State of art evidence in the treatment of systemic sclerosis

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Disclosures. Janet Pope has research grants from AbbVie, Bayer, BI, BMS, Frensenius Kabi, Lilly, Mallinckrodt Pharmaceuticals, Merck, Roche, Seattle Genetics. Dr Pope has consulted for AbbVie, Amgen, BI, BMS, Celltrion, EMERALD, Frensenius Kabi, Galapagos, Gilead, Janssen, Lilly, Mallinckrodt Pharmaceuticals, Medexus, Merck, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Roche, Sandoz, Samsung, Sanofi, Sobi, Teva, Viatris. Dr Pope has been a speaker or attended an advisory board for AbbVie, Amgen, BI, BMS, Frensenius Kabi, Galapagos, Gilead, Janssen, Lilly, Merck, Novartis, Pfizer, Sandoz, Sanofi, UCB. Christopher Denton has xxxxx. Sindhu Johnson has been a site investigator for clinical trials sponsored by Bayer, Boehringer Ingelheim, Corbus, Glaxo Smith Klein; and has served on advisory boards for Boehringer Ingelheim, Corbus and Ikaria. Dr. Johnson is supported by the Oscar and Eleonor Markovitz Scleroderma Research Fund and the Gurmej Kaur Dhanda Scleroderma Research Fund. Andreu Fernandez Codina has xxxx. Marie Hudson has xxxx.

There was no funding for this paper.

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Tables 6, Figures 2, Text box 1, References 99, 32 pages, 4675 word count

Introduction

This article reviews and critiques treatment for systemic sclerosis (SSc) including organ based and consideration for overall disease modification. A review was undertaken of recent and landmark trials for the treatment of skin, disease modification with autologous stem cell transplantation, lung involvement (interstitial lung disease and pulmonary hypertension), and Raynaud's phenomenon and digital ulcers. Several trials in SSc and consensus statements aid in the understanding of treatment order for various organs affected by SSc. Patients with SSc may be affected by gastrointestinal symptoms, inflammatory arthritis, renal crisis, cardiomyopathy, myopathy and calcinosis but these are beyond the scope of this article as fewer randomized controlled trials (RCTs) are available (1). There are some key organ systems that should be screened for in SSc (Table 1)

SSc is a rare autoimmune connective tissue disease that has significant morbidity and mortality due to fibrosis and vasculopathy (2). Patients are often characterized by the extent of skin involvement where limited cutaneous SSc (lcSSc) involves skin fibrosis distal to the elbows, knees and without truncal involvement but may have skin thickening on the face and neck, and diffuse cutaneous SSc (dcSSc) has both distal and proximal involvement (3). RCTs of disease modification are in general only enrolling patients with the dcSSc subset and often earlier in their disease. Whereas, RCTs of interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), Raynaud's phenomenon (RP) and digital ulcers (DU) include patients with either subset provided they meet entry criteria for trials.

Pharmacologic management of skin and overall disease modification in SSc

Skin

Skin fibrosis is one of the dominant clinical features of SSc. The extent of skin involvement is commonly used to subset the disease, with limited cutaneous SSc (lcSSc) affecting the distal limbs and face, and diffuse cutaneous SSc (dcSSc) extending to the proximal limbs and/or trunk. Although these subsets are often used as surrogates of disease severity and prognosis, both limited and diffuse skin involvement are associated with high functional and psychosocial impact. The extent of skin fibrosis in SSc is most commonly measured using the modified Rodnan skin score (mRSS), which measures skin thickness from 0-3 in 17 anatomic sites (range 0-51). A minimal clinically important difference in mRSS has been estimated to range between 3.5 to 5.3 points (4). In dcSSc, mRSS generally increases over the first 4 years of disease and regresses somewhat over time thereafter.

Skin involvement has been treated with a wide variety of standard immunosuppressants, of which only a few have been studied in randomized clinical trials (RCTs) (Table 2). Methotrexate was studied in 2 small RCTs (5,6) (Table 2), with the larger study (N=71) (5) reporting a between-group difference of approximately 5 points in the mRSS in favour of methotrexate ($p<0.17$). In both RCTs, relatively low doses of methotrexate were used (15

mg/week po or IM (5,6). Whether higher doses of methotrexate, which are now more commonly used in rheumatic diseases, could increase treatment effectiveness without significant increase in toxicity is unknown but often MTX 25mg/week is prescribed.

Cyclophosphamide has been studied in SSc in 11 RCTs (7). The Scleroderma Lung Study I was the only RCT that compared cyclophosphamide to placebo. The primary outcome was forced vital capacity (FVC); skin was a secondary outcome. In that study, one year of oral cyclophosphamide resulted in a between-groups difference in mRSS of 3 points in favour of cyclophosphamide (8). In the subsequent Scleroderma Lung Study II, mycophenolate was compared to cyclophosphamide (9). At 2 years, the difference between one-year of oral cyclophosphamide and two-years of mycophenolate on mRSS was 0.45. Figure 1 shows the effect size of the between groups difference in the mRSS from trials of immune suppression and autologous hematopoietic stem cell transplant (AHSCT).

Several placebo-controlled RCTs of biologics and targeted therapies with skin as primary endpoint have recently been reported, including tocilizumab (anti-IL-6), abatacept (T-cell co-stimulatory antagonist), riociguat (soluble guanylate cyclase stimulator), romilkimab (IL-4/IL-23 inhibitor), ziritaxestat (autotaxin-

LPA inhibitor) and belimumab (B-cell activating factor (BAFF) antagonist) (Table 2b). Between-group differences have been in the order of 2-5 points in favour of active treatment. Skin was a secondary outcome in a trial of lenabasum (CBD2 receptor agonist), which reached similar results in phase 2 but no effect vs placebo in phase 3 RESOLVE-1 RCT (10) (Table 2c). A Phase 3 study of the anti-fibrotic nintedanib also reported skin as a secondary outcome and found no difference compared to placebo (Table 2c).

The intervention with the largest effect on skin fibrosis to date is AHSCT, with between-group differences of approximately 10 points compared to 12 monthly infusions of cyclophosphamide (Table 3, Figure 1). Pre-post differences *by treatment group* were also large. In ASTIS, for example, AHSCT was associated with a -20 point difference in mRSS while intravenous cyclophosphamide was associated with a -9 point difference.

Disease modification

The vast majority of interventional studies in SSc have used organ-specific endpoints. In contrast, four open-label randomized clinical trials of AHSCT have used overall and event-free survival as primary or secondary outcomes (Table 3), thereby providing a lens into overall disease modification in SSc. Those trials included 292 patients followed for up to 10 years. Each trial had

distinctive mobilization and conditioning regimens. Control groups in ASSIST, ASTIS and SCOT were treated with monthly intravenous cyclophosphamide 0.5-1 g/m^2 for 6-12 months, while the Cardiac-Safe trial compared a fludarabine-based regimen with or without rituximab and/or IVIg.

