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Review article

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State-of-the-art evidence in the treatment of systemic sclerosis

Janet E. Pope[1,2] ✉, Christopher P. Denton[3], Sindhu R. Johnson[4,5], Andreu Fernandez-Codina[1,6,7], Marie Hudson[8,9] & Tatiana Nevskaya[1]

Abstract

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease with multi-organ involvement, fibrosis and vasculopathy. Treatment in SSc, including early diffuse cutaneous SSc (dcSSc) and the use of organ-specific therapies, has improved, as evident from randomized clinical trials. Treatments for early dcSSc include immunosuppressive agents such as mycophenolate mofetil, methotrexate, cyclophosphamide, rituximab and tocilizumab. Patients with rapidly progressive early dcSSc might be eligible for autologous haematopoietic stem cell transplantation, which can improve survival. Morbidity from interstitial lung disease and pulmonary arterial hypertension is improving with the use of proven therapies. Mycophenolate mofetil has surpassed cyclophosphamide as the initial treatment for SSc-interstitial lung disease. Nintedanib and possibly perfinidone can be considered in SSc pulmonary fibrosis. Pulmonary arterial hypertension is frequently treated with initial combination therapy (for example, with phosphodiesterase 5 inhibitors and endothelin receptor antagonists) and, if necessary, the addition of a prostacyclin analogue. Raynaud phenomenon and digital ulcers are treated with dihydropyridine calcium channel blockers (especially nifedipine), then phosphodiesterase 5 inhibitors or intravenous iloprost. Bosentan can reduce the development of new digital ulcers. Trial data for other manifestations are mostly lacking. Research is needed to develop targeted and highly effective treatments, best practices for organ-specific screening and early intervention, and sensitive outcome measurements.

Sections

[1]Division of Rheumatology, St Joseph's Health Care, London, ON, Canada. [2]Department of Medicine, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada. [3]Division of Medicine, University College London, London, UK. [4]Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital, Toronto, ON, Canada. [5]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada. [6]General Internal Medicine, Windsor Regional Hospital, Windsor, ON, Canada. [7]Critical Care, Emergency and Systemic Autoimmune Diseases, Hospital Clinic, Barcelona, Spain. [8]Department of Medicine, McGill University, Montreal, QC, Canada. [9]Division of Rheumatology and Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada. ✉e-mail: janet.pope@sjhc.london.on.ca

Key points

- Treatment of systemic sclerosis (SSc) is organ-based or aimed at disease modification.
- Autologous haematopoietic stem cell transplantation can improve survival in patients with early diffuse cutaneous SSc who are at high risk of mortality, such as those with very high skin scores (as measured by the modified Rodnan skin score) or moderate skin involvement and worsening interstitial lung disease (ILD).
- Immunosuppressives and some biologic agents can soften skin and change the natural history of early diffuse cutaneous SSc.
- Appropriate treatment for patients with early limited cutaneous SSc is unknown, and further research is needed.
- ILD is usually treated by the use of mycophenolate mofetil as the initial therapy and then other immunosuppressives or biologic agents, but if ILD is fibrotic and progressing, anti-fibrotic therapy can be added, such as nintedanib (and possibly pirfenidone).
- Raynaud phenomenon in SSc is treated with calcium channel blockers and then phosphodiesterase 5 inhibitors or intravenous iloprost.

Introduction

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease (CTD) that is associated with substantial morbidity and mortality due to fibrosis and vasculopathy; the estimated prevalence is 30–120 cases per million[1]. The disease is often characterized by the extent of skin involvement: limited cutaneous SSc (lcSSc) involves fibrosis of skin distal to the elbows and/or knees but without truncal involvement, although skin thickening might occur on the face and neck, whereas diffuse cutaneous SSc (dcSSc) involves skin both distal and proximal to the knees and/or elbows and/or truncal[2]. In addition, a small proportion of patients (1.5–8%) lack definite skin involvement, but develop major internal organ-based complications[3–5]; these patients, designated as having SSc sine scleroderma, often have a similar trajectory to the lcSSc subset. A potential 'prescleroderma' subset of patients has been described who have isolated Raynaud phenomenon, puffy fingers, specific antibodies against hallmark antigens or SSc-associated capillaroscopic changes. Up to half of these patients develop a defined CTD (including SSc) during long-term follow-up[6,7].

Nearly all patients with SSc have Raynaud phenomenon and half have digital ulcers[8]. Gastrointestinal involvement affects nearly 90% of patients with SSc, with the oesophagus being the most commonly involved area followed by the small bowel, colon and anorectum[9–11]. Some patients with gastrointestinal involvement as measured by pathology or functional tests can be asymptomatic; only 8% of these patients present with severe involvement leading to increased morbidity and mortality[8,12]. Malnutrition is the leading cause of mortality attributed to gastrointestinal tract involvement, although mechanical or pseudo-obstruction can also be life-threatening in the context of multi-organ involvement. Interstitial lung disease (ILD) is common (found in 40–75% based on lung function changes) but is progressive in 15–18% of patients[8,13,14]. Many other manifestations occur in SSc, such as pulmonary arterial hypertension (PAH), inflammatory arthritis, calcinosis, myopathy and/or myositis, cardiomyopathy, sicca symptoms and scleroderma renal crisis (SRC).

Owing to the relatively high frequency of certain disease complications and the fact that early intervention can change the natural history of these complications, screening for ILD and PAH is recommended (Table 1). In patients with early dcSSc, blood pressure should be monitored, especially if the patient has anti-RNA polymerase III antibodies (anti-RNAPIII), in order to detect and treat SRC early. Selected screening can also be performed when the index of suspicion of certain manifestations, such as cardiac involvement (beyond echocardiography, which is done for PAH screening, such as for arrhythmias), and paraneoplastic SSc, is high where cancer screening is performed.

Several SSc clinical trials and consensus statements guide treatments, and the order of their use, for various organ-based manifestations of SSc. Of note, randomized controlled trials (RCTs) of treatments that modify the overall disease (that is, improve the natural history and pathophysiology) and skin fibrosis generally consider only patients in the dcSSc subset and often only within 2–5 years from the onset of the first non-Raynaud phenomenon features, whereas RCTs of treatments for organ-based manifestations, such as ILD, PAH, Raynaud phenomenon and digital ulcers, include patients in either subset provided that they meet the entry criteria for the trials.

This article reviews and summarizes the current management of SSc, including screening for and treatment of organ-based manifestations such as skin, lung (ILD and PAH) and Raynaud phenomenon and digital ulcers, as well as consideration of overall disease modification with autologous haematopoietic stem cell transplantation (AHSCT). Although patients with SSc can also be affected by other symptoms, including gastrointestinal manifestations, SRC, arthritis, myopathy and cardiac involvement, these have not been included in this Review because data from RCTs are mostly lacking; we direct the reader to treatment algorithms devised by SSc experts that address these symptoms[15]. In addition, several treatments can improve disease pathophysiology and thus be considered to modify the overall disease, but in this article treatments are discussed according to the outcome measures used in studies; for example, mycophenolate mofetil (MMF) and cyclophosphamide might improve ILD and skin manifestations, whereas for AHSCT data are available on improvements in survival as well as skin, function and ILD. There may be a survival advantage when treating patients with early dcSSc with immunosuppressives, especially those not eligible for AHSCT, but proof within RCTs is lacking for immunosuppressive therapies.

Management of skin manifestations

Skin fibrosis is one of the dominant clinical features of SSc. The designations dcSSc and lcSSc are used as surrogates of disease severity and prognosis, but both subsets are associated with high functional and psychosocial impact. The extent of skin fibrosis in SSc is most commonly assessed using the modified Rodnan skin score (mRSS), which measures skin thickness on a scale of 0 to 3 at 17 anatomical sites (score range 0–51). The minimal clinically important difference in mRSS has been estimated to range between 3.5 and 5.3 points[16]. In dcSSc, mRSS generally increases over the first 4 years of the disease and regresses somewhat over time thereafter, although many patients do not follow this pattern as they may worsen later or not improve after 4 years of disease. It is difficult to predict which patients with early dcSSc will improve or worsen during a clinical trial with respect to skin involvement, but a large response to placebo (and many active therapies) is unlikely. Some prediction models

Table 1 | Screening for organ involvement in SSc[a]

Organ involvement	Screening strategy
Pulmonary arterial hypertension	a. Enrich a high-risk group: those with longer disease duration, older age and/or low diffusing capacity
	b. Various screening algorithms are available, including but not limited to echocardiography, pulmonary function testing, electrocardiography, NT-proBNP, 6-min walking distance
ILD	a. Patients who are positive for anti-topoisomerase 1 (Scl-70) antibodies have a higher frequency of ILD
	b. Patients especially in the dcSSc subset
	c. Investigate unidentified dyspnoea
	d. Screening is by history, physical examination, chest radiography, pulmonary function testing and high-resolution CT of the lungs where appropriate
Scleroderma renal crisis in patients with early dcSSc	a. Any patient who is positive for anti-RNAPIII is at a high risk of scleroderma renal crisis
	b. For many, this antibody test is not available, so all patients with early dcSSc should have regular blood pressure checks and home blood pressure monitoring should be encouraged
	c. Patients with active early dcSSc with other organ involvement, such as pericardial effusion, ILD, cardiac involvement, may be at a higher risk, and other risk factors include male sex, tendon friction rubs, rapidly progressive skin involvement and use of glucocorticoids
Other organ involvement and overlaps as appropriate	a. 15% rule: 1 in 6 patients with SSc have prevalent digital ulcers, complicated digital ulcers ever, inflammatory arthritis, myositis or myopathy, sicca symptoms or Sjögren syndrome
	b. 3% of cases of SSc overlap with rheumatoid arthritis; thus, if inflammatory arthritis is present, consider testing for rheumatoid factor and anti-citrullinated peptide antibody
	c. SSc can overlap with other connective tissue diseases including SLE, dermatomyositis, polymyositis and Sjögren syndrome; investigate where appropriate by history and physical examination, performing extractable nuclear antibodies to profile for overlaps and mixed connective tissue disease (RNP, SSA/Ro, SSB/La, Smith, Jo1, PM/Scl-70, other myositis antibodies) and for SLE overlap (complements C3, C4 and anti-DNA)
	d. Primary biliary cholangitis occurs in 8% of cases of lcSSc, usually in those positive for anti-centromere antibodies; alkaline phosphatase is elevated, generalized pruritis may occur
	e. Screen for cardiac involvement if there are arrhythmias and/or heart failure
	f. Consider premature atherosclerosis in patients with SSc, but routine screening is not recommended, so investigate as per usual care
	g. Screen for nutritional deficiencies if malabsorption is present or suspected owing to severe gastrointestinal involvement
	h. Screen for depression as it is elevated in patients with chronic diseases including SSc
	i. Osteoporosis is increased in SSc; perform a bone density scan if the index of suspicion of osteoporosis is moderate, consider vitamin D and calcium supplementation as per local guidelines
	j. Erectile dysfunction is frequent in men with SSc; screen by history and refer to urology where appropriate
Malignancy	a. Malignancy is a rare cause of SSc but screening should be pursued if the patient has rapidly progressive dcSSc and weight loss and is elderly and/or has other features that suggest that the SSc is paraneoplastic
	b. Anti-RNAPIII increases the risk of malignancy
	c. Other associations with malignancy are ILD, cyclophosphamide use, AHSCT
	d. Screening for malignancy should be performed as per local guidelines (Pap tests, mammograms, colon cancer screening) and periodic urine microscopy if exposed to cyclophosphamide
General health	a. Identification and treatment of cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, metabolic syndrome, smoking cessation, targeting ideal weight and encouraging regular exercise and a healthy diet
	b. Measure thyroid function if autoimmune thyroid disease is suspected

AHSCT, autologous haematopoietic stem cell transplantation; anti-RNAPIII, anti-RNA polymerase III antibody; dcSSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease; lcSSc, limited cutaneous systemic sclerosis; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. [a]Screening is recommended when earlier detection improves outcomes and the prevalence of a complication is high enough and the screen is widely available to warrant the cost/benefit ratio.

from the European Scleroderma Trials and Research (EUSTAR) database show that the initial mRSS on its own is a poor predictor of progression and that prediction is improved by simultaneously accounting for disease duration (those with a shorter disease duration were likely to be 'progressors') and autoantibody status (anti-RNAPIII-positive patients had the highest mRSS and reached peak mRSS earliest)[17].

