stabilisation or improvement in FVC at 6 months) nor in secondary outcomes (*i.e.* absolute change in FVC).

The scleroderma lung study III (SLS III) (NCT03221257) is near completion at the time of writing this manuscript and is designed to test the hypothesis that combining an anti-fibrotic therapy (PFD) with an immunosuppressive agent (MMF) since initiation of therapy can further stabilise or improve the progression of SSc-ILD compared with MMF alone.

Novel agents in early clinical development

Multiple other agents that are currently under clinical development for the treatment of pulmonary fibrosis (IPF) can be used for SSc-ILD, including pentraxin-2 analogs (81), connective tissue growth factor (CTGF) antagonists (82), G-protein receptors inhibitors (83), lysophosphatidic acid (LPA) inhibitors (84, 85) have shown early encouraging results; while others such as leukotriene antagonists, ROCK-2 inhibitors, and anti-integrin antibodies are already completing initial clinical trials in SSc patients.

Approach to patient treatment

As highlighted above, early diagnosis of SSc-ILD is a sine-qua-non-requirement to timely initiate therapy on these patients. A combination of HRCT, PFTs, and ECHO (the last one to screen for PAH) should be performed in the initial evaluation of all SSc patients, for screening of early ILD, followed by at least yearly PFTs follow up (or q 6 mo if ILD progression is suspected), ideally performed in the same centre to decrease technician/machine variability**.**

Although there is no consensus on how frequently HRCTs should be performed as a follow-up, serial CT is clinically useful to evaluate progression and the presence of fibrotic pattern and it is an irreplaceable tool for evaluating patients with overlapping patterns and pathologies (*i.e.* emphysema and ILD overlap or ILD with significant bronchial disease). Awareness of the clinician and the radiologist of early SSc-ILD CT features can help in recognising those cases.

Progression of SSc-ILD can be defined as a decline in FVC of 10% or more (ideally corroborated in a repeated PFT within 3–6 months of the prior one or progression of CT findings) or 6–10% worsening along with radiological worsening. In addition, especially in early cases, an isolated reduction in DLCO of >15% w/o evidence of PAH after comprehensive workup, can lead to suspect ILD progression and require re-imaging, especially if it is accompanied with otherwise non-significant decrease of FVC (5-9%) (86).

Patients with SSc-ILD progression should be treated, regardless of the severity of lung involvement given the overall irreversible nature of ILD progression. The SLSII study provided evidence that MMF is equally effective as CYC for halting SSc-ILD progression but is better tolerated. Consequently, MMF is the initial therapy preferred in many scleroderma centres, having displaced CYC as first-line therapy. Given the recent evidence that TCZ is also effective in slowing the progression of

ILD, it can be alternatively used when the patient is intolerant to more widely employed agents. Another alternative for these drug intolerant patients is initiation of NTD, if HRCT shows a fibrotic phenotype (69, 87).

Close follow-up is needed after starting first-line therapy. Subsequent addition of an antifibrotic agent (NTD) should be considered in patients who progress despite first-line immunosuppressive treatment.

Although there is no direct data of simultaneous initiation of both agents at the same time, the maximal benefit in the SENSIC study, was achieved by patients receiving the MMF+NTD combination. Consequently, this initial combination should be strongly considered in patients with rapid progression and moderate to severe pulmonary function restriction in the first evaluation. The antifibrotic+ immunosuppressant combination will likely become even more common following increased clinical experience with its use.

Despite other immunosuppressants/antifibrotic combinations, such as CYC+NTD and TCZ+NTD have not been studied, they are expected to serve the same purpose as MMF+NTD. Furthermore, in refractory cases, the addition of a 3rd agent can be attempted. The authors have clinical experience with the use of MMF+ rituximab+ NTD with encouraging results and good tolerance. The rationale behind this regimen is supported by few prospective and retrospective cohorts showing safety and efficacy of the MMF+ rituximab combination (88-90). Addition of TCZ as a third agent to MMF+ NTD may also serve the same purpose, but there is no clinical data in the efficacy or safety of the combination and our clinical experience is still limited. However, refractory patients should be also timely referred for lung transplantation.

We have observed that patients with SSc-ILD, developing COVID-19 pneumonia, may display notable acceleration of ILD progression. Whereas studies are needed to elucidate the severity and duration of this phenomenon, close lung monitoring after COVID-19 is recommended for SSc-ILD patients.

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