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Systemic-Sclerosis-Related Interstitial Lung Disease: A Review of the Literature and Recommended Approach for Clinical Pharmacists

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Abstract

Objective: To describe the efficacy, safety, and clinical utility of pharmacologic agents in the treatment of systemic sclerosis-related interstitial lung disease (SSc-ILD). **Data Sources:** A review of the literature was performed using the terms lung diseases, (interstitial/therapy) AND (scleroderma, systemic/therapy) OR (scleroderma, systemic) AND (lung diseases, interstitial/therapy) in PubMed, Ovid MEDLINE, CINAHL, and Web of Science. ClinicalTrials.gov was also searched to identify ongoing studies. The initial search was performed in October 2022, with follow-up searches performed in October 2023. **Study Selection and Data Abstraction:** Articles reviewed were limited to those written in the English language, human studies, and adult populations. **Data Synthesis:** A variety of therapeutic agents, including mycophenolate, azathioprine, cyclophosphamide (CYC), rituximab (RTX), nintedanib, and tocilizumab (TCZ) have slowed the rate of decline in forced vital capacity (FVC) and disease progression. Only nintedanib and TCZ have a labeled indication for SSc-ILD. Two agents, belimumab and pirfenidone, have shown encouraging results in smaller phase II and phase III studies, but have yet to be approved by the Food and Drug Administration. **Relevance to Patient Care and Clinical Practice:** Patients with pulmonary manifestations of SSc-ILD have worse outcomes and lower survival rates compared with those without. It is imperative that disease management be individualized to achieve optimal patient-centered care. Pharmacists are uniquely suited to support this individualized management. **Conclusion:** Numerous pharmacologic agents have been studied and repurposed in the treatment of SSc-ILD, with nintedanib and TCZ gaining approval to slow the rate of decline in pulmonary function in SSc-ILD. Other agents, including belimumab and pirfenidone, are on the horizon as potential treatment options; but further studies are needed to compare their efficacy and safety with the current standard of care.

Keywords

systemic sclerosis, interstitial lung disease, pharmacotherapy, review, literature evaluation, pharmacist role

Introduction

Systemic sclerosis (SSc) is a complex autoimmune chronic connective tissue disease (CTD) characterized by progressive fibrosis of the skin and internal organs.[1] Manifestations in organs other than the skin typically occur early in the course of the disease.[2] Interstitial lung disease (ILD) occurs in 35% to 52% of patients with SSc and typically develops within the first 5 years of SSc symptom onset.[3,4] Although the pathogenesis of SSc-ILD is not well understood, there is a combination of inflammation, epithelial damage, and fibroblast dysfunction that results in thickening of the

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pulmonary interstitum.[5] Approximately, 25% to 40% of patients with SSc who also develop ILD develop progressive disease with worsening fibrosis and poorer outcomes.[6,7] Risk factors predictive of disease progression in SSc-ILD include male sex, African-American ethnicity, diffuse cutaneous SSc, presence of anti-Scl-70/anti-topoisomerase I antibodies, baseline forced vital capacity (FVC) less than 70%, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) less than 50%, and cardiac involvement.[8] SSc-ILD also has variable disease state progression; many patients are often asymptomatic early on and may never progress to develop dyspnea, fatigue and nonproductive cough. However, others are at risk for rapid, life-threatening deterioration especially in the first 3 years of disease onset.[9] Progression can manifest as worsening respiratory symptoms, exercise tolerance, lung function (assessed with pulmonary function tests), and changes in high-resolution computed tomography (HRCT).[8]

The range in clinical features of SSc-ILD and heterogeneity in the patient population make diagnosis and treatment challenging. Furthermore, clinical trials have demonstrated that current therapies do not diminish disease-related inflammation or fibrosis consistently and that some patients experience progression despite treatment.[9-12] Treatment is also challenging for providers given the small sample sizes in primary literature, lack of established practice guidelines for SSc-ILD therapy, and variability in disease-state progression and response to treatment. Recently, an expert panel convened to address these issues with consensus recommendations for SSc-ILD management; however, there is still no established treatment algorithm that exists for these patients.[13]

Several therapies have been evaluated for the treatment of SSc-ILD, including immunosuppressive therapies, antifibrotic agents, immunomodulators, monoclonal antibodies, hematopoietic stem cell transplant, and lung transplant. Prior to 2019, primary treatment for SSc-ILD included the use of immunosuppressive therapies, such as azathioprine, CYC, methotrexate, and mycophenolate mofetil (MMF). In 2019, the tyrosine kinase inhibitor nintedanib was approved for the treatment of SSc-ILD.[14] More recently, tocilizumab (TCZ) was the first biologic agent approved for SSc-ILD.[15] Treatment decisions are typically made on a case-by-case basis, as such, there is a need to better understand the current evidence for treatment efficacy and safety. The objective of this review is to present existing literature on drug treatments for SSC-ILD. The review will include mechanism of action, dosing, critical adverse events, and specific key clinical characteristics that facilitate use of these medications for SSC-ILD.

Data Selection

A literature search was conducted using the following databases: PubMed, Ovid MEDLINE, CINAHL, and Web of Science. Search results were limited to the English language, human studies, and adult populations. Cited references were examined and journals dedicated to pulmonary research were also reviewed. No date restrictions were included as part of the search. Search terms included a combination of index terms and keywords for (lung diseases, interstitial/therapy) AND (scleroderma, systemic/therapy) OR (scleroderma, systemic) AND (lung diseases, interstitial/therapy). Medical subject headings (MeSHs) were included when available. A search of clinicaltrials.gov was also conducted to identify ongoing therapeutic studies. The condition terms searched included (systemic sclerosis with lung involvement) OR (systemic sclerosis pulmonary) OR (interstitial lung disease due to systemic disease). The initial search was performed in October 2022, with follow-up searches performed in October 2023.

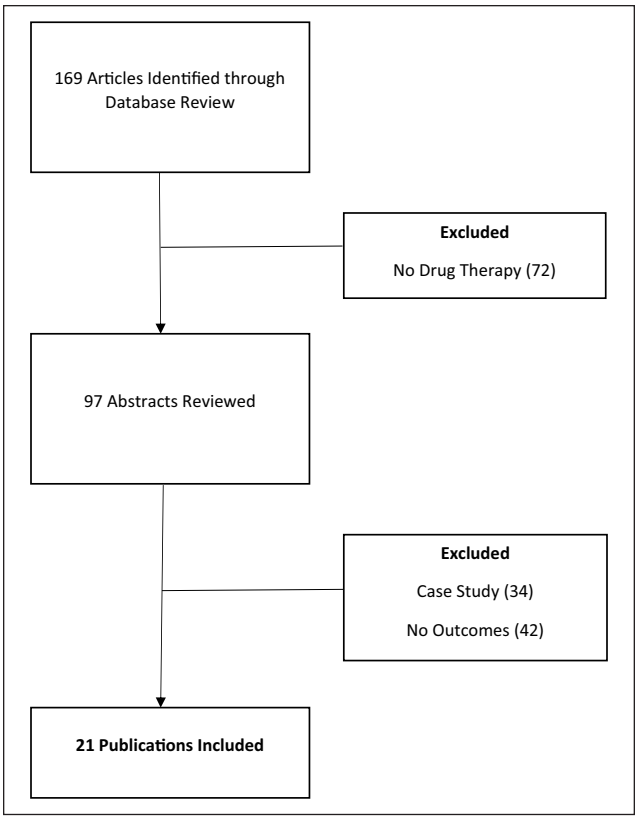

Figure 1. Study inclusion. References were identified through PubMed, Ovid, MEDLINE, CINAHL, and Web of Science databases. Search results were limited to English language, human studies, and adult populations.