A meta-analysis of the 3 studies comparing AHSCT to cyclophosphamide found that overall survival was significantly better with AHSCT (Hazard Ratio 0.61, 95% CI 0.40, 0.93) (11). Event-free survival was also clearly in favour of AHSCT (Table 3). Both ASSIST and ASTIS reported improvement in FVC while SCOT did not. This is possibly related to the use of total-body irradiation in the SCOT transplant regimen. On the other hand, by using a lower dose of cyclophosphamide, the rate of cardiac toxicity was lower in SCOT compared to ASSIST and ASTIS. Finally, trials and real-world data have shown that AHSCT is also associated with clinically significant improvements in health-related quality of life compared to controls (12).

However, AHSCT is consistently associated with increased risks of treatment-related mortality, with an overall estimate of approximately 10% (11), although treatment-related mortality with non-myeloablative appears to be earlier, and later with myeloablative transplant. AHSCT is also associated with higher risks of infections and hematological complications, and; is possibly associated with both early and late malignancies.

Thus, while AHSCT can be considered a disease-modifying treatment for SSc, this treatment should be reserved for carefully selected patients at high-risk of disease complications. Improved cardiac screening and less toxic transplant regimens have the potential to improve the safety of AHSCT. In the long term, the need for immune suppression in these patients and relapse rates need careful observation.

Lung

Management of interstitial lung disease in systemic sclerosis

Lung fibrosis is frequent in systemic sclerosis (SSc-ILD) and represents a major cause of morbidity and mortality. The timing and frequency of development of SSc-ILD has been examined in large well characterised SSc cohorts which have defined the natural history and outcomes. There are emerging clinical associations and laboratory characteristics that predict the development of SSc-ILD. Some patients remain stable whereas others develop progressive and severe lung fibrosis (25). The factors associated with development of lung fibrosis are summarised in Text Box 1. A simple schematic summarising the current approach to management of SSc-ILD is provided in Figure 2.

Epidemiology

Lung fibrosis occurs overall in approximately 40% of patients with SSc, but is clinically significant in approximately 20% of dcSSc and 12% of lcSSc (26). Pulmonary fibrosis has become the most common cause of SSc-related death due to improved outcomes in scleroderma renal crisis and pulmonary arterial hypertension (PAH)/pulmonary hypertension (PH) that were previously the

most frequently lethal complications (27). Lung fibrosis may be the presenting feature of SSc in some cases but most often develops within the first 3 years of onset of SSc. It is strongly associated with some autoantibodies, especially anti-topoisomerse-1 (Scl-70) and studies suggest that this risk is independent of the disease subset and important for case stratification (28). However, progressive lung fibrosis can occur throughout the disease course. There is a higher frequency of lung fibrosis in male patients, but this may in part be due to a higher frequency of dcSSc subset patients that are male.

Pathology and pathogenesis

It is likely that there are shared pathogenic mechanisms between various fibrotic manifestations of SSc including skin disease. This is consistent with the greater frequency of lung fibrosis in dcSSc. However initial disease may be driven by lung epithelial damage and immuno-inflammation. Recent studies have highlighted the potential role of monocytes and macrophages in determining the development of lung fibrosis and the adaptive immune system is also involved; based on studies of lymphocytes from bronchoalveolar lavage and the clear link to autoantibodies (29). In addition, B cell depletion is reported to show benefit supporting a potential role for B cells in pathogenesis (30). Epithelial damage from aspiration and reflux is also implicated and studies have associated CT evidence of oesophageal dilatation to the development and severity of SSc-ILD (31). Infections may also be important as well as other shared mechanisms in overlaps cases with other connective tissue diseases such as rheumatoid arthritis and Sjogren's syndrome or polymyositis. Histologically SSc-ILD is most often and nonspecific interstitial pneumonitis (NSIP) pattern ad this can be cellular or fibrotic. Extent of disease rather than histological classification appears to be most important in determining

progression and prognosis in SSc-ILD (32). Although if there is equal CT involvement, a SSc patient with usual interstitial pneumonitis (UIP) will have a worse outcome than NSIP.

Assessment of SSc-ILD – screening, diagnosis and evaluation

Screening is an essential part of effective management of SSc-ILD. This can be considered as primary screening in baseline assessment of all patients which may include CT assessment with prone images and high-resolution reconstruction to identify the earliest changes and differentiate from gravitational increases in interstitial abnormalities. Pulmonary function tests (PFTs) are important and need to be performed regularly but may be unreliable for screening due to the range of normal values and so all patients should have CT imaging (33). New imaging tools are being evaluated including PET scan, thoracic ultrasound or MRI (34). Hyperpolarized xenon has also been used and can be used to quantify gas exchange. Threshold of 70% FVC has been used to separate extensive and mild disease and appears to have prognostic value in several cohorts (25). Serial changes in PFT correlate to outcomes and are an important aspect of management. The threshold of 10% decrease in FVC or 5% with corroborative drop of 15% in DLco have bene applied from idiopathic pulmonary fibrosis (IPF) literature and predict survival. Changes in DLco or Kco are highly predictive of long-term outcome but changes over time appear only to be predictive over the next 2 years (36). Serum markers are looking promising, including the marker of epithelial damage KL-6 (37) and IL6, especially in early stage or less extensive SSc-ILD (38). Other potential markers of lung fibrosis include CCL18, CXCL4 and CCL2 (37). These have shown utility in research studies and in stratification although longitudinal changes have been less informative so far. Recent trials

suggest that elevated serum IL6, or acute phase response CRP, ESR or thrombocytosis may be predictive of the risk of lung fibrosis especially in early diffuse cutaneous SSc (39).

Treatment

Immunosuppression

Evidence supports the benefit from immunosuppression for SSc-ILD and this includes results from cohort studies and randomised placebo-controlled trials. The first trial was SLS I (40), and this was soon followed by FAST studying cyclophosphamide treatment (41). SLS II was designed to show superiority of MMF over 24 months of treatment compared to one year of cyclophosphamide and then no treatment; but showed equivalence. However, MMF was better tolerated and safer than oral cyclophosphamide (42). More recently, studies have shown benefit from MMF in the context of antifibrotic therapy. There is growing evidence supporting RTX as an alternative to cyclophosphamide that may be better tolerated (43). Autologous stem cell transplantation has been associated with benefit for lung function and fibrosis. This was seen most clearly in the SCOT trial (44).

