Treatment of interstitial lung disease in systemic sclerosis: guidelines and new clinical trial results

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Purpose of review
Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). The American College of Rheumatology (ACR), in conjunction with the American College of Chest Physicians (CHEST), recently published clinical practice guidelines for the treatment of adults with systemic autoimmune rheumatic disease-associated ILD, including SSc-ILD. Herein, we summarize evidence from randomized trials evaluating the safety and efficacy of pharmacologic therapies for the treatment of SSc-ILD.

Recent findings
In this review, we present findings from recent randomized controlled trials in SSc-ILD. The pharmacologic therapies discussed include immunosuppressive medications (mycophenolate, cyclophosphamide, rituximab, and tocilizumab) and antifibrotic medications (nintedanib and pirfenidone).

Summary
Randomized trials provide an evidence base for the SSc-ILD treatment recommendations put forth in the ACR/CHEST Guidelines for the treatment of ILD in people with systemic autoimmune rheumatic diseases. These guidelines will help inform clinical practice and highlight areas in which further research is needed.

Keywords
interstitial lung disease, mycophenolate, rituximab, systemic sclerosis, tocilizumab

Systemic sclerosis (SSc) is a complex systemic autoimmune rheumatic disease characterized by immune activation, vasculopathy and fibrosis. While its cause remains unknown, it is thought to occur in those with genetic susceptibility, and possibly, a second environmental exposure [1]. Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in SSc. Risk factors for the development of ILD include antitopoisomerase I antibodies, male sex and African–American race [2–4]. The American College of Rheumatology (ACR) and the American College of Chest Physicians (CHEST) conditionally recommend screening for ILD in people with SSc with pulmonary function tests (PFTs), which include spirometry, lung volumes and diffusion capacity for carbon monoxide (DLCO), as well as high-resolution computed tomography (CT) chest [5▪]. Once ILD is diagnosed, the ACR/CHEST ILD guidelines conditionally recommend monitoring with PFTs, high-resolution chest CT and ambulatory desaturation testing [5▪]. The guidelines suggest monitoring ILD with PFTs every 3–6 months in the first year, and then less frequently once stable. Monitoring ILD with ambulatory desaturation testing is suggested every 3–12 months, while monitoring ILD with high-resolution chest CT should occur as needed. Monitoring for ILD progression is best achieved in a shared-care model with pulmonology.

The past decade has seen significant advances in treatment options for SSc-ILD. The ACR/CHEST ILD guidelines for the treatment of ILD in SSc present a menu of options (Fig. 1) that are 'preferred' as well as those that could be considered 'additional' options [6▪]. While there have been many observational studies evaluating the effectiveness of pharmacologic agents for SSc-ILD, in this article, we summarize the randomized trials evaluating the efficacy

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KEY POINTS

- Randomized clinical trials provided an evidence base that informed the SSc-ILD treatment recommendations in the ACR/CHEST Guidelines for the treatment of ILD in people with systemic autoimmune rheumatic diseases.
- The ACR/CHEST Guidelines for the treatment of ILD in people with systemic autoimmune rheumatic diseases present a menu of options for the treatment of SSc-ILD.
- Mycophenolate was conditionally recommended as a first-line therapy for SSc-ILD.

and safety of pharmacologic therapies in SSc-ILD (Table 1).

MYCOPHENOLATE

Mycophenolate is conditionally recommended as a first-line treatment for SSc-ILD, and for progression of SSc-ILD if the first ILD treatment was not mycophenolate. There have been two randomized trials to support this recommendation.

