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Review

A Narrative Review of Therapeutic Options in Systemic Sclerosis Associated Interstitial Lung Disease

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Abstract: Background: Interstitial lung disease (ILD) has replaced scleroderma renal crisis as the leading cause of mortality in systemic sclerosis (SSc), with a 10-year mortality of 40%. There have been well-powered randomised control trials (RCTs) demonstrating the effect of cyclophosphamide (CYC), mycophenolic acid (MMF), nintedanib and tocilizumab (TCZ) in SSc-ILD but a paucity of sufficiently powered studies investigating other agents in the disease. **Methods:** This is a narrative review which examines the existing evidence for immunosuppressive treatments, transplant and adjunctive therapies in SSc-ILD by reviewing the key landmark trials in the last two decades. **Results:** MMF for 2 years is as effective as oral CYC for 1 year. Rituximab (RTX) is non-inferior to CYC. TCZ appears to have a beneficial effective regardless of the extent of lung involvement. **Conclusions:** There is now a strong evidence base supporting the use of MMF as the first line option in SSc-ILD. RTX, CYC and TCZ are viable therapeutic options if there is ILD progression on MMF. Anti-fibrotic and pulmonary arterial (PAH) treatments likely add long-term synergistic benefits. There remains a role for lung transplantation in select patients.

Keywords: systemic sclerosis; scleroderma; interstitial lung disease; rituximab; cyclophosphamide; tocilizumab; mycophenolic acid

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1. Introduction

SSc is an autoimmune connective tissue disease characterised by microvascular damage and progressive fibrosis of the skin and internal organs, including the heart, lungs, kidneys and the gastrointestinal tract [1–3]. Pulmonary fibrosis has replaced scleroderma renal crisis (SRC) as the leading cause of mortality in SSc, with a reported prevalence of up to 30% and a 10-year mortality of 40% [4]. A review of 9260 SSc patients from the European Trials and Research Group (EUSTAR)database revealed a prevalence of SSc-ILD of 50.2% [5]. Post-mortem studies suggest an even higher frequency of pulmonary involvement, with fibrosis reported in greater than 75% of cases [6].

While the aetiology and pathogenesis are not fully understood, the main risk factors for the progression of SSc-ILD are the diffuse cutaneous SSc (dcSSc) phenotype, the anti-Scl-70 antibody (anti-topoisomerase 1), male gender, African heritage, cardiac involvement and raised acute phase reactants [7,8]. Recent evidence from the EUSTAR cohort now clearly shows that ILD can appear at any time after SSc diagnosis, with stable incidence at any point during disease course, independent of disease duration [9]. This underscores the importance of continued interval screening for new-onset ILD in SSc.

The predominant pattern of ILD reported on high-resolution computed tomography (HRCT) in SSc is non-specific interstitial pneumonia (NSIP). It is observed in up to 75% of SSc-ILD cases and it is characterised by irregular ground-glass attenuation, traction bronchiectasis and sparing of the subpleural regions [10–12]. The consensus opinion is that NSIP in SSc-ILD represents inflammation rather than established fibrosis. Established fibrosis typically produces a usual interstitial pneumonia (UIP) pattern on HRCT. Therefore,

this suggests a degree of potential reversibility with timely immunosuppressive treatment in SSc-ILD.

The use of corticosteroids (CS) in SSc still remains controversial as there is an association with higher doses of CS and scleroderma renal crisis (SRC). To avoid this, and the sequelae of long-term CS, there is a real need to identify and stratify the best immunosuppressive agents for SSc-ILD. There have been well-powered RCTs demonstrating the effect of CYC, MMF, nintedanib and TCZ in SSc-ILD, but a paucity of sufficiently powered studies investigating other agents in the disease. This article will review the key landmark RCTs that have directed the treatment of SSc-ILD along with the American Thoracic Society (ATS), American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines for SSc-ILD.

2. Landmark Trials

Prior to the landmark RCTs demonstrating the efficacy of CYC and MMF in SSc-ILD, smaller cohort studies demonstrated that cyclosporine A (CYA) could be used to treat SSc. CYA was originally isolated from the fungus Tolypocladium inflatum in the 1970s and was introduced to solid organ transplant medicine and bone marrow transplantation in the 1980s [13]. An early Italian cohort study from 2001 of nine patients demonstrated that low-dose CyA treatment at 2.5 mg/kg/day was well tolerated without any significant negative effect on blood pressure and renal function [14]. There was a progressive improvement in lung score in seven patients with abnormal baseline pulmonary function prior to treatment. This improvement persisted beyond 3 years. Since this time, larger trials and RCTs have added greatly to the evidence base, which informs our choice of treatment options used today in clinical practice. The key landmark trials are highlighted in Table 1. The first of these is the large scleroderma lung study 1 (SLS), which investigated the role of CYC in the treatment of SSc-ILD.

Table 1. Landmark trials relating to SSc-ILD.

