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Review

Pharmacological treatments for SSc-ILD: Systematic review and critical appraisal of the evidence

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ABSTRACT

Many therapies have been investigated for systemic sclerosis-associated interstitial lung disease (SSc-ILD), including immunosuppressive therapies, antifibrotic agents, immunomodulators and monoclonal antibodies. There is a high unmet medical need to better understand the current evidence for treatment efficacy and safety. This systematic review aims to present the existing literature on different drug treatments investigated for SSc-ILD and to critically assess the level of evidence for these drugs.

A systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured literature search was performed for clinical trials and observational studies on the treatment of SSc-ILD with pharmaceutical interventions from 1 January 1990 to 15 December 2020. The quality of each reference was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria.

A total of 77 references were reviewed and 13 different treatments were identified. We found high-quality evidence for the use of cyclophosphamide, nintedanib, mycophenolate and tocilizumab. Therefore, we would posit that the clinical community has four valid options for treatment of SSc-ILD. Further research is mandatory to provide more evidence for the optimal treatment strategy in SSc-ILD, including the optimal time to initiate treatment, selection of patients for treatment and upfront combination therapy.

1. Introduction

Systemic sclerosis (SSc) is a rare, heterogeneous chronic connective tissue disease (CTD) characterised by progressive fibrosis of the skin and internal organs [1,2]. The clinical course is variable, but manifestations in organs other than the skin, including lungs, tend to occur early in the course of the disease [2,3]. Interstitial lung disease (ILD) is a common occurrence in SSc, affecting 35–52% of patients [4] (depending on the definition of ILD used [4]) and is responsible for 15–33% of deaths in SSc [5–7]. Previous studies suggest that most patients who develop ILD do so

Abbreviations: CI, confidence interval; CTD, connective tissue disease; dcSSc, diffuse cutaneous systemic sclerosis; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; GRADE, Grades of Recommendation Assessment Development and Evaluation; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRCT, high-resolution computed tomography; HSCT, haematopoietic stem cell transplant; IL-6, interleukin-6; ILD, interstitial lung disease; IV, intravenous; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; OR, odds ratio; POM, pomalidomide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QILD, quantitative ILD; QLF, quantitative lung fibrosis; RCT, randomised controlled trial; SLS, Scleroderma Lung Study; SSc, systemic sclerosis.

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within the first 5 years following the onset of SSc symptoms [8]. Of the patients who do develop ILD, 25–30% develop progressive disease, with worsening fibrosis and poorer outcomes [8].

Although most patients with SSc-associated ILD (SSc-ILD) experience a slow decline in lung function, some patients progress rapidly, with progression defined as declined lung function and signals of increased fibrosis on high-resolution computed tomography (HRCT) scans [9]. In the EUSTAR registry, 23–27% of patients with SSc-ILD experienced ILD progression during any 12-month period, and 67% experienced progression at any time over the mean 5-year follow-up period [10]. Due to this variable clinical course, treatment decisions need to be made on a case-by-case basis. However, although treatment recommendations are available [11], there is no established treatment algorithm for SSc-ILD.

Many therapies have been investigated for SSc-ILD, including immunosuppressive therapies, antifibrotic agents, immunomodulators, monoclonal antibodies, haemopoietic stem cell transplant (HSCT) and lung transplant. Given that there were no approved drug treatments available [11] until the approval of the tyrosine kinase inhibitor nintedanib in 2019 [12], patients with SSc-ILD had a high unmet medical need. The lack of approved therapies for SSc-ILD and known immune system involvement mainly lead to the use of immunosuppressive therapies such as cyclophosphamide, methotrexate and mycophenolate mofetil (MMF), as they are used for SSc. Methotrexate has been shown to improve skin score in early diffuse cutaneous SSc (dcSSc), but beneficial effects in other systems, including the lungs, have not yet been established [11]. The two most common drugs used in treatment of SSc are cyclophosphamide and MMF, supported by a positive randomised controlled trial (RCT) [13] and a negative RCT [14], respectively, but with similar efficacy results. The better safety and tolerability profile of MMF in the Scleroderma Lung Study (SLS) II and the toxicity of cyclophosphamide in the long term has made MMF the more commonly used drug in clinical practice for continued treatment. The latest available guidelines for SSc that included ILD recommended cyclophosphamide and HSCT as these were the only treatments with completed RCTs at that time. Additional drugs, such as nintedanib and tocilizumab, have been approved for slowing the rate of decline in pulmonary function in SSc-ILD (US label) [12,15] since the last guidelines were published.

Previous reviews in this area have focussed on a single treatment [16,17], or on ILD in other types of CTD or rheumatic diseases [18]. There is a need to better understand the current evidence for treatment efficacy and safety specifically in SSc-ILD. This systematic review aims to present the existing literature on different drug treatments investigated for SSc-ILD and to critically assess the level of evidence for these drugs.

2. Methods

2.1. Literature search

This systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the PRISMA 2009 checklist. A structured literature search was performed for studies on the treatment of SSc-ILD with pharmaceutical interventions. The PubMed database was searched from 1 January 1990 to 23 March 2020 (the date of the literature search); the search was updated on 15 December 2020. The search terms were '((systemic sclerosis OR SSc OR scleroderma) AND (interstitial lung disease OR ILD)) OR (SSc-ILD)'. Results were filtered to select clinical trials and observational studies only.

2.2. Study selection

The results were screened to select full peer-reviewed manuscripts of studies of SSc-ILD in humans, describing outcomes following pharmaceutical-based interventions. Studies of heterogeneous ILD populations (for example, CTD-associated ILD [CTD-ILD]) were selected if they included patients with SSc-ILD. Study designs, case reports, review articles, letters to the editor, conference abstracts, editorials and guidelines were excluded from the search results for consistency. Other exclusion criteria included preclinical studies, non-pharmaceutical interventions (for example, lung transplants) and studies not reporting outcomes. The reference lists of selected publications were manually searched for additional relevant publications that met the inclusion criteria above but did not appear in the original PubMed search.

2.3. Data extraction

Study information and outcomes data were independently extracted from each publication by one of three reviewers. Data collection included study design, sample size, treatment details, patient baseline characteristics, changes in pulmonary function, HRCT outcomes, patient function or quality of life measures, survival and safety outcomes.

2.4. Critical assessment of evidence

Each publication was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria [19] by one of three reviewers, independently checked and then agreed by all authors. GRADE assessments were conducted to assign the quality of evidence from each reference as high, moderate, low, or very low according to factors that include the study methodology, consistency and precision of the results, and directness of the evidence.

3. Results

3.1. Search results

In total, 124 publications were identified in the PubMed searches (Fig. 1). Screening of titles and abstracts resulted in 68 being excluded, leaving 56 publications. A manual search of the references of these selected articles found an additional 21 publications that met the inclusion criteria but were not identified in the PubMed search. A total of 77 publications were reviewed in full. There were 45 separate studies in SSc-ILD only (multiple publications for the same study not counted). Thirteen studies included SSc-ILD data as part of the larger patient population, with SSc-ILD results reported separately in eight of these. Thirteen different pharmaceutical interventions were identified and grouped together by type. See Table 1 for summary data and GRADE outcomes from these studies. Phase III data was available for nintedanib (N = 576) [20] and cyclophosphamide (N = 158) [13], and Phase II data is available for MMF (N = 142) [21]; tocilizumab had randomised Phase II data in SSc (N = 87) [22] and Phase III data in early dcSSc with raised inflammatory markers (N = 210) [23].

3.2. Nintedanib

We identified three publications evaluating nintedanib published in 2019 and 2020 [24–26]. Data from these studies are shown in Supplementary Table 1. Nintedanib was investigated in two Phase III placebo-controlled studies: one included only patients with SSc-ILD (N = 576) [24,26], whereas the other included patients with SSc-ILD as part of a wider progressive fibrosing ILD population (n = 39/663) and results for SSc-ILD were not reported separately [25]. In the nintedanib study in SSc-ILD, the median time from onset of first non-Raynaud symptom was 3.4 years, with a relatively equal split between dcSSc and limited cutaneous SSc [24], and almost half of the patients were receiving MMF at baseline. The certainty of the evidence for nintedanib was high [24,26] or moderate [25], based on the Phase III trials, suggesting high confidence in the finding that nintedanib significantly reduces the annual decline in forced vital capacity (FVC) in SSc-ILD or progressive fibrosing ILD including SSc-ILD.

