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Review

Ongoing clinical trials and treatment options for patients with systemic sclerosis–associated interstitial lung disease

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Abstract

SSc is a rare CTD that affects multiple organ systems, resulting in substantial morbidity and mortality. Evidence of interstitial lung disease (ILD) is seen in ~80% of patients with SSc. Currently there is no approved disease-modifying treatment for ILD and few effective treatment options are available. CYC is included in treatment guidelines, but it has limited efficacy and is associated with toxicity. MMF is becoming the most commonly used medication in clinical practice in North America and the UK, but its use is not universal. Newer agents targeting the pathogenic mechanisms underlying SSc-ILD, including fibrotic and inflammatory pathways, lymphocytes, cell–cell and cell–extracellular membrane interactions, hold promise for better treatment outcomes, including improved lung function, patient-related outcomes and quality of life. Here we review ongoing trials of established and novel agents that are currently recruiting patients with SSc-ILD.

Key words: abituzumab, bortezomib, dabigatran, interstitial lung disease, nintedanib, pirfenidone, pulmonary fibrosis, study design, systemic sclerosis

REVIEW

Rheumatology key messages

- There are no approved disease-modifying treatments for SSc-associated interstitial lung disease and few effective therapies.
- Newer agents show better outcomes in SSc-associated interstitial lung disease, including improved lung function.

Introduction

SSc is a rare CTD that affects multiple organ systems, resulting in substantial morbidity and mortality [1]. The pathogenesis of SSc is not fully understood, but may involve interactions between genetic susceptibility loci [including MHC class II genes and genes associated with extracellular matrix (ECM) metabolism and control of immune function] and environmental factors [2].

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The presentation and clinical course of SSc are heterogeneous, and the classification developed by the ACR and EULAR is based on the extent of skin fibrosis and pattern of internal organ involvement [3]. Patients with SSc can be subdivided into two main categories, limited (60% of patients) and diffuse cutaneous (30%), the remaining 10% of patients having rarer subtypes [1, 2, 4]. In dcSSc, fibrosis of the skin, lungs and other internal organs progresses rapidly, with early development of visceral organ complications. In contrast, lcSSc primarily features vascular manifestations with mild skin fibrosis, although organ fibrosis can be significant.

Key features of SSc are vasculopathy, dysregulation of innate and adaptive immunity, and fibrosis of skin and visceral organs [2]. Fibrosis results from a complex interplay of the immune system with activated fibroblasts, leading to ECM accumulation in skin and organs. While skin fibrosis is the most common feature, fibrosis of internal organs leads to organ damage and poor clinical outcome. Data from the European Scleroderma Trials

and Research (EUSTAR) group registry confirm that disease-related causes, particularly pulmonary fibrosis, pulmonary hypertension (PH) and heart disease, account for the majority of deaths in SSc [5]. However, survival has improved in recent decades, with a retrospective study in the UK showing that 5-year survival improved from 69% in patients with disease onset in 1990–93 to 84% in those with onset in 2000–03 ($P = 0.018$), as a result of more complete ascertainment of lung complications [6]. In a Canadian study published in 2010, 5- and 10-year survival was 95 and 92%, respectively, for lcSSc but only 81 and 65% for dcSSc [7].

Key organ systems are affected in SSc, including the musculoskeletal, skin, gastrointestinal and pulmonary systems [1, 3]. Musculoskeletal manifestations affect joints (arthralgia, synovitis, contractures), tendons (tendon friction rubs, tenosynovitis) and muscles (myalgia, muscle weakness, myositis), while skin manifestations include skin fibrosis and thickening, as well as RP, digital ulcers and calcinosis [1]. Gastrointestinal manifestations include dysphagia, heartburn, distension, bloating, abdominal pain, nausea, vomiting, diarrhoea, constipation and faecal incontinence [8].

The two most important forms of pulmonary involvement in SSc are interstitial lung disease (ILD) and PH. Around 80% of patients with SSc show lung fibrosis, with 25–30% developing progressive ILD [1]. Typical symptoms include cough, limited exercise tolerance, chest pain and dyspnoea [9]. Using high-resolution CT (HRCT), the most common findings of ILD include reticulation, ground-glass opacities and honeycombing [10]. Progression can lead to more extensive lung changes, with worsening of fibrosis.

Dyspnoea alone is insufficient to diagnose ILD, as there are other potential causes in patients with SSc [11]. Diagnosis involves pulmonary function tests (PFTs), diffusing capacity of the lung for carbon monoxide (DLCO) and imaging [12]. In SSc-ILD, initial PFTs may reveal a restrictive pattern, with reduced forced vital capacity (FVC) and a normal or slightly increased forced expiratory volume in 1 sec (FEV_1):FVC ratio. Importantly, PFTs may be normal in very early ILD and cannot be used to rule it out. DLCO is particularly important as it provides an assessment of the interstitial space between alveolar and endothelial surfaces and the integrity of the lung vascular bed. It is probably the most sensitive test of worsening pulmonary involvement in SSc, although it lacks specificity in differentiating ILD from pulmonary vascular disease. Reduced DLCO out of proportion to reduced FVC (e.g. FVC:DLCO ratio >1.6) suggests significant pulmonary vascular disease [13]. HRCT, unlike conventional radiography, has high sensitivity and specificity for detecting parenchymal involvement in patients with SSc, and is therefore mandatory for diagnosing SSc-ILD. HRCT should always include prone images to confirm that mild bibasilar changes are not due to atelectasis. Open lung biopsy is generally not performed.