In general, only patients with relatively early dcSSc are included in trials focused on skin disease; thus, the majority of patients with SSc would not be eligible for enrolment (for example, patients with lcSSc or dcSSc with disease duration greater than 2 to 5 years, depending on the study). Also, there is controversy about whether the skin score should be the primary outcome in trials[18]. A composite response measure can account for changes in other organs, global assessments and function; the ACR Composite Response Index in dcSSc (CRISS) has been developed and used in some RCTs in patients with early active dcSSc[19–21]. CRISS seems to be more sensitive to treatment effect than change in mRSS over a short period of time, and has been used as the primary efficacy outcome measure to discern early evidence of a treatment effect[18,22]. Also controversial is the use of mRSS response as a surrogate of organ changes such as in ILD trials. In that regard, though, treatment aimed at improving skin fibrosis could also be potentially disease modifying, as observational studies have suggested that treatment of skin disease is associated with improved internal organ involvement or less new organ involvement[23,24]. In the faSScinate study, improvements in mRSS with tocilizumab treatment from weeks 48 to 96 were accompanied by improvements in patient-reported outcomes, including the Health Assessment Questionnaire-Disability Index, patient global assessment of disease activity (on a visual analogue scale) and FACIT-Fatigue Scores[21].

Autologous haematopoietic stem cell transplantation

The intervention with the largest effect on skin fibrosis to date is AHSCT, with between-group differences in mRSS of approximately 10 points compared with 12 once-monthly infusions of cyclophosphamide (Fig. 1 and Supplementary Table 1). In the ASTIS trial, AHSCT was

associated with a 20-point reduction in mRSS, whereas intravenous cyclophosphamide was associated with a nine-point reduction. Figure 1 shows the effect size of the between-group difference in mRSS from selected trials of immunosuppression and AHSCT.

AHSCT is generally indicated for SSc in patients with aggressive disease portending poor prognosis, most commonly in early dcSSc with internal organ involvement in which the expected survival rate would be only 50% at 5 years. Careful selection of patients who have a poor prognosis but lack advanced organ involvement is pivotal, because of concerns arising from the toxicity of the procedure (for example, infections and treatment-related mortality) and durability of effect. In addition, few centres have expertise in AHSCT for SSc, and access to this treatment is a barrier even for eligible patients.

Most interventional studies in SSc have organ-specific end points. By contrast, four open-label RCTs of AHSCT used overall and event-free survival as primary or secondary outcomes[25–28] (Supplementary Tables 1,2), thereby providing an indication of overall disease modification. Those trials included 292 patients followed for up to 10 years. Each trial had distinctive mobilization and conditioning regimens (Supplementary Table 2). Patients in the control groups in the ASSIST[28], ASTIS[27] and SCOT[26] trials were treated with monthly intravenous cyclophosphamide 0.5–1 g/m^2 for 6–12 months, whereas the Cardiac Safe trial compared AHSCT with a fludarabine-based regimen with or without rituximab and/or intravenous immunoglobulin[25].

In the SCOT trial, mRSS improved in the majority of patients in the AHSCT arm (86%), but worsened or did not change in 3% and 11% of patients, respectively[26]. In the cyclophosphamide arm, mRSS improved, did not change or worsened in 49%, 33% and 18% of patients, respectively. In the ASTIS trial[27] the mean change in mRSS from baseline until 2 years' follow-up was significantly better in the AHSCT group (−19.9) than in the control group (−8.8) (difference 11.1, 95% CI 7.3–15.0; $P < 0.001$).

A meta-analysis of the three studies comparing AHSCT with cyclophosphamide found that overall survival was significantly better with AHSCT (hazard ratio 0.61; 95% CI 0.40–0.93)[29]. Event-free survival also clearly favoured AHSCT (Supplementary Table 1). Both ASSIST and ASTIS reported improvement in forced vital capacity (FVC) (mean difference 9.58, 95% CI 3.89–15.18), whereas the results of the SCOT trial did not show any difference in FVC reported as a categorical variable between the AHSCT and cyclophosphamide (control) arms. However, fewer patients randomized to receive AHSCT in the SCOT trial experienced respiratory failure ($n = 5$) compared with those randomized to receive cyclophosphamide ($n = 13$). Overall survival across the three studies was 77% in the cyclophosphamide groups and 91% in the AHSCT groups ($P = 0.19$). On the other hand, possibly owing to the use of a lower dose of cyclophosphamide in the AHSCT arm and/or other differences in the conditioning prior to transplantation, the rate of cardiac toxicity was lower in the SCOT trial than in the ASSIST and ASTIS trials. The treatment regimen in the control arm consisted of either pulsed intravenous cyclophosphamide 750 mg/m^2 monthly for 12 months in the ASTIS and SCOT trials (the first cyclophosphamide pulse was 500 mg/m^2), or pulsed intravenous cyclophosphamide 1 g/m^2 monthly for 6 months in the ASSIST trial. Cyclophosphamide at a total dose of 200 mg/kg with anti-thymocyte globulin was the standard conditioning regimen in those studies except for the SCOT trial, which used a cyclophosphamide dose of 120 mg/kg with total body irradiation and anti-thymocyte globulin.

Trials and real-world data have shown that AHSCT is also associated with clinically important improvements in health-related quality of life compared with conventional care[30]. Transplantation-associated cardiac toxicity is a current concern in AHSCT for SSc. Most conditioning regimens include high doses of cyclophosphamide that cause direct endothelial capillary damage, leading to acute myocardial injury. Attenuation of cyclophosphamide dose should be considered in patients with a low cardiac reserve. Pre-transplantation cardiac evaluation has been recommended by the European Society for Blood and Marrow and partners and, once incorporated by transplantation centres, should contribute to a reduction in transplantation-related mortality. The long-term efficacy of AHSCT in improving survival in SSc was confirmed in a retrospective study of 92 patients treated with AHSCT for SSc in the Netherlands, including 26 patients who had participated in the ASTIS trial[31]. Event-free survival estimates at 5, 10 and 15 years were 78%, 76% and 66%, respectively. Lung and skin involvement (as measured by mean FVC, diffusion capacity of the lungs for carbon monoxide (DLCO) and mRSS) improved significantly. Male sex, lower left ventricular ejection fraction and older age at baseline were identified as risk factors for events.

AHSCT is consistently associated with an increased risk of treatment-related mortality, with an overall estimate of approximately 5–10% (ref. [29]), although treatment-related mortality with non-myeloablative AHSCT appears to be less than with myeloablative transplantation, but the former option is not studied in RCTs. AHSCT is also associated with increased risks of infections and haematological complications, and can be associated with both early and late malignancies. In the SCOT study, 3 of 33 patients with SSc in the AHSCT group and 1 patient from the conventional-treatment control group developed cancer[26]. The ASTIS trial reported that 1 patient developed Epstein–Barr virus-related post-transplantation lymphoproliferative disease shortly after AHSCT; 5 non-transplanted patients with SSc from the cyclophosphamide (control) group also developed malignancies[27]. In a retrospective evaluation, the French Society for Bone Marrow Transplantation and Cellular Therapy reported that 4 (7%) of 56 patients with SSc who underwent AHSCT developed cancer (various solid tumours) over a median follow-up of 83 months[32]. Higher skin scores (mRSS >24) at baseline and older age at the time of transplantation were associated with lower rates of progression-free survival, suggesting that patients should be enrolled earlier in the disease course[33].

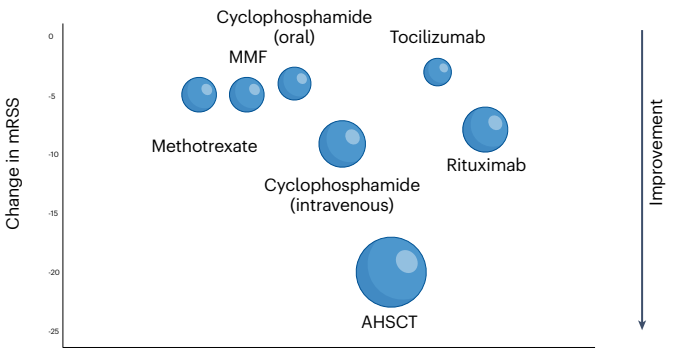

Fig. 1 | Treatment effect on skin in SSc. This figure illustrates the effects of immunosuppressive treatments on the skin in systemic sclerosis (SSc). Modified Rodnan skin score (mRSS) is measured on a scale of 0 to 51 points. The size of each circle reflects the effect size of the treatment (taking into consideration sample size and standard deviation), mirroring the change in mRSS from the smallest (the effect of tocilizumab treatment) to the largest (the effect of autologous haematopoietic stem cell transplantation (AHSCT), as seen in the ASTIS trial)[17]. MMF, mycophenolate mofetil.

Thus, although AHSCT can be considered a disease-modifying treatment for SSc, this treatment should be reserved for carefully selected patients at a high risk of disease complications. Consideration of referral for AHSCT is either a very high mRSS or moderate mRSS with worsening and/or moderate ILD in early dcSSc. Improved pre-transplantation screening for cardiac involvement and the use of less-toxic transplantation regimens have the potential to improve the safety of AHSCT. In the long term, the need for immunosuppression in patients who receive AHSCT and relapse rates require further study, and some protocols routinely add rituximab post-transplantation and/or MMF. Using cyclophosphamide as a control is not the standard of care, as MMF is more often used as initial immunosuppression in early dcSSc, especially if ILD is present. However, most patients referred for AHSCT have not responded to at least two immunosuppressive therapies before being referred for this treatment. One of two RCTs with cyclophosphamide treatment for SSc-ILD showed progression of restrictive lung disease 1 year after being stopped[34]. Another limitation of AHSCT is the cost of the procedure. In the USA, many insurers do not approve this intervention for SSc. Where the transplantation can be performed presents another barrier, as most sites will not perform AHSCT and many patients will not be assessed for this treatment owing to a lack of reimbursement, the distance to an expert site or other related concerns.

Immunosuppression

Skin involvement has been treated with a wide variety of standard immunosuppressants, of which only a few have been studied in RCTs[34–42] (Supplementary Table 1). Methotrexate was studied in two small RCTs[36,37] (Supplementary Table 1), with the larger study ($n = 71$)[36] reporting a between-group difference of approximately 5 points in mRSS in favour of methotrexate, compared with placebo ($P < 0.17$). In both RCTs, relatively low doses of methotrexate were used (15 mg per week)[36,37]. Whether higher doses of methotrexate, which are now more commonly used in rheumatic diseases, could increase the effectiveness of this treatment is unknown, but methotrexate 25 mg per week is often prescribed in patients with dcSSc.