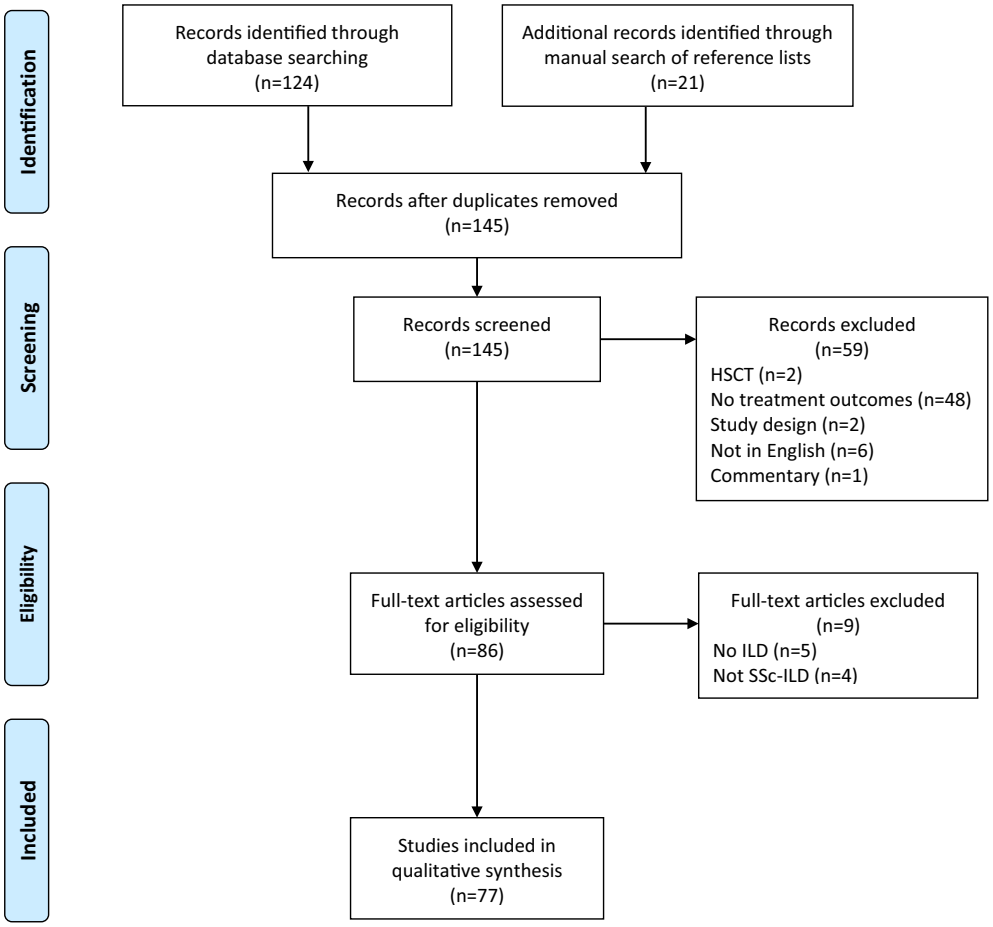

Fig. 1. PRISMA flowchart.
References were identified through searching of the PubMed database from 1 January 1990 to 15 December 2020 and through a manual search of reference lists. Records were excluded following screening of record titles and abstracts; additional records were excluded following review of the full text. ILD, interstitial lung disease; HSCT, haematopoietic stem cell transplant; SSc, systemic sclerosis.

3.2.1. *Lung function*

In patients with SSc-ILD, nintedanib (n = 288) significantly reduced the annual rate of decline of FVC compared with placebo (n = 288) (primary endpoint), with a between-group difference of 41.0 mL/year (95% confidence interval [CI] 2.9–79.0; P = 0.04; FVC% predicted difference 1.2%; 95% CI 0.1–2.2) [24]. Loss of FVC in mL/year was lowest in those patients that had been receiving MMF at baseline in both treatment arms, and nintedanib reduced the annual rate of decline of FVC both in patients receiving and those not receiving MMF [24]. In the study of nintedanib in progressive fibrosing ILD [25], patients with SSc-ILD were not analysed in isolation, although the results across the autoimmune subset have been presented [27].

3.3. *Tocilizumab*

We identified three references for tocilizumab, an interleukin-6 (IL-6) monoclonal antibody, which was investigated in two randomised, placebo-controlled studies with the first publication in 2016. Data from these studies are shown in Supplementary Table 2. The Phase II study investigated tocilizumab in patients with SSc with a mean baseline FVC % predicted of 80–82% (N = 87) [22,28], and the Phase III study investigated 210 patients with early dcSSc with raised inflammatory markers, including 136 with ILD by HRCT [23]. The quality of evidence was mixed, with high-quality evidence based on the Phase III trial [23], and low- or moderate-quality evidence based on the Phase II trial [22,28]. While the modified Rodnan skin score (mRSS) primary endpoint was not met in either trial, there is evidence that tocilizumab may have important, clinically relevant results on lung function.

3.3.1. *Lung function*

In the Phase III tocilizumab study in SSc, in which mRSS was the primary endpoint, there was a smaller decline in the secondary endpoint of FVC% predicted in the SSc-ILD subpopulation with tocilizumab (n = 104) compared with placebo (n = 106) at 48 weeks (between-group difference 3.4%; 95% CI 0.4–5.6; P = 0.002) [23]; these results were reflected in the overall population. Fewer participants treated with tocilizumab had a decline of ≥10% in FVC% predicted compared with placebo (9% vs 25%, respectively, of those with ILD and 5% vs 17%, respectively, of all patients). In the Phase II tocilizumab study, there was a smaller decline in FVC (an exploratory endpoint) for tocilizumab (n = 43) compared with placebo (n = 44) at 24 weeks (least square mean difference 136 mL; 95% CI 9–264; P = 0.0368); however, at 48 weeks the difference was not significant (least square mean difference 120 mL; 95% CI –23 to 262; P = 0.099) [22]. In the open-label extension of the Phase II study, 51 patients received tocilizumab for up to 96 weeks; no patients experienced a >10% decline in FVC% predicted at Week 96 [28]. Because neither tocilizumab study met its primary mRSS endpoint, all P-values were considered nominal.

3.3.2. *HRCT pattern*

In patients with ILD treated with tocilizumab in the Phase III study, there was a difference compared with placebo in change from baseline at 48 weeks in median quantitative lung fibrosis (QLF) for whole lung (−0.6; 95% CI 1.2 to −0.3; P = 0.0008) and most affected lobe (−1.6; 95% CI –3.3 to −0.4; P = 0.002), and quantitative ILD (QILD) for whole lung (−3.3; 95% CI –4.3 to −0.7; P = 0.008) scores on HRCT (P-values were nominal due to failure to meet primary endpoint) [23]. These results were reflected in the overall study population.

Table 1
Evidence profiles for treatments in SSc-ILD.