Overview of Landmark Trials in SSc-ILD					
Trial	**Year**	***n***	**Treatment**	**Comparator**	**Result**
SLS 1	2006	158	CYC (oral)	Placebo	Significant but modest beneficial effect on lung function Effect maintained through 24 months
SLS 2	2016	126	MMF	CYC (oral)	MMF for 2 years was as effective as oral CYC for 1 year MMF is safer and better tolerated with a lower toxicity profile
SENSCIS	2019	576	Nintedanib	Placebo	At 1-year the nintedanib group lost 52 mls from baseline FVC compared to 93 mls for the placebo group
FOCUSSCED	2020	210	TCZ (SC)	Placebo	TCZ appears to have a beneficial effect regardless of the extent of lung involvement
RECITAL (SSc-ILD Subgroup)	2023	37	RTX	CYC	RTX is non-inferior to CYC

2.1. Scleroderma Lung Study 1 (SLS1)

SLS1 was a 2-year double-blind, randomised, placebo-controlled trial funded by the National Institute of Health, which examined the effects of oral cyclophosphamide on pulmonary function in patients with SSc-ILD [15]. The trial enrolled 158 patients across 13 centres. It included those with mild to moderate ILD and evidence of active disease,

such as active alveolitis on bronchoalveolar lavage (BAL) or ground-glass opacities (GGOs), on HRCT. All patients included were deemed to have at least moderate dyspnoea.

The patients were randomised to either 12 months of CYC or 12 months of placebo followed by a 12-month observation period off treatment. Oral CYC was dosed at $\leq$ 2 mg per kg body weight. In total, 145 of 158 completed 6 months of treatment and were included in the analysis. The mean absolute difference in forced vital capacity (FVC) % predicted between the groups was 2.53% in favour of CYC ($p < 0.03$). This difference in FVC was maintained at 24 months. There was no significant difference between the two groups in diffusion capacity for carbon monoxide (DLCO).

Interestingly, while this difference may seem small, there were also treatment-related differences in dyspnoea scores and quality of life scores. The mean focal score, as per the transitional dyspnoea index, showed a clinically significant improvement (i.e., >1 unit) of $+1.4 \pm 0.23$ units in the CYC group compared with a clinically significant deterioration (i.e., >1 unit) of -1.5 ± 0.43 units in the placebo group. The CYC group also scored more favourably on the health assessment questionnaire (HAQ) disability score at the 12-month mark.

At oral CYC dosing $\leq$ 2 mg per kg body weight, the difference in adverse events between the two groups was perhaps lower than expected. The CYC group only experienced significantly more leukopenia and neutropenia than placebo. While the rate of haematuria was numerically higher in the CYC group, surprisingly, this difference was not statistically significant. Of course, a 2-year trial cannot account for the long-term effects of CYC. A particular concern is the established association between CYC treatment and bladder cancer. This is problematic when there are no clear guidelines as to how to best screen or monitor these patients for bladder cancer development years after initial treatment [16].

In summary, at the time of publication, given there was no reasonable alternative with a solid evidence base, the risk–benefit profile was in favour of CYC treatment in SSc-ILD patients. CYC demonstrated a favourable effect on lung volumes (i.e., FVC) but not gas transfer (i.e., DLCO). CYC did have a real, measurable effect on dyspnoea and quality of life scores. After the publication of SLS1 in 2006, CYC became the standard of care in SSc-ILD.

2.2. Scleroderma Lung Study 2 (SLS2)

SLS2 was a 2-year double-blind, parallel-group, RCT comparing MMF with oral CYC in 126 SSc-ILD patients [17]. Prior to SLS2, uncontrolled studies had shown that MMF had the potential to be an effective alternative to CYC, particularly given the demonstrated favourable safety profile in solid organ transplants [18]. SLS2 was designed to investigate the comparative efficacy and safety of MMF, administered for 2 years versus oral CYC, given for 1 year and followed thereafter by placebo for a further year.

The trial was performed in 14 US centres from 2009 to 2015. All patients enrolled had FVC values $\geq$45% and <80% predicted, exertional dyspnoea $\geq$ grade 2 on the Mahler Baseline Dyspnoea Index (BDI) and GGOs on HRCT. Notably, MMF was titrated up to 1.5 g BD in the treatment arm and oral CYC was titrated to a target dose of around 2 mg/kg/day, which was in line with SLS1.

It was hypothesised that a 2-year course of MMF would be safer, better tolerated and produce longer-lasting improvements than CYC. At 24 months, the mean values of FVC % predicted were similar in both groups: 2.17 vs. 2.86 ($p = 0.24$). While MMF compared favourably to CYC in terms of DLCO % predicted at 6 and 18 months, the 12 and 24-month results did not differ. Both CYC and MMF showed significant improvements in dyspnoea and disability, as per the health assessment questionnaire disability index (HAQ-DI). There was a 6-fold increased risk of leukopenia with CYC treatment compared to MMF, but there were no other differences in reported adverse events. The CYC group were 1.7 times more likely to discontinue treatment compared with the MMF group.