Patients with SSc should be monitored early in their condition, with serial spirometry and DLCO measurements throughout their disease. If ILD is confirmed, the change in lung function during treatment should be monitored [1, 11, 12]. Accounting for measurement error in FVC and DLCO, the OMERACT group defines progressive ILD as either a $\geqslant 10\%$ relative decline in FVC or a decline in FVC of 5–9% and in DLCO of $\geqslant 15\%$ [14]. The changes should be confirmed by repeat testing to show that they are sustained. This definition has recently been validated as a predictor of mortality in SSc-ILD [15].

Given the wide range of potential symptoms in patients with SSc, the management of SSc-ILD is of great relevance to clinicians across several therapy areas.

Unmet medical need in SSc-ILD

SSc remains difficult to treat, with limited options [16]. Few randomized studies have been conducted, effect sizes for existing drugs are small and there is no approved disease-modifying therapy. Patients may therefore receive several different immunosuppressive therapies for complications involving skin and internal organs. Their impact is modest, especially in the skin, and they are associated with adverse events [17–19] that have important lifestyle consequences. Local reimbursement and payment for multiple treatments are also factors to consider.

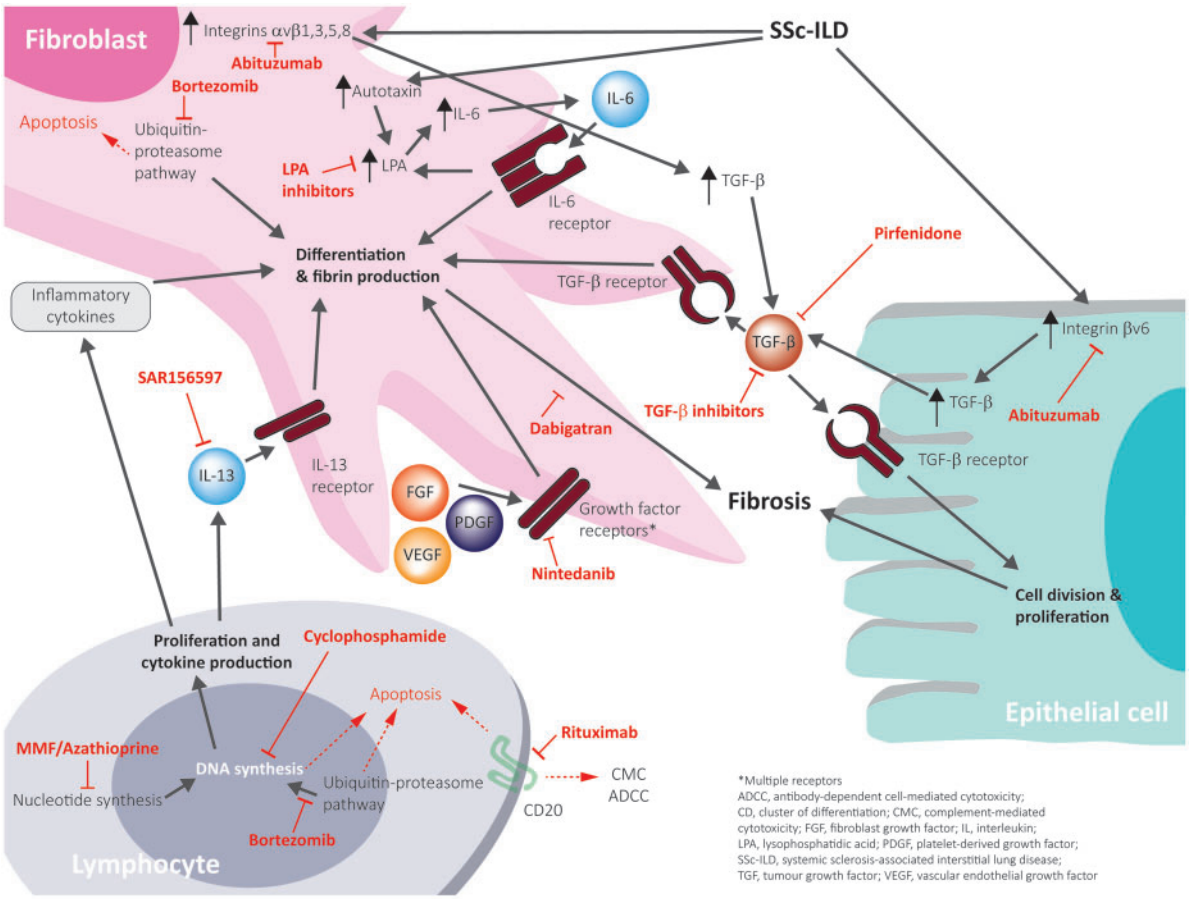
Treatments evaluated for SSc-ILD

CYC

CYC is a nitrogen mustard alkylating agent and potent immunosuppressive used to reduce inflammation and prevent fibrosis (Fig. 1) [20]. Efficacy in SSc-ILD was initially demonstrated in retrospective studies, suggesting that treatment could slow the decrease in FVC over time, potentially improving FVC in some patients [21]. However, results from observational studies are mixed, as not all studies show improved lung function [20, 22]. CYC has substantial toxicity, notably haemorrhagic cystitis and immunosuppression, as well an increased risk of malignancy, infection, nausea, vomiting and hair loss and less frequent cardiac, renal, genitourinary, pulmonary and hepatic toxicity [17].