The Scleroderma Lung Study II (SLS II) was a randomized, double-blind, parallel group trial conducted at 14 medical centers in the United States comparing mycophenolate mofetil (target dose 1500 mg twice daily) for 24 months to oral cyclophosphamide (target dose 2 mg/kg per day) for 12 months followed by placebo for 12 months [7]. The primary endpoint was the change in forced vital capacity as a percentage of the predicted normal value (FVC% predicted) over the course of 24 months. Both groups demonstrated a median improvement in FVC% predicted: 2.19% [95% confidence interval (95% CI) 0.53–3.84] in the mycophenolate mofetil group and 2.88% (95% CI 1.19–4.58) in the cyclophosphamide group, with no significant difference between groups $P = 0.24$. This trial has been highly influential in the treatment of SSc-ILD; however, its findings are frequently mislabelled and misinterpreted. Consumers of the medical literature frequently mislabel this study as a 'negative' trial and misinterpret these findings to suggest that mycophenolate and cyclophosphamide have the 'same' effect on FVC. This study was designed as a superiority trial (as opposed to a non-inferiority trial). As such, the correct interpretation of this study is that the investigators were unable to reject the null hypothesis of no treatment effect and could not demonstrate that mycophenolate is superior to cyclophosphamide [8]. Thus, it is incorrect to conclude that these medications have the same effect. Leukopenia ($n = 30$ versus $n = 4$ patients, $P < 0.05$) and thrombocytopenia (four versus zero patients, $P < 0.05$) occurred significantly more frequently in the cyclophosphamide group. There was no difference in proportion of participants with anemia or pneumonia between treatment arms. There were more serious adverse events in the mycophenolate arm ($n = 42$) than in the cyclophosphamide arm ($n = 36$), but more deaths in the cyclophosphamide arm ($n = 11$) than in the mycophenolate arm ($n = 5$). While some investigators use these data to justify mycophenolate as safer than cyclophosphamide, others question whether these differences are clinically significant.

Naidu *et al.* [9] conducted a double-blind, randomized, placebo-controlled pilot trial of mycophenolate mofetil 2000 mg twice daily compared to placebo among 41 patients with SSc-ILD. The primary outcome was median change from baseline FVC at 6 months. The FVC decreased by a median of 2.7% (range −21 to 9, $P = 0.31$) in the mycophenolate group and increased by a median of 1% (range -6

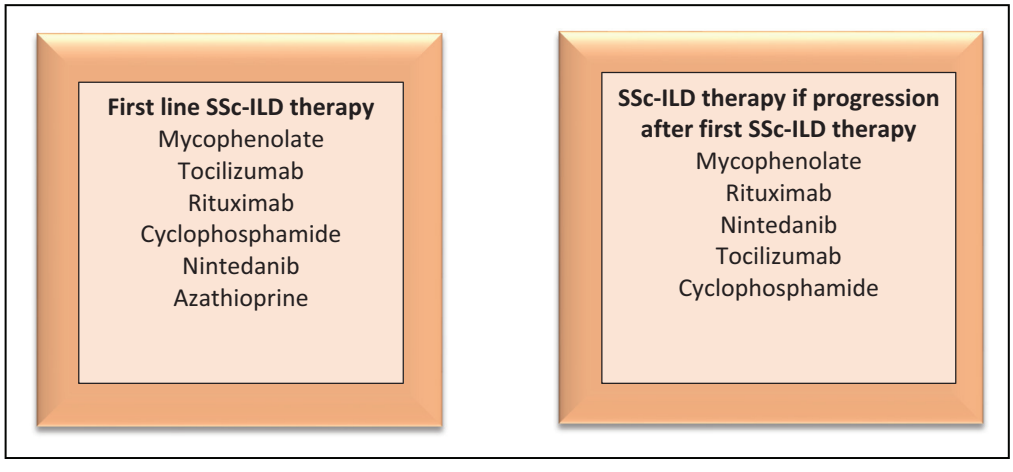

FIGURE 1. Pharmacologic options for the treatment of SSc-ILD.