The bottom line was that 65% of those in the CYC arm and 72% of those in the MMF arm had either stable or improving pulmonary function based on measured FVC predicted

values [17]. Ultimately, while there was no difference in all-cause mortality, MMF would become the first-line treatment in SSc-ILD given its better tolerance and more favourable safety profile.

2.3. SENSCIS

The Nintedanib for Systemic-Sclerosis-Associated Interstitial Lung Disease (SENSCIS) trial was a randomised, double-blind, placebo-controlled trial encompassing results from 32 countries. SENSCIS investigated the efficacy and safety of nintedanib in a cohort of 576 SSc-ILD patients [19]. Over half (51.9%) of the patients enrolled had dcSSc but all had HRCT evidence of $\geq$10% fibrosis of the lungs along with FVCs of at least 40% predicted and DLCOs of 30 to 89% predicted.

SENSCIS recruited all patients from November 2015 through October 2017. A key point to highlight here is that less than half (48.4%) of those enrolled were receiving MMF at baseline. SLS2, which showed the efficacy and favourable safety profile of MMF in SSc-ILD was published in 2016. The 48.4% figure on MMF at baseline is, therefore, perhaps still lower than one would expect, given the results from SLS2.

The treatment arm received nintedanib at 150 mg orally twice per day and the control arm received oral placebo tablets. The primary end point was the annual rate of FVC decline. The nintedanib group experienced an annual rate of FVC decline of −52.4 millilitres (mls) compared with −93.3 mls in the placebo group. The preserved 40.9 mls in the first year is a significant difference (p = 0.04).

A subgroup analysis showed that in patients receiving both MMF and nintedanib, the adjusted mean annual rate of decline in FVC was −40.2 mls versus −66.5 mls in those receiving MMF and placebo [20]. In those not receiving MMF, the annual rate of decline in FVC was −63.9 mls with nintedanib and −119.3 mls with placebo. These results suggest a synergistic effect of combining MMF and nintedanib on FVC.

However, SENSCIS failed to show a beneficial effect of nintedanib on patient-reported outcomes such as the Functional Assessment of Chronic Illness Therapy Dyspnoea Questionnaire (FACIT-Dyspnoea) and quality of life scores (HAQ-DI). Moreover, the tolerability of nintedanib from a gastrointestinal (GI) perspective proved problematic during SENSCIS, with diarrhoea experienced by 75.7% of the nintedanib group [19]. Even with anti-diarrhoeal agents, real-world experience suggests that at least a third of patients experience significant GI upset, so much so that continuing the medication can become problematic. Lastly, SENSCIS only demonstrated the effect of nintedanib in the first year of treatment and at the time of publication in 2019, it was unclear whether the effect would be cumulative over multiple years of treatment or not.

2.4. FOCUSSCED

The Tocilizumab in Systemic Sclerosis (FOCUSSCED) trial was a phase 3 placebo-controlled RCT investigating the effect of TCZ in patients with SSc and progressive skin disease [21]. In total, 210 patients were recruited from November 2015 to February 2017. Of these, 136 (65%) had ILD, and the majority with known fibrosis (77%) had pulmonary involvement with >10% of the volume of the lung fields affected on HRCT. However, the mean baseline FVC predicted was 80.3% in the TCZ group and 83.9% in the placebo group, which is only reflective of mild lung involvement. Similarly, the mean baseline DLCO was 74.4% in the TCZ group and 76.8% in the placebo group.

Patients were randomised to receive TCZ at 162 mg subcutaneous injection weekly or weekly placebo subcutaneous injection. PFTs and HRCT were performed at baseline and repeated at week 48. Among those with ILD at baseline, the least squares mean (LSM) change from baseline to week 48 in FVC was +0.07 in the TCZ group compared with −6.40 in the placebo group (p < 0.0001). This effect was also independent of the degree of fibrosis at the pre-treatment baseline. Therefore, TCZ appears to have a beneficial effect on SSc-ILD regardless of the extent of lung involvement prior to commencing treatment. However, this should be tempered by the fact that the patients enrolled in FOCUSSCED had milder

baseline ILD than in SLS1, SLS2 and SENSCIS. To illustrate this point, the SENSCIS cohort had a mean baseline FVC of 72% along with 35 to 37% baseline lung fibrosis on HRCT, whereas FOCUSSCED had a mean baseline FVC of 82% along with 2 to 17% baseline lung fibrosis on HRCT [19].

Lastly, there were no differences between TCZ and placebo for patient or physician-reported outcomes at 48 weeks. Importantly, this includes the HAQ-DI and the Saint George's Respiratory Questionnaire. Even if TCZ seems to have a numerically beneficial effect on ILD, this does not translate to improvement in quality-of-life metrics in this cohort of SSc patients with early baseline ILD.