Results

Search Results

Search results from these sources yielded 169 potential articles (Figure 1). References from selected articles were also reviewed. Articles were excluded if outcome data were not

available. A total of 97 abstracts were reviewed and 21 of these publications were included. Outcomes were compiled for the individual treatment options and are summarized in Table 1. A brief review of the treatment categories and the individual agents is provided below. Table 2 provides mechanism of action, dosing information, adverse events, and clinical pearls for the treatment options in SSc-ILD.

Immunosuppressants

The known immune system involvement in SSc-ILD has led to the use of immunosuppressive therapies, such as MMF/mycophenolic acid (MPA), azathioprine, and cyclophosphamide (CYC).[47] While methotrexate is used in the treatment of SSc-ILD, particularly with scleroderma, studies assessing its efficacy in patients with ILD have not observed significant improvements in pulmonary function tests during the treatment period.[48,49] Practitioners must be mindful of the screenings that should be completed prior to initiating these therapies. A baseline complete blood count with differential and a comprehensive metabolic panel should be obtained. Prescreening should be completed for infections, such as cytomegalovirus, Hepatitis B/C, human neurotrophic polyomavirus (JC virus), and tuberculosis. Patients should also complete all age-appropriate oncologic screenings. As these therapies have teratogenic properties, patients require counseling on the risks associated with potential pregnancies.[16,21,26,27,34]

Corticosteroids

Corticosteroids, commonly referred to as "glucocorticoids," are anti-inflammatory agents that mimic the effects of the naturally occurring hormone, cortisol.[50] Glucocorticoids are typically used at low doses ($\leq$ 10 mg/day of prednisone or equivalent) in combination with other immunosuppressive agents, as the efficacy of monotherapy is uncertain. The therapeutic use of corticosteroids in SSc-ILD is largely empirical and mimics strategies used in other inflammatory related disorders.[12] One study showed a trend toward stabilization of lung function with corticosteroid monotherapy compared with placebo, although the difference was not statistically significant.[17] Furthermore, higher doses of steroids should be avoided due to increased risk of precipitating a scleroderma renal crisis.[51,52] In an expert consensus for steroid use in SSc-ILD, only 11% of experts indicated they always used steroids; 28% would use sometimes and 24% would use occasionally. In the experts who would use steroids "always," 41% would treat with prednisone at $<$ 7.5mg/day and 42% would use for less than 3 months.[13]

MMF and Mycophenolate Sodium

MMF is the prodrug of mycophenolate acid (MPA), an inhibitor of inosine monophosphate dehydrogenase.[26,27] MMF and MPA have been used as steroid-sparing agents in the treatment of rheumatologic diseases and in the prevention of acute graft rejection in patients with solid organ transplants.[26-28] MMF emerged as an alternative treatment for SSc-ILD due to the long-term toxicity associated with CYC.[29] A meta-analysis of 4 retrospective studies evaluating the use of MMF in SSc-ILD found a statistically significant difference in FVC at baseline and 12 months after treatment (mean difference of 4.73 and 64.71% versus 69.44% of predicted normal value or 215mL).[30] Tashkin and colleagues designed the first study directly comparing CYC with MMF (Scleroderma Lung Study [SLS] II). Most patients in the MMF arm (72%) had improvements in FVC but the study design lacked a placebo arm.[10] A subsequent analysis, conducted by Volkham and colleagues, compared outcomes of patients in the MMF arm of SLS II with patients assigned to the placebo arm of SLS I.[22,29] A total of 64.4 and 71.7% of patients treated with MMF experienced improvements in FVC at 12- and 24-months, respectively.[29] When comparing MMF with other immunosuppressants for the treatment of SSc-ILD, efficacy tends to be similar. Since MMF is better tolerated by patients it tends to be utilized more in clinical practice.[10,29,30] MMF has primarily been evaluated in the SSc-ILD literature. However, practitioners may opt to use MPA over MMF in patients who already experience gastrointestinal related symptoms or who have drug-drug interactions. A meta-analysis comparing MMF with MPA showed no statistical difference favoring one over the other.[30]

Azathioprine

Azathioprine (AZA) is a purine analog that converts to the active metabolites mercaptopurine and thioguanine. AZA has been used historically as a second-line adjunctive therapy to prevent rejection after a kidney transplant and in the treatment of rheumatoid arthritis.[16] The studies evaluating AZA for SSC-ILD are mostly case reports and retrospective cohorts and the impact on rate of FVC decline remains unclear. The first use of AZA was explored in a retrospective case series which showed improved FVC at 12 months when AZA was combined with low dose prednisone for eleven patients.[18] In a randomized, double-blind placebo-controlled study, AZA or placebo was added to patients following CYC infusions of 600 mg/m^2 every 4 weeks for 6 months. The addition of AZA had a trend toward improving FVC in the 22 patients studied but was not statistically significant.[17] In a prospective cohort evaluating 18 patients, AZA was compared with MMF and found to have a similar rate of decline in FVC but the drug discontinuation of AZA was higher due to adverse effects.[37]

Cyclophosphamide

CYC is a nitrogen mustard that exerts its immunosuppressive effects via alkylation of DNA.[21] In addition, lower doses of CYC than those used to treat malignancies have

Table 1. Therapeutic Agents Used in the Treatment of SSc-ILD.