Antifibrotic therapies for SSc-ILD

Both of the antifibrotic agents licensed for use in IPF, nintedanib and pirfenidone have been tested in SSc-ILD trials. For nintedanib there are two relevant RCTs. SENSCIS defined benefit in terms of slowed progression and a numerically greater benefit for patients on concomitant mycophenolate mofetil (MMF) (45). Another large RCT of nintedanib showed superiority to placebo across a range of progressive ILDs including SSc (46). Pirfenidone has been less extensively evaluated but the LOTUSS clinic trial suggested that it is safe and well tolerated,

used in combination with immunosuppressive treatment (47). Pirfenidone showed benefit in the RELIEF study; a RCT of progressive fibrotic ILD including SSc patients that stopped due to slow recruitment (48). The larger Scleroderma Lung Study III (SLS III) will compare MMF alone with a combination of MMF and pirfenidone (49).

Tocilizumab has recently been approved by FDA to slow the rate of declining lung function in SSc-ILD based upon the results of a phase 3 focuSSced trial (50) that was designed to explore benefit for skin fibrosis which demonstrated skin improvement that was not quite statistically significant compared to placebo. However, there was less decline in lung function, compared with placebo, and this was corroborated by impact on visual read and quantitative CT scan. The mechanism of antifibrotic effect may be due to cross-talk between IL6 and more conventional profibrotic mediators such as TGFb (51).

Glucocorticoids are seldom used in SSc-ILD as they are not usually effective (except perhaps in overlaps with other CTDs) and have side effects (infections, osteoporosis, metabolic changes and may increase renal crisis especially in RNApol3 positive patients with early active dcSSc).

Supportive – oxygen, infection, reflux, associated PH

In addition to potential disease modifying therapies, it is important to manage factors that may aggravate the SSc-ILD such as gatroesophageal reflux disease (GERD) and intercurrent infection. Intercurrent infection should be promptly treated. Some patients may benefit from prophylactic antibiotics if they have frequent pulmonary infections. Oxygen is used if there is hypoxia. Oxygen can reduce dyspnoea, especially associated with exertion, and may mitigate development of pulmonary hypertension. Associated PH is important as it portends a very poor

outcome and may require additional treatment. There are concerns that ventilation:perfusion (V;Q) mismatch may be aggravated but judicious use of pulmonary vasodilators may be beneficial (29). Although RCTs are lacking, encouraging regular cardiovascular exercise and targeting ideal body weight may be helpful.

Lung transplantation for ILD

For end stage lung fibrosis transplantation is the only treatment that may improve long term outcome. However, the availability of donors and concerns about comorbidity limit lung transplantation in SSc. Reflux that may predispose to post transplant bronchiolitis is a particular concern. Recent cohort studies suggest outcomes after lung transplant are comparable to other chronic diseases in age and sex matched patients and so this option should be considered in severe or poor prognosis cases (52).

Thus, although remaining an important complication and cause of death in SSc, lung fibrosis is now more manageable and better understood, with evidence-based treatment including two FDA approved drugs. It is likely that early intervention and combination therapies will be needed to impact on long term survival. Case stratification will be important in balancing benefits and side effects and well as ensuring appropriate use of high-cost drugs. Better understanding of emerging new imaging techniques and more validation of circulating biomarkers will underpin future management.

PAH/PH in SSc

Pulmonary hypertension (PH) is a leading cause of death in SSc.(53) SSc-associated pulmonary arterial hypertension (SSc-PAH) is the most common etiology of PH in SSc, however PH can be the consequence of left-sided heart disease, interstitial lung disease, pulmonary veno-occlusive disease (PVOD) or pulmonary embolism(54) (Table 4). SSc-PAH occurs more frequently in older patients, those with longer disease duration and in African ancestry and is associated with positive anticentromere antibodies, anti-topoisomerase I, U3-RNP antibodies, erythrocyte sedimentation rate, immunoglobulin G, digital ulcerations/pitting (55). PVOD is characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules leading to hydrostatic pulmonary edema. Clinical features suggestive of PVOD include severe hypoxia, pleural effusions, interlobular septal thickening, poorly defined parenchymal opacities and lymphadenopathy. Pulmonary embolism in SSc can be acute, associated with ILD or rarely chronic (chronic thromboembolic pulmonary hypertension (CTEPH) (56). Echocardiogram is recommended as the first-line screening test for SSc-PH, followed by measurement of hemodynamics by right heart catheterization to confirm the diagnosis. There are several other PAH screening algorithms (57). Historically, SSc-PH was associated with a median survival of 12 months (56). Advances in the management of SSc-PAH, specifically the development of PH-specific therapies, have led to improvements in hemodynamics, exercise capacity, World Health Organization functional class, health related quality of life and survival (Table 5). However, survival at 5 years post PAH diagnosis is still poor (57).

Non-Pharmacologic Strategies

SSc-PH patients should be counselled against smoking tobacco and marijuana, receive routine vaccinations, exercise as tolerated and discuss contraception. If hypoxic, they need oxygen. However, one should note that SSc-PAH is rarely a hypoxic disease. If a SSc-PH patient is hypoxic, one should investigate for a cause of the hypoxia (e.g. PVOD, ILD, PE) (58). SSc-PH patients with right ventricular overload and fluid retention, should be counselled on a reduced salt diet, and may need diuretics and/or inotropic agents.

Pharmacologic 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.(59) Although anticoagulation is recommended in idiopathic PAH (60). However, SSc-PAH patients should not be anticoagulated due to conflicting evidence and bleeding risk.(61) Using a propensity score matched SSc cohort, warfarin did not confer a survival benefit.(62) In a post-hoc analysis of the COMPERA trial, SSc-PAH had a statistically nonsignificant trend towards worse survival among those taking anticoagulants compared with patients not on anticoagulant therapy (3-year survival 62% versus 74%; hazard ratio (HR) 1.82, 95%CI 0.94-3.54). For these reasons, anticoagulation is not routinely given to SSc-PH patients.

PH specific therapies

Four groups of PH specific therapies may be considered in the treatment of SSc-PAH: endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5 inhibitors), soluble guanylate cyclase stimulators and prostaglandin analogues.

ERA. PAH is associated with elevated levels of endothelin-1, a potent vasoconstrictor and mitogen, however, it remains uncertain if the elevated levels of endothelin-1 is a cause or consequence of PAH. Three oral endothelial receptor antagonists (bosentan, ambrisentan, macitentan) are available that target this pathway. A recent systematic review of bosentan trials in SSc-PAH patients found bosentan may improve exercise capacity, and hemodynamics (pulmonary arterial pressure, pulmonary vascular resistance).(63) ERA therapies require regular monitoring of liver enzymes and hemoglobin levels because of the risk of hepatotoxicity and anemia. It is uncertain which ERA will be most effective within an individual.

PDE-5 inhibitors. PDE-5 inhibitors enhance the NO-cGMP pathway, slowing cGMP degradation and resulting in both pulmonary vasodilatory and antiproliferative effects. Three PDE-5 inhibitors are available (sildenafil, tadalafil, vardenafil) albeit 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 hemodynamics, functional class and exercise capacity (64).