2.5. RECITAL

The Rituximab versus Intravenous Cyclophosphamide in Patients with Connective Tissue Disease-associated Interstitial Lung Disease (RECITAL) trial was a phase 2b randomised, double-blind, multicentre UK-based trial that aimed to assess whether or not RTX is superior to CYC in severe or progressive connective tissue disease-associated ILD (CTD-ILD). This included three broad groups: idiopathic inflammatory myopathies (IIM), mixed connective tissue disease (MCTD) and SSc. This was unusual as the RECITAL trial published the end results as a composite of the three diseases showing the effect of RTX in CTD-ILD.

SSc accounted for 38% of the trial recruits (37/97). The subgroup analysis of SSc-ILD patients was presented at the American College of Rheumatology (ACR) Congress in Philadelphia in November 2022. It reported a 24-week change from baseline FVC of −26.0 mls (95% CI −186.8, 134.6) in the RTX group versus −3.3 mls (95% CI −154.8, 148.2) in the CYC group.

These results did not support their hypothesis that RTX is superior to CYC in this patient group. However, RECITAL does support the idea that RTX is non-inferior to CYC. Given SLS2 showed that CYC and MMF are similar in terms of efficacy, this does support the idea of RTX as a second-line agent in SSc-ILD along with CYC [18,22].

3. Guidelines

3.1. American Thoracic Society

The updated American Thoracic Society (ATS) guidelines from 2023 make a strong recommendation for the use of MMF in SSc-ILD but only a conditional recommendation for the use of CYC in the treatment of SSc-ILD [23]. Similarly, RTX, TCZ, nintedanib, as well as the combination of MMF and nintedanib, were all given only conditional recommendations. Pirfenidone was met with the consensus opinion that further research is required to increase the evidence base before any recommendation can be made.

3.2. American College of Rheumatology

The new ACR guidelines from 2023 recommend MMF as the preferred first-line treatment. Alternatively, TCZ and RTX may be used as a first-line treatment [24]. Additional options thereafter include CYC and azathioprine (AZA). ACR also makes a conditional recommendation for the use of nintedanib in SSc-ILD. Importantly, there is a strong recommendation against the use of glucocorticoids as a first-line treatment. Lastly, there is a conditional recommendation for referral to an experienced centre for autologous haematopoietic stem cell transplant (AHSCT) if ILD is progressing on first-line treatment.

3.3. European League against Rheumatism

The updated European League Against Rheumatism (EULAR) guidelines place MMF, RTX and CYC in the same group as a first-line treatment [25]. TCZ is categorised as a second-line treatment. Nintedanib is also strongly recommended. While HSCT is included in the first-line group for reserve patients, there is no mention yet of chimeric antigen receptor T cell (CAR-T) treatment as it is still a nascent medical technology.

The treatment recommendations for SSc-ILD from above guidelines are compared in Table 2.

Table 2. Comparison of SSc-ILD treatment guidelines.

Comparison of SSc-ILD Treatment Guidelines					
Guideline	**1st Line**	**2nd Line**	**Anti-Fibrotics**	**HSCT**	**CAR-T**
ATS [23]	MMF	CYC RTX TCZ	Nintedanib (Conditional)	N/A	N/A
ACR & CHEST [24]	MMF TCZ RTX	CYC AZA	Nintedanib (Conditional)	Consider if progressing despite 1st line	N/A
EULAR [25]	RTX MMF CYC	TCZ	Nintedanib (May use in conjunction with 1st line immunosuppression)	Consider in severe cases	N/A

4. Screening and Treatment Paradigm

A recent modified Delphi consensus from a panel of expert pulmonologists and rheumatologists in the field recommends ILD screening in all systemic sclerosis patients [26]. Initial screening should include a history of respiratory symptoms, chest auscultation for crackles, HRCT Thorax and PFTs. Routine screening for pulmonary hypertension should be part of the process when dyspnoea is not explained by the progression of ILD.

Often, treatment criteria will focus on a combination of PFT results and HRCT evidence of ILD. The same expert panel suggest the commencement of treatment if FVC < 80% with any degree of ILD or symptoms, or there is >20% total lung involvement on HRCT, or there is >10% lung involvement on HRCT with abnormal PFTs. They also recommended initiating treatment in high-risk patients with early diffuse cutaneous disease and any evidence of mild ILD.

The ACR systemic autoimmune rheumatic disease (SARD) ILD guidelines offer practical advice regarding the frequency of monitoring for progression in SSc-ILD [23]. PFT testing with spirometry, lung volumes and diffusion capacity should be performed every 3–6 months for the first year and then less frequently once stable. Ambulatory desaturation testing can be performed every 3–12 months, and interval HRCT should be guided by PFT trend. CXR, 6 min walk test and bronchoscopy are generally not helpful and are conditionally recommended against in this guideline, except in a few exceptional circumstances, where they provide additional diagnostic utility.