Medication	Mechanism of action	Dosing information	ADEs	Clinical pearls
Azathioprine[16-18]	Purine analog that converts into the active metabolites mercaptopurine and thioguanine, which block purine synthesis and incorporate into replicating DNA to halt cellular division of inflammatory cells	Goal dose of 2-2.5 mg/kg (based on actual body weight) Reduced dose recommended in those with thiopurine-s-methyltransferase deficiency	Common: leukopenia (28%), nausea/vomiting (12%) Rare: risk of infection (< 1%)	Requires screening for thiopurine-s-methyltransferase deficiency prior to initiation due to increased risk of ADEs
Belimumab[19,20]	Fully human B-cell inhibiting monoclonal antibody. Acts as a B-lymphocyte stimulator-specific (BLys) antibody and binds to soluble BLys to inhibit autoreactive B cells, leading to cellular apoptosis	IV: 10 mg/kg IV infusion every 2 weeks × 3 doses, then every 4 weeks thereafter SQ: 200-400 mg once weekly	Common: nausea (15%), diarrhea (12%), pyrexia (10%), and nasopharyngitis and bronchitis (9%) Warnings and precautions: serious infections (including tuberculosis and progressive multifocal leukoencephalopathy), hypersensitivity reactions, depression, suicidality	Currently FDA-approved for the treatment of lupus nephritis and systemic lupus erythematosus
Cyclophosphamide[21,22]	Nitrogen mustard exerts immunosuppressive effects via DNA alkylation. Lower doses than those traditionally used to treat malignancies have demonstrated selective modulation of T-lymphocytes, leading to decreased inflammatory response and skin fibrosis	IV: 600 mg/m^2 every 4 weeks (maximum 1200 mg/dose) PO: 1 mg/kg/day (rounded to the nearest 25 mg) with increase to 2 mg/kg/day based on response and tolerability	Common: Myelosuppression, nausea, vomiting, diarrhea, abdominal pain, alopecia, skin rash Warnings and precautions: hemorrhagic cystitis, pulmonary toxicity, malignancy, cardiotoxicity (especially in those >55 years of age)	Treatment should be limited to 6 months for CYC IV and 12 months with CYC PO. Pregnancy should be avoided due to risk of fetal harm, and contraception should be used during and for at least 4 months after treatment in males and up to 1 year after treatment completion in females. CYC has also been associated with infertility
Imatinib[23-25]	Tyrosine kinase inhibitor that acts on Brc-Abl, the abnormal fusion gene on the Philadelphia chromosome in chronic myeloid leukemia. Thought to have downstream effects on other tyrosine kinase inhibitors involved in fibrosis, including transforming growth factor-beta and platelet-derived growth factors	Doses range from 100 to 800 mg PO per day	Common: fluid retention (62%), nausea (50%), muscle cramps (50%), diarrhea (45%), fatigue (39%), and headache (37%) Warnings and precautions: hematologic toxicities, hepatotoxicity, dermatologic toxicities (including Stevens-Johnsons syndrome), teratogenicity when administered to pregnant patients	Greater rates of drug toxicity and discontinuation demonstrated in patients receiving > 400 mg/day, limiting utility
Mycophenolate[10,26-30]	Inhibits inosine monophosphate dehydrogenase to deplete guanosine nucleotides and block DNA synthesis of B-lymphocytes and T-lymphocyte, ultimately leading to decreased cellular proliferation and immunosuppressive effects	MMF: initial dose of 500 mg twice daily, titrated to 1500 mg twice daily as tolerated EC-MPS: initial dose of 360 mg twice daily, titrated to 1080 mg twice daily as tolerated	Common: abdominal pain (14%-63%), constipation (38%-44%), diarrhea (24%-53%), dyspepsia (9%-23%), nausea (27%-56%), headache (11%-59%), hypertension (18%-79%), sleep disorders (3%-52%) Warnings and precautions: Leukopenia (19%-46%), leukocytosis (22%-43%), thrombocytopenia (24%-38%)	Classified under REMS drug safety program. Should be used by providers experienced in immunosuppressive therapy given risk of serious infection, malignancy, and fetal toxicity. EC-MPS may be preferred in patients experiencing gastrointestinal-related symptoms due to a lower risk of ADEs, or in patients on proton-pump inhibitors

Table 1. (continued)

Medication	Mechanism of action	Dosing information	ADEs	Clinical pearls
Nintedanib[14,31,32]	Small molecule kinase inhibitor that binds multiple growth factors overstimulated during lung repair. This leads to inhibition of fibroblast proliferation	150 mg PO twice daily Can be reduced to 100 mg twice daily if ADEs are severe	Common: diarrhea (76%), nausea/vomiting (32%), increased liver enzymes (13%-14%), fatigue (10%-11%), weight loss (10%-12%) Warnings and precautions: cardiovascular events, including myocardial infarction and arterial thrombosis, drug-induced liver injury	Nintedanib can cause fetal harm when administered to pregnant patients; contraception should be used during treatment and up to 3 months after the last dose
Pirfenidone[33]	Mechanism of action not entirely known; thought to exert antifibrotic effects through inhibition of transforming growth factor-beta to decrease fibroblast proliferation	Goal dose of 801 mg 3 times per day titrated over a 2-week period Dose reduction may be required in those experiencing ADEs, or taking moderate or strong CYP1A2 inhibitors, such as ciprofloxacin or fluvoxamine	Common: nausea (36%), diarrhea (26%), abdominal pain (24%), upper respiratory tract infection (27%), rash (30%), and fatigue (26%) Warnings and precautions: Drug-induced liver injury, severe cutaneous ADEs (including Stevens-Johnson syndrome and toxic epidermal necrolysis)	Smoking has demonstrated decreased exposure to pirfenidone, which may alter its effectiveness. Patients should be instructed to stop smoking prior to treatment initiation
Rituximab[34,35]	Chimeric anti-CD20 monoclonal antibody that acts on B-lymphocytes to mediate cell lysis and decrease autoantibodies	Two doses of 1000 mg IV 14 days apart, then repeat every 6 months	Common: Pruritus/rash (17%), night sweats (15%), hypophosphatemia (12%-21%), abdominal pain/diarrhea (10%-17%), nausea (8%-23%), hepatic (17%), arthralgias (6%-13%), and muscle spasms (17%) Warnings and precautions: Reactivation of hepatitis B, serious/fatal infections (including bacterial, fungal, or viral), progressive multifocal leukoencephalopathy, infusion-related reactions (including, angioedema, hypotension, acute respiratory distress syndrome, and ventricular fibrillation)	Not FDA-approved in the treatment of SSc-ILD, but used off-label
Tocilizumab[15]	IL-6 receptor antagonist that leads to reduction in cytokine release and inhibition of a variety of immunologic responses	162 mg weekly via self-administered subcutaneously injection	Common: Increased cholesterol (19%-20%), constipation (6%-13%), injection site reactions (7%-10%), upper respiratory tract infections and nasopharyngitis (5%-8%) Warnings and precautions: neutropenia, thrombocytopenia, serious infections (including tuberculosis and herpes zoster), gastrointestinal perforation, hepatic injury or failure, hypersensitivity reactions, demyelinating disorders	Therapy should not be initiated in patients with an absolute neutrophil count $< 2000/mm^3$, platelet count $< 100\,000/mm^3$, or if liver enzymes are more than 1.5 times the upper limit of normal. A baseline lipid panel should be obtained due to the risk of lipid elevations

Abbreviations: ADE, adverse drug effect; CYC, cyclophosphamide; EC-MFS, enteric-coated mycophenolate sodium; FDA, Food and Drug Administration; IL-6, interleukin-6; ILD, interstitial lung disease; IV, intravenous; MMF, mycophenolate mofetil; PO, oral; REMS, Risk Evaluation and Mitigation Strategy; RTX, rituximab; SQ, subcutaneous; SSc, systemic sclerosis; TCZ, tocilizumab.