Soluble guanylate cyclase stimulators. Riociguat, a soluble guanylate cyclase stimulator, enhances cGMP production resulting in antiproliferative and antiremodelling effects. In the PATENT-1 trial, patients with CTD-PAH (largely SSc-PAH), riociguat improved hemodynamics, functional class, and six minute walk distance (65).

Prostaglandin analogues. Prostaglandin is a potent vasodilator and inhibitor of platelet aggregation. Patients with PH have reduced levels of prostacyclin. Prostaglandin analogues evaluated for the treatment of PH include beraprost, epoprostenol, iloprost, and trepostinil. Epoprostenol, a prostacyclin analogue, has a short half-life which requires continuous intravenous administration. Challenges include the need to aseptically reconstitute the medication, need for an indwelling central venous catheter and side effects. For this reason, it is generally reserved for the more advanced disease. Selexipag is an oral selective IP receptor (prostacyclin receptor) agonist with comparable effects as endogenous prostacyclin.

Combination dual oral therapy with an ERA and PDE-5 inhibitor is the first line treatment in SSc-PAH. Historically, initial monotherapy with one oral agent was recommended, but now is only used in selected low-risk patients. Any ERA may be combined with a PDE-5 inhibitor. For instance, combination ambrisentan and tadalafil are used as the Ambition trial of PAH patients found a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy (HR 0.50 (95%CI 0.35 to 0.72, $p<0.001$)).(66) Post-hoc analyses of the SSc-PAH subgroup demonstrated a reduction in the risk of clinical failure compared with single

agent therapy (SSc-PAH HR 0.44; 95% CI 0.22-0.89).(67) Similarly macitentan and sildenafil or tadalafil have been combined for enhanced efficacy compared to monotherapy (60,68). If there is an intolerance or contraindication to a medication, an alternative medication within the same class may be used.(69) Two agents with a similar mechanism of action are not combined. One should note that bosentan can increase the metabolism and result in the reduction in plasma concentration of sildenafil. As such, this may not be a preferred combination. Combination of a PDE5 inhibitor and riociguat are not recommended due to the increased risk of hypotension. Patients with functional class IV limitation may be considered for combination triple therapy with an ERA, PDE-5 inhibit and prostaglandin analogue. Treatment is often altered according to brain naturetic peptide (BNP), walk distance, pulmonary artery hemodynamics and functional class (for dyspnea). There is a trend of starting with two PAH therapies and adding a third if the patient has poor prognostic factors (68,69).

Lung transplantation

In SSc-PH patients with end stage lung disease, particularly those progressing despite therapy, one can consider double lung or heart-lung transplantation. Lung transplantation is performed to prolong survival and improve quality of life. Survival post transplantation has improved over time, with survival estimates of 93% 1-year post transplantation (52,60). Other surgical options may include right to left shunt or atrial septostomy.

Raynaud's phenomenon and digital ulcers

Raynaud's phenomenon (RP) is present in >95% of patients with SSc (70). Digital ulcers (DU) occur in half the patients with SSc and 15% cross sectionally, and often DU are multiple (1). RP and especially DU have a high burden of disability and loss of quality of life (71). Pathophysiology for both manifestations is similar including due to ischemia from damaged digital arteries (72). Treatment of RP and DU is similar. However, there are some drugs that may prevent DU but don't enhance healing. Management goals of DU include preventing tissue loss, avoiding/treating infection, treating pain and reducing ischemia. Evaluating the efficacy of treatment for RP is challenging as outcome measurements are not uniform and clinical trial endpoints might be improbable (73). The 2016 British Rheumatology Society and EULAR/EUSTAR guidelines only provide specific recommendations for first line treatment (74,75). Treatment algorithms for DU and RP were developed (76), often adding treatment rather than switching. We provide an integrative table suggesting different lines of treatment and the grade of recommendation for each choice according to the scientific evidence available (77) (Table 6). Side effects and dosing can be found in a separate review (78).

Non-pharmacological measures for RP and DU

Since RP plays a key role in the appearance of DU, some preventive general recommendations can be useful both for RP and DU. Alternative diagnoses such as atherosclerosis, thrombosis, hyperviscosity, or thoracic outlet syndrome are important to consider when suspected. When indicated specific diagnostic procedures should be undertaken. To reduce the frequency and severity of the attacks, avoiding some known RP triggers such as cold, trauma, stress, smoking, vibration injury or certain drugs (bleomycin, clonidine, ergot alkaloids) could be helpful. Proper

clothing in the cold is suggested such as warm clothing including a coat, mittens, wearing a hat, dry insulated footwear, hand/foot warmers, etc., based on expert opinion (79).

Alternative treatments

Non-conventional therapeutic approaches to RP treatment including acupuncture, antioxidants, biofeedback, essential fatty acids, Ginkgo biloba, L-arginine, laser, glucosaminoglycans and therapeutic gloves have inconclusive results. A systematic review showed that the quality of these studies was low and only ceramic impregnated gloves might improve RP minimally (80).

RP management

Dihydrophyridine calcium channel blockers (CCB) constitute the first line of treatment due to some clinical benefit, price, and acceptable side effects. A meta-analysis pooled 38 RCTs, including 554 patients with secondary RP most of whom had SSc (81). Nifedipine was the most studied CCB. CCBs significantly reduced the number and frequency of attacks. Higher doses may be more effective.

Phosphodiesterase-5 inhibitors (PDE5i) increase the availability of nitric oxide by inhibiting its metabolism. Side effects include hypotension, headache and they are contraindicated in patients taking nitrates. The price is significantly higher than for CCB, and PDE5i might not be reimbursed in some countries. Sildenafil and tadalafil reduced the frequency, duration, and severity (using the Raynaud condition score, a visual analog scale) of RP attacks in 6 RCTs in secondary Raynaud's (244 patients) (82).

Prostanoids constitute an advanced treatment. Side effects can include tachycardia, hypotension, jaw pain, GI side effects and headache. Intravenous iloprost is the only prostanoid that showed with improvement in RP in trials wich included over 300 SSc patients (83). Infusion dosing and days have variable schemes (84). Alprostadil seems to have negative long term benefit but may be an alternative (85).

Topical nitrates, like nitroglycerin or glyceryl trinitrate showed clinical or blood flow improvement according to a meta-analysis including approximately 200 patients with secondary RP (86). Headache might be a limiting side effect and combination with PDE5i is contraindicated. Losartan (an angiotensin II receptor blocker) (87), aspirin (88), atorvastatin (89), and fluoxetine (90) among others, may or may not be useful.

Surgical/Procedural treatments are limited to small observational studies for RP improvement in SSc patients performing a surgical digital sympathectomy or abdominal fat grafting in the fingertips. Finally, two small randomized clinical trials with conflicting results have studied the use of botulinum toxin injections on the interdigital web spaces (91,92).