We present our preferred treatment hierarchy in Figure 1. MMF is our preferred first-line agent, given the lower relative toxicity when compared with CYC. MMF is also an oral therapy that can be very beneficial and convenient for the patient. Nintedanib may also be offered in conjunction with MMF if tolerated from a gastrointestinal perspective. We will discuss lung transplant, HSCT and the potential of CAR-T cells in a separate section as rescue treatments.

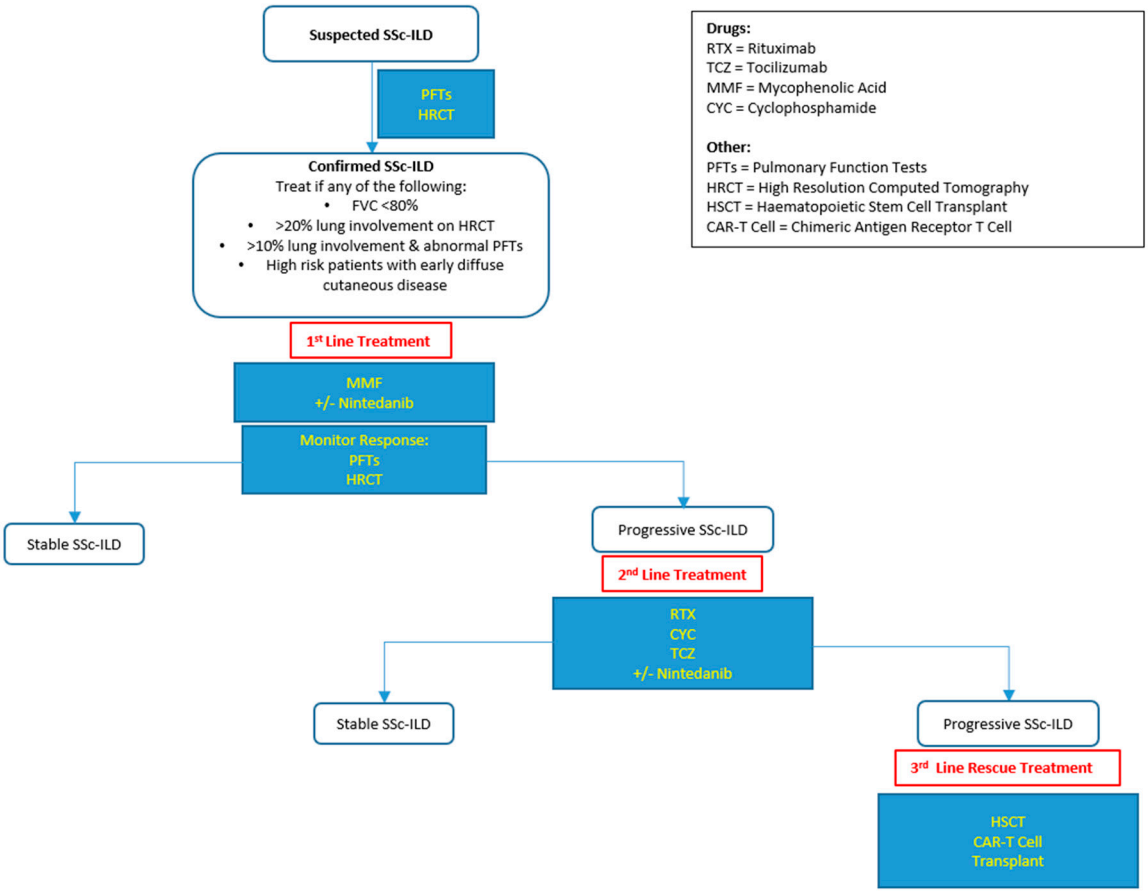

Figure 1. Proposed SSc-ILD treatment hierarchy.

5. Transplant

5.1. Lung Transplant

Historically, SSc-ILD patients were deemed to be poor candidates given the systemic nature of the disease and the concerns of high extra pulmonary morbidity and mortality [27]. While the immunosuppressive treatment paradigm has come a long way, there remains the grave concern of graft failure and death from bronchiolitis obliterans (BO). This fear is compounded by studies suggesting a link between gastro-oesophageal reflux (GORD) and BO; it is well established that gastrointestinal dysmotility and GORD are often features of SSc, hence the concern [28].

Data from the International Society for Heart and Lung Transplantation (ISHLT) from 2019 reported that only 0.9% of all lung transplants were for connective tissue disease (CTD)-related ILD and lower still for SSc-ILD specifically [29]. Despite this, the recent evidence base suggests that SSc-ILD patients have similar short- and long-term survival with lung transplant when compared to patients with other forms of pulmonary fibrosis. A retrospective cohort study from the University of Pittsburgh Medical Centre (UPMC) compared the post-transplant outcomes of 72 SSc-ILD patients with 311 patients with other forms of interstitial lung disease. Interestingly, they found the 1-year survival of 81% for SSc compared well with the 79% 1-year survival rate in the other causes of the ILD group. Similarly, the 5-year survival rate was favourable for the SSc-ILD patient compared to other causes of ILD: 66% vs. 58% [30]. A second retrospective cohort study from the University of California Los Angeles (UCLA) group again showed reassuring survival data. The group of SSc-ILD patients was smaller at 35, but they demonstrated 1-, 3- and 5-year survival rates post-transplant of 94%, 77% and 70%, respectively. These results were comparable to those seen in patients with other forms of ILD. Notably, 60% of the SSc-ILD patients in this

cohort had severe oesophageal dysmotility. This perhaps suggests that previous fears of GORD-related BO and graft failure were overestimated [31].