Table 2. Summary of Clinical Trials Evaluating Efficacy of Therapies for SSc-ILD.

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Liossis et al[36] Prospective, single-arm, OL trial	Adults with early diffuse SSc and pulmonary involvement	Age ≥ 18 years and identification of ground-glass opacities on HRCT	Clinically significant infection, leukopenia (defined as white blood cell count < 4000 WBCs/mcL), pregnancy, history of malignancy	MMF 1000 mg/day (with option to titrate to 2000 mg/day) plus prednisolone 7.5-10 mg/day ($N = 6$)	Change in DLCO from pretreatment to 4-6 months of MMF treatment	DLCO and FVC improved significantly in all patients after 4-6 months of therapy (mean pretreatment DLCO 64.2% vs post-treatment DLCO 75.4% predicted, $P = 0.033$; mean pretreatment FVC 65.6% vs posttreatment 76.2% predicted, $P = 0.057$), apart from FVC in 1 patient	No serious adverse events, including clinically significant infections or leukopenia, were reported
Owen et al, [37] Prospective cohort trial	Adults with SSc-ILD on therapy for ≥3 months	Registered in the Australian Scleroderma Cohort Study, age ≥ 18 years, diagnosis of SSc-ILD (meeting ACR criteria for SSc and having interstitial abnormalities on HRCT), taking MMF or AZA for at least 3 months	Patients not meeting inclusion criteria; no specific exclusions reported	MMF 2000 mg/day ($N = 18$) AZA 100 mg/kg/day ($N = 29$)	Change in absolute FVC	Rate of decline in FVC was similar between groups (median absolute FVC 2.13 at 12 months from 2.12 at baseline [95% CI = 1.79, 2.56, $P = 0.86$] in MMF compared with median absolute FVC of 2.54 at 12 months from 2.51 at baseline [95% CI = 1.91, 3.02, $P = 0.09$]) in AZA	Overall number of ADEs were similar between groups treated with at least 12 months of drug therapy (13.8% in AZA vs 16.6% in MMF), however, rate of drug discontinuation due to ADEs was higher in those receiving AZA compared with MMF (26.5% vs 18.2%, respectively)
Tashkin et al[10] DB, R, PG trial	Adults 18-75 years old with SSc-ILD and FVC < 80% but ≥45% of predicted	Age 18-75 years, FVC < 80% but ≥45% of predicted, ground-glass opacities on HRCT, onset of first non-Raynaud's symptom of SSc within previous 7 years	FVC < 45% of predicted, FEV1/FVC ratio < 65%, pulmonary hypertension, smoking within the previous 6 months, persistent leukopenia or thrombocytopenia, uncontrolled heart failure, pregnancy and/or lactation, prior use of CYC or MMF for more than 8 weeks, malignancy or other serious concomitant medical illness	MMF 3000 mg/day for 24 months ($N = 69$) CYC 1.8-2.3 mg/kg/day PO with evening placebo for 12 months, then placebo BID for 12 months ($N = 73$)	Change in % predicated FVC from baseline to 24 months	There was no difference in change in % predicted FVC between groups (2.88% and 2.19% predicted for CYC and MMF, respectively [95% CI = −3.1, 1.7, $P = 0.24$])	Leukopenia (51 events vs 5 events), thrombocytopenia (7 events vs 0 events), and anemia (26 events vs 18 events) occurred more in patients receiving CYC compared with MMF, however, more serious ADEs were seen in those who received MMF (42 events vs 36 events)

(continued)

Table 2. (continued)

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Volkmann et al[29] R, DB, PC trial	Adults enrolled in the MMF arm of the SLS II trial and the placebo arm of the SLS I trial	Age ≥ 18 years, disease duration ≤ 7 years from onset of first non-Raynaud's symptom, FVC 40%-85% of predicted, DLCO ≥40% of predicted, evidence of ground-glass opacities on HRCT	FVC < 40% of predicted, Fev1/FVC ratio < 65%, pulmonary hypertension, DLCO < 40% of predicted, previous use of MMF or CYC, other serious concomitant medical illness, inability to use appropriate contraception if of child bearing age	MMF 3000 mg/day in divided doses ($N = 69$) from SLS II Matching placebo ($N = 79$) from SLS I	Change in % predicted FVC	Improvement in FVC was seen in 64.4% and 71.7% of patients treated with MMF at 12 and 24 months, respectively. Only 28.8% and 37.5% of patients treated with placebo saw improvements at 12 and 24 months	More patients experienced serious ADEs in the placebo group compared with MMF (38 vs 27 events)
Naidu et al[38] DB, R, PC trial	Adults with mild SSc-ILD not previously on immunosuppression within 3 years of enrollment	Age ≥ 18 years, features of ILD on HRCT with < 20% involvement, baseline FVC ≥ 70% of predicted, fulfilled ACR criteria for SSc	Received immunosuppression in the last 3 years, severe pulmonary arterial hypertension, pregnancy, or lactation, abnormalities on HRCT not related to ILD, decompensated heart failure, active infection	MMF 2000 mg/day ($N = 20$) Matching placebo BID ($N = 22$)	Change in FVC from baseline to 6 months	This study demonstrated no difference in lung function as measure by change in FVC (−2.7% [95% CI = −21, 9] vs 1% [95% CI = −6, 10], $P = 0.131$) in patients taking MMF compared with placebo	There were no differences in rates of adverse events per patient (1.6 episodes per subject in MMF vs 1.14 episodes per subject in placebo, $P = 0.147$). More patients taking MMF reported diarrhea (15 episodes) compared with placebo (7 episodes)
Dheda et al[18] Retrospective case series	Adults with SSc-ILD with progressive pulmonary symptoms and/or FVC < 70% of predicted	Fulfill ACR criteria for SSc; diagnosis of ILD confirmed with presence of clinical symptoms, abnormal PFTs, and evidence of ILD on HRCT; received AZA for at least 3 months	Patients not meeting inclusion criteria; no specific exclusions reported	AZA plus low-dose prednisone (no doses described) ($N = 11$)	Response to treatment, defined as improved if FVC increased by ≥10% from baseline and stable if remained within 10% of baseline	Mean FVC improved from a baseline of 54.25 ± 3.53% to 63.38 ± 6.15% at 12 months. At 12 months of treatment, 5 of 8 patients were classified as improved and 3 of 8 were classified as stable	Three patients receiving AZA dropped out of the study due to ADEs (one due to nausea, one due to leukopenia, and one due to development of tuberculosis after 6 months of treatment)
Tashkin et al[22] DB, R, PC trial	Scleroderma-related ILD with FVC between 45% and 85% of predicted and grade 2 exertional dyspnea	Age ≥ 18 years, fulfill ACR criteria for SSc, FVC ≥ 85% predicted, dyspnea on exertion, SSc duration ≤ 7 years, ≥2% neutrophils or ≥3% eosinophils in screening bronchoalveolar lavage fluid and/or ground-glass opacities on HRCT	FVC < 45% predicted, DLCO < 30% predicted, persistent unexplained hematuria, history or persistent leukopenia or thrombocytopenia, serum creatinine ≥2.0 mg/dL, pregnancy, uncontrolled heart failure, active infection, prior use of oral CYC for >4 weeks or prior administration of ≥2 doses of intravenous CYC	CYC 2 mg/kg/day PO ($N = 79$) Matching placebo ($N = 79$)	FVC at 12 months	One year of treatment with CYC demonstrated improvement in lung function (adjusted mean absolute difference in FVC of 2.53% [95% CI = 0.28, 4.79, $P < 0.03$), but no improvement in gas exchange compared with placebo (absolute difference in % predicted DLCO −1.04%, $P = 0.43$)	Hematuria (9 events vs 3 events), leukopenia (19 events vs 0 events), and neutropenia (7 events vs 0 events) were more common in the first year of treatment in the CYC group, but were similar at 24 months (hematuria: 1 event vs 2 events, leukopenia: 0 events vs 0 events, and neutropenia: 0 events vs 0 events)