CYC in patients with SSc, restrictive lung physiology, dyspnoea and evidence of inflammatory ILD was evaluated in the Scleroderma Lung Study (SLS) I [23] (Table 1). In this randomized, double-blind trial, 158 patients received daily CYC ($\leqslant 2$ mg/kg) or placebo for 1 year and were followed for an additional year. The primary endpoint was FVC (percentage of predicted value, adjusted for baseline FVC) at 12 months, with a mean absolute treatment difference of 2.53% (95% CI 0.28, 4.79; $P < 0.03$) favouring CYC [23]. There were also benefits in total lung capacity, dyspnoea and quality of life (QoL). Benefits of CYC on pulmonary function continued to increase for 18 months (i.e. 6 months after treatment was withdrawn), with a positive effect on dyspnoea for 2 years [24]. However, adverse events (AEs), including

Fig. 1 Modes of action of existing and future candidate agents for the treatment of SSc-ILD



SSc-ILD has many potential targets for therapeutic agents [18, 20, 22, 50, 56, 64, 67, 70, 73–75, 77–79].

haematuria, leukopenia and neutropenia, were more frequent with CYC *vs* placebo [23].

In a second placebo-controlled trial [the Fibrosing Alveolitis in Scleroderma Trial (FAST)], 45 patients were randomized to placebo or active treatment (prednisolone 20 mg on alternate days and six infusions at 4-week intervals of CYC 600 mg/m^2 followed by AZA 2.5 mg/kg/day as maintenance therapy) [25]. The primary endpoints were the change in the percentage predicted FVC and haemoglobin-corrected DLCO, but after 12 months there were no significant differences in lung parameters between the two arms. There was, however, a trend to significance in treatment difference for FVC change (4.2% in favour of active treatment; $P = 0.08$) and no increase in serious AEs with active treatment.

Based on these two trials, EULAR guidelines state that CYC may be considered for the treatment of SSc-ILD [26].

MMF

MMF is a prodrug of MPA that inhibits a metabolic pathway essential for lymphocyte function (Fig. 1) [18]. Extensive prospective and retrospective studies in SSc-ILD suggest that MMF may be effective in improving or stabilizing ILD [18]. In the recent SLS II study, 142 patients with SSc-ILD were randomized to oral MMF (titrated to a target dose of 1500 mg twice daily) for 24 months or oral CYC (titrated to a target dose of 2.0 mg/kg/day) for 12 months followed by placebo for 12 months (Table 1) [27]. The primary endpoint was the percentage predicted FVC at 24 months, and improvement was positive in both treatment arms (MMF 2.2%, CYC 2.9%). While the between-treatment difference was not statistically significant, the difference from baseline was statistically significant for both treatments. Leucopenia and thrombocytopenia were more frequent with CYC (41 and 6%, respectively) than MMF (6 and 0%) and fewer MMF-treated patients withdrew from treatment or met criteria for treatment failure. Time to stopping treatment due largely to AEs was significantly shorter with CYC ($P = 0.019$) (27). Of course, these data do not allow us to draw comparisons between MMF and the short courses of i.v. CYC that have previously been tested in this setting. In a large retrospective analysis in the UK, 109 MMF-treated patients with dcSSc (61 with lung involvement) were compared with 63 patients (40 with lung involvement) receiving other immunosuppressive agents [6]. In the 5 years after starting treatment there was a significantly lower

Table 1 Key randomized controlled trials in patients with SSc and ILD

Study drug (study)	Design	Treatment arms	*n*	Primary endpoint	Key findings
CYC (SLS I [23])	1-year, randomized, double-blind, placebo-controlled trial plus 1 additional year of follow-up without study medication	CYC ⩽2 mg/kg; placebo	158	FVC[a] at 12 months	Mean absolute difference in adjusted 12-month FVC[a]: 2.53% (95% CI 0.28, 4.79), favouring CYC ($P < 0.03$) Difference in FVC[a] maintained at 12 months Additional treatment-related benefits on skin thickening and QoL
AZA (FAST [25])	12-month randomized, double-blind, placebo-controlled trial	Prednisone 20 mg on alternate days + monthly CYC 600 mg/m^2 (6 months), then AZA 2.5 mg/kg/day; placebo	45	Change in FVC[a] and corrected DLCO at 1 year	Adjusted relative treatment effect for FVC[a] was 4.19% in favour of AZA ($P = 0.08$) No improvements in DLCO or secondary outcome measures were identified
MMF (SLS II [27])	2-year randomized, double-blind, active comparator/placebo-controlled trial	MMF 1500 mg twice a day (24 months) CYC 2 mg/kg/day (12 months) then placebo (12 months)	142	Change in FVC[a] at 24 months	FVC[a] improved by 2.19 (95% CI 0.53, 3.84) in the MMF arm and 2.88 (95% CI 1.19, 4.58) in the CYC arm ($P = 0.24$) Leucopenia and thrombocytopenia were more frequent with CYC than MMF Fewer patients receiving MMF than CYC prematurely withdrew from study drug or met pre-specified criteria for treatment failure
Bosentan (BUILD-2 [34])	12-month randomized, double-blind, placebo-controlled trial	Bosentan 125 mg twice a day; placebo	163	Change in 6MWD at 12 months	No significant difference in 6MWD change between treatment arms at month 12 (bosentan −12 months, placebo +9 months) FVC and DLCO remained stable in most patients Significant worsening of lung function occurred in 26% of patients receiving placebo and 23% receiving bosentan
Pirfenidone (LOTUSS [72])	16-week randomized, open-label comparison of two titration schedules	Pirfenidone 801 mg three times a day (2-week titration); pirfenidone 801 mg three times a day (4-week titration)	63	Safety and tolerability	Incidence of TEAE was similar with the two titration schedules More patients discontinued treatment because of TEAEs in the 2-week arm ($n = 5$) than in the 4-week arm ($n = 1$) Addition of MMF did not appear to affect tolerability