Table 1. Summary of randomized trials evaluating pharmacologic treatments in SSc-ILD

References	Medications and doses[a]	Sample size[b]	Measure of effect
Naidu *et al.* [9]	Mycophenolate mofetil up to 2000 mg twice daily Placebo	15 Mycophenolate 19 Placebo	FVC decreased by a median of 2.7% (range – 21 to 9; $P=0.307$) in the mycophenolate group and increased by a median of 1% (range – 6 to 10; $P=0.222$) in the placebo group. The mean absolute difference in FVC change from baseline to 6 months between mycophenolate and placebo groups was 3.1% (95% CI −1.0 to 7.3; $P=0.13$).
Tashkin *et al.* [7]	Mycophenolate mofetil (target dose 1500 mg twice daily) for 24 months Oral cyclophosphamide (target dose 2 mg/kg per day) for 12 months followed by placebo for 12 months	63 Mycophenolate 63 Cyclophosphamide	FVC% improved from baseline to 24 months by 2.19 in the mycophenolate mofetil group (95% CI 0.53–3.84) and 2.88 in the cyclophosphamide group (95% CI 1.19–4.58). The course of the FVC% did not differ significantly between the two treatment groups ($P=0.24$), indicating that the trial was negative for the primary endpoint.
Tashkin *et al.* [10]	Oral cyclophosphamide ($\leq$2 mg/kg of body weight per day) Placebo	73 Cyclophosphamide 72 Placebo	Adjusted 12-month FVC% predicted between the cyclophosphamide and placebo groups was 2.53% (95% CI 0.28 to 4.79, $P<0.03$) favoring cyclophosphamide
Hoyles *et al.* [12]	IV cyclophosphamide 600 mg/m^2 (mean dose 1050 mg) at 4-week intervals for 6 months, followed by oral azathioprine at 2.5 mg/kg/day (maximum 200 mg/day) Placebo	19 Cyclophosphamide + Azathioprine 18 Placebo	The between-group difference adjusted for baseline FVC was 4.19% ($P=0.08$).
Nadashkevich *et al.* [13]	Oral cyclophosphamide 2 mg/kg daily Azathioprine (2.5 mg/kg daily	30 Cyclophosphamide 30 Azathioprine	No change in FVC in the cyclophosphamide group: baseline 90.3 versus 92.5% at 6 months, $P=$ not significant Worsening in FVC in the azathioprine group: baseline 91.7 versus 87.3%, $P=0.01$
Sircar *et al.* [14]	IV cyclophosphamide 500 mg/m^2 monthly for 6 months Rituximab 1000 mg at 0 and 15 days.	30 Cyclophosphamide 30 Rituximab	Percentage mean FVC in the rituximab group improved from 61.3 to 67.5 and declined in the cyclophosphamide group from 59.3 to 58.1 at 6 months ($P=0.003$).
Maher *et al.* [16]	Rituximab 1000 mg at weeks 0 and 15 days Cyclophosphamide (600 mg/m^2 body surface area every 4 weeks intravenously for 6 months)	49 Rituximab 48 Cyclophosphamide	Between-group difference in FVC at 24 weeks was –40 ml ($P=0.49$)
Khanna *et al.* [17]	Tocilizumab 162 mg subcutaneous weekly Placebo	43 Tocilizumab 44 Placebo	Smaller decline in FVC in tocilizumab group (-34 ml) versus placebo group (-171 ml) at 24 weeks (least square mean difference 136 ml ($P=0.04$))
Khanna *et al.* [18]	Tocilizumab 162 mg subcutaneous weekly Placebo	104 Tocilizumab 106 Placebo	Least square mean difference in FVC −4.6 in the placebo group and −0.4 in the tocilizumab group (difference 4.2, $P=0{\cdot}0002$)
Acharya *et al.* [21]	Pirfenidone 2400 mg a day Placebo	17 Pirfenidone 17 Placebo	Stabilization/improvement in FVC occurred in 94.1% pirfenidone group versus 76.5% placebo group ($P=0.33$)

[a]Please note that as of this writing, the only FDA-approved medications for the treatment of SSc-ILD are tocilizumab and nintedanib. All other medications discussed in this manuscript are off label for the treatment of SSc-ILD.
[b]Numbers of participants analyzed for the primary outcome. The trials report higher numbers of subjects that were recruited or randomized, but the number of individuals analyzed for the primary outcome is small due to withdrawal or loss to follow-up.