(continued)

Table 2. (continued)

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Hoyles et al[17] Multicenter, DB, R, PC trial	Adults with SSc-associated pulmonary fibrosis	Age 18-75 years, fulfill the ACR criteria for SSc, have SSc-associated pulmonary fibrosis indicate by HCRT or lung biopsy	Previously treated with AZA or CYC for > 3 months, previous treatment with high-dose oral corticosteroids 3 months prior to study entry, poorly controlled diabetes or osteoporosis, likely to require lung transplantation within 1 year, pregnancy or lactation, alcohol or drug use	CYC 600 mg/m^2 IV every 4 weeks x 6, prednisone 20 mg qOD for induction, and AZA 2.5 mg/kg/day ($N = 22$) CYC 600 mg/m^2 IV every 4 weeks $\times$ 6, prednisone 20 mg qOD for induction, and matching placebo ($N = 23$)	Change in % predicted FVC and DLCO	FVC trended toward a significant improvement at 1 year after adjustment for baseline (82.5 $\pm$ 11.3 in treatment group vs 78.0 $\pm$ 21.6 % predicted in placebo, $P = 0.08$), but no significant changes were seen in other pulmonary function parameters	ADEs in the treatment group were relatively low and unsustained. The most common transient adverse events in the treatment group included nausea (36.4%), mood disturbances (18.2%), mouth ulceration (13.6%), rash (13.6%), abnormal LFTs (9.1%), and diarrhea (9.1%). Serious adverse events, including infection, were similar between groups
Sircar et al[39] OL, R trial	Adults with diffuse cutaneous SSc and ILD	Age 18-60 years, diagnosis of diffuse cutaneous SSc meeting the ACR criteria, ILD indicate on HRCT and PFTs, onset of SSc symptoms within 3 years of study inclusion	Receipt of any immunosuppression prior to study, pregnancy or lactation, active infection, presence of hepatitis B or C, HIV infection, active tuberculosis, uncontrolled heart failure, moderate to severe pulmonary hypertension, FVC < 45% predicted, persistent unexplained hematuria, thrombocytopenia, or leukopenia	CYC mg/m^2 IV every 4 weeks $\times$ 6, followed by MMF or AZA plus prednisolone 10 mg/day ($N = 32$) RTX 1000 mg IV on days 0, 15, and at 6 months plus prednisolone 10 mg/day ($N = 32$)	FVC % predicted at 24 weeks	Mean difference in change in % predicted FVC favored RTX (9.46% [95% CI = 3.01, 15.90, $P = 0.003$) along with changes in skin and disease severity scores	There were significantly fewer adverse drug effects reported in patients who received RTX compared with CYC (30% in RTX vs 70% in CYC $P = 0.02$)
Maher et al[40] R, DB, DD phase 2b trial	Adults with severe or progressive CTD-ILD	Age 18-80 years; diagnosis of SSc, idiopathic inflammatory myositis, or mixed CTD with associated severe of progressive ILD evident on HRCT	Previous receipt of CYC or RTX, current use of noncorticosteroid immunosuppression, history of obstructive lung disease with FEV1/FVC ratio of < 0.7	CYC 600 mg/m^2 every 4 weeks $\times$ 20 weeks follow by placebo ($N = 49$) RTX 1000 mg IV on days 0 and 15 followed by placebo every 4 weeks ($N = 48$)	Change in FVC from baseline to 24 weeks	RTX was not found to be superior to CYC in the treatment of CTD-ILD (mean adjusted difference −40 [95% CI −153 to 74, $P = 0.493$]), however, both agents showed improvement in lung function (change from baseline FVC 99 mL in RTX vs 97 mL in CYC)	There were fewer side effects experienced in the RTX group compared with CYC (646 vs 445 events). Most common ADEs included gastrointestinal disorders (26% CYC vs 16% RTX), respiratory disorders (15% vs 23%), administration site reactions (14% vs 12%), and infections (8% vs 10%)

(continued)

Table 2. (continued)

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Narváez et al[41] Retrospective cohort trial	Adults with ongoing progressive SSc-ILD despite receiving immunosuppression	Fulfill ACR criteria for SSc, diagnosis of ILD via HRCT, received off-label RTX	Patients not meeting inclusion criteria; no specific exclusions reported	RTX 1000 mg IV on days 0, 15, and optionally at ≥6 months plus MMF (doses ranging from 1000 to 2000 mg/day) (N = 24)	Change in % predicted FVC and DLCO from baseline to 1 and 2 years	Mean % predicted FVC improved by 8.8% at 1 year (95% CI = −13.7, −3.9, P = 0.001) and 11.1% at 2 years (95% CI = −17.6, −4.5, P = 0.003) from baseline. DLCO improved by 4.6% at 1 year (95% CI = −8.2, −0.8, P = 0.018) and 8.7% at 2 years (95% CI −13.9 to −3.6, P = 0.003) from baseline	ADEs occurred in 9 of 24 patients, but were severe in only 3 patients, who withdrew treatment as a result. The most frequent side effects reported included respiratory or urinary tract infections (33%), IgG and/or IgM hypogammaglobulinemia (25%), and transient moderate to severe neutropenia (8%)
Khanna et al[42] R, DB, PC trial	Adults with diffuse cutaneous SSc, including those with ILD	Classified according to ACR criteria, duration of ≤ 60 months, mRSS of 10-35 units at screening, elevated acute phase reaction and active disease	FVC of ≤ 55% of predicted, DLCO ≤ 45% of predicted, pregnancy or lactation, major surgery within 8 weeks before or within 12 months after screening, previous treatment with any interleukin-6 inhibitor, class 2 or higher pulmonary hypertension, any significant cardiovascular disease (arrhythmia, congestive heart failure, unstable angina, uncontrolled hypertension, or myocardial infarction within 6 months prior to screening)	TCZ 162 mg SQ weekly × 48 weeks (N = 105) Matching placebo (N = 107)	Difference in change from baseline in mRSS at week 48	LSM change of −4.4 in placebo and −6.1 in TCZ (adjusted difference in LSM −1.7 [95% CI = −3.8, 0.3, P = 0.10])	Adverse effects were similar across both groups, with 77% of participants reporting at least 1 ADE in the placebo group compared with 86% in the TCZ group. The most common ADE was infection (50% in placebo vs 52% in TCZ)
Roofeh et al[43] Post hoc analysis of the focuSSced trial	Participants from the focuSSced trial with ILD	Same as the focuSSced trial (see Khanna et al[42])	Same as the focuSSced trial (see Khanna et al[42])	TCZ 162 mg SQ weekly (N = 68) Matching placebo (N = 68)	Change in % predicted FVC from baseline to week 48	Those who received TCZ demonstrated preserved FVC over 48 weeks compared with those who received placebo (LSM change, −0.1% for TCZ vs −6.3% for placebo). This was consistent across all subgroups, including those who did and did not have ILD, however, given that this is a post hoc analysis all results should be considered as hypothesis generating	No ADE information was reported in this analysis