(continued)

Table 1 Continued

Study drug (study)	Design	Treatment arms	*n*	Primary endpoint	Key findings
Pomalidomide (CC-4047 [37])	52-week randomized, placebo-controlled trial	Pomalidomide 1 mg/day; placebo	22	52-week change in FVC[a], mRSS, and UCLA SCTC GIT total score	FVC[a] deteriorated in both treatment arms (pomalidomide −5.2%, placebo −2.7%) mRSS improved in both treatment arms (pomalidomide −2.7, placebo −3.7) UCLA SCTC GIT 2.0 changed by +0.1 and 0.0 in the pomalidomide and placebo arms, respectively Observed changes in all three co-primary efficacy endpoints favoured placebo
SCOT [40]	54-month randomized, open-label, active comparator study	CYC 750 mg/m^2/month; post-myeloablation CD34$^+$-selected autologous HSCT	75	GRCS at 54 months[b]	GRCS comparisons favoured HSCT (48 months, P = 0.008; 54 months, P = 0.013) At 54 months, EFS was 50% with CYC and 79% with HSCT (P = 0.021) and overall survival was 77% and 91% (P = 0.19), respectively Treatment-related mortality at 54 months was 0% with CYC and 3% with HSCT
ASTIS [41]	Randomized, open-label, active comparator survival study	CYC 750 mg/m^2/month; post-myeloablation CD34$^+$-selected autologous HSCT	156	EFS[c]	During follow-up (median 5.8 years), 53 events occurred (HSCT, n = 22; CYC, n = 31) During the first year there were more events in the HSCT arm (n = 13, including 8 treatment-related deaths) than in the control arm (n = 8, no treatment-related deaths) At 4 years, 15 events had occurred cumulatively in the HSCT group *vs* 20 events in the control group

[a]Expressed as a percentage of predicted value. [b]Patients ordered based on a hierarchy of outcomes: death, EFS, FVC, scleroderma HAQ and mRSS. [c]Defined as time from randomization until death or persistent major organ failure. 6MWD: 6-minute walking distance; ASTIS: Autologous Stem Cell Transplantation International Scleroderma; BUILD: Bosentan in Interstitial Lung Disease in Systemic Sclerosis; EFS: event-free survival; FAST: Fibrosing Alveolitis in Scleroderma Trial; LOTUSS: An Open-Label, RandOmized, Phase 2 STUdy of the Safety and Tolerability of Pirfenidone when Administered to Patients with Systemic Sclerosis-Related Interstitial Lung Disease; SCOT: Scleroderma: Cyclophosphamide or Transplantation; SLS: Scleroderma Lung Study; TEAE: treatment-emergent adverse event; UCLA SCTC GIT: University of California, Los Angeles, Scleroderma Clinical Trial Consortium Gastrointestinal Tract.

frequency of clinically significant pulmonary fibrosis in the MMF arm ($P = 0.037$) and significantly better 5-year survival from disease onset ($P = 0.027$) and start of treatment ($P = 0.012$). There were no significant differences in modified Rodnan skin score (mRSS) and FVC change.

While generally well tolerated, MMF is associated with gastrointestinal disturbances, myelosuppression and increased risk of infection [18, 22]. An enteric formulation, mycophenolate sodium, has been developed to reduce the incidence of gastrointestinal side effects [28].

MMF is often the initial treatment of choice for patients with SSc-ILD [22]. It is not, however, included in the 2013 EULAR guidelines [26], which were developed before SLS II was published.

AZA

AZA is a non-selective immunosuppressant acting primarily in lymphocytes to block purine synthesis and DNA replication [29]. It has been evaluated in an open-label study in 60 patients randomized to CYC (2 mg/kg/day for 12 months followed by 1 mg/kg/day maintenance) or AZA (2.5 mg/kg/day for 12 months followed by 2 mg/kg/day maintenance) [30]. AZA was associated with significant worsening of FVC and DLCO and is no longer considered a first-line treatment option for SSc-ILD. Several observational studies have shown, however, that AZA maintenance therapy after CYC induction can stabilize lung function [12].