Cyclophosphamide has been studied in SSc in 11 RCTs[43], including intravenous and oral routes of administration. The Scleroderma Lung Study I (SLS I) was the only RCT that compared cyclophosphamide with placebo. The primary outcome was FVC at 12 months; improvement of skin disease was a secondary outcome. In that study, 1 year of oral cyclophosphamide treatment resulted in a between-group difference in mRSS of 3 points in favour of cyclophosphamide[34]. In the subsequent SLS II, MMF was compared with cyclophosphamide[35]. Skin thickening as measured by mRSS improved from baseline to 24 months in both arms (−5.35 change in mRSS with oral cyclophosphamide treatment for 1 year and no treatment for a second year, and −4.90 change in mRSS with MMF over 2 years). The skin improved (as measured by a reduction in mRSS) in 73.6% of study participants treated with cyclophosphamide and 71.7% of those treated with MMF and improved by ≥5 units in 78% of the cyclophosphamide group and 64% of the MMF group.

Several placebo-controlled RCTs of biologic agents and targeted therapies with skin as the primary end point have been published over the past few years, including rituximab (anti-CD20), tocilizumab (anti-IL-6), abatacept (T cell co-stimulatory antagonist), riociguat (soluble guanylate cyclase (sGC) stimulator), romilkimab (IL-4/IL-13 inhibitor), ziritaxestat (autotaxin inhibitor that reduces lysophosphatidic acid) and belimumab (B cell-activating factor antagonist)[38–42,44] (Supplementary Table 1). In some of these trials, between-group differences in mRSS have been in the order of 2–8 points in favour of active treatment; some were statistically significant. Skin was a secondary outcome in an RCT of lenabasum (cannabinoid receptor 2 agonist), which achieved positive results in phase II but had no difference on skin versus placebo in phase III[45] (Supplementary Table 1). A phase III study of the anti-fibrotic nintedanib, the SENSCIS trial, also reported a change in skin thickening (mRSS) as a secondary outcome and found no difference compared with placebo for skin, but did slow progression of lung function (the primary outcome)[46] (Supplementary Table 1). Preliminary results of small studies with tofacitinib, other Janus kinase inhibitors and brentuximab are promising, but definitive studies will be needed to confirm these findings[21,41,47–49].

In practice, the most common first-line drug for skin manifestations in patients with dcSSc is MMF; although change in mRSS has not been a primary outcome in RCTs of MMF, it is chosen because of the positive benefits for ILD[50]. Methotrexate is also commonly used as an alternative first-line treatment, or second-line after MMF. If the patient worsens, other treatments, such as rituximab, tocilizumab, cyclophosphamide or AHSCT, can be considered[15]. There has been some consensus on treatment for skin disease in dcSSc but this could change as more data accumulate for various medications and if access to biologic agents improves[15,51]. Data suggest that immunosuppressive therapy after AHSCT could reduce recurrence and/or worsening of SSc; the duration of treatment is unknown but might be long term[52,53]. The optimal selection of immunosuppressive treatment post-transplantation and which patients to treat (if everyone or selected individuals stratified by risk of recurrence) are yet to be determined[54]. Most treatments for skin disease have only a weak effect, so new treatments or a different paradigm, such as combination or induction therapy, are urgently needed. If the risk of lung involvement is not high, initial treatment seems to be either MMF or methotrexate, and if skin worsens or is more severe, then adding rituximab, tocilizumab or switching to oral or cyclophosphamide can be considered for patients who are not eligible for or who do not have access to AHSCT. Many prescribers do not have access to tocilizumab and in some jurisdictions access to rituximab is restricted.

Management of lung manifestations

Interstitial lung disease

Lung fibrosis occurs in approximately one-third of patients with SSc, but is clinically meaningful in 20% of patients with dcSSc and 12% of patients with lcSSc[55]. ILD in SSc is often manifested as pulmonary fibrosis, which has become the most common cause of SSc-related death following improvements in outcomes in SRC and pulmonary hypertension (PH, including PAH), which were previously the most frequent lethal complications[56,57]. Lung involvement can develop at any time and prognosis may be worse if onset is within the first 3 years of SSc. In an early SSc group in the EUSTAR database, 50% showed significant or moderate progression of ILD[58]. A 2022 study from the EUSTAR registry reported that progression of ILD can occur at any disease duration[59].

Clinical associations and laboratory characteristics that predict the development of SSc-ILD are emerging. It is strongly associated with some autoantibodies, especially anti-topoisomerase 1 (anti-Scl-70) antibodies, and studies suggest that this risk is independent of the disease subset and is important for case stratification[60]. The frequency of lung fibrosis is higher in male patients, but this could be attributable in part to a higher frequency of the dcSSc subset in this patient group. Gastroesophageal reflux disease (GERD) with reflux into the lungs worsens ILD[61,62]. Some patients remain stable, whereas others develop progressive and severe lung fibrosis[63].

A simple schematic summarizing the current approach to management of SSc-ILD is provided in Fig. 2 and Table 2.

Screening for SSc-ILD. Screening is an essential part of effective management of SSc-ILD; it can be considered as primary screening in the baseline assessment of all patients, which can include a chest radiograph, pulmonary function tests (PFTs) and CT assessment with prone images and high-resolution reconstruction to identify early changes. However, there is no standardized timing of PFTs and high-resolution CT. PFTs are important and need to be performed regularly, particularly in early dcSSc, but can be unreliable for screening, possibly because of the range of normal values, and test variability, especially if patients are unable to perform testing reliably owing to significant oral involvement[64]. Some SSc experts suggest that all patients with SSc should have a baseline high-resolution CT of the lungs, whereas others order these tests only for high-risk patients (for example, those with crackles/rales on auscultation, abnormal PFTs, abnormal chest radiographs or anti-topoisomerase 1 antibody positivity) (Table 1), although the clinical and functional abnormalities can be late findings in ILD.

Several imaging tools are being evaluated for assessment of SSc-ILD including PET, thoracic ultrasonography or MRI[65]. Hyperpolarized xenon MRI has been studied to quantify gas exchange. For PFTs, a threshold of 70% FVC has been used to separate extensive disease from mild disease, and has prognostic value in several cohorts[63]. Serial changes in PFTs correlate with outcomes (for lungs and survival) and PFTs are ordered at intervals to also screen for PH[66,67]. The thresholds of 10% decrease in FVC, or 5% with a corroborative drop of 15% in DLCO, have been applied from idiopathic pulmonary fibrosis literature and predict survival. Changes in DLCO or carbon monoxide transfer coefficient are highly predictive of long-term outcome, and are especially predictive over the next 2 years[66]. Serum markers are looking promising, including KL-6 (ref. [68]), a marker of epithelial damage, and IL-6, especially in early-stage or less-extensive SSc-ILD[69,70]. Other potential markers of lung fibrosis include CCL18, CXCL4 and CCL2 (ref. [68]). All of these biomarkers have shown utility in research studies and in stratification, although longitudinal changes have been less informative so far. Studies suggest that elevated serum concentrations of IL-6, the acute phase reactant C-reactive protein, erythrocyte sedimentation rate and thrombocytosis could be predictive of the risk of lung fibrosis, especially in early dcSSc[71].

Immunosuppressive treatment for SSc-ILD. Evidence including results from cohort studies and placebo-controlled RCTs supports the benefit of immunosuppression for SSc-ILD (reviewed elsewhere[72,73]). The first trial studying cyclophosphamide treatment in SSc lung disease was SLS I[34], which was soon followed, also in 2006, by the Fibrosing Alveolitis in Scleroderma Trial (FAST)[74] (Table 2). The results of SLS II, which compared cyclophosphamide with MMF, were published in 2016 (ref. [35]), and the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) RCT[46], which evaluated the anti-fibrotic nintedanib in the context of MMF treatment, was published in 2019. The primary end point outcomes for these lung-related RCTs in SSc were between-group difference in change in FVC (expressed as percentage of predicted change) at 12 months (SLS I) and at 24 months (SLS II), change in FVC and corrected DLCO at 1 year (FAST), and the annual rate of FVC decline (millilitres per year) over 52 weeks (SENSCIS). As discussed earlier, 2 years of MMF treatment had similar efficacy to 1 year of oral cyclophosphamide and then no treatment in the SLS II trial, but was better tolerated and safer[35]. There is benefit from combining MMF with anti-fibrotic therapy, as less worsening of FVC was observed in the SENSCIS trial for the subset of patients on both MMF and nintedanib compared with those treated with either one alone (and the worst group with respect to progression of FVC was the group with no MMF background therapy and placebo) in an exploratory analysis[46]. There is growing evidence supporting rituximab as an alternative to cyclophosphamide that might be better tolerated[75–78]. AHSCT has been associated with benefits related to lung function and fibrosis; these benefits were seen most clearly in the SCOT trial[26].

Tocilizumab, which targets the IL-6 signalling pathway, was approved by the FDA in 2021 to slow the rate of declining lung function in SSc-ILD. This approval was based on the results of the phase III focuSSced trial[41], which demonstrated improvements in skin fibrosis that were not quite statistically significant compared with placebo; however, there was less of a decline in lung function and quantitative CT changes. The mechanism of the anti-fibrotic effect of tocilizumab could be attributable to crosstalk between IL-6 and more conventional pro-fibrotic mediators such as TGFβ[79]. The phase II STRATUS trial randomly allocated patients with SSc-ILD on background MMF to receive the monoclonal antibody abituzumab, which targets integrin alpha-V, or placebo; however, the trial was stopped prematurely because of slow enrolment so analyses of efficacy for ILD were underpowered[80]. In the RECITAL trial, patients with CTD who also had ILD were randomized to receive either rituximab or cyclophosphamide; rituximab was not superior to cyclophosphamide but had fewer adverse events, and the two treatments reduced the mean

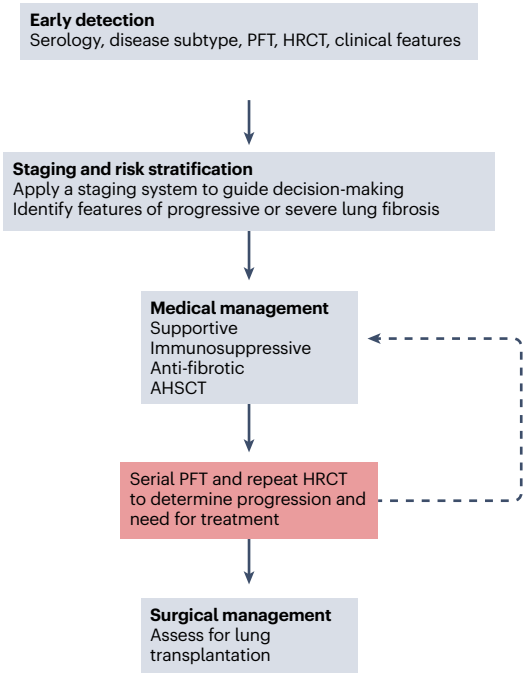

Fig. 2 | Overview of management of lung fibrosis in SSc. The pathway for patients with systemic sclerosis (SSc) requires screening and early detection of interstitial lung disease (ILD) together with staging and risk stratification. Treatment generally involves immunosuppression and supportive measures together with anti-fibrotic therapies in appropriate cases (Table 2). In established lung fibrosis, use of a simple staging system[63] can help with treatment decision-making but longitudinal monitoring of lung function tests and CT imaging is important to detect progressive disease and assess treatment response. AHSCT, autologous haematopoietic stem cell transplantation; HRCT, high-resolution CT; PFT, pulmonary function testing.

FVC at 24 weeks[81]. Azathioprine has been considered in ILD treatment if MMF is not tolerated, as it has been used for maintenance after induction with cyclophosphamide or if ILD is mild[74].

Glucocorticoids are seldom used in SSc-ILD as they are not usually effective (except perhaps in overlaps with other CTDs) and have adverse effects such as infections, osteoporosis and metabolic changes, and they can also increase SRC, especially in anti-RNAPIII-positive patients with early active dcSSc.