Reference	Treatment	Summary of results	Quality of evidence
Nintedanib			
Distler, et al. N Engl J Med 2019 [24]	Nintedanib 150 mg BID (n = 288) Placebo (n = 288) N = 576	Nintedanib reduced the annual rate of decline in FVC (mL) compared with placebo	High
Flaherty, et al. N Engl J Med 2019 [25]	Nintedanib 150 mg BID (n = 332) Placebo (n = 331) N = 663	Nintedanib reduced the annual rate of decline in FVC (mL) compared with placebo	High
Seibold, et al. Ann Rheum Dis 2020 [26]	Nintedanib 150 mg BID (n = 288) Placebo (n = 288) N = 576	The safety profile of nintedanib in SSc-ILD in the SENSCIS trial was consistent with the safety profile in IPF	Moderate
Tocilizumab			
Khanna, et al. Lancet 2016 [22]	Tocilizumab 162 mg/week SC for 48 weeks (n = 43) Placebo (n = 44) N = 87	Tocilizumab did not meet the primary endpoint of improving mRSS compared with placebo in the faSScinate trial. In the exploratory FVC endpoint, tocilizumab reduced pulmonary function decline compared with placebo	Moderate
Khanna, et al. Ann Rheum Dis 2018 [28]	Tocilizumab 162 mg/week SC for 48 weeks open-label extension 24/44 placebo-tocilizumab and 27/43 continuous-tocilizumab pts. completed Week 96 N = 51	FVC stabilisation seen in the double-blind period of the faSScinate trial was also observed in placebo-treated pts. who transitioned to tocilizumab in the open-label extension	Low
Khanna, et al. Lancet Respir Med 2020 [23]	Tocilizumab 162 mg/week SC for 48 weeks (n = 104) Placebo (n = 106) N = 210	Tocilizumab did not meet the primary endpoint of improving mRSS compared with placebo in the focuSSced trial. For the secondary endpoint of FVC%pred, there was some evidence that tocilizumab reduced pulmonary function decline	High
Mycophenolate			
Swigris, et al. Chest 2006 [36]	MMF median dose of 2000 mg/day in divided doses Prednisone median dose of 12.5 mg/day N = 28	MMF maintained pulmonary physiology without increase in the median daily dose of glucocorticoids	Very low
Liossis, et al. Rheumatology 2006 [45]	MMF 500 mg BID for 1 month, then 2000 mg/day Prednisolone 10 mg/day N = 6	MMF improved lung function parameters, with significant improvements in DLco at 6 months compared with pre-treatment. Improvement of GGO on chest HRCT	Very low
Vanthuyne, et al. Clin Exp Rheumatol 2007 [46]	MMF 500 mg BID for 1 week, then 1 g BID MP IV pulse 15 mg/kg, 3 consecutive days, then 5 additional monthly pulses Glucocorticoids 5–10 mg/day N = 16	This immunosuppressive regimen significantly improved FEV_1 and DLco. There were non-significant improvements in GGO	Low
Nihtyanova, et al. Rheumatology 2007 [39]	MMF n = 109 Control group n = 63 N = 172	Significantly lower frequency of clinically significant pulmonary fibrosis in the MMF-treated cohort. Significantly better 5-year survival from disease onset and from start of treatment. No significant difference in median change in FVC%pred	Very low
Gerbino, et al. Chest 2008 [40]	MMF >1 g/day (majority received 2 g/day in divided doses) N = 13	MMF was associated with a significant improvement in VC. DLco did not change significantly during MMF treatment	Very low
Zamora, et al. Respir Med 2008 [41]	MMF 2 g/day for ≥12 months N = 17	Treatment of pts. with SSc-ILD for up to 24 months with MMF was generally associated with stable pulmonary function	Very low
Simeón-Aznar, et al. Clin Rheumatol 2011 [38]	MS Week 1: 360 mg BID, then 720 mg BID for 12 months Prednisone 5 mg/day N = 14	After 12 months of MS therapy, median values for FVC, FEV_1 and DLco did not change significantly and fulfilled the definition of stable disease by the American Thoracic Society	Very low
Panopoulos, et al. Lung 2013 [35]	Mycophenolate (MMF n = 3; MS n = 7) 1500 mg/day, 22–72 months CYC 90 mg/day, 17–55 months (n = 10) MTX (n = 3) or no treatment (n = 3) N = 26	FVC, TLC and DLco did not change significantly in either mycophenolate or CYC group after 1 or 2 years. A deterioration of lung HRCT findings at 2 years was noticed after mycophenolate but not after CYC. The study does not support replacement of CYC with mycophenolate for pts. with SSc-ILD	Low
Fischer, et al. J Rheumatol 2013 [37]	MMF 3000 mg/day in 65% pts.; <2000 mg/day in 4 pts.; <3000 mg/day in remaining pts. Prednisone at MMF initiation 20 mg/day, reduced to 5 mg/day after 9–12 months N = 125	Treatment with MMF was associated with either stable or improved pulmonary physiology over a median 2.5 years of follow-up	Low
Yilmaz, et al. Int J Rheum Dis 2014 [43]	CYC 750 mg/m^2 monthly IV injections/oral equivalent for 6–12 months Oral AZA 2 mg/kg/day as maintenance at 6 months if there was a good response. If there was an inadequate response, MMF 500 mg BID for 1 month and then, if tolerated, 1500–2000 mg/day N = 12	PFTs and imaging scores were stabilised by MMF in SSc-ILD pts. who were inadequate responders to CYC	Very low

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Table 1 (*continued*)

Reference	Treatment	Summary of results	Quality of evidence
Iudici, et al. Semin Arthritis Rheum 2015 [44]	CYC weekly pulses of 500 mg up to 20 pulses. Oral corticosteroids, proton pump inhibitors, calcium channel blockers, antiplatelet agents and vitamin D. Mesna 100 mg and oral trimethoprim-sulfamethoxazole 160–180 mg CYC responders: AZA 2 mg/kg/day; CYC non-responders: MMF 2 g/day N = 39	The incidence of improvement or stabilisation of lung function parameters was significantly higher in AZA-treated than in MMF-treated pts.	Low
Launay, et al. J Scleroderma Relat Disord 2016 [42]	CYC 6–12 monthly pulses of 0.6 g/m^2 (n = 7) or 0.7 g/m^2 (n = 13) MMF maintenance 2 g/day (n = 12) or 3 g/day (n = 8) N = 20	CYC followed by maintenance MMF for worsening SSc-ILD was associated with improvement or stabilisation of PFTs in 55% of pts. after 12 months of MMF	Very low
Tashkin, et al. Lancet Respir Med 2016 [14]	MMF 1500 mg BID for 24 months (n = 69) Oral CYC 2.0 mg/kg/day for 12 months followed by placebo for 12 months (n = 73) N = 142	In SLS II, there was no significant clinical efficacy observed for MMF vs CYC at 24 months, but it was better tolerated	High
Volkmann, et al. Arthritis Res Ther 2016 [34]	MMF 1500 mg BID for 24 months (n = 65) Oral CYC 2.0 mg/kg/day for 12 months followed by placebo for 12 months (n = 71) N = 136	Plasma CXCL4 decreased significantly from baseline to 12 months in all pts. in SLS II, with no between-treatment differences (CYC vs MMF)	Moderate
Tashkin, et al. Chest 2017 [29]	MMF 1500 mg BID for 24 months (n = 69) Oral CYC 2.0 mg/kg/day for 12 months followed by placebo for 12 months (n = 73) N = 142	In SLS II, frequent cough correlated with both the presence and severity of GERD and ILD at baseline and improved in parallel with improvements in both ILD and GERD over 2 years of MMF or CYC therapy	Moderate
Goldin, et al. Ann Am Thorac Soc 2018 [31]	MMF <3.0 g BID, for 2 years (n = 50); n = 48 completed 24 months of treatment CYC 1.8–2.3 mg QD, for 1 year followed by 1-year placebo (n = 47); n = 32 completed 24 months of treatment N = 97	In SLS II, CYC treatment for 1 year followed by placebo, or MMF treatment for 2 years was associated with a significant improvement in the extent of HRCT SSc-ILD assessed by computer-aided diagnosis scores	High
Namas, et al. Arthritis Care Res 2018 [32]	SLS I: CYC oral ≤2 mg/kg/day (n = 73) vs placebo (n = 72) for 1 year SLS II: MMF ≤3 g/day for 2 years (n = 69) vs CYC oral ≤2 mg/kg/day for 1 year, followed by placebo BID for 1 year (n = 73) N = 287 (SLS I n = 145; SLS II n = 142)	In SLS II, MMF and CYC treatment resulted in improvements in mRSS in pts. with dcSSc over 24 months	High
Volkmann, et al. Ann Rheum Dis 2019 [30]	SLS I: 1-year oral CYC (n = 79) vs placebo (n = 79) SLS II: 1-year oral CYC (n = 73), 1-year placebo vs 2 years of MMF (n = 69) N = 300	In addition to traditional mortality risk factors in SSc (skin score and age), SLS I and II found that a decline in FVC and DLco over 2 years is a better predictor of mortality than baseline FVC and DLco	Moderate
Volkmann et al. ACR Open Rheumatol 2020 [33]	MMF 1500 mg BID for 24 months (n = 69) Oral CYC 2.0 mg/kg/day for 12 months followed by placebo for 12 months (n = 73) N = 142	In SLS II, MMF and CYC treatment improved overall HRQoL in pts. with SSc-ILD	Moderate
Cyclophosphamide			
Silver, et al. J Rheumatol 1993 [94]	Oral CYC (1–2 mg/kg/day) and low-dose prednisone (<10 mg/day) N = 14	The majority of pts. treated with oral CYC and low-dose prednisone showed significant improvements in FVC at 12 months, which were maintained in those completing 24 months of treatment; there was no significant improvement in DLco but it remained stable in the majority of cases	Very low
Akesson, et al. Arthritis Rheum 1994 [95]	Initial daily dose of oral CYC (2.0–2.5 mg/kg) and prednisolone (30 mg/day; range 10–40; tapered to between 5 mg every other day and 10 mg/day over 10 weeks) N = 18	VC and Cst improved after treatment, with reduced skin involvement; the improvements mainly occurred in pts. with biochemical evidence of an acute-phase reaction	Very low
Schnabel, et al. Arthritis Rheum 1998 [96]	6–9 cycles of IV pulse CYC (0.5 g/m^2 of body surface area) q4w and oral prednisolone, starting at 50 mg/day, tapered over 3 weeks to 5–7.5 mg N = 6	IV pulse CYC is effective and well tolerated in rapidly progressive ILD due to CVD; advantage over daily oral therapy is a lower cumulative CYC dose and less treatment-associated morbidity. CYC treatment should be confined to pts. with indices of high inflammatory activity	Very low
Varai, et al. J Rheumatol 1998 [66]	IV CYC (1 g) monthly for 48 weeks N = 5	Intermittent treatment with IV CYC reduces the severity of dyspnoea but fails to improve FVC or DLco, or to resolve radiological abnormalities, in pts. with SSc	Very low
Davas, et al. Clin Rheumatol 1999 [56]	Monthly CYC pulse (750 mg/m^2) for 12 months (n = 8) or oral CYC 2–2.5 mg/kg/day for 12 months (n = 8); all pts. received prednisone 10 mg/day N = 16	CYC pulse therapy was effective in suppressing active alveolitis; not possible to compare pulse vs oral therapy because of different HRCT patterns but oral therapy also appeared to be effective	Very low
White, et al. Ann Intern Med 2000 [58]	Oral CYC (1–1.5 mg/kg of body weight, increased as tolerated up to 2 mg/kg per day) or IV CYC monthly (800–1400 mg for 6–9 months) N = 103	Lung inflammation identifies pts. who are more likely to have worsening lung function; lung function outcomes and survival improve in pts. with alveolitis who have CYC treatment	Very low
Giacomelli, et al. J Rheumatol 2002 [60]	IV CYC (1000 mg/m^2 of body surface monthly for 6 months) and oral prednisone (25 mg/day for first month and 5 mg/day of maintenance dosage for remaining 5 months) N = 23	CYC pulse stabilised alveolitis in the majority of cases; the association with prednisone may help to control disease evolution in the lung. CYC plus prednisone did not change FVC but, at least in part, improved DLco	Very low