to 10, $P = 0.22$) in the placebo group. The mean absolute difference in FVC change from baseline to 6 months between groups was 3.1% ($P = 0.13$) and not statistically significant. The inability to demonstrate a beneficial effect of mycophenolate over placebo on FVC may include the small sample size, that 6 months of follow-up was too short to detect a treatment effect or that the maximum dose of mycophenolate (3 g/day) was not used. Despite these potential limitations, it is notable that the magnitude of the treatment effect in this trial was comparable to that observed in SLS II. There was no significant difference in the frequency of adverse events between the mycophenolate and placebo groups.

The combined trial evidence suggests that mycophenolate confers a modest beneficial effect on FVC, or at least, results in stabilization of FVC. Moreover, mycophenolate has a more favorable adverse effect profile relative to other options. Furthermore, rheumatologists and pulmonologists have considerable experience with mycophenolate and mycophenolate has a relatively lower cost compared to other options. The combination of evidence, favorable adverse effect profile, experience and cost led to mycophenolate being conditionally recommended for the treatment of SSc-ILD.

CYCLOPHOSPHAMIDE

The Scleroderma Lung Study I (SLS I) was a double-blind, randomized, placebo-controlled trial comparing oral cyclophosphamide (≤2 mg per kilogram per day) to placebo, conducted at 13 US centers [10]. The primary outcome was the FVC% predicted at 12 months, after adjustment for the baseline FVC. Seventy-three participants in the cyclophosphamide group and 72 participants in the placebo group were evaluated for the primary outcome. The mean absolute difference in adjusted 12-month FVC% predicted between the cyclophosphamide and placebo groups was 2.53% (95% CI 0.28–4.79, $P < 0.03$) favoring cyclophosphamide. Oral cyclophosphamide resulted in a modest beneficial effect or stabilization of FVC at 12 months but the effects on FVC collapsed by 24 months [11]. There was a greater frequency of adverse events in the cyclophosphamide group, but the difference in serious adverse events between the two groups was not significant. Leukopenia ($n = 19$ versus $n = 0$ patients, $P < 0.05$) and neutropenia ($n = 7$ patients versus $n = 0$ patients, $P < 0.05$) were more common in the cyclophosphamide group than in the placebo group, with no statistically significant differences in hematuria, anemia or pneumonia between groups.

Hoyles *et al.* [12] reported a double-blind, randomized, placebo-controlled trial comparing intravenous cyclophosphamide 600 mg/m^2 (mean dose 1050 mg) every 4 weeks for 6 months, followed by oral azathioprine 2.5 mg/kg/day (maximum 200 mg/day) to placebo. The cyclophosphamide group also received prednisolone 20 mg orally on alternate days. Nineteen patients received cyclophosphamide followed by azathioprine, and 18 patients received placebo for 1 year. The primary outcome measures were change in FVC% predicted and change in DLCO. The between-group difference adjusted for baseline FVC was 4.19% ($P = 0.08$). Although not statistically significant, the magnitude of this modest effect on FVC is comparable to that observed in SLS I. No bone marrow suppression or hemorrhagic cystitis was observed.

Nadashkevich *et al.* [13] reported a randomized, unblinded, trial conducted in Canada and the Ukraine, comparing oral cyclophosphamide (2 mg/kg daily for 12 months followed by a maintenance dose of 1 mg/kg daily) to azathioprine (2.5 mg/kg daily for 12 months followed by a maintenance dose of 2 mg/kg daily). There was no significant change in FVC% predicted in the cyclophosphamide group (baseline 90.3 versus 92.5% at 6 months, $P =$ not significant), whereas there was a statistically significant worsening in FVC% predicted in the azathioprine group (baseline 91.7 versus 87.3%, $P = 0.01$).