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Table 2. (continued)

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Khanna et al[44] OL extension of the focuSSced trial	Participants from the focuSSced trial opting to extend trial participation	Same as the focuSSced trial (see Khanna et al[42])	Same as the focuSSced trial (see Khanna et al[42])	Patients who continued TCZ 162 mg SQ weekly ($N = 92$) Patients newly initiated on TCZ 162 mg SQ weekly ($N = 89$)	Change in mRSS from week 48 to 96	Improvement in mRSS was seen in both groups during the open-label period (mean change in placebo-TCZ −2.5 [95% CI = −3.3, 1.6] and −2.3 [95% CI = −3.2, −1.5] in continuous-TCZ), including the subgroup of patients with SSc-ILD (mean change = −3.1 [95% CI = −4.1, –2.0] in placebo-TCZ and −2.3 [95% CI = −3.2, −1.4] in continuous-TCZ)	Rates of ADEs were similar between groups (77.5% experience at least 1 ADE in placebo-TCZ vs 71.7% in continuous-TCZ), with infections listed as the most frequently reported ADE (46.1% in placebo-TCZ vs 39.1% in continuous-TCZ)
Distler et al[31] R, DB, PC trial	Adults with SSc-ILD	Age ≥ 18 years, SSc meeting ACR criteria, onset of first non-Raynaud's symptom within 7 years, ILD diagnosed based on HRCT, FVC ≥50%, DLCO 30%-89% of predicted	AST, ALT, or total bilirubin >1.5 times the upper limit of normal; FEV1/FVC < 0.7; pulmonary hypertension; bleeding risk; history of scleroderma renal crisis; history of myocardial infarction or unstable angina ≤ 6 months prior to screening; history of thrombotic event	Nintedanib 150 mg BID ($N = 288$) Matching placebo BID ($N = 288$)	Annual rate of decline in FVC over 52 weeks	Patients who received nintedanib had a significantly lower rate of decline in FVC compared with those who received placebo (−52.4 ± 13.8 vs −93.3 ± 13.5 [95% CI = 2.9, 79.0, $P = 0.04$]). The absolute difference in annual rate of decline observed across both groups was smaller than expected, likely due to half the population receiving MMF at baseline	Rates of adverse effects in both the continuation and initiation groups were similar (98.3% in nintedanib vs 95.8% in placebo), including serious adverse effects. The most common adverse effect was diarrhea (75.7% in nintedanib vs 31.6% in placebo). In addition, a pooled analysis of change in FVC over time showed improvement in both groups
Allanore et al[32] OL extension trial	Patients with SSc-ILD who completed the SENSCIS trial and attended 28-day follow-up, or completed a DDI study of nintedanib and oral contraceptives	Onset of first non-Raynaud symptom ≤ 7 years prior to study enrollment, ≥10% extent of fibrotic ILD on HRCT, FVC ≥40% predicted	AST or ALT > 3 times the upper limit of normal or bilirubin > 2 times the upper limit of normal, patients at risk of bleeding, patients with major thromboembolic events following completion of the parent trial	Patients who continued nintedanib 150 mg BID ($N = 197$) Patients newly initiated on nintedanib 150 mg BID ($N = 247$)	Absolute change in FVC from baseline to 52 weeks	52 weeks were −58.3 ± 15.5 mL in those continuing nintedanib and −51.3 ± 11.2 mL in those newly initiated	Adverse events were similar between the patients who continued nintedanib (21.3%) and those who newly initiated (24.3%). The most common adverse effect was diarrhea (68.0% in continuation vs 68.8% in newly initiated group). The most frequent serious adverse event was pneumonia (4.1% in continuation vs 1.6% in newly initiated)

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Table 2. (continued)

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Khanna et al[24] OL, pilot trial		Age 18-80 years, meet ACR criteria for SSc, >10 years from first non-Raynaud's symptom, FVC < 85% of predicted, dyspnea on exertion, presence of ground-glass opacities on HRCT	FVC ≤ 50% of predicted or DLCO ≤ 35% of predicted; pulmonary hypertension; persistent leukopenia, neutropenia, or thrombocytopenia, abnormal liver function tests, grade III/IV New York Heart Association criteria	Imatinib 100 mg/day with goal of titrating to 400-600 mg/day ($N = 20$)	Safety of daily imatinib	Of the 20 patients enrolled, 12 completed the study, 7 dropped out, and 1 was lost to follow-up. Of the 7 who dropped out, 5 were related to ADEs from imatinib. Three of these patients had ADEs related to imatinib classified as serious	The most common ADEs reported include nausea/vomiting (45%), pedal edema (45%), fatigue (35%), facial edema (35%), new-onset proteinuria (30%), diarrhea (25%), upper respiratory infection (20%), and generalized rash (20%). ADEs were managed by either decreasing the dose, drug holiday, or separating into divided doses
Fraticelli et al[25] Multicenter, P, OL, phase 2 trial	Adults with SSc and active lung involvement and resistance to conventional immunosuppressant	Age 18-80 years, SSc meeting ACR criteria, presence of active interstitial alveolitis, resistance to conventional immunosuppressants, use of acceptable birth control	Severe pulmonary fibrosis, CTD other than SSc, smoking, pregnancy or lactation, evidence of hepatitis B or C, hepatic disease, moderate or severe renal failure, severe heart failure	Imatinib 200 mg/day ($N = 26$)	Improvement of pulmonary involvement after 6 months	Lung involvement improved in 4 patients, worsened in 7 patients, and was stable in 15 patients after 6 months of treatment (73.07% had improved or stable lung disease at 6 months)	The most common ADEs reported were lower limb edema (19.2%), cough (19.2%), infections, (19.2%), and urticaria/rash (15.3%). Four serious ADEs requiring drug discontinuation were reported; however, none of them were deemed to be related to imatinib
Gordon et al[20] R, DB, PC pilot trial	Patients with diffuse SSc on a background of MMF therapy	Age ≥ 18 years, fulfill ACR criteria for SSc, disease duration < 3 years since first non-Raynaud's symptom, baseline mRSS ≥ 16	DLCO < 30% predicted, ejection fraction < 50%, receiving MMF for > 3 months, previously received RTX or belimumab, require prednisone > 10 mg/day	Belimumab 10 mg/kg IV every 2 weeks × 3, then every 4 weeks until week 48 plus MMF 2000 mg/day ($N = 10$) Matching IV placebo plus MMF as above ($N = 10$)	Difference in median change in mRSS after 52 weeks	Both groups had significant improvements in mRSS scores; however, there was no statistically significant difference in median change between groups (−10 [IQR = −13 to −9] in belimumab group vs −3.0 [IQR = −15 to −1] in placebo [$P = 0.411$])	There was no difference between groups in total number of ADEs (53 in belimumab vs 56 in placebo, $P = 0.868$), including number of infections (18 vs 16, $P = 0.818$)