Digital ulcer treatment and prevention

There is weak evidence for healing of digital ulcers. In one small randomized clinical trial comparing intravenous iloprost vs oral nifedipine, iloprost reduced the number of DU (83,84). Healing and prevention of DU often have CCB as first line therapy with limited data (75).

A meta-analysis on PDE5i including 3 studies (sildenafil and tadalafil) showed a beneficial effect in DU number reduction and DU improvement (93). Regarding DU prevention, results are unclear,

as one placebo controlled clinical trial with tadalafil was positive (94), while another with sildenafil was negative (95). Cost and off label use might limit its use.

Bosentan, a dual endotelin receptor antagonist, prevented new DU, especially in SSc patients with a DU count ≥4 at baseline (96). Unfortunately, it did not improve DU healing. Intravenous prostacyclin agonists seemed to yield better DU healing and decrease new DU but these were exploratory endpoints of RP RCTs (83,84). Atorvastatin in a small trial seemed to prevent new DU (89) but is not in guidelines for prevention of DU (75).

Surgical/procedural. Small trials support the use of fat grafting (97) for healing DU and botulinum toxin infiltrations for DU healing and prevention (92). There is anecdotal evidence to support digital sympathectomy for DU healing and prevention (98).

Wound care by specialized nurses and physicians may be needed. There is no standardized dressing protocol for SSc DUs. Antibiotics should be added only when infection is suspected, Pain needs to be controlled. In case of gangrene or osteomyelitis, amputation may be appropriate.

Conclusions

There are several proven organ-based treatments for SSc including improving skin and survival, treating ILD, PAH, Raynaud's and some evidence for DU prevention and treatment. However, proven treatment for many patients is lacking such as those with lcSSc or later dcSSc where immune modulation data are mostly absent, and several SSc complications. Even where treatment exists, there is often a slowing of progressive lung fibrosis or PH in patients with these diagnoses. However, research has improved the care of people living with SSc.

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Textbox 1. Predictors of severe lung fibrosis in SSc

- Diffuse pattern of skin involvement
- Less than three years' disease duration
- Autoantibody profile
  - Scl-70 (anti-topoisomerase-1 autoantibody)
  - Anti Th/to
  - Anti PM-Scl
  - Anti-U11/U12
- Severe gastro-oesophageal reflux
- Elevated KL-6
  - epithelial injury marker

Figure 2. Overview of management of lung fibrosis in systemic sclerosis (SSc-ILD)

The pathway for patients with SSc requires screening and early detection of ILD together with staging and risk stratification. Treatment generally involves immunosuppression and supportive measures together with antifibrotic therapies in appropriate cases. In established lung fibrosis using the published UK-RSA Staging system (25) can help making treatment decisions but longitudinal monitoring of lung function tests and CT imaging is important to detect progressive disease and assess treatment response.

Table 1 Screening in Systemic Sclerosis

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

1. Screen for pulmonary arterial hypertension (PAH) periodically/regularly
    a. Enrich a high risk group – longer disease duration, older, low diffusing capacity
    b. There are various screening algorithms including but not limited to: echocardiography, pulmonary function testing, ECG, (pro)brain naturetic peptide (BNP), 6 minute walk distance (6MWD)
2. Screen for interstitial lung disease (ILD)
    a. Patients who are Topoisomerase1 positive have a higher frequency of ILD
    b. Patients especially in the dcSSc subset
    c. Investigate: unidentified dyspnea
    d. Screening is by history, physical examination, chest radiograph, pulmonary function testing, and high resolution CT scan of the lungs where appropriate
3. Screen for scleroderma renal crisis (SRC) in early dcSSc patients
    a. Any patient who is RNApolymerase3 positive is at high risk of SRC
    b. For many, this antibody is not available so all early dcSSc should have regular blood pressure checks and encourage home BP monitoring
    c. Early dcSSc active patients with other organ involvement such as pericardial effusion, ILD, cardiac involvement may be at higher risk, male, tendon friction rubs, rapidly progressive skin involvement, use of glucocorticoids
4. Screen for other organ involvement and overlaps as appropriate
    a. 15% rule (1): 1 in 6 patients with SSc have prevalent digital ulcer(s), complicated digital ulcers ever, myositis or myopathy, sicca or Sjogren's, inflammatory arthritis
    b. 3% of SSc overlap with RA
    c. SSc may overlap with other CTDs: SLE, dermatomyositis, polymyositis, Sjogren's syndrome
    d. Primary biliary cholangitis (PBC) occurs in 8% of lcSSc, usually in anticentromere antibody positive, alkaline phosphatase is elevated, generalized pruritis may occur (99)

Table 2 Randomized trials in diffuse cutaneous systemic sclerosis
Table 2a. Randomized trials of standard immunosuppression

Trial (year) Intervention Phase N	Main inclusion criteria	Primary outcome	Mean disease duration	Antibody profile	Mean skin score at baseline	ΔmRSS
SLS II (2016)(9) MMF vs oral CYC Phase 2 N=142 (randomized 1:1)	ILD	ΔFVC at 24 mos	MMF 2.6 yrs CYC 2.5 yrs	ATA 46% RNAPIII 13% ACA 2%	MMF 15 CYC 14	Change at 24 mos (including dcSSc and lcSSc): MMF - 4.90 CYC -5.35 Difference 0.45 (95% CI -1.7, 2.6)
SLS I (2006)(8) Oral CYC vs PBO Phase 3 N=158 (randomized 1:1)	ILD	ΔFVC at 12 mos	CYC 3.2 yrs PBO 3.1 yrs		CYC 16 PBO 14	Difference at 12 mos in dcSSc: -3.06 (95% CI -3.54, -0.52, p=0.008)
Methotrexate (2001)(5) MTX vs PBO Phase NA N=71 (randomized 1:1)	DcSSc < 3 years duration	ΔmRSS (0-78) at 12 mos	MTX 6.3 mos PBO 7.3 mos		MTX 28 PBO 27	Difference at 12 mos: Complete case analysis: MTX – 6.3 PBO – 1.1 p < 0.17 ITT analysis: MTX -4.3 PBO 1.8 p<0.009
Methotrexate (1996)(6) MTX vs PBO Phase NA N=29 (randomized 1:1)	Disease duration < 3 years	ΔTotal skin score (0-104) at 24 weeks	MTX 3.2 yrs PBO 3.2 yrs	ATA MTX 53% PBO 58%	MTX 20.2 PBO 20.7	MTX -0.7 PBO 1.2 p=0.06

Table 2b. Randomized trials of targeted therapies and biologics with skin as primary endpoint