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Table 1 (*continued*)

Reference	Treatment	Summary of results	Quality of evidence
Griffiths, et al. J Rheumatol 2002 [68]	Six pulses of IV CYC (15 mg/kg) and IV MP (10 mg/kg) given at 3–4 weekly intervals N = 14	Treatment with IV CYC and MP may stabilise disease activity during the course of treatment and for 6 months afterwards; however, in the long term, deterioration still occurred in most pts., sometimes at a significant rate	Very low
Pakas, et al. J Rheumatol 2002 [69]	Monthly IV CYC and prednisolone at low dose (<10 mg/day; n = 12) or high dose (1 mg/kg/day for 4 weeks, tapered by 5 mg/day on alternating days q2w; n = 16) N = 28	IV pulse CYC with high doses of prednisolone is effective in improving clinical, physiological and radiological evolution of SSc-ILD, with reversal of underlying alveolitis	Very low
Kowal-Bielecka, et al. Ann Rheum Dis 2005 [59]	IV CYC (1.0 g every 30 days) for 6 months; pts. also received prednisone (<10 mg/day) N = 21	IV CYC stabilised or improved functional status and lung function. Pts with SSc-ILD and neutrophilic alveolitis showed greater improvements than pts. with normal levels of granulocytes in the bronchoalveolar lavage fluid	Very low
Tashkin, et al. N Engl J Med 2006 [13]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 145/158 completed ≥6 months of treatment	In SLS I, 1 year of oral CYC had a significant but modest beneficial effect on lung function, dyspnoea, mRSS and HRQoL; effects on lung function were maintained for 24 months	High
Airò, et al. Clin Exp Rheumatol 2007 [61]	Induction therapy: 8 IV pulses over 6 months (CYC 750 mg and 6-MP 125 mg q3w) Maintenance therapy: further cycles at 4 (3 pulses), 6 (3 pulses) and 9 weeks (3 pulses); total CYC dosage of 12.75 g over 18 months N = 13	Initial improvement in lung function tests (particularly FVC) in the first 6 months; no further improvement observed during the maintenance phase	Very low
Beretta, et al. Clin Rheumatol 2007 [97]	Oral CYC 2 mg/kg/day for 1 year and prednisone 25 mg for 3 months (then tapered to 5 mg/day) N = 33	Oral CYC is effective in ameliorating and/or stabilising lung function, with beneficial effects lasting up to 1 year after interruption; higher efficacy was observed with lower HRCT grade	Very low
Khanna, et al. Arthritis Rheum 2007 [52]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 158	In SLS I, 1 year of treatment with oral CYC leads to an improvement in HRQoL in pts. with scleroderma lung disease	Very low
Tashkin, et al. Am J Respir Crit Care Med 2007 [48]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 145/158 completed ≥6 months of treatment	In SLS I, CYC improved lung function, skin scores, dyspnoea and health status/disability for at least 12 months; however, except for a sustained impact on dyspnoea, these effects waned and were no longer apparent at 24 months	Moderate
Yiannopoulos, et al. Rheumatol Int 2007 [67]	Monthly IV pulses of CYC (750–1000 mg/m^2) and 1 g of MP N = 13	Combination of IV pulses of CYC and MP is well tolerated and effective, mainly in stabilising respiratory function; this goal is more realistic when treatment is given before significant functional compromise has ensued	Moderate
Simeón-Aznar, et al. Open Respir Med J 2008 [62]	IV CYC (0.50–0.75 g/m^2 of body surface area) each month for 6 months and oral prednisone (50 mg/day for 1 week, tapered to 5–7.5 mg over 6 weeks) 7/10 pts.: same IV CYC dose was continued bimonthly for 6 months and then quarterly during the second year N = 10	An IV CYC pulse regimen over 24 months may stabilise pulmonary activity in pts. with SSc-ILD during treatment and for a median of 26.5 months thereafter	Very low
Strange, et al. Am J Respir Crit Care Med 2008 [53]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 141	The presence of an abnormal lavage defined pts. with more advanced ILD but added no additional value to physiological and HRCT findings as a predictor of progression or treatment response in SLS I	High
Goldin, et al. Chest 2009 [47]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 98	In SLS I, 1-year course of treatment with CYC was associated with treatment-related changes in fibrosis scores on HRCT scans, which correlated with other measures of treatment response	High
Wanchu, et al. Int J Rheum Dis 2009 [98]	Monthly CYC pulses (750 mg/m^2) for 6 months followed by 3-monthly maintenance pulses and oral prednisolone (1 mg/kg body weight, tapered to 7.5 mg/day) N = 36	Pulse CYC and high-dose prednisolone can improve or stabilise lung function irrespective of presence of ground-glass appearance on HRCT	Very low
Furuya, et al. Rheumatology 2010 [99]	Six courses of CYC IV (0.5 g/m^2) q4w and prednisolone (≤30 mg/day; tapered gradually) (n = 12); control group on prednisolone alone (n = 7) N = 19	Low-dose IV CYC induces endothelial progenitor cell mobilisation, which may contribute to the efficacy for treating SSc- ILD	Very low
Domiciano, et al. Clin Rheumatol 2011 [63]	CYC monthly infusions (1 g/m^2/dose) for 12 months ± prednisone 60 mg/day (Month 1, tapered down to 10 mg/day by end of Month 2) N = 18	CYC stabilised lung function for 3 years after the 1-year treatment period; prednisone did not further improve lung fibrosis but may reduce skin involvement during the first year of treatment	Very low
Kim, et al. Eur Radiol 2011 [50]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 83	Quantitative fibrosis scoring for the extent of reticular pattern used in the present analysis of HRCT data obtained at baseline and after 1 year of treatment confirmed the beneficial treatment effect of CYC in SLS I	High
Mittoo, et al. Open Rheumatol J 2011 [100]	At least 6 months of CYC treatment (record review; typically, daily oral CYC 1 mg/kg of body weight, titrated to 2 mg/kg depending on tolerability) N = 38	While the majority of pts. treated with CYC for active ILD experienced long-term lung function stability and survived, more than a third of pts. experienced lung function decline, death, or required a lung transplant	Very low