RITUXIMAB

Sircar *et al.* [14] conducted a randomized trial comparing monthly intravenous cyclophosphamide 500 mg/m^2 for 24 weeks to two doses of rituximab 1000 mg at 0 and 15 days. The primary outcome was FVC% predicted at 6 months. The mean FVC% predicted in the rituximab group improved from 61.3 to 67.5% and declined in the cyclophosphamide group from 59.3 to 58.1% at 6 months ($P = 0.003$). Serious adverse events were more common in the cyclophosphamide group.

The DESIRES trial was a double-blind, randomized, placebo-controlled trial conducted at four centers in Japan comparing rituximab (375 mg/m^2) weekly for 4 weeks to placebo [15]. The primary endpoint was the absolute change in mRSS at 24 weeks. One of the secondary endpoints was absolute change in FVC% predicted at 24 weeks. Twenty-seven patients in the rituximab group and 22 patients in the placebo group received at least one dose and completed 24 weeks of follow-up. The absolute change in mRSS was lower in the rituximab group than in the placebo group (-6.3 versus 2.14, $P < 0.0001$). The absolute change in FVC% predicted was 0.09% in the rituximab group and -2.87% in the placebo group ($P = 0.044$). Adverse events were

similar in both groups. The most common adverse event was upper respiratory infection ($n = 11$ rituximab group, $n = 10$ placebo group).

The RECITAL trial was a randomized, double-blind, double-dummy, controlled trial comparing rituximab (1000 mg at weeks 0 and 2 intravenously) to cyclophosphamide (600 mg/m^2 body surface area every 4 weeks intravenously for 6 months) in patients with severe or progressive ILD related to SSc, idiopathic inflammatory myositis or mixed connective tissue disease conducted at 11 centers in the United Kingdom [16]. The primary endpoint was change in FVC at 24 weeks compared with baseline. Forty-eight participants in the cyclophosphamide group and 49 in the rituximab group received at least one dose of treatment. At 24 weeks, FVC was improved from baseline in both the cyclophosphamide group (unadjusted mean increase 99 ml) and the rituximab group (97 ml). The difference in the primary endpoint at 24 weeks was -40 ml ($P = 0.49$) between the rituximab and cyclophosphamide groups. Gastrointestinal and respiratory issues were the most commonly reported adverse events in both groups. This trial was unable to demonstrate that rituximab is superior to cyclophosphamide, as both treatments resulted in increased FVC.

TOCILIZUMAB

The faSScinate study was a multicenter, international, randomized, double-blind, placebo-controlled phase 2 trial comparing subcutaneous tocilizumab 162 mg weekly to placebo [17]. The primary endpoint was the difference in mean change from baseline in mRSS at 24 weeks. Change in FVC at 48 weeks was an exploratory endpoint. Forty-three patients were assigned to tocilizumab and 44 assigned to placebo. The least squares mean change in mRSS at 24 weeks was -3.92 in the tocilizumab group and -1.22 in the placebo group (difference -2.70, $P = 0.09$). Fewer patients in the tocilizumab group than in the placebo group had a decline in FVC% predicted at 48 weeks ($P = 0.04$). Serious infections were more common in the tocilizumab group ($n = 7$ [16%]) than in the placebo group ($n = 2$ [5%]).

The focuSSced trial was a multicenter, international, randomized, double-blind, placebo-controlled phase 3 trial comparing tocilizumab 162 mg subcutaneous weekly to placebo for 48 weeks [18]. The primary outcome was the difference in change in mRSS from baseline to week 48. FVC% predicted at week 48 was a secondary outcome. The adjusted difference in mRSS was -1.73 ($P = 0.10$). The least square mean change from baseline in FVC% predicted was −4.6 in the placebo group and −0.4 in the tocilizumab group with a difference of 4.2 ($P = 0.0002$). There were 54 (52%) adverse events in the tocilizumab group and 53 (50%) in the placebo group.

The combined data suggest that tocilizumab has a modest beneficial effect or preserves lung function in people with early SSc-ILD, specifically those with diffuse cutaneous SSc and elevated acute-phase reactants. These data led to the approval of tocilizumab for SSc-ILD by the US Food and Drug administration.