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Table 2. (continued)

Authors Methods	Patient population	Inclusion criteria	Key exclusion criteria	Regimen	Primary endpoint	Outcomes	Adverse events
Khanna et al[45] OL, phase 2 trial	Adults with SSc-ILD	Age 18-75 years old, fulfills criteria of ACR for SSc, evidence of ILD on HRCT, disease duration < 7 years from first non-Raynaud's symptom, FVC ≥ 50%, DLCO ≥40%	Pulmonary arterial hypertension, right atrial or ventricular enlargement of left ventricular dysfunction, underlying liver disease, moderate to severe gastroesophageal reflux	Pirfenidone 801 mg TID titrated over 2 weeks (N = 32) Pirfenidone 801 mg TID titrated over 4 weeks (N = 31)	TEAEs related to pirfenidone	Most patients completed the study, with 6 patients withdrawing due to adverse effects. Rates of ADEs were similar between groups, with 96.8% of patients experiencing at least 1 TEAE. Four serious ADEs were reported; 3 were deemed to be not related to pirfenidone and 1 (intestinal obstruction) possibly related to pirfenidone	ADEs were reported as "mild, moderate, or severe." Rates were similar between the 2 titration groups, with nausea (50.0% in 2-week vs 48.4% in 4-week) headache (43.8% vs 45.2%), fatigue (40.7% vs 32.2%), diarrhea (28.2% vs 32.3%), and vomiting (28.1% vs 29.1%)
Acharya et al[46] R, DB trial	Adults with SSc and ILD	Fulfill ACR criteria for SSc, ILD confirmed on HRCT, FVC 50%-80% of predicted, DLCO > 30% of predicted, disease duration < 7 years since onset of first non-Raynaud's symptom, no new immunosuppressive treatment initiated in the previous 6 months	Coexistent inflammatory myopathy, severe pulmonary arterial hypertension requiring specific therapy, persistent cytopenia, clinically significant heart failure, previous use of biologics, abnormal liver function tests	Pirfenidone titrated to a target of 2400 mg/day (N = 17) Matching placebo (N = 17)	Proportion of subjects with improvement or stabilization in FVC at 6 months	After 6 months of treatment, more patients in the pirfenidone group had stabilization or improvement in FVC, however, this difference was not statistically significant (94.1% in pirfenidone vs 76.5% in placebo [95% CI = −0.07, 0.41, P = 0.335])	There were no significant differences in ADEs seen between groups. Gastrointestinal effects were the most common ADEs reported (8 events in pirfenidone vs 5 in placebo), leading to discontinuation in 2 patients receiving pirfenidone

Abbreviations: ACR, American College of Rheumatology; ADE, adverse drug effect; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZA, azathioprine; BID, twice daily; DB, double-blind; DD, double dummy; DDI, drug-drug interaction; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; LSM, least squares mean; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; OL, open-label; PC, placebo-controlled; PG, parallel group; PO, oral; qOD, every other day; R, randomized; RTX, rituximab; SQ, subcutaneous; SSc, systemic sclerosis; TEAE, treatment-emergent adverse effect; WBC, white blood cell; 6MWT, 6-minute walk test.

demonstrated selective modulation of T-lymphocytes, leading to decreased inflammatory response and skin fibrosis in the treatment of scleroderma.[53] Historically, CYC was frequently used as an effective treatment for individuals with severe or rapidly progressive SSc-ILD; however, its use has been limited by severe toxicities. The earliest report of CYC was published in 1993 and most of the studies did not find a significant effect on the rate of FVC decline at 12 months, but there have been significant improvements seen in HRCT scans.[22,54,55] The SLS I study had a mean absolute difference in FVC% predicted at 12 months of 2.53% for CYC compared with placebo.[22] There was no significant difference in CYC compared with MMF for impact on FVC% decline in the follow-up SLS II study. However, a greater number of patients on CYC prematurely withdrew from the study (32 vs 20), failed treatment (2 vs 0), and had more significant adverse effects (34 vs 4) compared with MMF.[10]

Rituximab

Rituximab (RTX) has been used as part of a chemotherapy regimen for non-Hodgkin lymphomas and in conjunction with methotrexate in the treatment of rheumatoid arthritis.[34] It is often used off-label as rescue therapy in treatment-refractory SSc-ILD and administered intravenously.[35] In small open-label studies, RTX was associated with significant improvements in FVC in patients with SSc-ILD; however, there were no significant improvements in HRCT scores at 24 weeks.[56-58] A retrospective cohort evaluating RTX plus MMF in 24 patients demonstrated improvements in FVC and DLCO at years 1 and 2 (8.8%/4.6% and 11.1%/8.7%, respectively).41 There was also an open-label, randomized controlled trial which favored RTX for change in FVC% predicted when compared with CYC plus MMF or CYC plus AZA.[39] A more recent trial failed to demonstrate the superiority of RTX compared with CYC in the treatment of CTD-ILD (mean adjusted difference −40 [95% CI = −153, 74], $P = 0.493$). However, both agents did show improvements in FVC (change of 99 mL for RTX vs 97 mL for CYC) and there were fewer adverse effects in the RTX group (646 vs 445).[40]

Tocilizumab

TCZ is an antagonist of the interleukin-6 (IL-6) receptor. Inhibition of IL-6 receptors leads to a reduction in cytokine release and prevents unwanted immune responses. TCZ was approved for use in SSc-ILD to slow the rate of decline in pulmonary function in March 2021.[15] A phase III study evaluated 136 patients with early SSc-ILD by HRCT. In this study, there was a smaller decline in the secondary endpoint of FVC at 48 weeks (between group difference 3.4%). Patients treated with TCZ also had a difference compared with placebo in median HRCT scores at 48 weeks.[42]