Table 2 | Treatment of ILD in systemic sclerosis

Treatment type	Medication and dose
Immunosuppression	Oral MMF (2–3 g per day) or azathioprine (150 mg per day)
	Intravenous cyclophosphamide (600 mg/m^2) or oral cyclophosphamide 100–150 mg per day
	Rituximab two intravenous infusions 2 weeks apart, then one infusion every 6 months
	Tocilizumab 162 mg subcutaneously once per week or 4–8 mg/kg intravenously monthly
	Other immunosuppressants may improve pulmonary function or reduce onset of ILD such as methotrexate but there are fewer data than for MMF
	Assess eligibility for clinical trial protocols
Anti-fibrotic therapy	Nintedanib 150 mg twice a day; reduce if not tolerated to 100 mg twice a day
	May consider pirfenidone (fewer data and may not be approved in many jurisdictions for this indication); increase to 801 mg three times per day as tolerated; if not tolerated, reduce dose
	Assess eligibility for clinical trial protocols
Rigorous anti-reflux therapy and treatment of dysphagia	Proton pump inhibitor as first-line treatment, often exceeding the maximum approved dose
	H2 antagonist, prokinetic drugs, sucralfate, antacids
	Lifestyle modification: raise the head of the bed, no food after supper, chew food well, eat slowly, drink water with eating, avoid foods that trigger reflux or worsen dysphagia
	Oesophageal dilations when required
	Fundoplication surgery if severe reflux with aspiration
Other interventions	Smoking cessation
	Vaccinations (influenza, COVID-19, pneumococcal)
	Oxygen if hypoxia or desaturation with exercise or when lying down
	Exercise programme, pulmonary rehabilitation
	Early intervention for infection
	Antibiotic prophylaxis; i.e., azithromycin 250 mg three times per week if recurrent pulmonary infections or severe bronchiectasis
	Pneumocystis jirovecii pneumonia prophylaxis if significant immune suppression; i.e., trimethoprim plus sulfamethoxazole double-strength three times a week
	Identification and treatment of concomitant pulmonary hypertension
	Consider referral for lung transplantation

ILD, interstitial lung disease; MMF, mycophenolate mofetil.

Anti-fibrotic therapies for SSc-ILD. Both of the anti-fibrotic agents licensed for use in idiopathic pulmonary fibrosis, nintedanib and pirfenidone, have been tested in SSc-ILD trials. Nintedanib is approved in many countries for SSc-ILD, whereas pirfenidone is not. For nintedanib, there are two relevant RCTs. In the SENSCIS trial, MMF use was not randomized: if patients were on stable MMF therapy at the time of randomization to treatment with nintedanib or placebo (approximately half the patients in the study), MMF was continued. Concomitant treatment with MMF showed a potential benefit on lung function, slowing the decline in FVC in the placebo group as well as increasing the magnitude of the effect of nintedanib in the experimental group[46]. Another large RCT of nintedanib, the INBUILD trial, showed the superiority of nintedanib over placebo across a range of progressive ILDs, including SSc[82]. Pirfenidone has been less extensively evaluated in SSc-ILD, but the LOTUSS clinic trial suggested that it is safe and well tolerated when used in combination with immunosuppressive treatment[83]. Pirfenidone showed benefit in the RELIEF study, an RCT of progressive fibrotic ILD that included patients with SSc, although this trial was stopped owing to slow recruitment[84]. The SLS III trial compared MMF alone with a combination of MMF and pirfenidone[85] Unfortunately, only one-third of the calculated sample size (51 of 150) was recruited and there were no differences between MMF versus MMF plus pirfenidone at 18 months. However, there was a more rapid improvement of FVC% predicted at 6 months in the combination group and there were numerically more improvements in patient-reported outcomes and HRCT but more adverse effects.

Supportive interventions for SSc-ILD. In addition to potential disease-modifying therapies, it is important to manage factors that might aggravate SSc-ILD, such as GERD and intercurrent infection. GERD should be aggressively treated to avoid worsening of ILD due to aspiration. Those with severe oesophageal involvement, including symptoms of aspiration, severe reflux (awakening due to reflux or choking) and significant dysphagia, are at an increased risk of ILD progression in SSc[61,62]. Treatments include not eating after dinner, sleeping with the head raised, high doses of proton pump inhibitors, promotility agents and oesophageal dilations. Fundoplication surgery may be considered for severe reflux. Intercurrent infection should be promptly treated. Some patients could benefit from prophylactic antibiotics if they have frequent pulmonary infections. Occasionally, prevention of *Pneumocystis jirovecii* pneumonia with sulfamethoxazole and trimethoprim is prescribed in patients with SSc-ILD with significant immune suppression or who are on high doses of glucocorticoids. All vaccines should be up to date, especially Pneumovax 23 (which protects against bacterial infections), the pneumococcal vaccine Prevnar 13 or 20, influenza vaccine and COVID-19 vaccine. Oxygen is used if hypoxia is present, including constant use and in some circumstances only higher doses with activity and lying down/sleeping, depending on when desaturation occurs. Oxygen can reduce dyspnoea, especially when associated with exertion, and can mitigate the development of PH. PH secondary to ILD has a very poor prognosis as it is usually group 3 PH (that is, PH associated with hypoxia and lung disease). Patients with group 3 PH might require additional treatment of the ILD (for example, with nintedanib for progressive pulmonary fibrosis) and also treatment of PH (for example, with the vasodilator treprostinil). There are concerns that pulmonary vasodilators can aggravate ventilation:perfusion mismatch but judicious use of these agents may be beneficial[86]. PH secondary to ILD was the focus of a positive RCT published in 2021, in which inhaled treprostinil improved exercise capacity from baseline (the primary

efficacy end point), as assessed by 6-min walk distance (6MWD), as well as a significant reduction in levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP, which is associated with improved survival in PH) and time to clinical worsening[87]. Although RCTs are lacking, regular cardiovascular exercise and targeting ideal body weight could be helpful and should be encouraged. Exercise in SSc-ILD, including pulmonary rehabilitation, can improve symptoms and quality of life[88].

Lung transplantation for SSc-ILD. For end-stage lung fibrosis, transplantation is the only treatment that can improve long-term outcomes. However, the availability of donors and concerns about comorbidity limit the use of lung transplantation in SSc. Reflux is a particular concern because it can predispose to post-transplantation bronchiolitis. Results of cohort studies suggest that outcomes after lung transplantation in SSc are comparable with those in other chronic diseases in age- and sex-matched patients, and so this option should be considered in cases of severe disease or poor prognosis[89,90]. Unfortunately, survival with lung transplantation for pulmonary fibrosis is approximately 81% and 66% at 1 year and 5 years, respectively[90].

Outlook for treatment of SSc-ILD. Data from the SENSCIS trial found that a decline in FVC increased hospitalizations and death, and a decrease in FVC of 3% was associated with 43% higher hospitalization and mortality[91]. Thus, although remaining an important complication and cause of death in SSc, lung fibrosis is now better understood and more manageable, with evidence-based treatment including medications to slow progression of fibrosis (nintedanib and possibly pirfenidone) and to potentially prevent ILD changes in early dcSSc (tocilizumab). Other biologics such as rituximab seem to decrease and/or improve SSc-ILD; there are now several RCTs that demonstrate improvement in lung function in SSc with rituximab treatment.

Treatment algorithms and guidelines suggest MMF as first-line therapy for SSc-ILD, followed by consideration of cyclophosphamide, rituximab, tocilizumab or AHSCT and, if progressive pulmonary fibrosis is present, the use of an anti-fibrotic agent[15,46,82]. Most patients will not have access to tocilizumab for slowing ILD as it is not reimbursed in many jurisdictions for this indication.

It is likely that early intervention and the use of combination therapies will be needed to impact long-term survival. Case stratification will be important for balancing the benefits and adverse effects of therapies, as well as ensuring the appropriate use of high-cost drugs. Better understanding of emerging new imaging techniques and more validation of circulating biomarkers will underpin future management. Data on early intervention with MMF in mild ILD are mixed[92,93]. Early use of immunosuppression may delay ILD onset[94].

Pulmonary hypertension and pulmonary arterial hypertension

PH is an important cause of death in SSc[95] and occurs in approximately 15–18% of patients[8,11,96]. PH is classified into five groups as defined by the WHO classification scheme, with group 1 consisting of PAH. SSc-associated PAH (SSc-PAH) is the most common aetiology of PH in SSc and accounts for about two-thirds of cases (occurring in 8–15% of all patients). However, PH can also be the consequence of left-sided heart disease (group 2), ILD with hypoxia (group 3), pulmonary veno-occlusive disease (PVOD) (group 1) or less frequently pulmonary embolism (group 4); group 5 PH is due to unknown causes so is not relevant in patients with SSc[97]. SSc-PAH occurs more frequently in older patients, those with longer disease duration and is associated with positivity for anti-centromere, anti-topoisomerase I and anti-U3-RNP antibodies, elevated erythrocyte sedimentation rate and IgG levels, and digital ulcers and/or pitting scars on fingertips[98]. Some studies have found PAH to be more prevalent in lcSSc, but this finding could be related to patients in this group starting at a more advanced age than patients with dcSSc and living longer – both are risk factors associated with SSc-PAH. African ancestry may increase the risk of PAH in SSc.

PVOD is characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules, leading to hydrostatic pulmonary oedema. Clinical features suggestive of PVOD include severe hypoxia, pleural effusions, interlobular septal thickening, poorly defined parenchymal opacities and lymphadenopathy. PVOD is under-diagnosed as it requires an open lung biopsy to make a definitive diagnosis. In one study of SSc-PAH, 7 out of 59 patients (11%) had two or more signs of PVOD on CT[99]. Pulmonary embolism in SSc can be acute, associated with ILD or, rarely, chronic (chronic thromboembolic pulmonary hypertension)[100]. The work-up of suspected PAH in SSc includes ruling out pulmonary emboli and chronic thromboembolic pulmonary hypertension, which occurs in approximately 0.56% of patients after pulmonary embolism[101], although it is a very rare cause of PH in SSc. Echocardiography is recommended as the first-line screening test for SSc-associated PH, but several other PAH screening algorithms are available[102] (Table 1). A very low DLCO (<46% with parenchymal lung disease and <73% without parenchymal lung disease) and decreasing DLCO are suggestive of PAH. Historically, SSc-PAH was associated with a median survival of 1 to 2 years[100]. Advances in the management of SSc-PAH, specifically the development of PH-specific therapies, have led to improvements in haemodynamics, exercise capacity, WHO functional class, health-related quality of life and survival (Table 3). However, survival at 5 years after diagnosis of PAH is still poor[102].

Non-pharmacological strategies. Patients with SSc who have PH should be counselled against smoking tobacco and marijuana, receive routine vaccinations, exercise regularly as tolerated and discuss contraception. If hypoxic, they need oxygen. If a patient with SSc and PH is considerably hypoxic, one should investigate for a cause of the hypoxia (such as PVOD, ILD or pulmonary emboli)[103]; PAH can be associated with hypoxia at the end stage. Patients with SSc and PH with right ventricular overload and fluid retention should be counselled to follow a reduced-salt diet. Discussion of prognosis with patients is important, and providing support personnel (such as social workers and nurses) and palliative care may be needed.

Pharmacological strategies. The treatment of SSc-PAH has evolved over the past two decades with the development of new treatment options and a stronger evidence base[104]. Although anti-coagulation is recommended in idiopathic PAH[105], anti-coagulation is not routinely administered to patients with SSc-associated PH as there is no evidence of improved survival and the risk of bleeding is high, such as in the gut due to erosive oesophagitis and gastric antral vascular ectasia[106,107]. RCTs could benefit future recommendations with respect to anti-coagulation as they are currently lacking.