Corticosteroids

Corticosteroid monotherapy is ineffective, but corticosteroids are often combined with immunosuppressants because of their anti-inflammatory properties [12]. Furthermore, chronic use of moderate to high doses (>15 mg/day) has been associated with a higher risk of scleroderma renal crisis, regardless of other immunosuppressive therapy [31, 32]. As SSc-ILD generally involves fibrotic non-specific interstitial pneumonia or usual interstitial pneumonia (>95% of cases), the use of moderate to high doses of steroids is questionable. Consequently, clinical trials have used doses of prednisone of up to 10 mg/day, while physicians in the USA avoid prednisone for management of ILD. In Europe, oral prednisolone doses up to 10 mg are often given, although efficacy is uncertain. This practice is supported by inclusion of prednisolone in the FAST, as described above [25].

Bosentan

Endothelin 1 (ET-1) is implicated in the pathophysiology of lung fibrosis and elevated levels have been detected in plasma and bronchoalveolar lavage fluid from patients with SSc-ILD [33]. There is therefore a rationale for evaluating drugs targeting ET-1 or its receptors.

Bosetan Use in Interstitial Lung Disease 2 (BUILD-2) was a randomized, double-blind, placebo-controlled trial in 163 patients with SSc-ILD, predicted DLCO <80% and a 6-min walk distance of either 150–500 m or >500 m with a decrease in oxygen saturation [34]. Patients were randomized to the ET-1 receptor antagonist bosentan (62.5 mg twice a day, increasing to 125 mg twice a day after 4 weeks) or placebo. Despite the clear rationale and large population, there was no significant difference in the 6-min walk distance change at week 12 (primary endpoint) between the bosentan (−12 ± 100 m) and placebo (+9 ± 84 m) arms. Furthermore, bosentan had no effect on time to death or worsening PFTs [hazard ratio (HR) 1.10 (95% CI 0.56, 2.14)] or clinically significant worsening at month 12 [relative risk 0.88 (95% CI 0.50, 1.56)].

Pomalidomide

Pomalidomide is an immunomodulator related to thalidomide with a range of effects, including anti-inflammatory properties resulting from inhibition of cyclooxygenase-2 production and prostaglandin generation in lipopolysaccharide-stimulated monocytes [35]. It also has direct and indirect cytotoxic activity and is licensed for the treatment of relapsed and refractory multiple myeloma [36].

Based on the anti-fibrotic activity in pre-clinical models, 23 patients with SSc-ILD were randomized to pomalidomide or placebo in a phase 2 study (Table 1) [37]. At week 52, changes in FVC%, mRSS and University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 instrument total score all favoured placebo, so the study was terminated early for lack of efficacy.

Rituximab

Rituximab is a CD20-targeted mAb causing rapid B cell depletion and immunosuppression [38]. It is licensed for treatment of non-Hodgkin lymphoma and chronic lymphocytic leukaemia, RA and granulomatosis with polyangiitis. In a 1-year, proof-of-principle study, eight patients with SSc-ILD received standard therapy plus 4 weekly infusions of rituximab 375 mg/m^2 at baseline and at 24 weeks, while six additional patients received standard therapy only [39]. After 1 year there were significant increases in FVC ($P = 0.002$) and DLCO ($P = 0.023$) in the rituximab-treated patients compared with declines with standard therapy. The mRSS also improved significantly from baseline in the rituximab arm ($P < 0.001$).

Autologous haematopoietic stem cell transplantation

Autologous haematopoietic stem cell transplantation (HSCT) as a means of 'resetting' the immune system has shown promise in phase I and II studies in SSc-ILD [22]. In the Scleroderma: Cyclophosphamide or Transplantation study, 75 patients with dcSSc and a high risk of lung and/or renal involvement were randomized to receive monthly CYC (750 mg/m^2) or myeloablation (800 cGy total body irradiation with lung and kidney shielding, 120 mg/kg CYC and 90 mg/kg antithymocyte globulin) followed by CD34$^+$-selected autologous HSCT (Table 1) [40]. The primary endpoint was a global rank composite score at 54 months that ordered patients based on a hierarchy of death, event-free survival, FVC, scleroderma HAQ and mRSS. At 48 months ($P = 0.008$) and 54 months ($P = 0.013$), global rank composite score comparisons favoured HSCT. In addition, event-free

survival at 54 months was 50 and 79% in the CYC and HSCT arms, respectively ($P = 0.021$), and more patients who received HSCT survived to 54 months (91%) compared with CYC (77%). Serious AEs were similar in both study arms, although grade 3+ AEs, including cytopenia and herpes zoster, were more common with HSCT [40].

In the Autologous Stem Cell Transplantation International Scleroderma study, 156 patients with early dcSSc were randomized to HSCT or i.v. pulse CYC (Table 1) [41]. The primary endpoint was event-free survival (time from randomization until death or persistent major organ failure). Despite an increase in treatment-related mortality in the first year in the HSCT arm (eight deaths *vs* none with CYC), there were significantly fewer cumulative events in the HSCT arm after 4 years [19 *vs* 26%; time-varying HR 0.34 (95% CI 0.16, 0.74)]. Based on these promising results, HSCT is recommended for the treatment of carefully selected patients with rapidly progressive SSc at risk of organ failure [26]. In particular, HSCT with intensive immunosuppression has a substantial benefit as rescue therapy in some patients with SSc, especially those with lung fibrosis and poor prognosis [1, 42].