NINTEDANIB

The largest study of SSc-ILD to date – the SENSCIS trial – was a multicenter, international, randomized, placebo-controlled trial [19]. Five hundred seventy-six SSc-ILD patients were randomized to receive nintedanib 150 mg twice daily or placebo [20]. About 48.4% of patients had been treated with mycophenolate for at least 6 months before enrollment. The adjusted annual rate of change in FVC over 52 weeks was -52.4 ml/year in the nintedanib group compared to -93.3 ml/year in the placebo group (difference: 40.9 ml/year; $P = 0.03$) [20]. Nintedanib, in combination with mycophenolate, provided greater numerical preservation of lung function than mycophenolate in combination with placebo, but this was not statistically significant ($P = 0.45$) and SENSCIS was not powered to detect differences in the primary outcome based on baseline mycophenolate use. Diarrhea was reported in 76% ($n = 106$) of the nintedanib group and 34% ($n = 48$) of the placebo group among those taking mycophenolate at baseline. More data are needed regarding the benefits of initial combination therapy versus a sequential approach in the treatment of SSc-ILD.

PIRFENIDONE

Acharya *et al.* [21] report a double-blind, randomized, placebo-controlled, pilot study comparing pirfenidone 2400 mg per day to placebo for 6 months. The primary outcome was the proportion of subjects with stabilization or improvement in FVC at 6 months. Thirty-four individuals were enrolled. Stabilization/improvement in FVC occurred in 16 (94.1%) of the pirfenidone group and 13 (76.5%) of the placebo group ($P = 0.33$). The median absolute change in FVC% predicted was −0.55 in the pirfenidone group and 1.0 in the placebo group ($P = 0.51$). Common adverse events were gastrointestinal issues and skin rash. This pilot study was unable to demonstrate a beneficial effect of pirfenidone over placebo in improving/stabilizing FVC.

The RELIEF trial was a multicenter, double-blind, randomized, placebo-controlled trial conducted at 17

centers in Germany. One-hundred twenty-seven patients with progressive fibrotic ILD eight 8 (6%) with SSc-ILD were randomized to pirfenidone (titrated up to 801 mg three times per day) or matched placebo, in addition to background therapy [22]. The primary endpoint was change in FVC% predicted from baseline to week 48. The trial was prematurely terminated due to an interim analysis for futility prompted by slow recruitment. Analysis of the available data suggested treatment with pirfenidone resulted in a significantly smaller decline from baseline to week 48 in FVC% predicted than placebo ($P = 0.04$). Analysis of the SSc-ILD patients was not conducted due to the small sample size.

The Scleroderma Lung Study III was a multicenter, double-blind, placebo-controlled, phase 2 trial evaluating combination mycophenolate mofetil and pirfenidone compared to mycophenolate mofetil and placebo in SSc-ILD [23]. The primary endpoint was the change from baseline in FVC% predicted over 18 months. The investigators were unable to recruit to the prespecified sample size of 150 individuals due to the COVID-19 pandemic and the impact of prior medication use on eligibility. Twenty-seven participants were randomized to mycophenolate with pirfenidone and 24 were randomized to mycophenolate with placebo. Over 18 months, there was a 2.24% improvement in the mycophenolate mofetil with placebo group and a 2.09% improvement in the mycophenolate mofetil with pirfenidone group, and no statistically significant difference between groups ($P = 0.93$). About 74.1% of individuals on mycophenolate with pirfenidone compared to 29.2% on mycophenolate with placebo had adverse events of special interest (gastrointestinal: 55.6 versus 20.8%, photosensitivity: 14.8 versus 0%).

In summary, clinical trials in SSc-ILD provide an evidence base to inform the ACR/CHEST guidelines for the treatment of SSc-ILD. There are several treatments that provide a modest beneficial effect or stabilize FVC. The choice of pharmacologic option will necessitate shared decision making with the individual patient based on values, preferences, cost and extra-pulmonary manifestation.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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