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Table 1 (*continued*)

Reference	Treatment	Summary of results	Quality of evidence
Roth, et al. Arthritis Rheum 2011 [49]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) vs placebo N = 158 (12 months: n = 136; 18 months: n = 112)	In SLS I, FIBmax score, mRSS and BDI were independent correlates of the change in FVC%pred over time; severity of reticular infiltrates on baseline HRCT and baseline mRSS may be predictive of response to CYC therapy	High
Tochimoto, et al. Mod Rheumatol 2011 [65]	IV CYC (0.4 g/m^2 body surface area monthly) and prednisolone (0.8 mg/kg/day for 1 month, tapered to 10 mg/day) N = 13	IV CYC and oral prednisolone improved dyspnoea, HRCT score and FVC%pred in all pts. for 1 year after treatment began; >1 year post-therapy, ILD recurred in approximately half of the pts	Very low
Pérez Campos, et al. Reumatol Clin 2012 [70]	IV CYC (0.75 mg–1 g/m^2 body surface area; maximum dose 1 g) monthly for 6 months and bimonthly for the remaining 6 months and low-dose prednisone (1 mg/kg/day for 4 weeks, tapered to 5 mg q2w up to 10 mg) OR high-dose oral prednisone (10 mg/day) N = 13	A combination of CYC with low-dose steroids is effective in ILD, especially in active disease; results did not show differences between the high- and low-dose groups but differences in disease severity between the groups at baseline may have affected the findings	Very low
Theodore, et al. Chest 2012 [54]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 156	Cough is a common symptom and correlates with the extent of fibrosis; its frequency decreased significantly in response to CYC but returned to baseline 1 year after withdrawal of treatment in SLS I	Very low
Kim, et al. Ann Rheum Dis 2016 [51]	Oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year vs placebo N = 83	In SLS I, changes in quantitative HRCT measures of ILD provided a sensitive indication of disease progression and response to treatment	High
Sumida, et al. J Dermatol 2018 [101]	One pulse of IV CYC (500 mg/m^2/month for 6 months; first pulse decreased to 70% in some cases for safety reasons) and prednisolone (increased up to or started from 20, 25 or 30 mg/day prior to IV CYC therapy) N = 32	ILD severity/activity before treatment and variability of serum KL-6 and SP-D levels during treatment may be useful to predict therapeutic effects of IV CYC on SSc-ILD	Very low
van den Hombergh, et al. Clin Rheumatol 2018 [64]	IV CYC pulses (750 mg/m^2) monthly N = 75	CYC followed by maintenance therapy stabilises pulmonary function over a 3-year period; extent of ILD, proportion of ground glass, SSc disease duration and baseline DLco <60% did not influence the effect of CYC on pulmonary function	Low
Volkmann, et al. J Rheumatol 2019 [55]	SLS I: oral CYC (1 mg/kg/day, increased every month up to a maximum of 2 mg/kg/day) for 1 year (n = 79) SLS II: oral CYC 2.0 mg/kg/day for 12 months followed by placebo for 1 year (n = 69) N = 148	In both SLS I and II, treatment with CYC for 1 year led to similar improvements in pulmonary function, although effects were not maintained after cessation of CYC	Low
Bruni, et al. Clin Exp Rheum 2020 [57]	Oral CYC for ≥6 months with 12 months of follow-up after last administration of CYC (n = 149) IV CYC for ≥6 months with 12 months of follow-up after last administration of CYC (n = 153) N = 302	No difference in pulmonary function, ILD progression or skin score was found between IV CYC and oral CYC after 1 year in pts. from the EUSTAR registry and SLS I and SLS II	Low
Other immunosuppressive therapies			
Azathioprine			
Hoyles, et al. Arthritis Rheum 2006 [72]	IV CYC (600 mg/m^2) monthly for 6 months plus 20 mg oral prednisolone on alternate days followed by oral AZA (2.5 mg/kg/day), or placebo (N = 45)	Combination therapy with IV CYC, low-dose prednisolone and AZA may help to stabilise lung function in a subgroup of pts. with SSc-ILD	Low
Bérezné, et al. J Rheumatol 2008 [71]	IV CYC (0.6 g/m^2) monthly for 6 months followed by oral AZA (2–3 mg/kg/day) for 18 months (N = 27)	In pts. with worsening ILD, CYC followed by AZA treatment was associated with stable/improved PFT in 70% of pts. at 6 months and 51.8% at 2 years	Very low
Kundu, et al. Indian J Chest Dis Allied Sci 2016 [73]	IV CYC (600 mg/m^2) monthly for 6 months with oral prednisolone (10 mg) daily, then AZA (2–3 mg/kg/day) with same dose of steroid for 1 year N = 9	IV pulse CYC therapy for 6 months followed by AZA therapy with low-dose steroids is associated with significant improvement in lung function and 6MWD	Very low
Rituximab			
Daoussis, et al. Rheumatology 2010 [74]	2 cycles of RTX at baseline and 24 weeks or standard treatment (N = 14)	RTX treatment may improve lung function in pts. with SSc-ILD	Very low
Daoussis, et al. Clin Exp Rheumatol 2012 [75]	1 cycle of RTX at baseline, 6, 12 and 18 months N = 8	Long-term RTX therapy may have beneficial effects on skin and lung disease in pts. with dcSSc-ILD	Very low
Keir, et al. Eur Respir J 2012 [78]	RTX (1000 mg on days 0 and 14) preceded by treatment with IV hydrocortisone and chlorphenamine N = 8	RTX may be an effective therapy for pts. with very severe unresponsive CTD-ILD	Moderate
Jordan, et al. Ann Rheum Dis 2015 [77]	RTX (various doses). 75% of pts. received 2 x infusions (1000 mg) within 2 weeks N = 63	A comparison of RTX vs untreated matched control pts. with SSc, including pts. with ILD, revealed that RTX treatment is associated with beneficial effects on skin and lung fibrosis	Very low
Daoussis, et al. Semin Arthritis Rheum 2017 [76]	≥2 cycles of RTX, every 6 months or conventional treatment N = 33	RTX treatment has significant beneficial effects on lung function and skin fibrosis in pts. with SSc-ILD	Very low

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Table 1 (*continued*)