Trial (year) Intervention Phase N	Main inclusion criteria	Skin outcome	Mean disease duration	Antibody profile	Mean mRSS at baseline	∆mRSS
RISE-SSc (2020)(13) Riociguat vs PBO Phase 2b N=121 (randomized 1:1)	DcSSc Duration ≤ 18 months mRSS 10-22	∆mRSS at 12 mos	Riociguat 9.5 mos Placebo 8.6 mos	ATA 41% RNAP 22%	17	Mean ∆mRS at week 52: Riociguat: -2.09 Placebo: –0.77 LSM difference 2.34 (95% CI 4.99, 0.30; p=0.08)
ASSET (2020)(14) Abatacept vs PBO Phase 2 N=88 (randomized 1:1)	DcSSc and Duration ≤18 months with mRSS 10-35 or Duration 18-36 months with mRSS 15-45 and either progressive skin disease or tendon friction rubs	∆mRSS at 12 mos	Abatacept 20 mos Placebo:18 mos		Abatacept 23 Placebo 22	Adjusted mean ∆mRSS at week 52: Abatacept: -6.24 Placebo: -4.49 Adjusted mean treatment difference −1.75 (p=0.28)
FocuSSced (2020)(15) Tocilizumab vs PBO Phase 3 N=210 (randomized 1:1)	DcSSc Duration ≤5 years mRSS 10-35 units “Active” disease	∆mRSS at week 48	TCZ 23.1 mos Placebo 22.2 mos	ATA 50.5% RNAP 17.5% ACA 8.5%	TCZ 20.3 Placebo 20.4	LSM ∆mRSS at week 48: TCZ : -6.14 Placebo: - 4.41 Adjusted difference –1.73 (95% CI 3.78, 0.32; p=0·10)
Romilkimab (2020)(16) Romilkimab vs PBO Phase 2 N=97 (randomized 1:1)	DcSSc	∆mRSS at week 24	Romilkimab 19 mos Placebo 22 mos		Romilkimab 21 Placebo 21	LSM ∆mRSS at week 24: Romilkimab: –4.8 Placebo: –2.5 Mean difference –2.31 (90% CI –4.32, –0.31; p=0.0291, one-sided)
NOVESA (2020) (abstract only)(17) Ziritaxestat vs PBO Phase 2a	DcSSc mRSS > 10	∆mRSS at week 24	Ziri 18 mos Placebo 31 mos		Ziri 27 Placebo 23	LSM difference (95% CI) was –2.8 (–5.6, –0.1; p=0.04) in favour of ziri

N=33 (randomized 2:1)						
Belimumab (2017)(18) Belimumab vs PBO Phase 2 N=20 (randomized 1:1)	Duration < 3 years mRSS ≥16	∆median mRSS at week 52	Belimumab 11.7 mos Placebo 9 mos	Scl70 25% RNAP 50%	Belimumab 27 Placebo 28	∆median mRSS at week 52: Belimumab: - 10 Placebo: - 3 p-value 0.41

Table 2c Recent randomized trials in which skin was secondary outcome

al ervention ase	Inclusion Criteria	Primary outcome	Disease duration	Antibody profile	Mean mRSS	∆mRSS
nabasum 020)(19) nabasum vs O ase 2 42 ndomized 1:1)	DcSSc Duration ≤ 3 years or 3-6 years with elevated inflammatory markers, mRSS ≥ 16 progressive skin disease	Safety CRISS	Mean: Lenabasum 34 mos Placebo 34 mos		Lenabasum 24 Placebo 26	Lenabasum -4.6 Placebo -2.0 Mean difference −2.6 at week 16 (p=0.09, on-sided and p=0.17, two-sided)
NSCIS 019)(20) ntedanib vs O ase 3 576	ILD Duration < 7 years	∆FVC at week 52	Median: Nintedanib 3.4 yrs Placebo 3.5 yrs	ATA 61%	DcSSc: Nintedanib 17 PBO 16 LcSSc: Nintedanib 5 PBO 5	Adjusted mean ∆mRSS at week 5 Nintedanib −2.17 Placebo −1.96 in Difference −0.21, 95% CI −0.94 to 0.53

Table 3 Trials in stem cell transplantation in poor prognosis diffuse cutaneous systemic sclerosis (dcSSc)
Table 3a. Randomized trials of Autologous Hematopoetic Stem Cell Transplantation (AHSCT)

Trial Intervention Phase N	Inclusion Criteria	Skin outcome	Mean disease duration	Antibody profile	Mean mRSS at baseline	∆mRSS
"Cardiac Safe AHSCT" (2021)(21) Fludarabine-based regimen±RTX± IVIg Phase 2/3 N=42	i. dcSSc, mRSS > 14, lung or GI disease OR ii. lcSSc with mRSS < 14 AND lung disease AND iii. scleroderma heart disease	Flu/Cy/ATG vs Flu/Cy/ATG/RTX ± IVIG: ∆mRSS at 12 mos (secondary) Flu/Cy/ATG/RTX 1000 mg vs Flu/Cy/ATG/RTX 500 mg/IVIG: ∆mRSS at 6 mos (secondary)	Flu/Cy/ATG 69 mos Flu/Cy/ATG/RTX ± IVIG 71 mos	Flu/Cy/ATG ATA 8/14 RNAP 2/14 Flu/Cy/ATG/RTX ± IVIG ATA 11/28 RNAP 9/28	Flu/Cy/ATG 18 Flu/Cy/ATG/RTX 1000 mg 16 Flu/Cy/ATG/RTX 500 mg/IVIG 20	At 12 mos: Flu/Cy/ATG -11.7 vs Flu/Cy/ATG/RTX ± IVIG -9.4 At 6 mos: Flu/Cy/ATG/RTX 1000 mg -5.4 vs Flu/Cy/ATG/RTX 500 mg/IVIG -8.5
ASTIS (2014)(22) Non-myeloablative AHSCT vs CYC Phase 3 N=156	dcSSc, minimum mRSS ≥ 15, < 4 yrs of disease and heart, lung, kidney disease; or mRSS ≥ 20 and < 2 yrs of disease	∆mRSS at 24 mos (secondary)	AHSCT 1.4 yrs CyP 1.5 yrs	AHSCT ATA 67% CyP ATA 81%	AHSCT 25 CyP 26	AHSCT -20 CyP -9
ASSIST (2011)(23) Non-myeloablative AHSCT vs CYC Phase 2 N=19	i. dcSSc, mRSS > 14, lung or GI disease OR ii. lcSSc with mRSS < 14 AND lung disease	Secondary: ∆mRSS at 12 mos (secondary)	AHSCT 14 mos CyP 18 mos	AHSCT ATA 5/10 CyP ATA 7/9	AHSCT 28 CyP 19	AHSCT -13 CyP +3

Table 3b. Disease modification with AHSCT in active diffuse cutaneous systemic sclerosis