Non-pharmacological and symptomatic treatment options

The cardinal respiratory symptom of SSc-ILD is dyspnoea. Measures that may be useful for treating disabling dyspnoea not responding adequately to pharmacotherapy for SSc-ILD include supplemental oxygen therapy for dyspnoea associated with significant oxygen desaturation $<88\%$ either at rest or during exertion, pulmonary rehabilitation and, for intractable dyspnoea at rest, opiates. The data available from randomized clinical trials concerning the efficacy of supplemental oxygen therapy (compared with air) were derived from patients mainly with idiopathic pulmonary fibrosis, but also included patients with ILD due to other causes, including SSc. The results are mixed, with some studies showing a significantly greater effect than placebo in improving exercise performance (that is mainly limited by dyspnoea) and others not, while one study showed a significant benefit for resting dyspnoea [43]. Data regarding the benefits of pulmonary rehabilitation are derived largely from chronic obstructive pulmonary disease, but some studies have examined its role in ILD. The results of these studies have largely shown significant improvements in 6-min walk distance and health-related QoL, with variable improvement in dyspnoea at rest and during exercise [44, 45]. Despite a lack of published data in SSc-ILD, patients are routinely referred for pulmonary rehabilitation to improve functional exercise capacity and dyspnoea. Multiple randomized controlled trials and systematic reviews have shown significant reductions in intractable dyspnoea with oral or parenteral opioids in patients with advanced disease, including ILD [46]. Anxiolytics might be of added benefit to minimize dyspnoea associated with anxiety.

Lung transplantation is usually reserved for patients who are non-responsive to immunosuppressive therapy for their ILD (with or without associated PH). In SSc-ILD, consideration for lung transplantation is limited by the high prevalence of comorbid oesophageal dysfunction, which likely increases the risk of allograft dysfunction [47]. However, recent data suggest that survival outcomes may be comparable to those in non-SSc diffuse fibrotic lung disease due to better management of oesophageal dysmotility. The 1-, 3- and 5-year post-lung transplant survival rates for SSc-ILD in a recent retrospective review from a large, single-centre database were 94, 77 and 70%, respectively, similar to rates in other groups [47].

Gastro-oesophageal reflux can be associated with silent aspiration that may result in worsening of ILD [48]. Patients with ILD should be advised to follow non-pharmacological and pharmacological management strategies for gastro-oesophageal reflux, if appropriate.

Ongoing clinical trials in SSc-ILD

Several drugs are under investigation for SSc-ILD, including existing and novel agents (Table 2). Examples of previously investigated agents are MMF and rituximab. MMF is being investigated in the phase 3 MYILD study (ClinicalTrials.gov: NCT02896205) in patients with SSc and early, mild ILD (defined as FVC $\geqslant 70\%$ of predicted). The primary endpoint is FVC, and secondary endpoints include FVC according to antibody (anti-centromere and anti-topoisomerase1) profile, QoL (36-item Short Form), Mahler Transition Dyspnoea Index and adverse events. Rituximab is being investigated in the double-blind phase 3 RECITAL study (ClinicalTrials.gov: NCT01862926), in which 116 patients will be randomized to rituximab (two 1 g i.v. infusions at an interval of 2 weeks) or cyclophosphamide (600 mg/m^2/month for up to 6 months) [49]. The study will enrol patients with connective tissue disease (SSc, idiopathic interstitial myopathy or MCTD) and ILD and is expected to be completed in November 2020.

Novel agents for treatment of SSc-ILD

Abituzumab

Integrins are heterodimeric transmembrane glycoproteins consisting of one α and one β subunit. Integrins mediate cell–cell and cell–ECM interactions, including cell cycle progression, cellular invasion and migration, signalling and regulation of gene transcription [50–54]. One important subfamily contains the αv integrins, which are involved in the regulation of cell–ECM adhesion, cellular proliferation and migration and activation of TGF-β [54, 55]. These properties of αv integrins are the basis for their involvement in several forms of cancer and led to the development of specific inhibitors. TGF-β plays a pivotal role in the regulation of lung fibrosis, and inhibition of TGF-β can protect against lung fibrosis in animal models of lung disease [56]. Notably, integrins βv3, βv5 and βv6 are upregulated in the epithelium of some patients with SSc-ILD