Pulmonary hypertension-specific therapies. Four groups of PH-specific therapies can be considered in the treatment of SSc-PAH: endothelin receptor (ETR) antagonists, phosphodiesterase 5 (PDE5) inhibitors, sGC stimulators and prostacyclin analogues and receptor agonists.

Table 3 | Pulmonary hypertension-specific therapies

Therapy	Dosing
Endothelin receptor antagonists	
Ambrisentan	5–10 mg daily orally
Bosentan	62.5–125 mg, twice per day orally
Macitentan	10 mg daily orally
Phosphodiesterase 5 inhibitors	
Sildenafil	20 mg three times per day orally
Tadalafil	40 mg daily orally
Prostacyclin analogues	
Epoprostenol	1–12 ng/kg/min continuous intravenous infusion via central venous catheter Dose titrated up every 1–2 weeks
Iloprost, inhaled	Initial dose: 2.5 µg inhaled; if well-tolerated, then 5 µg subsequent doses 6–9 times per day as needed; not more than once every 2 h while awake Maintenance: 2.5–5 µg per dose; not to exceed 45 µg per day
Iloprost, intravenous[a]	Intravenous infusion over 6 h daily at 0.5–2.0 ng/kg /min
Selexipag	200 to 1600 µg twice per day orally
Treprostinil, subcutaneous	0.625 to 1.25 ng/kg/min continuous intravenous infusion via central venous catheter or continuous subcutaneous infusion
Trepostinil, inhaled	18 µg inhaled four times per day
Soluble guanylate cyclase stimulator	
Riociguat	Initial dose: 0.5–1 mg three times per day orally, titrated up by 0.5 mg three times per day every 2 weeks to a maximum dose of 2.5 mg three times per day orally

[a]Only approved for pulmonary arterial hypertension in New Zealand; used off-label in Germany for pulmonary arterial hypertension.

PAH is associated with elevated levels of endothelin 1, a strong vasoconstrictor and mitogen; however, it remains uncertain if elevated levels of endothelin 1 are a cause or consequence of PAH. Three oral ETR antagonists are available that target this pathway: bosentan, ambrisentan and macitentan. A 2021 systematic review of bosentan trials in patients with SSc-PAH found that bosentan might improve exercise capacity and haemodynamics (pulmonary arterial pressure and pulmonary vascular resistance)[108]. ETR antagonist therapies require regular monitoring of liver enzymes and haemoglobin levels because of the risk of hepatotoxicity and anaemia. It is uncertain which ETR antagonist will be most effective within an individual. Toxicity studies in animals have shown severe teratogenic effects of ETR antagonists, particularly craniofacial malformations; however, a 2019 systematic review of cases describing exposure to ETR antagonists during pregnancy (18 articles describing 39 cases) found no foetal congenital abnormalities[109]. Overall, pregnancy is dangerous for the mother if she has SSc-PAH, owing to increased cardiac output and the possibility of worsening hypoxia, so it should be avoided.

PDE5 inhibitors enhance the nitric oxide–cyclic GMP (cGMP) pathway, slowing cGMP degradation and resulting in both pulmonary vasodilatory and anti-proliferative effects. Three PDE5 inhibitors are available, sildenafil, tadalafil and vardenafil, although vardenafil has not been tested in patients with SSc-PAH. In a post hoc subgroup analysis of 84 patients with CTD-PAH in the SUPER-1 double-blind placebo-controlled trial, sildenafil improved haemodynamics, functional class and exercise capacity[108].

The sGC stimulator riociguat enhances cGMP production, resulting in anti-proliferative and anti-remodelling effects. In the PATENT-1 trial, which included patients with CTD-PAH (largely SSc-PAH), riociguat improved haemodynamics, functional class and 6MWD[110].

Prostacyclin (also called prostaglandin I_2) is a vasodilator and it inhibits platelet aggregation. Patients with PH have reduced levels of prostacyclin. Prostacyclin analogues evaluated for the treatment of PAH include epoprostenol (administered intravenously), iloprost (inhaled), beraprost (orally administered), and trepostinil (inhaled or chronic subcutaneously). Epoprostenol has a short half-life, which necessitates continuous intravenous administration. Challenges include the need to aseptically reconstitute the medication, the need for an indwelling central venous catheter, and adverse effects; for these reasons, use of epoprostenol is generally reserved for the treatment of advanced disease. Selexipag is an oral selective prostacyclin receptor agonist with effects comparable to those of endogenous prostacyclin. Oral selixipag is easier to use than continuous intravenous or subcutaneous prostacyclin analogues and patients do not experience rebound if it is suddenly discontinued compared with epoprostenol, but its use depends on access and reimbursement.

Combination oral therapy with an ETR antagonist and a PDE5 inhibitor is often first-line treatment in SSc-PAH[111] (Fig. 3). Historically, initial monotherapy with one oral agent was recommended, but now this approach is used only in selected low-risk patients (REVEAL risk score ≤6 (ref. [105])). Any ETR antagonist can be combined with a PDE5 inhibitor. For instance, combination therapy with ambrisentan and tadalafil in patients with PAH in the AMBITION trial led to a significantly lower risk of clinical-failure events than ambrisentan monotherapy or tadalafil monotherapy (HR 0.50, 95% CI 0.35–0.72; $P < 0.001$)[112]. Post-hoc analyses of the SSc-PAH subgroup demonstrated a reduction in treatment failure with combination therapy compared with single-agent therapy (HR 0.44, 95% CI 0.22–0.89)[112]. Similarly, combining macitentan with sildenafil or tadalafil has enhanced efficacy compared with monotherapy[105,113]. If there is an intolerance or contraindication to a medication, an alternative medication within the same class can be used[114]. Two agents with a similar mechanism of action are not combined. Of note, bosentan can increase the metabolism of sildenafil and result in a reduction in the plasma concentration of sildenafil[115]; as such, this combination might not be preferred. Combination of a PDE5 inhibitor with the sGC stimulator riociguat is not recommended owing to an increased risk of hypotension. Patients with functional class IV (the most severe patients) can be considered for combination triple therapy with an ETR antagonist, a PDE5 inhibitor and a prostaglandin analogue. Treatment is often altered according to several targets such as changes in NT-proBNP, 6MWD, pulmonary artery haemodynamics and functional class (for dyspnoea). There is a trend of starting with two PAH-specific therapies and adding a third if the patient has poor prognostic factors[113,114].

Surgical options. In patients with SSc and PH with end-stage lung disease, particularly those with progressive disease despite therapy, double-lung or heart–lung transplantation can be considered. Lung transplantation is performed to prolong survival and improve quality of life. Survival post-transplantation has improved over time, with

estimates of 93% survival 1-year post-transplantation[89,105]. Other surgical options can include right-to-left shunt or atrial septostomy, which is done only rarely, such as in cases of severe right heart failure while awaiting transplantation.

Outlook for management of pulmonary hypertension and pulmonary arterial hypertension in SSc. Combination treatment with PAH-specific therapies at the time of diagnosis of PAH, as well as treating to a target with risk stratification of patients, has improved outcomes; however, more studies are needed in order to alter the prognosis at ≥5 years after PAH onset in SSc, as the mortality increases dramatically. Risk stratification has been used in PAH to estimate mortality and guide treatment in order to reduce risk (such as treating to a target of low risk in a series of parameters where possible). Stratification is done on clinical assessment and on imaging such as echocardiography and haemodynamics with right heart catheterization[105,111]. Treatment targets are often multiple such as improving 6MWD, NT-proBNP, symptoms, functional class, echocardiograms, right heart catheterization, exercise testing and prevention or treatment of heart failure and hypoxia.

In an underpowered RCT, B cell depletion therapy with rituximab added to the standard of care in SSc-PAH did not meet the end point (significant change in 6MWD at 24 weeks) but had some possible benefit such as improving functional exercise capacity at week 48 (ref. [116]). More data are needed to determine if the paradigm of treatment without immunosuppression for PAH as a complication in SSc should change.

Management of Raynaud phenomenon and digital ulcers

Raynaud phenomenon is present in >95% of patients with SSc[117]. Digital ulcers occur in half of patients with SSc during the course of the disease and 10% report a new digital ulcer within the preceding 12 months[118,119]. The frequency of digital ulcers in SSc cohorts, cross sectionally, is 15% and often digital ulcers are multiple[8]. Raynaud phenomenon and especially digital ulcers are associated with a high burden of disability and loss of quality of life[120]. Pathophysiology for both manifestations is similar, including structural alterations in digital arteries[121]. Treatment of Raynaud phenomenon and digital ulcers is also similar. However, there are some drugs that might prevent digital ulcers but do not enhance healing. The goals of digital ulcer management include preventing tissue loss, avoiding and/or treating infection, treating pain and reducing ischaemia. Evaluating the efficacy of treatment for Raynaud phenomenon is challenging, as outcome measurements are not uniform and clinical trial end points might be improbable[122]. The EULAR–EUSTAR and 2016 British Society for Rheumatology guidelines provide specific recommendations only for first-line treatment[51,123]. Treatment algorithms for digital ulcers and Raynaud phenomenon were developed[15], often adding treatment rather than switching. We provide an integrative algorithm suggesting different lines of treatment and the grade of recommendation for each choice according to the scientific evidence available[124] (Fig. 4). Adverse effects and dosing can be found in a separate review[125].

Raynaud phenomenon management

Nifedipine, a dihydropyridine calcium channel blocker (CCB), is a first-line treatment for Raynaud phenomenon as it has some clinical benefit, low cost and acceptable adverse effects. Other CCBs (primarily the dihydropyridine type of CCBs) can be considered if there is a lack of benefit from or tolerability of nifedipine. A meta-analysis pooled findings from 38 RCTs that included 554 patients with secondary Raynaud phenomenon, most of whom had SSc[126]. Nifedipine was the most frequently studied CCB. CCBs significantly reduced the number and frequency of attacks, and higher doses could be more effective than lower doses.