Trial Phase N	Mobilization	Conditioning	Global outcome	Results	Treatment-related deaths	Incidence of cancer
"Cardiac Safe AHSCT" (2021)(21) Phase 2/3 N=42	CYC 2 g/m^2	Flu/Cy/ATG Flu/Cy/ATG/RTX 1000 mg Flu/Cy/ATG/RTX 500 mg/IVIG	Primary: Overall survival at 1 year	Flu/Cy/ATG 86% vs Flu/Cy/ATG/RTX ± IVIG 96% p=0.25 Flu/Cy/ATG/RTX 1000 mg 93% vs Flu/Cy/ATG/RTX 500 mg/IVIG 100% p=NS	Flu/Cy/ATG 0 vs Flu/Cy/ATG/RTX ± IVIG 4% p=0.99	
SCOT (2018)(24) Phase 2 N=75	G-CSF only CD34+ selected	Treatment: Myeloablative AHSCT • TBI 800cGy • CYC 120 mg/kg • eATG 90 mg/kg Comparator: CYC 500-750 mg IV monthly x 12 months	Primary: Global rank composite score (GRCS; higher scores better) Secondary: Overall survival Event-free survival	Median GRCS (ITT) at 54 months: AHSCT 17 CYC -6 P=0.01 Overall survival (per-protocol) at 72 months: AHSCT 86% CYC 51% p=0.02 EFS (per-protocol) at 54 months: AHSCT 79% CYC 50% p=0.02	6% (both late, from MDS)	AHSCT 8% (including 2 late occurrences of myelodysplastic syndrome) CYC 3%
ASTIS (2014)(22) Phase 3 N=156	CYC 4 g/m^2 CD34+ selected	Treatment: Non-myeloablative AHSCT • CYC 200 mg/kg • rATG 7.5 mg/kg	Primary: Event-free survival Secondary: Overall survival	Event-free survival at 4 yrs: AHSCT 81% CYC 74% (hazard ratio 0.34, 95% CI, 0.16-0.74; p=0.006)	10% (within one year, predominantly from cardiac dysfunction)	AHSCT 0 CYC 4%

		Comparator: CYC 750 mg/m^2 IV monthly x 12 months		Overall survival at 4 yrs: AHSCT 83.5% CYC 74% (hazard ratio 0.29, 95%CI, 0.13-0.64; p=0.002)		
ASSIST (2011)(23) Phase 2 N=19	CYC 2 g/m^2 No selection	Treatment: Non-myeloablative AHSCT: • CYC 200 mg/kg • rATG 6.5 mg/kg Comparator: CYC 1 g/m^2 IV x 6 months	Secondary: Overall survival	No deaths in either group at mean 2.6 years follow up		

Table 4. Etiologies of Pulmonary Hypertension in Systemic Sclerosis

Etiology	World Health Organization Classification
Pulmonary arterial hypertension	Group 1
Pulmonary Hypertension due to left-sided heart disease	Group 2
Pulmonary Hypertension associated with interstitial lung disease	Group 3
Pulmonary veno-occlusive disease (PVOD)	Group 1
Pulmonary hypertension due to pulmonary embolism	If chromic thromboembolic pulmonary hypertension (CTEPH), then Group 4

Table 5. Pulmonary Hypertension Specific Therapies

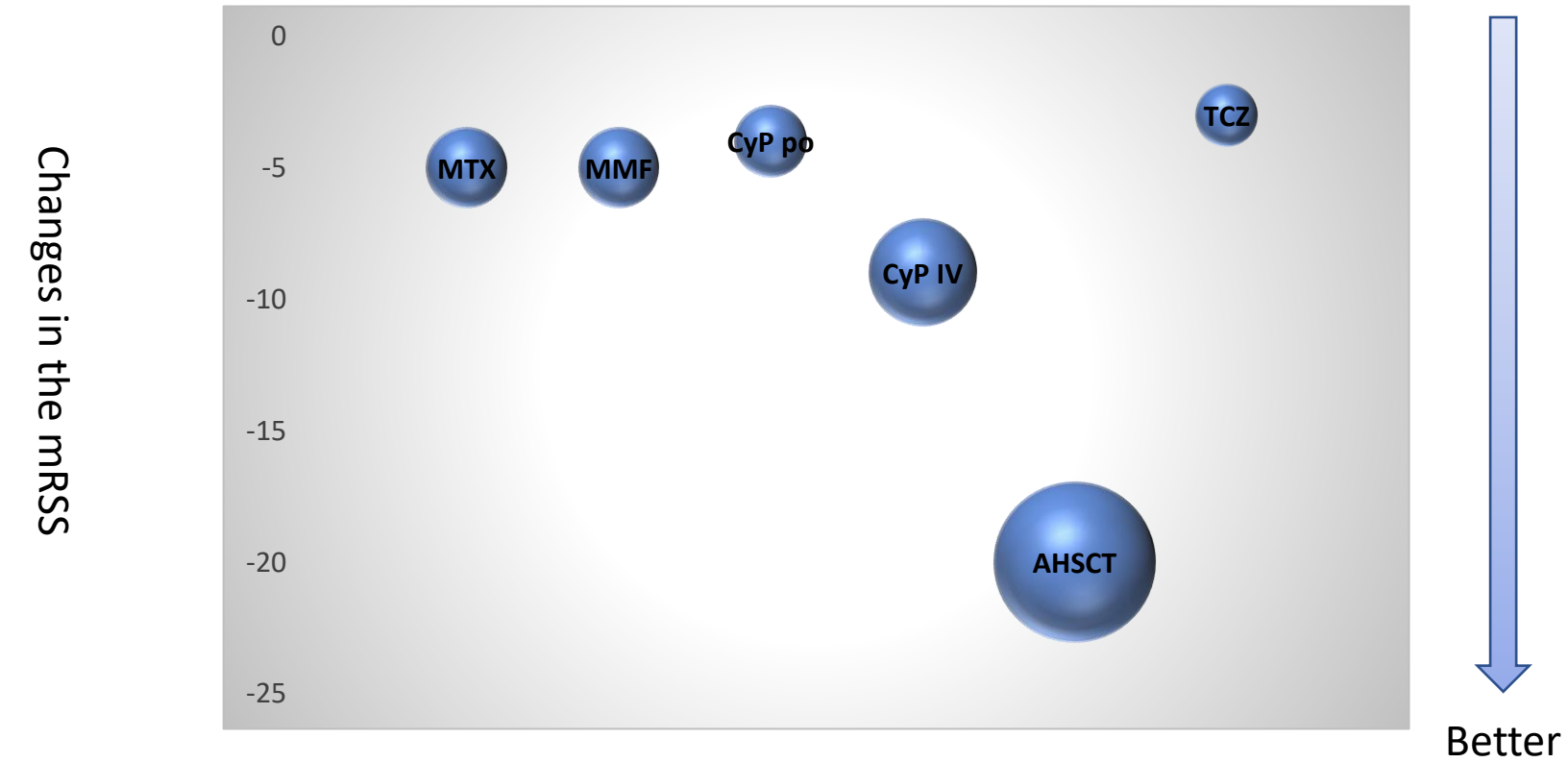
Therapy	Dosing
Endothelin Receptor Antagonists	
Ambrisentan	5 to 10 mg daily po
Bosentan	62.5 to 125 mg, two times daily po
Macitentan	10 mg per day po
Phosphodiesterase-5 inhibitors	
Sildenafil	20 mg three times daily po
Tadalafil	40 mg daily po
Prostacyclin analogue	
Epoprostenol	1 to 12 nanograms/kg/minute continuous intravenous infusion via central venous catheter Dose titrated up every one to two weeks
Iloprost	2.5 to 5 micrograms inhaled six to nine times daily
Selexipag	200 to 1600 micrograms twice daily po
Treprostinil	0.625 to 1.25 nanograms/kg/minute continuous intravenous infusion via central venous catheter or continuous subcutaneous infusion
Soluble guanylate cyclase stimulator	
Riociguat	Initial dose 0.5 to 1 mg three times daily orally, titrated up by 0.5 mg three times per day every two weeks to a maximum dose of 2.5 mg three times daily po