Table 2 Ongoing studies in patients with SSc-ILD

Study drug	Mode of action	ClinicalTrials.gov identifier	Phase	Status	Start date	Patient population	Treatment arms	Estimated enrolment	Duration (until primary endpoint)	Primary endpoint
Abituzumab	Anti-integrin monoclonal antibody	NCT02745145	II	Recruiting	April 2016	SSc-ILD Stable MMF/MPS therapy	Abituzumab 500 mg every 4 weeks Abituzumab 1500 mg every 4 weeks Placebo	175	52 weeks[a]	FVC
Bortezomib	Proteasome inhibitor	NCT02370693	II	Recruiting	March 2016	SSc with pulmonary fibrosis	Bortezomib 1.3 mg/m^2/week + MMF 1.5 g twice a day MMF 1.5 g twice a day	30	48 weeks	Adverse events
Dabigatran	Direct thrombin inhibitor	NCT02426229	I	Recruiting	February 2016	SSc-ILD	Dabigatran 75 mg twice a day	15	6 months	Composite safety endpoint
MMF	Metabolic inhibitor of lymphocytes	NCT02896205	III	Recruiting	October 2016	Early SSc-ILD	MMF 2 g/day Placebo	60	6 months	FVC
Nintedanib	Growth factor receptor tyrosine kinase inhibitor	NCT02597933	III	Recruiting	November 2015	SSc-ILD	Nintedanib 150 mg twice a day Placebo	520	52 weeks	FVC
Pirfenidone	Anti-fibrotic, and inhibitor of inflammatory cytokines	NCT03221257	II	Recruiting	Q4 2017	SSc-ILD	MMF + pirfenidoneMMF + placebo	150	18 months	FVC
Rituximab	Anti-CD20 mAb	NCT01862926	III	Recruiting	November 2014	Connective tissue disease + ILD	Rituximab (two 1-g infusions) CYC 600 mg/m^2/month	116	48 weeks	FVC
SAR156597	Anti-IL-4/IL-13 mAb	NCT02921971	II	Recruiting	November 2016	dcSSc	SAR156597 Placebo	94	24 weeks	mRSS
Tocilizumab	Anti-IL6 receptor mAb	NCT02453256	III	Recruiting	August 2015	SSc	Tocilizumab 162 mg/week s.c.	210	48 weeks[a]	mRSS

[a]The 48-week double-blind period will be followed by a 48-week open-label period in which all patients will receive tocilizumab 162 mg/week. MPS: mycophenolate sodium.

[57–59]. Integrin αv is involved in activating TGF-β, a key mediator of fibrosis.

Abituzumab (EMD 525797; DI17E6) is a novel, humanized monoclonal IgG2 antibody to the αv subunit [50]. It inhibits binding to αv heterodimers, preventing ECM attachment, cell motility and apoptosis, without cross-reacting with other integrins (Fig. 1). In a phase 1, placebo-controlled, dose-escalation study in healthy male volunteers, the pharmacokinetics of abituzumab appeared to be dose dependent, especially at lower doses [60].

Abituzumab has been studied in several phase 1/2 oncology trials, demonstrating good safety and tolerability, with potential anti-tumour activity in tumours with high integrin αvβ6 expression [61–63]. A phase 2 study of abituzumab is currently recruiting ∼175 patients with SSc-ILD and DLCO ⩾30% predicted, FVC 40–85% predicted, FVC:DLCO ratio <1.8 and ⩾5% lung fibrosis on HRCT (ClinicalTrials.gov: NCT02745145; Eudra-CT: 2015-005023-11) (Table 2). The study will assess abituzumab plus immunosuppression and patients must have been receiving a stable dose of MMF (1.5–3 g/day) or mycophenolate sodium (1080–2160 mg/day) for ⩾2 months before screening. The primary endpoint is the annual rate of absolute FVC change in volume (millilitres). Secondary endpoints include the following: 52-week changes in breathlessness [as assessed by the Mahler Transition Dyspnoea Index and St George's Respiratory Questionnaire (SGRQ)]; mRSS (in patients with diffuse cutaneous skin involvement at baseline); quantitative lung fibrosis in the region of highest severity; 104-week changes in DLCO, CO transfer coefficient, quantitative lung fibrosis and extent of ILD on HRCT; clinically meaningful progression of SSc-ILD at weeks 52 and 104; and overall survival (assessed until death or end of trial).

Bortezomib

Bortezomib inhibits the ubiquitin–proteasome proteolytic pathway (Fig. 1), which degrades most short-lived intracellular proteins involved in cellular processes such as the cell cycle, differentiation and death, DNA repair, transcription, signal transduction, morphogenesis, metabolism and antigen presentation [64]. It is licensed for treatment of multiple myeloma and mantle cell lymphoma and is under investigation for treatment of solid tumours [64].

Bortezomib has immunomodulatory effects involving immune cells, tumour-associated ligands and lymphocyte-activating receptors and cytokine signalling pathways [64]. In a mouse model, bortezomib promoted normal repair and prevented the development of skin and lung fibrosis after injury, a process related to inhibition of TGF-β_1-mediated target gene expression [65]. A phase 2, placebo-controlled study of bortezomib plus MMF *vs* MMF is currently recruiting (ClinicalTrials.gov: NCT02370693) (Table 2). Eligible patients have diffuse or limited SSc and evidence of pulmonary fibrosis at high risk of progression, with or without progressive skin disease. The primary endpoint is safety and tolerability, with secondary endpoints including QoL (Promis-29, 36-item Short Form and SGRQ dyspnoea score), mRSS, FVC and serum biomarkers at 48 weeks.

Dabigatran

Vascular injury is central to SSc pathogenesis and, combined with matrix deposition, leads to tissue hypoxia [66]. This in turn leads to epithelial–mesenchymal transition via TGF-β signalling or hypoxia-inducible factor 1, and a vicious cycle of increasing fibrogenesis. Vascular injury is also associated with activation of the coagulation cascade and generation of thrombin, a potent stimulus for myofibroblast differentiation [66]. Dabigatran is a direct thrombin inhibitor that reversibly binds thrombin's active site, preventing conversion of fibrinogen to fibrin (Fig. 1) [67]. It is licensed for primary prevention of venous thromboembolic events after joint replacement surgery, prevention of stroke and systemic embolism in non-valvular atrial fibrillation and treatment of deep vein thrombosis and pulmonary embolism.