The 2021 ISHLT consensus document proposed that lung transplant is now a viable option for a select group of patients with CTD, including those with advanced SSc-ILD [29]. The combined 2023 ACR and American College of Chest Physicians (CHEST) guideline for the treatment of SARD-ILD makes a conditional recommendation for referral for lung transplant after failure of all immunosuppressive treatments and consideration of suitability for HSCT [23]. Interestingly, the 2017 EULAR recommendations for the treatment of systemic sclerosis, which are due to be updated, do not mention lung transplant at all, although it does acknowledge HSCT as a viable option [32]. The 2019 European Respiratory Society (ERS) evidence-based consensus recommendations for the identification and management of interstitial lung disease in systemic sclerosis do acknowledge the role of lung transplant in these patients [33]. After the progression of ILD despite MMF or CYC treatment, these patients may then be considered candidates for either rituximab, lung transplant or HSCT.

5.2. HSCT

Hematopoietic stell cell transplant (HSCT) has been used in severe refractory autoimmune diseases for the past quarter of a century. While the introduction of biologic therapies in recent times has reduced the role of HSCT, there remain a few diseases where HSCT may still be used. SSc-ILD is one of those rare diseases where HSCT features in the treatment guidelines.

There are three RCTs demonstrating the clear benefits of HSCT in progressive diffuse SSc. This are shown in Table 3. While not all patients in these trials have ILD, the impact of treatment on lung disease is reported as a secondary outcome. All three trials demonstrated a beneficial effect on FVC with HSCT treatment compared to the comparator groups of CYC monotherapy. Notably, at least in the context of these short RCTs, there does not appear to be the same beneficial effect on DLCO.

Table 3. Overview of HSCT RCTs in SSc.

Study	*n*	Baseline ILD on HRCT	Baseline FVC	Trial End FVC
ASSIST [34]	HSCT *n* = 10 CYC *n* = 9	HSCT 70% CYC 89%	Median FVC %pred. HSCT 62% CYC 67%	Median Change at 1 yr HSCT +20% CYC −9%
ASTIS [35]	HSCT *n* = 79 CYC *n* = 77	HSCT 87% CYC 80%	Mean FVC %pred. HSCT 82% CYC 81%	Mean Change at 2 yrs HSCT +6.3% CYC −2.8%
SCOT [36]	HSCT *n* = 36 CYC *n* = 39	HSCT 100% CYC 95%	Mean FVC %pred. HSCT 74% CYC 74%	Change at 54 Months HSCT 13/36 improved (↑FVC >10%) HSCT 4/36 decline (↓FVC ≥10%) CYC 8/39 improved (↑FVC >10%) CYC 8/39 decline (↓FVC ≥10%)

The ASSIST study (American Scleroderma Stem Cell versus Immune Suppression Trial) defined an increase of greater than 10% in FVC at 12 months as a significant improvement. Overall, 80% of the HSCT treatment group (n = 8) met this threshold, whereas the CYC group (n = 9) showed a mean decrease in FVC [34].

The ASTIS trial (Autologous Stem Cell Transplantation International Scleroderma) demonstrated a mean increase in FVC of +6.3% at 2 years in the HSCT group (n = 79) compared with a mean decrease of −2.8% in the CYC control group (n = 77) (p = 0.004) [35].

The SCOT trial (Scleroderma: Cyclophosphamide Or Transplantation) randomised 36 patients to the HSCT arm and 39 to the CYC arm [36]. It defined a significant improvement in FVC at the trial end of 54 months to be an increase of greater than 10%. It also defined a significant decline in FVC at the trial end to be a decrease of $\geq$10%. Overall, 13/36 HSCT patients experienced a significant improvement, and only 4/36 HSCT patients experienced a significant decline in FVC. This compares favourably to the CYC group, where 8/39 patients experienced a significant improvement, and 7/39 experienced a significant decline.

While many large observational studies exist, they tell us little about the efficacy of HSCT compared to first-line treatments and, as a result, are less insightful. Both the combined guidelines from ACR and CHEST and the guidelines from EULAR recommend HSCT for the treatment of SSc-ILD patients. The ACR and CHEST guidelines recommend HSCT if ILD is progressing despite the trial of first-line treatments, MMF, TCZ and RTX [24]. The EULAR recommendations make a more general recommendation to consider HSCT in severe cases of SSc-ILD. However, the EULAR peer review report for their guidelines has deemed the quality of the scientific evidence for HSCT in SSc-ILD to be grade A or excellent [32]. Notably, the ATS guidelines for SSc-ILD do not make any reference to HSCT as a treatment option [33].