Reference	Treatment	Summary of results	Quality of evidence
Sircar, et al. Rheumatology 2018 [79]	IV CYC (500 mg/m^2) q4w for 24 weeks vs two RTX pulses (1000 mg on Day 0 and Day 15) N = 60	Treatment with RTX was associated with significant improvements in lung and skin disease in pts. with early SSc-ILD (<2 years' duration)	Moderate
Pomalidomide			
Hsu, et al. J Rheumatol 2018 [80]	POM (1 mg QD) or placebo for 52 weeks (N = 22)	POM was not linked to clinical benefits in pts. with SSc-ILD. The study was terminated early due to recruitment problems and there were too few enrolled pts. to draw meaningful conclusions	Very low
Other tyrosine kinase inhibitors			
Imatinib mesylate			
Sabnani, et al. Rheumatology 2008 [84]	Imatinib 200 mg/day CYC 500 mg q3w N = 5	Clinical improvement with imatinib plus CYC was only seen in the 1 pt. with mild restrictive disease	Very low
Spiera, et al. Ann Rheum Dis 2011 [85]	Imatinib 400 mg/day N = 30 (ILD = 16)	Imatinib significantly improved skin thickening. Lung parameters remained stable in pts. with ILD	Very low
Khanna, et al. Arthritis Rheum 2011 [82]	Imatinib >600 mg/day N = 20	Imatinib significantly improved skin thickening. There was a trend towards improved lung function	Very low
Fraticelli, et al. Arthritis Res Ther 2014 [81]	Imatinib 200 mg/day N = 26	Lung function and HRCT assessments stabilised in the majority of pts. following treatment with imatinib	Low
Dasatinib			
Martyanov, et al. PLoS One 2017 [83]	Dasatinib 100 mg/day N = 31	There was no significant clinical efficacy observed for dasatinib. An inflammatory gene expression subset was associated with worsening skin fibrosis, lung fibrosis and pulmonary function	High
Other treatments			
D-penicillamine			
Steen, et al. Arthritis Rheum 1994 [87]	High-dose prednisone ≥30 mg/day for ≥4 months or ≥ 60 mg/day for 2 months (n = 21), IST other than CYC (AZA ≥50 mg/day or MTX ≥7.5 mg/week for at least 6 months) (n = 16), CYC ≥50 mg/day for at least 6 months or monthly IV 500–750 mg/m^2 for at least 6 months (n = 14), D-penicillamine ≥250 mg/day for more than months (n = 37), no drug (n = 34) N = 122	Pts. treated with CYC showed significant improvement in lung function compared with other ISTs, prednisone or D-penicillamine	Very low
Bosentan			
Seibold, et al. Arthritis Rheum 2010 [86]	Bosentan 62.5 mg BID then 125 mg BID after 4 weeks or placebo N = 163	In pts. with SSc-ILD, lung function parameters remained stable at 12 months in the majority of pts. in both placebo and bosentan groups. There was no significant difference in 6MWD between bosentan and placebo groups	High
Pirfenidone			
Khanna, et al. J Rheumatol 2016 [88]	Pirfenidone for 16 weeks (titration for 2 vs 4 weeks: 801 mg/day starting dose finishing at 2403 mg/day maintenance dose) N = 63	Pirfenidone treatment (either titration group) had no significant effect on lung function, skin thickening or patient-reported outcomes. However, 96.8% of pts. experienced one or more treatment-emergent AE	Low
Riociguat			
Khanna, et al. Ann Rheum Dis 2020 [89]	Riociguat 0.5–2.5 mg orally three times daily (individually assessed q2w) (n = 60) Placebo (n = 61) N = 122	Riociguat did not significantly benefit mRSS compared with placebo in the RISE-SSc trial	Moderate

%pred, percent predicted; 6MWD, 6-min walking distance; AE, adverse event; AZA, azathioprine; BDI, Baseline Dyspnoea Index; BID, twice daily; Cst, static lung compliance; CTD, connective tissue disease; CVD, cardiovascular disease; CXCL4, chemokine (C-X-C motif) ligand 4; CYC, cyclophosphamide; dcSSc, diffuse cutaneous systemic sclerosis; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FIBmax, maximum fibrosis score on HRCT; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; HRQoL, health-related quality of life; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IST, immunosuppressive therapy; IV, intravenous; KL-6, Krebs von den Lungen-6; MMF, mycophenolate mofetil; MP, methylprednisolone; mRSS, modified Rodnan skin score; MS, mycophenolate sodium; MTX, methotrexate; PFT, pulmonary function tests; POM, pomalidomide; pts., patients; q2/3/4w, every 2/3/4 weeks; QD, once daily; RTX, rituximab; SC, subcutaneous; SLS, Scleroderma Lung Study; SP-D, surfactant protein D; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease; TLC, total lung capacity; VC, vital capacity.

3.4. Mycophenolate

We identified 19 references investigating mycophenolate in the literature search, with the earliest published in 2006. Data from these studies are shown in Supplementary Table 3. The efficacy of MMF was investigated in the Phase II SLS II study, an RCT evaluating MMF for 2 years against oral cyclophosphamide for 1 year followed by 1 year of placebo in SSc-ILD (N = 142) [14]. Seven analyses of the SLS II trial [14,29–34] presented high- or moderate-quality evidence, suggesting that while there was no difference in clinical efficacy compared with cyclophosphamide after 2 years, MMF was better tolerated and significantly reduced the extent of SSc-ILD on HRCT but did not result in improvement in lung fibrosis [14,31]. However, mycophenolate was mostly investigated in smaller cohorts or observational studies [35–46] with very low- or low-quality evidence.

3.4.1. Lung function

For most studies, including SLS II [14], the baseline mean FVC% predicted was >60%, with Nihtyanova et al. and Iudici et al. reporting baseline FVC% predicted >80% [39,44]. The effect of MMF on lung function was non-significant in most studies, including in SLS II where FVC% predicted improved from baseline by +2.17% in the MMF arm (n = 69) and +2.86% in the cyclophosphamide arm (n = 73), with no significant difference found (N = 126; P = 0.24) [14]. However, significant improvement in mean FVC% predicted from baseline was demonstrated in a cohort of patients with CTD-ILD (N = 125) treated with MMF for 156 weeks (+7.3%; P = 0.004) [37]. Gerbino et al. also demonstrated that MMF treatment significantly improved FVC% predicted by a mean of 4% per year (P = 0.002) in a small cohort of patients with SSc-ILD (N = 13) [40].

Liossis et al. showed that MMF significantly improved mean diffusing capacity for carbon monoxide (DLco) % predicted compared with pre-treatment after 4–6 months in patients with dcSSc-associated alveolitis of recent onset (N = 6; 75.4% vs 64.2%, respectively, P = 0.033) [45]. Vanthuyne et al. also observed significant improvements in DLco% predicted when patients with early SSc-ILD or extensive skin disease were treated with MMF in combination with methylprednisolone and glucocorticoids for 12 months [46].

3.4.2. HRCT pattern

In SLS II, treatment with MMF or cyclophosphamide was not significantly correlated with changes in QLF scores. However, QILD score in the whole lung was improved in both the MMF (−2.51; 95% CI −4.9 to −0.15; n = 51) and cyclophosphamide arms (−2.78; 95% CI −5.17 to −0.40; n = 47) [14]. Goldin et al. demonstrated that both MMF and cyclophosphamide treatments were associated with a significant improvement in QILD score in the whole lung (pooled group: −2.51%; 95% CI −4.00 to −1.03; P = 0.001), with no significant differences observed between the two treatments [31], and FVC% predicted was significantly correlated with change in the extent of fibrosis on HRCT assessed by computer-aided diagnosis scores [31].

In studies that recruited patients with early SSc-ILD (N = 5–16), there were non-significant improvements in ground-glass opacities by chest HRCT following MMF treatment [45,46]. In a small case series (N = 12), 54.5% of patients with SSc-ILD who experienced an inadequate response to cyclophosphamide, MMF treatment led to stabilisation of the Warrick score (a semi-quantitative scoring system composed of a severity and extent score calculated across four pulmonary zones) [43]. However, a study of patients with progressive SSc-ILD found a similar deterioration in Warrick score at 2 years of 2.7 and 2.0 for MMF and cyclophosphamide, respectively [35].