In normal lung fibroblasts, dabigatran inhibits thrombin-induced differentiation to the myofibroblast phenotype, while in fibroblasts from patients with SSc, dabigatran decreases connective tissue growth factor, α-smooth muscle actin and collagen type I [68]. In a mouse model of lung injury, dabigatran attenuated the development of injury-induced pulmonary fibrosis, with marked anti-inflammatory and anti-fibrotic effects [69]. Dabigatran (75 mg twice a day) is being investigated in an open-label phase 1 study in ∼15 patients with SSc-ILD (Table 2). The primary endpoint is a composite safety measure of complete blood counts, comprehensive metabolic profile and coagulation studies, while the main secondary endpoint is a composite efficacy measure comprising skin score and dermal fibroblast biology.

Nintedanib

Nintedanib is a small-molecule tyrosine kinase inhibitor acting on the PDGF, fibroblast growth factor and VEGF receptors (Fig. 1) [70]. It interferes with fibrosis, including fibroblast proliferation, migration and differentiation, and secretion of ECM. Nintedanib is licensed for use in idiopathic pulmonary fibrosis (IPF) and is being investigated in SSc-ILD in the phase 3 SENSCIS study (ClinicalTrials.gov: NCT02597933) [71]. Patients are randomized to nintedanib 150 mg twice a day or placebo and, to reflect real-world management, patients receiving concomitant prednisone 10 mg/day and/or a stable dose of MMF or MTX are eligible. The primary endpoint is the annual rate of FVC decline at week 52, with key secondary endpoints including absolute changes from baseline in mRSS and SGRQ at week 52.

Pirfenidone

Pirfenidone has anti-fibrotic and anti-inflammatory properties resulting from inhibition of IL-1β, IL-6, TNF-α and PDGF [22]. It is licensed for treatment of IPF and was investigated in the randomized, open-label, phase 2 LOTUSS study (ClinicalTrials.gov: NCT01933334) in 63 patients with SSc-ILD [72] to assess tolerability

(Table 1). Patients received pirfenidone for 16 weeks using either a 2- or 4-week titration schedule (starting dose 801 mg/day, maintenance dose 2403 mg/day). As pirfenidone is associated with an increased incidence of photosensitivity, patients were instructed to avoid or minimize sun exposure, use sunblock and wear protective clothing. AEs were similar to those previously reported in IPF, most commonly nausea, headache and fatigue. Tolerability was generally better with the 4-week titration schedule, and addition of MMF had no adverse impact on tolerability. FVC% and DLCO were evaluated as exploratory endpoints and remained stable throughout the study [72].

This led to the launch of the SLS III study (ClinicalTrials.gov: NCT03221257), which is assessing whether the combination of immunosuppressive therapy with MMF and anti-fibrotic therapy with pirfenidone has greater efficacy than the immunosuppressant alone (Table 1). The primary hypothesis is that the rapid onset and anti-fibrotic effects of pirfenidone, as observed in IPF, will complement the delayed anti-inflammatory and immunosuppressive effects of MMF to produce a significantly more rapid and/or greater improvement in lung function. The primary endpoint is the change in predicted FVC% during the 18-month treatment period. Secondary endpoints include the change in mRSS, extent of fibrosis and total ILD on HRCT, predicted DLCO%, Transitional Dyspnoea Index and other patient-reported outcomes and time to achieve $\geqslant$3% improvement from baseline in predicted FVC%. Identification of biomarkers is an exploratory endpoint. SLS III began recruiting patients in November 2017.

Other agents

Several other agents are being investigated in patients with SSc. While these studies are not specific to SSc-ILD, they will include pulmonary endpoints. For example, tocilizumab is an anti-IL-6 receptor humanized mAb that blocks IL-6-mediated signalling (Fig. 1), implicated in SSc pathogenesis in animal models [73]. It is licensed for treatment of RA and is being investigated in the phase 3 focuSSced study in SSc (ClinicalTrials.gov: NCT02453 256; Table 2). SAR156597 is a mAb targeting IL-4 and IL-13 (Fig. 1). The latter is associated with fibrogenic remodelling, and SAR156597 is currently in phase 2 development for the treatment of IPF [74, 75]. A phase 2 proof-of-concept, placebo-controlled study of SAR156597 is also under way in patients with dcSSc (ClinicalTrials.gov: NCT02921971; Table 2).

In conclusion, SSc-ILD is a severely debilitating disease with high mortality in extensive disease. There is no approved disease-modifying treatment and few effective treatment options are available. Key issues include variable response rates, including non-response in some patients, slow response and drug toxicity. While CYC is an option in the EULAR recommendations [26], it has limited efficacy and issues with toxicity and is not licensed for SSc-ILD. MMF is the most commonly used medication in current best practice. Newer agents hold promise for better treatment outcomes, including improved lung function, patient-related outcomes and QoL. In addition, an article highlighting points to consider when designing clinical trials in SSc has recently been published by the EUSTAR research group [76].

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