6. CAR-T Cells

Autologous chimeric antigen receptor (CAR)-T cell therapy is a nascent treatment beginning to gain traction in the treatment of autoimmune rheumatic diseases. While it has been hailed as a transformative medical technology in the world of haematology, it is showing early promise in the treatment of systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM) and now also SSc.

The group pioneering this technology in Europe is the Friedrich-Alexander University Hospital Erlangen-Nürnberg group. The early results with their first seven patients were presented at EULAR's 2024 Congress in Vienna in June, and their results were published in their scientific abstract for the conference [37]. This small group included seven diffuse systemic sclerosis patients ranging in age from 23 to 60. Overall, six out of seven were positive for anti-Scl70 and one was positive for RNA polymerase 3. Notably, all had interstitial lung disease, three had cardiac involvement and one had renal involvement. Prior treatments included MMF, MTX, RTX and cyclophosphamide. Interestingly, CAR-T cell treatment did not completely deplete circulating autoantibodies in all patients. Nevertheless, serial PFTs showed reassuring stability in both FVC and DLCO up to 400 days post initial CAR-T treatment. One patient also had positron emission tomography (PET) performed at baseline prior to treatment and then again at 3 months after treatment. The 3-month follow-up PET showed markedly reduced uptake throughout the lung fields. It should be noted that all seven patients have not received any form of immunosuppressive maintenance treatment since their initial CAR-T cell infusions.

These are very promising results in a small cohort of severe refractory SSc patients. To see the efficacy of CAR-T cell therapy pitted against the current standard of care in an RCT of treatment naïve SSc-ILD patients would be fascinating. The logistics and granting of ethics for such a trial may prove difficult to obtain for the time being. The question of whether CAR-T and HSCT are competitive or complementary is not so easy to answer at present. It is too early yet to truly appreciate the potential toxicity, morbidity and mortality with CAR-T cell therapy compared to HSCT. SSc-ILD patients may very well be one of those niche cohorts that could benefit in the future from this promising medical technology.

7. Adjunctive Therapies and Other Considerations

7.1. Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) affects approximately 30% of SSc-ILD patients [38]. A meta-analysis of 22 studies reported survival rates of 81% for 1 year, 64% for 2 years and 52% for 3 years in SSc-ILD patients with PAH [39]. There are currently four major categories of medication for PAH and they are shown in Table 4. These are prostacyclin

analogues, phosphodiesterase inhibitors (PDE5i), endothelin receptor antagonists (ERAs) and guanylate cyclase stimulators.

Table 4. PAH therapeutics in SSc-ILD.

PAH Therapeutics in SSc-ILD	
Prostacyclin Analogues	Epoprostenol Treprostinil Iloprost
Phosphodiesterase Inhibitors	Sildenafil Tadalafil
Endothelin Receptor Antagonists	Bosentan Ambrisentan Macitentan
Guanylate Cyclase Stimulators	Riociguat

Combination therapy is now routine in clinical practice in idiopathic pulmonary arterial hypertension (IPAH). The evidence base is growing for the use of combination therapy in SSc-PAH. The AMBITION trial, which included a small cohort of CTD patients, demonstrated that a combination of ambrisentan and tadalafil improved haemodynamics, 6 min walk test (6MWT) distance and reduced the risk of clinical deterioration when compared to monotherapy [40]. A small prospective, open-label trial of 24 patients with SSc-PAH without prior PAH treatment demonstrated improvements in haemodynamics, 6MWT distance and right ventricle (RV) structure and function with combination treatment with ambrisentan and tadalafil [41]. The follow-up ATPAHSS-O trial, which again solely focused on SSc-PAH patients, showed improvements in RV and left ventricle (LV) function on cardiac MRI along with 6MWT distance, pro-BNP and haemodynamics with ambrisentan and tadalafil combination treatment [42].

While the current EULAR SSc guidelines give PDE5i, ERAs and prostanoids a strong level A recommendation, the eagerly awaited updated EULAR SSc guidelines are set to give riociguat a level B recommendation for PAH treatment [25]. The role of both anticoagulation and corticosteroids in SSc-PAH remains contentious, and neither are commonly used in clinical practice.

7.2. Oxygen

There is no specific guidance for SSc-ILD patients and supplemental oxygen. In clinical practice, oxygen is provided to those patients with severe hypoxaemia at rest, as is the case with all forms of ILD. While there is no evidence to suggest supplemental oxygen provides a survival benefit in SSc-ILD, there is evidence showing that ambulatory oxygen does improve quality of life and reduce dyspnoea. AmbOX was a prospective, open-label, mixed-method, crossover randomised controlled clinical trial carried out at three centres across the United Kingdom [43]. Approximately 10% of the patients enrolled in this trial had CTD. This trial used the King's Brief Interstitial Lung Disease questionnaire (K-BILD). It demonstrated that ambulatory oxygen seemed to be associated with improved health-related quality of life measures in patients with ILD, including CTD-ILD. While we do not have similar robust trials solely in SSc-ILD, we assume for now that these results are translatable and applicable to SSc-ILD patients.