PDE5 inhibition increases the availability of nitric oxide by inhibiting its metabolism. Sildenafil and tadalafil reduced the frequency,

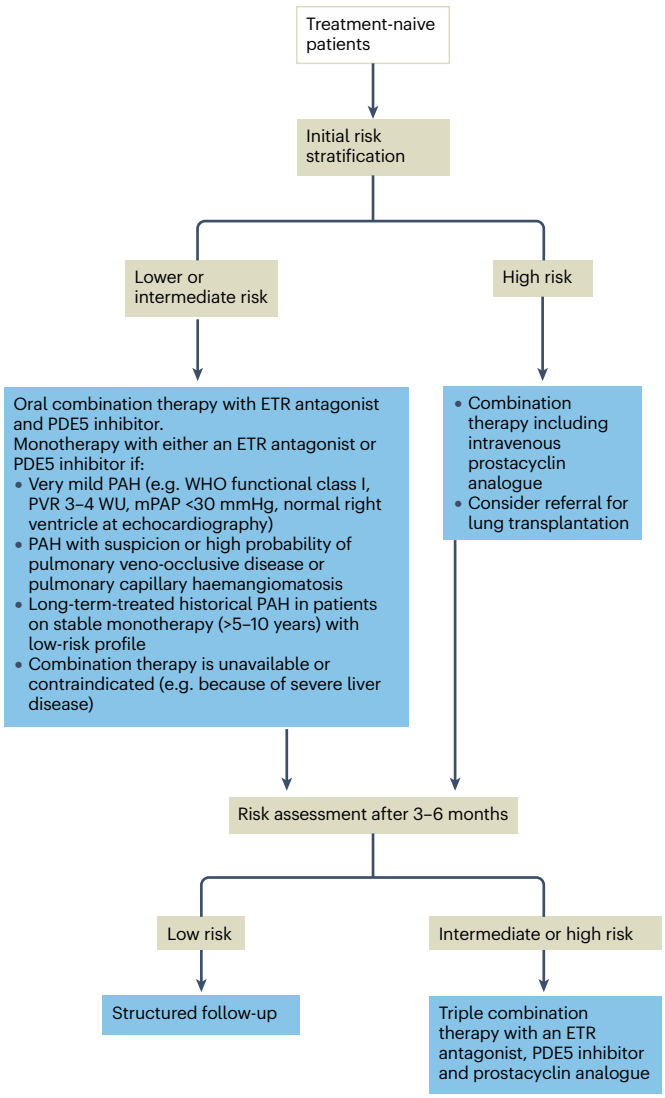

Fig. 3 | Pulmonary hypertension treatment algorithm in SSc. Treatment of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) is guided by risk stratification, which uses information from clinical assessments and imaging. Risk is graded using the REVEAL 2.0 calculator (involving 14 variables): a REVEAL score ≤6 corresponds with a low risk, a score of 7 or 8 corresponds to an intermediate risk and a score ≥9 indicates a high risk[149]. Four groups of pulmonary hypertension-specific therapies can be considered in the treatment of SSc-PAH: endothelin receptor (ETR) antagonists, phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase (sGC) stimulators, and prostacyclin analogues and receptor agonists. Combination oral therapy with an ETR antagonist and a PDE5 inhibitor is often first-line treatment in SSc-PAH. Historically, initial monotherapy with one oral agent was recommended, but now this approach is used only in selected low-risk patients. BMPR2, bone morphogenetic protein receptor type 2; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

duration, and severity (using the Raynaud condition score, a visual analogue scale) of Raynaud phenomenon attacks in six RCTs in secondary Raynaud phenomenon (244 patients)[127]. However, the price of PDE5 inhibitors is substantially higher than that of CCBs, and PDE5 inhibitors might not be reimbursed in some countries.

Prostacyclin analogues constitute an advanced treatment. Adverse effects can include tachycardia, hypotension, jaw pain, gastrointestinal side effects and headache. In a systematic review of RCTs, which included over 300 patients with SSc, intravenous iloprost was the only prostacyclin analogue that improved Raynaud phenomenon[128]. Infusion dosing and number of days of treatment have variable schemes[129]. The vasodilator alprostadil (prostaglandin E_1) seems to have no long-term benefit but could be an alternative to iloprost for short-term treatment such as in severe digital ischaemia[130].

Topical nitrates, such as nitroglycerin or glyceryl trinitrate, showed clinical or blood flow improvement according to a meta-analysis of studies including approximately 200 patients with secondary Raynaud phenomenon[131]. Headache might be a limiting adverse effect, and combination with a PDE5 inhibitor is contraindicated. Losartan (an angiotensin II receptor blocker)[132], aspirin[133], atorvastatin[134] and fluoxetine (a selective serotonin reuptake inhibitor)[135], among others, might help some patients, but are not included in the EUSTAR–EULAR recommendations as they have either a small benefit or potential adverse effects[51].

Evidence for surgical and/or procedural treatments improving Raynaud phenomenon in patients with SSc is limited to small observational studies of a surgical digital sympathectomy[136] or abdominal fat grafting to the fingertips[137]. Finally, two small RCTs have studied the use of botulinum toxin injections on interdigital web spaces, with conflicting results[138,139].

Digital ulcer treatment and prevention

There is weak evidence for interventions that promote the healing of digital ulcers. In one small RCT comparing intravenous iloprost with oral nifedipine, iloprost reduced the number of digital ulcers[128,129]. For the healing and prevention of digital ulcers, a CCB is often first-line therapy, on the basis of limited data[51].

A meta-analysis including three studies of PDE5 inhibitors (sildenafil and tadalafil) showed that these drugs have a beneficial effect in improving and reducing the number of digital ulcers[140]. Regarding the prevention of digital ulcers, the results are unclear, as one placebo-controlled clinical trial with tadalafil was positive[141], whereas another with sildenafil was negative[142]. The cost and off-label use of PDE5 inhibitors might limit their use.

Bosentan, a dual ETR antagonist, prevented new digital ulcers, especially in patients with SSc and a digital ulcer count ≥4 at baseline[143]. Unfortunately, it did not improve the healing of digital ulcers. Intravenous prostacyclin analogues seemed to yield better effects on healing and decreasing new digital ulcers, but these were exploratory end points in Raynaud phenomenon RCTs[128,129]. Atorvastatin seemed to prevent new digital ulcers in a small trial[134] but is not included in guidelines for the prevention of digital ulcers[51].

The results of small trials support the use of fat grafting[144] for healing digital ulcers and botulinum toxin infiltrations for the healing and prevention of digital ulcers[139]. There is also evidence to support the use of digital sympathectomy for digital ulcer healing and prevention[145].

Wound care by specialized nurses and physicians could be needed. There is no standardized dressing protocol for SSc digital ulcers. Antibiotics should be added only when infection is suspected, and pain needs to be controlled. In patients with SSc who have digital ulcers, gangrene and osteomyelitis occur in 22.5% and 11% of cases, respectively, at any time during the course of the disease[146]. In the case of gangrene or osteomyelitis, amputation might be required.

Non-pharmacological measures for Raynaud phenomenon and digital ulcers

Since Raynaud phenomenon has a key role in the appearance of digital ulcers, some general preventive recommendations can be useful for both Raynaud phenomenon and digital ulcers. When indicated,

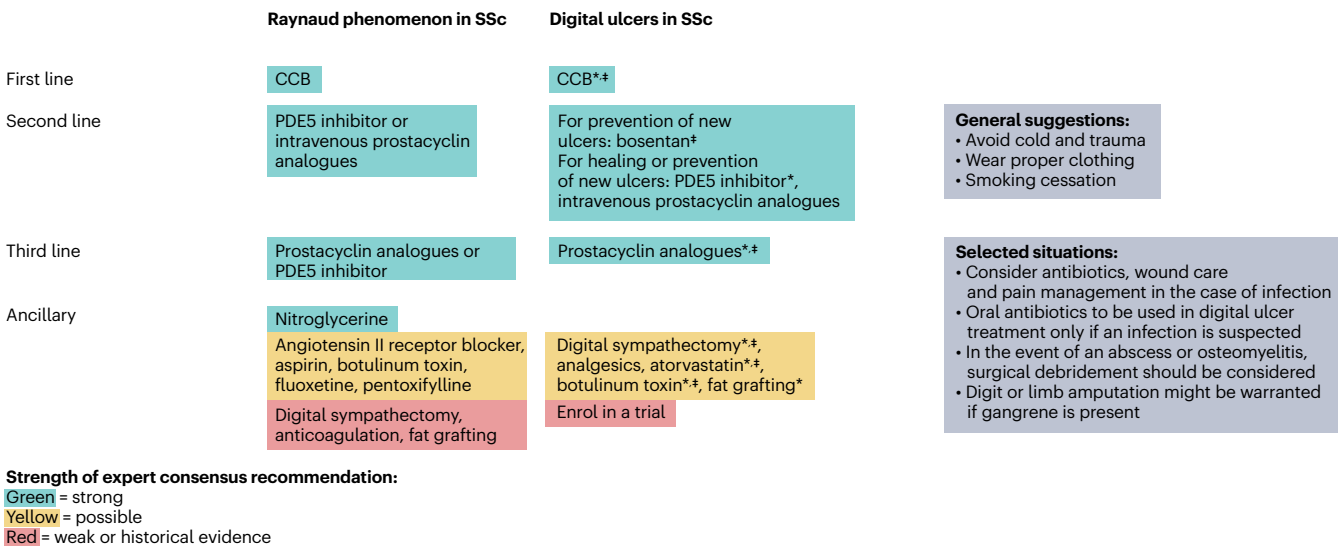

Fig. 4 | Management of Raynaud phenomenon and digital ulcers in SSc. Treatment of Raynaud phenomenon and digital ulcers is similar, although some drugs might prevent digital ulcers but not enhance their healing. This algorithm suggests different lines of treatment and the strength of each recommendation according to the scientific evidence available: strong (green), possible (yellow) and based on weak or historical evidence (red). CCB, calcium channel blocker; PDE5, phosphodiesterase 5; SSc systemic sclerosis. *Effective in digital ulcer healing. ‡Effective in digital ulcer prevention.

specific diagnostic procedures should be undertaken. To reduce the frequency and severity of the attacks, avoiding some known Raynaud phenomenon triggers, such as cold, trauma, stress, smoking, vibration injury or certain drugs (for example, bleomycin, clonidine and ergot alkaloids), could be helpful. Wearing of proper (warm) clothing in cold conditions is suggested, such as a coat, mittens, hat, dry insulated footwear and hand and/or foot warmers, based on expert opinion[147]. Physical therapy can be used to stimulate blood flow, for example, by teaching patients exercises to generate heat to prevent the onset of symptoms, as well as biofeedback and laser treatment. Biofeedback and deep oscillation (electromechanical stimulation of deep tissues) are being studied in an RCT (NCT00946738).

Alternative treatments

Non-conventional therapeutic approaches to Raynaud phenomenon treatment include acupuncture, antioxidants, biofeedback, essential fatty acids, *Ginkgo biloba*, L-arginine, laser, glucosaminoglycans and therapeutic gloves, although studies of these interventions have had inconclusive results. A systematic review showed that the quality of these studies was low, and only ceramic-impregnated gloves were shown to potentially improve Raynaud phenomenon, with minimal benefit[148].

Outlook for management of Raynaud phenomenon and digital ulcers in SSc

Raynaud phenomenon is associated with pain and complications in SSc, so other treatments are needed to reduce tissue loss, functional impairment and other complications. Several targets have been identified in the skin and blood of patients with SSc, which could lead to clinical trial development. Additionally, combining targets and/or therapies could lead to better responses than with monotherapy.

Conclusions

There are several proven organ-based treatments for SSc, including those that improve skin involvement and survival, ILD, PAH and Raynaud phenomenon, and some evidence supports therapies for digital ulcer prevention and treatment. However, for many patients proven treatment is lacking, such as those with lcSSc or later-stage dcSSc, for which data on immunomodulation are mostly absent, and several SSc complications. Even where treatment exists, there is often a slowing of progressive lung fibrosis or pulmonary hypertension in patients with these diagnoses. However, research has improved the care of people living with SSc. Several SSc trials are registered; for example, on ClinicalTrials.gov, 524 studies on SSc are listed; at least 40 are trials of treatment interventions that are recruiting patients. Ongoing and future research should be directed at elucidating pathophysiology and identifying new targets, effective screening for early identification of disease (including organ-based complications), optimizing outcome measurements and trial design to aid in differentiating the effects of experimental treatments from those of placebo or standard of care, and considering pragmatic trials within clinical care to ascertain the optimal order of treatment options.