Table 7. Management of Raynaud's phenomenon and digital ulcers in systemic sclerosis

	First line	Second line	Third line	Ancillary
Raynaud's phenomenon in SSc	CCB	PDE5i	Prostanoids	Nitroglycerine
				ARB
				Aspirin
				Botulinum toxin
				Fluoxetine
				Pentoxifylline
				Digital sympathectomy
				Anticoagulation
				Fat grafting
				Digital sympathectomy[H,P]
Digital ulcers in SSc	CCB[H,P]	Bosentan[P]	Prostanoids[H,P]	Analgesics
		PDE5i[H]		Atorvastatin[H,P]
				Botulinum toxin[H,P]
				Fat grafting[H]
				Digital sympathectomy[H,P]
General suggestions	-Avoid cold and trauma -Proper clothing -Smoking cessation -Rule out macrovascular involvement			
Selected situations	-Consider antibiotics, wound care and pain management in case of infection -Treatment with oral antibiotics in DU only if an infection is suspected -In the event of an abscess or osteomyelitis surgical debridement should be considered -Digit or limb amputation might be warranted if gangrene is present			

Recommendation expert consensus: strong (green), possible (yellow), weak or historical evidence (red)
[H]:Effective in digital ulcer healing; [P]:Effective in digital ulcer prevention; CCB: calcium channel blockers; PDE5i: phosphodiesterase-5 inhibitors; ARB: angiotensin receptor blocker

Treatment effect in systemic sclerosis on skin



Immune suppressive treatment and their effects on skin in SSc

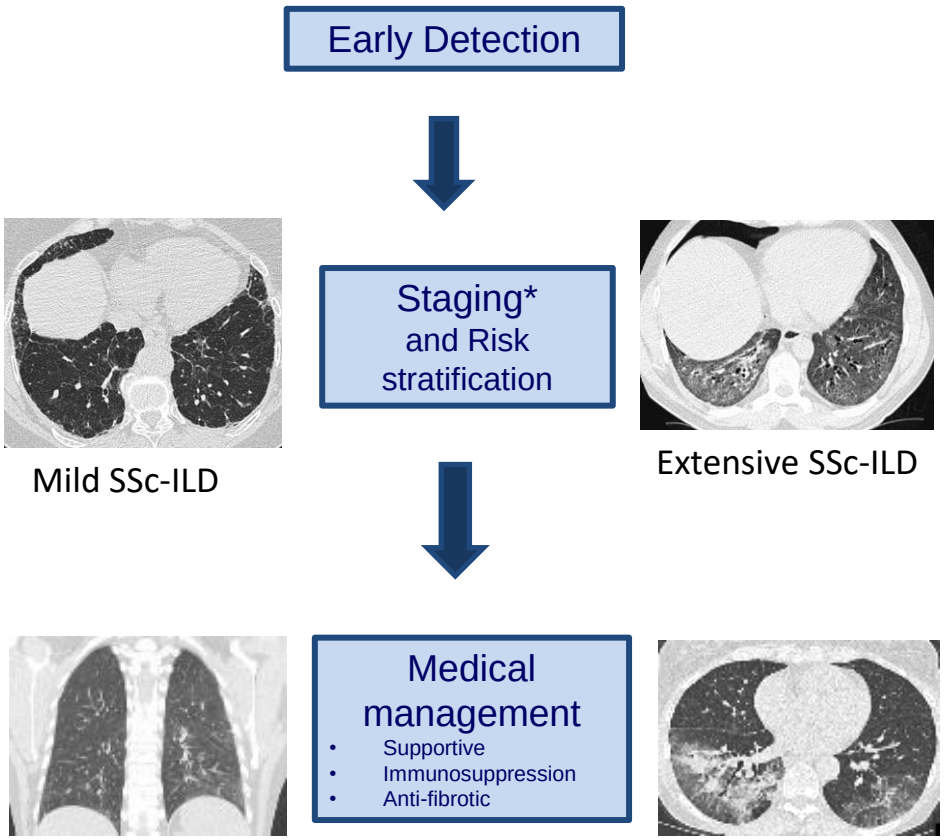
Modified Rodnan skin score mRSS (0 to 51 points)

MTX methotrexate, MMF mycophenolate mofetil, CyP cyclophosphamide, po oral, IV intravenous, TCZ tocilizumab, AHSCT autologous hematopoietic stem cell transplant, SSc systemic sclerosis

Figure 1

Overview of management of lung fibrosis in systemic sclerosis (SSc-ILD)

- Early detection
  - Serology, subset, PFT, HRCT, clinical features
- Staging
  - UK-RSA Staging system applied[1]
- Risk stratification
  - Investigational features of progressive or severe lung fibrosis
- Immunosuppression
  - Oral MMF (2g/d) or azathioprine (150mg/d)
  - Increase MMF to 3g/day or iv cyclophosphamide (600mg/m^2)
  - Rituximab (currently for overlap CTD)
  - Tocilizumab*
- Antifibrotic therapy
  - Nintedanib
  - Tocilizumab *
  - ?Pirfenidone
  - Eligibility for clinical trial protocols
- Rigorous anti-reflux therapy
  - PPI, H2 antagonist, prokinetic drugs
  - Raising head of bed, no food after supper
  - Esophageal dilations when required
- Other interventions
  - Oxygen
  - Exercise
  - Antibiotic prophylaxis – i.e. azithromycin 250mg x3/week
  - Identification and treatment of pulmonary hypertension
  - Consider referral for lung transplantation



Serial PFT and repeat HRCT to determine progression and need for treatment