7.3. Pulmonary Rehabilitation

Many SSc-ILD patients are referred for pulmonary rehabilitation but there is a paucity of evidence to suggest that this improves quality of life. There are, however, a few small single-centre trials that demonstrate an improvement in aerobic capacity with moderate-intensity exercise. These studies were performed in SSc patients rather than specifically SSc-ILD patients [44,45].

7.4. GORD Treatment

In addition to immunosuppressive therapies, the management of GORD in SSc-ILD patients is paramount. The oesophageal involvement, reflux and gastric dysmotility seen in dcSSc all increase the risk of aspiration pneumonitis, which can cause ILD progression [46,47]. Apart from the conservative measures of smaller meals, eating dinner well before lying supine to sleep at night and raising the head of the bed, the use of proton pump inhibitors (PPI) and pro-motility agents may be beneficial.

7.5. Pneumocystis Jirovecii Pneumonia Prophylaxis

The risk of pneumocystis jirovecii pneumonia (PJP) should be carefully considered in SSc-ILD patients on strong or combination immunosuppression or high-dose corticosteroids. The mortality rate with PJP in patients with rheumatic diseases is 39.6%, and this may be even higher in SSc-ILD patients. There is a risk of medication-related adverse events with PJP prophylaxis, regardless of whether co-trimoxazole, dapsone or atovaquone is prescribed. In general, the number needed to harm (NNH) with first-line PJP prophylaxis, co-trimoxazole, is 131. Fortunately, the number needed to treat (NNT) in SSc to prevent one case of PJP is 36 [48]. This shows a favourable risk–benefit ratio that supports the prescribing of PJP prophylaxis in SSc-ILD patients with strong immunosuppression.

7.6. Vaccination

Seasonal influenza vaccines and SARS-CoV-2 vaccines are strongly recommended for SSc-ILD patients. It is also prudent for SSc-ILD patients to strongly consider receiving the pneumococcal polysaccharide (Pneumovax 23) vaccine, which protects against the 23 serotypes of streptococcus pneumoniae. A booster shot is not required for 5 years after initial vaccination. The Centre for Disease Control (CDC) recommend respiratory syncytial virus (RSV) vaccination for all adults 75 years of age and older and adults with certain risk factors between the ages of 60 and 75 [49]. Given the morbidity and mortality associated with RSV in patients with ILD, SSc-ILD patients should again strongly consider the RSV vaccine.

A comprehensive review article from Italy goes further, identifying SSc-ILD patients as a frail immunocompromised cohort who are overlooked by the current vaccination literature and guidelines [50]. It makes a strong recommendation for vaccination in SSc-ILD patients against the six following pathogens: SARS-CoV-2, influenza, streptococcus pneumoniae, neisseria meningitidis, haemophilus influenzae and diphtheria–tetanus–pertussis.

7.7. Symptomatic Dyspnoea Management

There are no specific high-quality trials examining the effect of low-dose opioids or benzodiazepines (BDZs) on dyspnoea in SSc-ILD patients. Again, it is assumed that evidence from trials in other forms of ILD demonstrating a beneficial effect on dyspnoea is applicable to SSc-ILD patients. In one longitudinal study in fibrosing ILD patients on long-term oxygen, both opioids and low-dose BDZs appear to be safe [51].

8. Conclusions

There is a strong evidence base now for the use of MMF as a first-line treatment in SSc-ILD. RTX, CYC and TCZ are advised if there is ILD progression on MMF. Antifibrotic treatment with nintedanib likely adds synergistic long-term benefits and may be used if tolerated from a GI perspective. SSc-ILD patients may still be considered for lung transplant despite concerns regarding GORD, BO and graft failure. Careful assessment and consideration for PPIs and pro-kinetics should be made on a case-by-case basis to minimise GORD and the risk of aspiration. There is also a favourable risk–benefit ratio that supports the prescribing of PJP prophylaxis in patients on strong immunosuppression.

CAR-T cell therapy is a promising medical technology that may replace HSCT in the coming decades for select SSc-ILD cases. PAH is common in SSc-ILD patients, and while

current guidelines give a strong recommendation for PDE5i, ERAs and prostanoids, it is likely that future guidelines will recommend combination therapy if tolerated.

Seasonal influenza and SARS-CoV-2 vaccines are strongly recommended. Consideration should be given for both the pneumococcal polysaccharide vaccine and the RSV vaccine. In addition to long-term oxygen or ambulatory oxygen, low-dose opioids and low-dose BDZs may be appropriate to reduce dyspnoea and improve quality of life.

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