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References

1. Martin Calderon, L. & Pope, J. E. Scleroderma epidemiology update. *Curr. Opin. Rheumatol.* **33**, 122–127 (2021).
2. LeRoy, E. C. et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J. Rheumatol.* **15**, 202–205 (1988).
3. Hunzelmann, N. et al. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. *Rheumatology* **47**, 1185–1192 (2008).
4. De Almeida Chaves, S. et al. Sine scleroderma, limited cutaneous, and diffused cutaneous systemic sclerosis survival and predictors of mortality. *Arthritis Res. Ther.* **23**, 295 (2021).
5. Marangoni, R. G. et al. Systemic sclerosis sine scleroderma: distinct features in a large Brazilian cohort. *Rheumatology* **52**, 1520–1524 (2013).
6. Koenig, M. et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. *Arthritis Rheum.* **58**, 3902–3912 (2008).
7. Bellando-Randone, S. et al. Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for very early diagnosis of systemic sclerosis (VEDOSS). *Lancet Rheumatol.* **3**, e834–e843 (2021).
8. Muangchan, C. et al. The 15% rule in scleroderma: the frequency of severe organ complications in systemic sclerosis. A systematic review. *J. Rheumatol.* **40**, 1545–1556 (2013).
9. Akesson, A. & Wollheim, F. A. Organ manifestations in 100 patients with progressive systemic sclerosis: a comparison between the CREST syndrome and diffuse scleroderma. *Br. J. Rheumatol.* **28**, 281–286 (1989).
10. Thoua, N. M. et al. Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre. *Rheumatology* **49**, 1770–1775 (2010).
11. Fretheim, H. et al. Multidimensional tracking of phenotypes and organ involvement in a complete nationwide systemic sclerosis cohort. *Rheumatology* **59**, 2920–2929 (2020).
12. Steen, V. D. & Medsger, T. A. Jr Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum.* **43**, 2437–2444 (2000).
13. Bussone, G. & Mouthon, L. Interstitial lung disease in systemic sclerosis. *Autoimmun. Rev.* **10**, 248–255 (2011).
14. Pope, J. E. et al. Systemic sclerosis and associated interstitial lung disease in Ontario, Canada: an examination of prevalence and survival over 10 years. *J. Rheumatol.* **48**, 1427–1434 (2021).
15. Fernandez-Codina, A. et al. Treatment algorithms for systemic sclerosis according to experts. *Arthritis Rheumatol.* **70**, 1820–1828 (2018).
16. Khanna, D. et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J. Scleroderma Relat. Disord.* **2**, 11–18 (2017).
17. Herrick, A. L. et al. Patterns and predictors of skin score change in early diffuse systemic sclerosis from the European Scleroderma Observational Study. *Ann. Rheum. Dis.* **77**, 563–570 (2018).
18. Khanna, D. et al. The American College of Rheumatology provisional composite response index for clinical trials in early diffuse cutaneous systemic sclerosis. *Arthritis Care Res.* **68**, 167–178 (2016).
19. Spiera, R. et al. Safety and efficacy of lenabasum in a phase II, randomized, placebo-controlled trial in adults with systemic sclerosis. *Arthritis Rheumatol.* **72**, 1350–1360 (2020).
20. Chung, L. et al. Safety and efficacy of abatacept in early diffuse cutaneous systemic sclerosis (ASSET): open-label extension of a phase 2, double-blind randomised trial. *Lancet Rheumatol.* **2**, e743–e753 (2020).
21. Khanna, D. et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* **387**, 2630–2640 (2016).
22. Khanna, D. et al. Evaluation of American college of rheumatology provisional composite response index in systemic sclerosis (ACR CRISS) in a phase 3 randomized controlled trial [abstract]. *Arthritis Rheumatol.* **70**, 2938 (2018).
23. Nevskaya, T. et al. Skin improvement is a surrogate for favourable changes in other organ systems in early diffuse cutaneous systemic sclerosis. *Rheumatology* **59**, 1715–1724 (2020).
24. Zheng, B. et al. Changes in skin score in early diffuse cutaneous systemic sclerosis are associated with changes in global disease severity. *Rheumatology* **59**, 398–406 (2020).
25. Burt, R. K. et al. Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: a pilot safety study that decreases neutropenic interval to 5 days. *Bone Marrow Transpl.* **56**, 50–59 (2021).
26. Sullivan, K. M. et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N. Engl. J. Med.* **378**, 35–47 (2018).
27. van Laar, J. M. et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* **311**, 2490–2498 (2014).
28. Burt, R. K. et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* **378**, 498–506 (2011).
29. Shouval, R. et al. Autologous hematopoietic stem cell transplantation for systemic sclerosis: a systematic review and meta-analysis. *Biol. Blood Marrow Transpl.* **24**, 937–944 (2018).
30. Maltez, N. et al. Association of autologous hematopoietic stem cell transplantation in systemic sclerosis with marked improvement in health-related quality of life. *Arthritis Rheumatol.* **73**, 305–314 (2021).
31. van Bijnen, S. et al. Predictive factors for treatment-related mortality and major adverse events after autologous haematopoietic stem cell transplantation for systemic sclerosis: results of a long-term follow-up multicentre study. *Ann. Rheum. Dis.* **79**, 1084–1089 (2020).

32. Guillaume-Jugnot, P. et al. Autologous haematopoietic stem cell transplantation (AHSCT) in autoimmune disease adult patients in France: analysis of the long-term outcome from the French society for bone marrow transplantation and cellular therapy (SFGM-TC). *Clin. Rheumatol.* **38**, 1501–1511 (2019).
33. Henes, J. et al. Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow transplantation autoimmune disease working party. *Haematologica* **106**, 375–383 (2021).
34. Tashkin, D. P. et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N. Engl. J. Med.* **354**, 2655–2666 (2006).
35. Tashkin, D. P. et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir. Med.* **4**, 708–719 (2016).
36. Pope, J. E. et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum.* **44**, 1351–1358 (2001).
37. van den Hoogen, F. H. et al. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br. J. Rheumatol.* **35**, 364–372 (1996).
38. Gordon, J. K. et al. Belimumab for the treatment of early diffuse systemic sclerosis: results of a randomized, double-blind, placebo-controlled, pilot trial. *Arthritis Rheumatol.* **70**, 308–316 (2018).
39. Khanna, D. et al. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol.* **72**, 125–136 (2020).
40. Khanna, D. et al. A phase 2a randomized, double-blind, placebo-controlled study of ziritaxestat in early diffuse cutaneous systemic sclerosis (NOVESA) [abstract]. *Arthritis Rheumatol.* **72**, L09 (2020).
41. Khanna, D. et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir. Med.* **8**, 963–974 (2020).
42. Khanna, D. et al. Riociguat in patients with early diffuse cutaneous systemic sclerosis (RISE-SSc): randomised, double-blind, placebo-controlled multicentre trial. *Ann. Rheum. Dis.* **79**, 618–625 (2020).
43. Hudson, M. et al. Cyclophosphamide for the treatment of skin fibrosis in systemic sclerosis: a systematic review [abstract]. *Arthritis Rheumatol.* **71**, 2593 (2019).
44. Allanore, Y. et al. A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis. *Ann. Rheum. Dis.* **79**, 1600–1607 (2020).
45. GlobeNewswire. Corbus Pharmaceuticals announces topline results from RESOLVE-1 phase 3 study of lenabasum for treatment of systemic sclerosis. *GlobeNewswire* https://www.globenewswire.com/news-release/2020/09/08/2089940/0/en/Corbus-Pharmaceuticals-Announces-Topline-Results-from-RESOLVE-1-Phase-3-Study-of-Lenabasum-for-Treatment-of-Systemic-Sclerosis.html (2020).
46. Distler, O. et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N. Engl. J. Med.* **380**, 2518–2528 (2019).
47. Fernandez-Codina, A., Nevskaya, T. & Pope, J. Brentuximab vedontin for skin involvement in refractory diffuse cutaneous systemic sclerosis, interim results of a phase IIb open-label trial. *Ann. Rheum. Dis.* **80**, 103–104 (2021).
48. Khanna, D. et al. Tofacitinib in early diffuse cutaneous systemic sclerosis — results of phase I/II investigator-initiated, double-blind randomized placebo-controlled trial [abstract 863]. *Arthritis Rheumatol.* **71**, 1493–1495 (2019).
49. Karalilova, R. V. et al. Tofacitinib in the treatment of skin and musculoskeletal involvement in patients with systemic sclerosis, evaluated by ultrasound. *Rheumatol. Int.* **41**, 1743–1753 (2021).
50. Hoa, S. et al. Association between immunosuppressive therapy and course of mild interstitial lung disease in systemic sclerosis. *Rheumatology* **59**, 1108–1117 (2020).
51. Kowal-Bielecka, O. et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann. Rheum. Dis.* **76**, 1327–1339 (2017).
52. Gernert, M. et al. Immunosuppressive therapy after autologous hematopoietic stem cell transplantation in systemic sclerosis patients-high efficacy of rituximab. *Front. Immunol.* **12**, 817893 (2021).
53. Gressenberger, P. et al. Rituximab as a treatment option after autologous hematopoietic stem cell transplantation in a patient with systemic sclerosis. *J. Pers. Med.* **11**, 600 (2021).
54. Arruda, L. C. et al. Resetting the immune response after autologous hematopoietic stem cell transplantation for autoimmune diseases. *Curr. Res. Transl. Med.* **64**, 107–113 (2016).
55. Nihtyanova, S. I. et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol.* **66**, 1625–1635 (2014).
56. Steen, V. D. & Medsger, T. A. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann. Rheum. Dis.* **66**, 940–944 (2007).
57. Elhai, M. et al. Mapping and predicting mortality from systemic sclerosis. *Ann. Rheum. Dis.* **76**, 1897–1905 (2017).
58. Hoffmann-Vold, A. M. et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann. Rheum. Dis.* **80**, 219–227 (2021).
59. Hoffmann-Vold, A. M. et al. POS0063 Progressive interstitial lung disease is frequent also in late disease stages in systemic sclerosis patients from EUSTAR. *Ann. Rheum. Dis.* **81**, 248 (2022).
60. Nihtyanova, S. I. et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. *Arthritis Rheumatol.* **72**, 465–476 (2020).
61. Savarino, E. et al. Possible connection between gastroesophageal reflux and interstitial pulmonary fibrosis in patients with systemic sclerosis. *Recenti Prog. Med.* **100**, 512–516 (2009).
62. Zhang, X. J. et al. Association of gastroesophageal factors and worsening of forced vital capacity in systemic sclerosis. *J. Rheumatol.* **40**, 850–858 (2013).
63. Goh, N. S. et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am. J. Respir. Crit. Care Med.* **177**, 1248–1254 (2008).
64. Hoffmann-Vold, A. M. et al. Assessment of recent evidence for the management of patients with systemic sclerosis-associated interstitial lung disease: a systematic review. *ERJ Open Res* **7**, 00235-2020 (2021).
65. Montesi, S. B. & Caravan, P. Novel imaging approaches in systemic sclerosis-associated interstitial lung disease. *Curr. Rheumatol. Rep.* **21**, 25 (2019).
66. Goh, N. S. et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol.* **69**, 1670–1678 (2017).
67. Volkmann, E. R. et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. *Ann. Rheum. Dis.* **78**, 122–130 (2019).
68. Stock, C. J. W. et al. Serum markers of pulmonary epithelial damage in systemic sclerosis-associated interstitial lung disease and disease progression. *Respirology* **26**, 461–468 (2021).
69. De Lauretis, A. et al. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. *J. Rheumatol.* **40**, 435–446 (2013).
70. Renaud, L. et al. Prominence of IL6, IGF, TLR, and bioenergetics pathway perturbation in lung tissues of scleroderma patients with pulmonary fibrosis. *Front. Immunol.* **11**, 383 (2020).
71. Bonhomme, O. et al. Biomarkers in systemic sclerosis-associated interstitial lung disease: review of the literature. *Rheumatology* **58**, 1534–1546 (2019).
72. Roofeh, D. et al. Management of systemic sclerosis-associated interstitial lung disease. *Curr. Opin. Rheumatol.* **31**, 241–249 (2019).
73. Bukiri, H. & Volkmann, E. R. Current advances in the treatment of systemic sclerosis. *Curr. Opin. Pharmacol.* **64**, 102211 (2022).
74. Hoyles, R. K. et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum.* **54**, 3962–3970 (2006).
75. Ebata, S. et al. Safety and efficacy of rituximab for systemic sclerosis: a double-blind, parallel-group comparison, investigators initiated confirmatory randomized clinical trial (DESIRES Study) [abstract]. *Arthritis Rheumatol.* **73**, 0496 (2021).
76. Hughes, M., Denton, C. P. & Khanna, D. Rituximab for the treatment of systemic sclerosis-interstitial lung disease. *Rheumatology* **60**, 489–491 (2021).
77. Goswami, R. P. et al. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. *Rheumatology* **60**, 557–567 (2021).
78. Sircar, G. et al. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. *Rheumatology* **57**, 2106–2113 (2018).
79. Denton, C. P. et al. Therapeutic interleukin-6 blockade reverses transforming growth factor-beta pathway activation in dermal fibroblasts: insights from the faSScinate clinical trial in systemic sclerosis. *Ann. Rheum. Dis.* **77**, 1362–1371 (2018).
80. Khanna, D. et al. STRATUS: a phase II study of abituzumab in patients with systemic sclerosis-associated interstitial lung disease. *J. Rheumatol.* **48**, 1295–1298 (2021).
81. Maher, T. M. et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir. Med.* **11**, 45–54 (2023).
82. Flaherty, K. R. et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N. Engl. J. Med.* **381**, 1718–1727 (2019).
83. Khanna, D. et al. An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. *J. Rheumatol.* **43**, 1672–1679 (2016).
84. Behr, J. et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir. Med.* **9**, 476–486 (2021).
85. Khanna, D. et al. Combination therapy of mycophenolate mofetil and pirfenidone vs. mycophenolate alone: results from the Scleroderma Lung Study III [abstract]. *Arthritis Rheumatol.* **74**, 0520 (2022).
86. Perelas, A. et al. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir. Med.* **8**, 304–320 (2020).
87. Waxman, A. et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N. Engl. J. Med.* **384**, 325–334 (2021).
88. Hoffmann-Vold, A. M. et al. The need for a holistic approach for SSc-ILD — achievements and ambiguity in a devastating disease. *Respir. Res.* **21**, 197 (2020).
89. Bernstein, E. J. et al. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. *Arthritis Rheumatol.* **67**, 1314–1322 (2015).
90. Crespo, M. M. et al. Lung transplant in patients with scleroderma compared with pulmonary fibrosis. Short- and long-term outcomes. *Ann. Am. Thorac. Soc.* **13**, 84–92 (2016).