3.5. Cyclophosphamide

We identified 33 publications covering 23 different studies that evaluated cyclophosphamide, with the earliest report on cyclophosphamide published in 1993. Eleven publications were analyses of SLS I, a landmark Phase III study evaluating oral cyclophosphamide versus placebo in patients with SSc and ILD over 1 year [13,47–54]. Cyclophosphamide was either administered as intravenous (IV) pulses (doses most commonly ranging from 0.5–1.0 g/m^2 body surface area) or orally (generally 1–2 mg/kg/day). Data from these studies are shown in Supplementary Table 4. In 19 of the 33 publications, cyclophosphamide was administered alongside steroid treatment, most commonly prednisone/prednisolone (16/19) or methylprednisolone (3/19). Prednisone/prednisolone therapy was administered either at low dose (<10 mg/day) or high dose (10–60 mg/day, but generally tapered down to 5–10 mg/day where possible).

For cyclophosphamide, the certainty of evidence was generally very low or low (23/33 references). Studies with high-quality evidence did not find a significant effect of cyclophosphamide on FVC% predicted at 12 months; however, there was significant improvement in fibrosis on HRCT scans [47–51,53,54]. Moderate-quality evidence found that cyclophosphamide significantly improved Health Assessment Questionnaire-Disability Index (HAQ-DI) scores at 12 months, with a higher proportion of patients achieving a minimally clinically important difference [48,52]. This is in alignment with the assessment of HAQ-DI evidence in a previous systematic review focussing on cyclophosphamide [16].

3.5.1. Lung function

Out of the 33 studies, 28 reported lung function data, although results were variable across studies. In SLS I, there was a smaller decline in FVC% predicted at 12 months in the cyclophosphamide arm (n = 79) compared with placebo (n = 79) (−1.0 ± 0.92 vs −2.6 ± 0.9) [13]. The mean absolute difference in FVC% predicted at 12 months for cyclophosphamide compared with placebo was 2.53% (95% CI 0.28–4.79; P < 0.03); this difference was also seen at 24 months [13]. A comparison of the cyclophosphamide arms from SLS I and SLS II using an inferential joint model approach found significant improvement from baseline in lung function at 3–12 months, but not after that time point [55].

Davas et al. found that more patients showed an improvement in pulmonary function with IV cyclophosphamide pulse therapy (7/8) than oral cyclophosphamide (3/8) [56], although direct comparisons were not possible due to different HRCT patterns. However, Bruni et al. found no difference in either pulmonary function or ILD progression (oral n = 149, IV pulse n = 153) [57]. Several studies noted that IV cyclophosphamide treatment was particularly effective in the short term in patients with alveolitis, associated with improvement or stabilisation of FVC and DLco over time (n = 8–39) [56,58–61]. While SLS I showed improvement/stabilisation in lung function only over the first 3–12 months, in other smaller studies (n = 10–75) lung function was maintained for 2–4 years, with a mean change in FVC% predicted ranging from −4.45% to +5.0% [62–65].

3.5.2. HRCT pattern

Sixteen studies reported HRCT findings beyond baseline. Again, results were inconsistent between studies, with some showing conflicting data or that HRCT patterns did not improve with cyclophosphamide treatment [59,60,62,66,67], while others demonstrated stabilisation/improvement of HRCT scores [47,50,51,56,65,68–70]. In SLS I, improvement in FVC was correlated with improvement in QLF scores after 12 months of cyclophosphamide treatment (n = 41): −0.40 (P = 0.0003) for highest QLF score zone at baseline and −0.33 (P = 0.003) for whole lung [50]. Cyclophosphamide (n = 49) treatment also significantly influenced improved HRCT outcomes when adjusting for covariates (odds ratio [OR] 3.26, 95% CI 1.30–8.17; P = 0.012) [47]; however, there was no correlation between baseline maximum fibrosis score over the lung regions assessed and fibrosis outcomes (OR 0.81, 95% CI 0.52–1.25; P = 0.331), and no treatment effect on ground-glass opacities or honeycombing. Van den Hombergh et al. showed that HRCT scores for ground glass at baseline were not predictive of the therapeutic

effect of cyclophosphamide on lung function (N = 75) [64].

3.6. Other immunosuppressive therapies

We identified ten studies investigating other immunosuppressive treatments for SSc-ILD, including azathioprine [71–73] rituximab [74–79] and pomalidomide [80], with the earliest publications in 2008, 2010 and 2018, respectively. Data from these studies are shown in Supplementary Table 5. Rituximab was investigated in one single-arm study (N = 8) [75], compared with either standard of care (N = 14–51) [74,76] or cyclophosphamide (N = 60) [79], and in two observational studies (N = 8–63) [77,78]. There were two observational studies (N = 9–45) and one placebo-controlled study (N = 27) investigating the safety and efficacy of azathioprine following cyclophosphamide in patients with SSc-ILD [71–73]. A Phase II study investigating the efficacy and safety of pomalidomide in patients with SSc-ILD did not show any beneficial effects on skin or lung disease; however, the study was terminated early and patient numbers were too low (N = 23) to make accurate conclusions [80].

The quality of evidence was low or very low for azathioprine [71–73], pomalidomide [80] and four out of six rituximab studies [74–76]. There were two moderately rated studies on rituximab: there was moderate evidence that rituximab stabilised or improved lung function after 6 months of treatment [77,79]; however, other studies with similar findings were very low quality [74,75]. In a recent systematic review of rituximab in CTD-ILD, including SSc-ILD, the authors concluded that while it was a promising therapeutic tool, more data were needed from multicentre prospective trials [17]. This matches our assessment of the quality of the evidence for rituximab in SSc-ILD.

3.6.1. Lung function

Rituximab treatment was associated with significant improvements in FVC after both 1 year (n = 8) [74] and 2 years (n = 8–33) [75,76] of treatment in patients with SSc-ILD. In an observational study using the EUSTAR cohort, rituximab treatment was associated with preventing further FVC decline from baseline in patients with SSc-ILD (N = 9) compared with matched controls (P = 0.02) [77]. In an open-label randomised study, rituximab (n = 30), but not cyclophosphamide (n = 30), was associated with a significant increase in FVC% predicted [79]. In patients treated with azathioprine following cyclophosphamide therapy, a 2-year experimental study (N = 27) and a 1-year observational study (N = 9) showed beneficial effects on lung function [71,73]; however, there was no improvement in a 1-year experimental study with 45 patients [72].

3.6.2. HRCT pattern

Only three studies reported HRCT results following immunosuppressive treatment [72,74,75]. There were no significant improvements in serial HRCT scans in patients with SSc-ILD who were treated with oral prednisolone, cyclophosphamide and azathioprine at 1 year (n = 22) [72]. In a small study of 18 patients with SSc-ILD, there were no significant improvements in HRCT scores at 24 weeks following rituximab treatment [74]. In another rituximab study, a 5–10% decrease in ground-glass lesions was reported in 5 out of 8 patients [75].

3.7. Other tyrosine kinase inhibitors

We identified five publications investigating two additional tyrosine kinase inhibitors during the literature search: imatinib mesylate and dasatinib. The earliest publication for each treatment was in 2008 and 2017, respectively. Data from these studies are shown in Supplementary Table 6. The evidence for imatinib and dasatinib was rated low or very low quality [81–85]. Imatinib mesylate was investigated in SSc-ILD in four studies, including one Phase I/IIa study (N = 20) [82], two Phase II studies (both N = 30) [81,85] and a small case series (N = 5) [84], with doses ranging from 200 to 600 mg once daily, either as monotherapy or in combination with cyclophosphamide. There was one Phase I/II single-arm safety/biomarker study investigating dasatinib in SSc-ILD (N = 31) [83]. Most patients in these studies had a baseline FVC% predicted >70%, except the Khanna et al. imatinib study, where the baseline mean value was <70% [82].

3.7.1. Lung function

Two imatinib studies reported on changes in lung function. In Spiera et al. [85], a mean increase of 2.1% in FVC% predicted from baseline at 12 months was reported for the 16/30 patients with ILD. In Fraticelli et al. [81], 4/26 patients had a good response at 6 months of treatment, defined as an increase in FVC >15%, and/or increase in DLco >15% and partial pressure of oxygen >90%, and HRCT pattern unchanged or improved from baseline; 19/26 patients had stabilised ILD. In the single-arm dasatinib study, there were significant differences in FVC and DLco at 6 months between patients classed as improvers (n = 3) and non-improvers (n = 9). Improvers had stable FVC and DLco at 6 months, whereas non-improvers had a decline in both these measures (P = 0.1289 and P = 0.0195, respectively) [83].