Tyrosine Kinase Inhibitors

Nintedanib. Nintedanib is a small molecule kinase inhibitor that binds multiple growth factors that are overstimulated during lung repair, ultimately leading to inhibition of fibroblast proliferation and migration.[14] Nintedanib was approved by the United States Food and Drug Administration (FDA) for the treatment of idiopathic pulmonary fibrosis in 2014 and for chronic fibrosing ILD with a progressive phenotype in 2019. It also has a labeled indication for SSc-ILD to slow the rate of decline in pulmonary function.[14] Distler and colleagues conducted the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, a randomized, double-blind placebo-controlled trial evaluating nintedanib in SSc-ILD. Nintedanib significantly reduced the rate of decline of FVC compared with placebo with a mean difference of 41 mL/year.[31] An open-label extension of SENSCIS conducted by Allanore and colleagues found FVC improvements at 52 weeks for patients with SSc-ILD continuing therapy ($n = 197$) and newly initiated ($n = 247$) (−58.3 ± 15.5 mL and −51.3 ± 11.2 mL, respectively).[32]

Imatinib. Imatinib is a tyrosine kinase inhibitor that acts on Bcr-Abl, the abnormal fusion gene on the Philadelphia chromosome in chronic myeloid leukemia.[23] Imatinib also has downstream effects on the other tyrosine kinases involved in fibrosis, including transforming growth factor-beta and platelet-derived growth factors. Although originally developed for leukemias, the effect of imatinib on key signaling molecules in the pathogenesis of fibrosis led to evaluation of use in SSc-ILD. However, clinical trials have demonstrated significant adverse effects which limit its utility in this disease state.[24,25] A phase I/II study assessed the safety of imatinib in patients with SSc-ILD. Seven of the 20 patients evaluated discontinued therapy due to adverse events, including fatigue, facial/lower extremity edema, nausea and vomiting, diarrhea, generalized rash, and new-onset proteinuria. The median dosage was 400 mg per day and treatment with imatinib showed a trend toward improvement in FVC% predicted (1.74%).[24] In a phase II pilot study, 30 patients with SSc-ILD and unresponsive to CYC were treated with imatinib 200 mg per day for 6 months. Of the 26 patients who completed the study, 19 (73.07%) of patients improved or stabilized lung disease and 7 (26.93%) worsened. Adverse events occurred in less than 20% of the patients, with only 3 cases of serious adverse events requiring drug discontinuation.[25]

Relevance to Patient Care and Clinical Practice

Patients with SSc-ILD have worse 5-year and 10-year survival rates than those with SSc alone since greater lung involvement is associated with higher mortality rates.[3,59] Therefore, it is imperative that SSc-ILD be managed with the best treatment options. However, treatment proves to be

difficult as many of the studies have included retrospective case reviews and open-label observational studies with surprisingly few randomized control trials. Moreover, many of the randomized control trials have small sample sizes. Only the European League Against Rheumatism guidelines for the management of SSc provide a recommendation for the treatment of patients with SSc-ILD; these guidelines were last updated in 2017 and only include data published through 2014.[60] Recently, a Delphi study was conducted to develop consensus recommendations for the management of SSc-ILD based on expert physician opinions.[13] Although some of the recommendations from this expert panel align with the findings from the treatment literature, practitioners need to remember that the Delphi technique is a systematic process of forecasting that relies purely on expert opinion to generate findings.[61]

The consensus recommendations were published in January 2023 and identify shifts in the treatment of SSc-ILD. For one, MMF is now preferred over CYC due to a more favorable long-term adverse effect profile.[13] This is not surprising given the studies evaluating MMF in SSc-ILD compared with CYC, AZA, and RTX show comparable efficacy but a better safety profile.[10,17,37,39-41] Nintedanib was recommended as initial therapy in patients with longstanding progressive SSc-ILD and as add-on therapy in patients who continue to have progressive lung fibrosis following failure of immunosuppressive agents.[13] This recommendation is likely impacted by the SENSCIS trials, which showed lower rates of decline in FVC.[8,32] Not surprisingly, there was a lack of consensus on the use of TCZ; this was likely influenced by recent publication of the data and/or inexperience with the medication.[13] Based on a review of the recent studies, TCZ may be considered in patients with early SSc-ILD and elevated acute-phase reactants or in those who do not tolerate immunosuppressants and/or antifibrotics.[42,44] The panel provided no recommendations regarding ongoing studies.[13]

Currently, there are ongoing trials for the treatment of SSc-ILD with pirfenidone, an antifibrotic used for idiopathic pulmonary fibrosis, and belimumab, a monoclonal antibody currently approved for the treatment of lupus and lupus nephritis.[19,33] Although pirfenidone is not currently indicated for SSc-ILD, new practice guidelines for the treatment of progressive pulmonary fibrosis recommended further research into the efficacy and safety of pirfenidone in "specific types of interstitial lung disease manifesting as progressive pulmonary fibrosis."[62] In a phase III trial of belimumab compared with placebo in patients with systemic lupus erythematosus, 53% of patients receiving belimumab 1 mg/kg and 58% of patients receiving belimumab 10 mg/kg demonstrated a reduction in disease activity scores compared with 46% of patients in the placebo group.[63] In addition, a pilot study assessing belimumab against placebo in patients with diffuse SSc on a background of MMF therapy showed substantial improvement in mRSS scores (−10 in belimumab vs −3 in placebo), but the median change was not significantly different between groups.[20] As a result, in February 2023, the FDA granted belimumab Orphan Drug Designation for the potential treatment of SSc.[19]

Given the conflicting treatment data and ongoing research, there is an opportunity to include pharmacists in the management of SSc-ILD regardless of the regimen chosen. Pharmacists are uniquely suited to provide counseling on drug-drug/drug-food interactions and adverse effect management. Pharmacists may also aid in overseeing laboratory monitoring and providing recommendations on dose reductions and drug holidays. By providing supportive care recommendations, pharmacists can collaborate with the patient and other team members to prevent premature drug discontinuation that may lead to disease progression. Furthermore, pharmacists can assist with insurance coverage and cost of these medications which are often a barrier to access.

Conclusion

Currently, MMF is the preferred immunosuppressant used for the treatment of SSc-ILD based on the efficacy and safety profiles. Several medications have been studied and successfully repurposed for the treatment of SSc-ILD. Most notably, TCZ and nintedanib have emerged as the first FDA-approved agents to treat this rare disease. Given the promising data in small trials and ongoing phase II trials, both pirfenidone and belimumab may provide additional treatment options for SSc-ILD. This disease state and the complex regimens used provide an excellent opportunity for pharmacists to participate in patient management. This review provides pharmacists with a succinct overview of the extensive literature and practical considerations for the management of SSc-ILD.

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