91. Kreuter, M. et al. Impact of lung function decline on time to hospitalisation events in systemic sclerosis-associated interstitial lung disease (SSc-ILD): a joint model analysis. *Arthritis Res. Ther.* **24**, 19 (2022).
92. Hoa, S. et al. Association between immunosuppressive therapy and incident risk of interstitial lung disease in systemic sclerosis. *Chest* **160**, 2158–2162 (2021).
93. Naidu, G. S. R. S. N. K. et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. *Rheumatol. Int.* **40**, 207–216 (2020).
94. Yomono, K. & Kuwana, M. Outcomes in patients with systemic sclerosis undergoing early vs delayed intervention with potential disease-modifying therapies. *Rheumatology* **61**, 3677–3685 (2022).
95. Vonk, M. C., Vandecasteele, E. & van Dijk, A. P. Pulmonary hypertension in connective tissue diseases, new evidence and challenges. *Eur. J. Clin. Invest.* **51**, e13453 (2021).
96. Morrisroe, K. et al. Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme. *Arthritis Res. Ther.* **19**, 42 (2017).
97. Simonneau, G. et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* **53**, 1801913 (2019).
98. Jiang, Y., Turk, M. A. & Pope, J. E. Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). *Autoimmun. Rev.* **19**, 102602 (2020).
99. Connolly, M. J. et al. Prognostic significance of computed tomography criteria for pulmonary veno-occlusive disease in systemic sclerosis-pulmonary arterial hypertension. *Rheumatology* **56**, 2197–2203 (2017).
100. Johnson, S. R. et al. Venous thromboembolism in systemic sclerosis: prevalence, risk factors, and effect on survival. *J. Rheumatol.* **45**, 942–946 (2018).
101. Ende-Verhaar, Y. M. et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur. Respir. J.* **49**, 1601792 (2017).
102. Weatherald, J. et al. Screening for pulmonary arterial hypertension in systemic sclerosis. *Eur. Respir. Rev.* **28**, 190023 (2019).
103. Lee, P. et al. Mortality in systemic sclerosis (scleroderma). *Q. J. Med.* **82**, 139–148 (1992).
104. Johnson, S. R. et al. Pulmonary veno-occlusive disease and scleroderma associated pulmonary hypertension. *J. Rheumatol.* **33**, 2347–2350 (2006).
105. Galie, N. et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur. Heart J.* **37**, 67–119 (2016).
106. Johnson, S. R., Granton, J. T. & Mehta, S. Thrombotic arteriopathy and anticoagulation in pulmonary hypertension. *Chest* **130**, 545–552 (2006).
107. Johnson, S. R., Mehta, S. & Granton, J. T. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. *Eur. Respir. J.* **28**, 999–1004 (2006).
108. Lei, Y. et al. The effects of oral treatment for systemic sclerosis related pulmonary arterial hypertension: a systematic review and meta-analysis. *Mod. Rheumatol.* **31**, 151–161 (2021).
109. Hitzerd, E. et al. Endothelin receptor antagonism during preeclampsia: a matter of timing? *Clin. Sci.* **133**, 1341–1352 (2019).
110. Humbert, M. et al. Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. *Ann. Rheum. Dis.* **76**, 422–426 (2017).
111. Galie, N. et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur. Respir. J.* **53**, 1801889 (2019).
112. Galie, N. et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N. Engl. J. Med.* **373**, 834–844 (2015).
113. Belge, C. & Delcroix, M. Treatment of pulmonary arterial hypertension with the dual endothelin receptor antagonist macitentan: clinical evidence and experience. *Ther. Adv. Respir. Dis.* **13**, 1753466618823440 (2019).
114. Coghlan, J. G. et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann. Rheum. Dis.* **76**, 1219–1227 (2017).
115. Paul, G. A. et al. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br. J. Clin. Pharmacol.* **60**, 107–112 (2005).
116. Zamanian, R. T. et al. Safety and efficacy of B-cell depletion with rituximab for the treatment of systemic sclerosis-associated pulmonary arterial hypertension: a multicenter, double-blind, randomized, placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* **204**, 209–221 (2021).
117. Meier, F. M. et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann. Rheum. Dis.* **71**, 1355–1360 (2012).
118. Hughes, M. & Herrick, A. L. Digital ulcers in systemic sclerosis. *Rheumatology* **56**, 14–25 (2017).
119. Khimdas, S. et al. Associations with digital ulcers in a large cohort of systemic sclerosis: results from the Canadian Scleroderma Research Group registry. *Arthritis Care Res.* **63**, 142–149 (2011).
120. Merkel, P. A. et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum.* **46**, 2410–2420 (2002).
121. Hughes, M. et al. Raynaud phenomenon and digital ulcers in systemic sclerosis. *Nat. Rev. Rheumatol.* **16**, 208–221 (2020).
122. Pauling, J. D. The challenge of establishing treatment efficacy for cutaneous vascular manifestations of systemic sclerosis. *Expert. Rev. Clin. Immunol.* **14**, 431–442 (2018).
123. Denton, C. P. et al. BSR and BHPR guidelines for the treatment of systemic sclerosis. *Rheumatology* **55**, 1906–1910 (2016).
124. University of Oxford. Oxford Centre for Evidence-Based Medicine: levels of evidence (March 2009). *CEBM* https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (2009).
125. Fernández-Codina, A., Cañas-Ruano, E. & Pope, J. E. Management of Raynaud's phenomenon in systemic sclerosis — a practical approach. *J. Scleroderma Relat. Disord.* **4**, 102–110 (2019).
126. Rirash, F. et al. Calcium channel blockers for primary and secondary Raynaud's phenomenon. *Cochrane Database Syst. Rev.* **12**, CD000467 (2017).
127. Roustit, M. et al. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann. Rheum. Dis.* **72**, 1696–1699 (2013).
128. Pope, J. et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst. Rev.* **1998**, CD000953 (2000).
129. Ingegnoli, F. et al. Practical suggestions on intravenous iloprost in Raynaud's phenomenon and digital ulcer secondary to systemic sclerosis: systematic literature review and expert consensus. *Semin. Arthritis Rheum.* **48**, 686–693 (2019).
130. Marasini, B. et al. Comparison between iloprost and alprostadil in the treatment of Raynaud's phenomenon. *Scand. J. Rheumatol.* **33**, 253–256 (2004).
131. Curtiss, P. et al. A systematic review and meta-analysis of the effects of topical nitrates in the treatment of primary and secondary Raynaud's phenomenon. *J. Am. Acad. Dermatol.* **78**, 1110–1118.e3 (2018).
132. Dziadzio, M. et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum.* **42**, 2646–2655 (1999).
133. van der Meer, J. et al. A double-blind controlled trial of low dose acetylsalicylic acid and dipyridamole in the treatment of Raynaud's phenomenon. *VASA Suppl.* **18**, 71–75 (1987).
134. Abou-Raya, A., Abou-Raya, S. & Helmii, M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J. Rheumatol.* **35**, 1801–1808 (2008).
135. Coleiro, B. et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology* **40**, 1038–1043 (2001).
136. Wasserman, A. & Brahn, E. Systemic sclerosis: bilateral improvement of Raynaud's phenomenon with unilateral digital sympathectomy. *Semin. Arthritis Rheum.* **40**, 137–146 (2010).
137. Bank, J. et al. Fat grafting to the hand in patients with Raynaud phenomenon: a novel therapeutic modality. *Plast. Reconstr. Surg.* **133**, 1109–1118 (2014).
138. Motegi, S. I. et al. Efficacy of botulinum toxin B injection for Raynaud's phenomenon and digital ulcers in patients with systemic sclerosis. *Acta Derm. Venereol.* **97**, 843–850 (2017).
139. Bello, R. J. et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: a randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol.* **69**, 1661–1669 (2017).
140. Tingey, T. et al. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. *Arthritis Care Res.* **65**, 1460–1471 (2013).
141. Shenoy, P. D. et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology* **49**, 2420–2428 (2010).
142. Hachulla, E. et al. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. *Ann. Rheum. Dis.* **75**, 1009–1015 (2016).
143. Matucci-Cerinic, M. et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **70**, 32–38 (2011).
144. Del Papa, N. et al. Regional grafting of autologous adipose tissue is effective in inducing prompt healing of indolent digital ulcers in patients with systemic sclerosis: results of a monocentric randomized controlled study. *Arthritis Res. Ther.* **21**, 7 (2019).
145. Momeni, A. et al. Surgical treatment of systemic sclerosis — is it justified to offer peripheral sympathectomy earlier in the disease process? *Microsurgery* **35**, 441–446 (2015).
146. Allanore, Y. et al. Clinical characteristics and predictors of gangrene in patients with systemic sclerosis and digital ulcers in the Digital Ulcer Outcome Registry: a prospective, observational cohort. *Ann. Rheum. Dis.* **75**, 1736–1740 (2016).
147. Hughes, M. et al. Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. *Rheumatology* **54**, 2015–2024 (2015).
148. Malenfant, D., Catton, M. & Pope, J. E. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. *Rheumatology* **48**, 791–795 (2009).
149. Benza, R. L. et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* **141**, 354–362 (2012).

Author contributions

All authors contributed to all aspects of the article.

Competing interests

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