3.7.2. HRCT pattern

Only two studies reported HRCT results. After 6 months of imatinib treatment, there was a significant reduction in the number of lung segments with ground-glass opacities compared with baseline in stabilised patients (n = 15; P = 0.0002), but not in the number of lung segments with honeycombing [81]. In patients treated with dasatinib, 23/31 patients had matched baseline and 6-month follow-up HRCT scans [83]. Of these, improved or stable HRCT scores were observed in the most severe lobe in 9/23 patients and in the whole lung in 10/23 patients. In the most severe lobe, 39% of patients showed no progression in ILD by quantitative HRCT following dasatinib treatment.

3.8. Other treatments

We identified four studies in the literature search investigating other treatments for SSc-ILD: bosentan, riociguat, pirfenidone and D-penicillamine [86–89]. Data from these studies are shown in Supplementary Table 7. Bosentan, a nonselective endothelin receptor antagonist, was investigated in a randomised, placebo-controlled Phase II/III study in SSc-ILD (N = 163), where the primary endpoint was change in 6-min walking distance, and secondary endpoints included changes in pulmonary function tests, published in 2010 [86]. The soluble guanylate cyclase inhibitor riociguat was investigated in a Phase IIb placebo-controlled trial of patients with dcSSc at high risk of skin fibrosis progression, including a subset of patients with ILD (n = 25/121) [89]. The quality of evidence for bosentan and riociguat was assessed to be high and moderate, respectively, although neither study met its primary endpoint [86,89]. An open-label Phase II trial investigated the safety and tolerability of the antifibrotic pirfenidone, using two different dose-titration schedules (2 weeks vs 4 weeks) in patients with SSc-ILD (N = 63) published in 2016 [88]. The quality of evidence for pirfenidone was low, and the study found no significant differences between treatment groups [88]. D-penicillamine was investigated in a retrospective observational study (N = 122) comparing cyclophosphamide, D-penicillamine, prednisone and other immunosuppressive treatments used to treat SSc-ILD as well as a no-treatment group published in 1994 [87]. The evidence from Steen et al.'s study was assessed as very low quality, suggesting low confidence in the findings that only cyclophosphamide had a significant effect on lung function over 2 years [87].

3.8.1. Lung function

In Seibold et al., the change in median FVC% predicted from baseline at 12 months was similar between groups: −1.6% for the bosentan group (n = 77) and −1.2% for the placebo group (n = 86), representing a median treatment effect of −0.9% (95% CI −3.41.2; P = 0.422) [86]. Riociguat (n = 60) reduced decline in FVC% predicted at 52 weeks by

4.9% compared with placebo (n = 61) in the ILD subgroup [89]. In the pirfenidone study, FVC% predicted was similar between the two titration groups after 16 weeks of treatment (change from baseline in both groups: −0.6 [standard deviation 8.91]) [88]. In addition, the change in DLco% predicted after 16 weeks for the 2-week (n = 32) and 4-week (n = 31) titration groups was 0.7 (9.57) and 3.2 (10.00), respectively [88].

In Steen et al., out of the five treatment groups, the cyclophosphamide-only group (n = 14) showed improvement in FVC% predicted ($P < 0.05$). In the D-penicillamine group (n = 37), FVC% predicted and DLco% predicted remained stable (FVC 55% predicted at baseline and final recorded value) [87]. The treatment groups had lower baseline FVC% predicted (47–59%) compared with the other studies, which ranged from 68% to 93% [86–89].

4. Discussion

ILD secondary to SSc has emerged as the leading cause of morbidity and mortality in SSc [5–7]. Accordingly, there have been a large number of interventional studies evaluating candidate therapies. These studies have included retrospective case reviews and open-label observational studies, but surprisingly few RCTs. This diversity in the reporting of potential therapies lends itself to standardised assessment of the quality of evidence.

In the present critical assessment of published evidence from the last 30 years, we found high-quality evidence for the use of cyclophosphamide, nintedanib, mycophenolate and tocilizumab. We would posit that the clinical community has four options for treatment of SSc-ILD. Nintedanib has been shown to reduce decline in pulmonary function, both alone and in combination with MMF. Based on data from tocilizumab in SSc [22,23,28], including patients with ILD [23], there is evidence for an important, clinically relevant effect on lung function in patients with early diffuse cutaneous disease and raised inflammatory markers. Both nintedanib and tocilizumab have been approved for slowing the rate of decline in pulmonary function in patients with SSc-ILD (the latter in the US only). Treatment with cyclophosphamide and MMF has been shown to preserve pulmonary function. However, treatment with cyclophosphamide is limited in duration due to its toxicity. MMF, in our opinion, should be considered particularly in combination with targeted agents. Some of the other treatments discussed may also have potential.

In SSc and SSc-ILD we are mainly interested in reducing or stopping the ongoing processes that lead to irreversible damage and loss of function, whether inflammatory, fibrotic or both, thereby slowing down clinical deterioration. This was achieved as the primary endpoint in nintedanib clinical trials, and as secondary or exploratory endpoints in the tocilizumab trials. Long-term follow-up of lung function and markers of inflammation and/or fibrosis are essential parameters for selecting the most reliable approach in patients with ILD.

As outlined in our review, there are many different endpoints that can be assessed. Different patient subgroups may also require different treatments. Future approaches may stratify patients as more data become available.

4.1. Future and other treatments

Several clinical trials are investigating possible future treatments for SSc-ILD. The SLS III trial is a Phase II study investigating MMF in combination with pirfenidone (NCT03221257). Another Phase II placebo-controlled trial of MMF combination therapy (NCT02370693) is investigating MMF with or without the proteasome inhibitor bortezomib. Other treatments that have been studied but lack data include a Phase III trial of the phosphodiesterase 5 inhibitor tadalafil (NCT01553981) that completed in 2015 (although no results have been published) and a dose-comparison trial of abituzumab (an immunoglobulin G2 monoclonal antibody targeted at the integrin CD51) in patients receiving a steady dose of MMF that was terminated due to difficulty in recruitment (NCT02745145).

Autologous HSCT is another potential treatment option, although as a non-drug-based treatment it was excluded from the current literature review. One single-centre study and two larger RCTs have shown improvement of skin involvement and stabilisation of lung function in patients with SSc, including SSc-ILD [90–92]. Event-free and overall survival were improved in patients treated with HSCT compared with cyclophosphamide in both trials, with survival benefits maintained at 5–10 years [91,92]. However, HSCT was associated with increased treatment-related mortality in the first few years after treatment. In view of the high risk of treatment-related side effects, the European League Against Rheumatism guidelines recommend careful selection of patients with rapidly progressive SSc at risk of organ failure for HSCT treatment, and state that the experience of the medical team is of key importance [11].

In the current treatment approaches discussed in this review, there has been no stratification on markers for disease. Instead, there has effectively been a blanket approach with immunosuppressive therapy. Disease marker-led treatment stratification could be useful for better targeting patients, with which drug or treatment combination determined for each patient based on markers for inflammation or fibrosis. More data from long-term follow-up of markers would also give insight into disease progression and treatment efficacy over time. These questions may inform future clinical research approaches.

4.2. Conclusions

The literature to date leaves a number of critical questions unanswered. Is there an hierarchy of effectiveness that should influence selection of therapy? Are there effective combinations of therapy that provide optimum results? If combination therapy is employed, is there a preferred order of drug initiation? In the nintedanib study [93], nintedanib reduced the loss of pulmonary function both in those who were and were not using MMF at baseline, with no heterogeneity in treatment effect between the subgroups, but there are few other data addressing this question. What clinical, laboratory and HRCT findings might lead to identification of subsets most likely to benefit from one therapy versus another?

Further research is required to provide more evidence for the optimal treatment strategy in SSc-ILD, including the optimal time to initiate treatment, selection of patients for treatment and upfront combination therapy.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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