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Evidence-based management of rapidly progressing systemic sclerosis

Dinesh Khanna, MD, MS, Assistant Professor of Medicine In-Residence [a,*], Christopher P. Denton, PhD, FRCP, Professor of Medicine [b]

[a] UCLA Scleroderma Program, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[b] Centre for Rheumatology, Royal Free Hospital, London, UK

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Systemic sclerosis has the highest case-specific mortality of any of the auto-immune rheumatic diseases, as well as causing major morbidity. It is a major clinical challenge and one that has previously provoked substantial nihilism due to the limited therapeutic options available and the perceived lack of evidence for clinical effectiveness of those treatments that are currently in use. However, this situation is changing; there are emerging data supporting efficacy for some treatment approaches for this patient group together with a growing number of exciting potential novel approaches to treatment that are moving into the clinical arena. Some of the recent clinical trials are reviewed and discussed in detail.

The major mortality and much of the morbidity of systemic sclerosis (SSc) arises through the development of specific complications of the disease including organ-based complications such as cardiopulmonary, renal or gastrointestinal manifestations. The frequency and diverse nature of these complications makes systematic assessment and long-term follow up essential to good management of SSc. In addition, it is essential that accurate baseline assessment of each case is undertaken to define the extent and pattern of disease and to ascertain the likelihood of progression and risk of severe life-threatening complications. Current approaches to assessment and follow-up of severe progressive SSc are summarised below.

* Corresponding author. Division of Rheumatology, Department of Medicine, David Geffen School of Medicine 1000 Veteran Avenue, Rm 32-59 Rehabilitation Building, Los Angeles, CA 90095, USA. Tel.: +1 310 825-3061; Fax: +1 310 206 8606.
E-mail address: dkhanna@mednet.ucla.edu (D. Khanna).

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Assessment of skin disease

Skin fibrosis is a hallmark feature of SSc. Depending on the extent of skin sclerosis, the disease is classified into two major subsets – limited cutaneous SSc (limited SSc) when only skin distal to the elbows and knees (with or without face involvement) is affected and diffuse cutaneous SSc (diffuse SSc) when the skin thickening includes distal areas and also spreads proximally. These patients are also at risk from other complications of SSc.

The majority of cases of rapidly progressive SSc can be classified to the diffuse subset as there is almost always progression to involve proximal limbs or trunk. Nevertheless, it is important to consider that almost all cases will, at some point, have had less extensive skin involvement. For this reason, determining the duration of disease, as defined by the first non-Raynaud disease sign or symptom (such as joint pain and swelling, reflux disease and digital ulcer) is critical to assessment of cases of SSc. In addition, tendon friction rubs (TFRs), a 'leathery crepitus' on palpation of knees, wrists, fingers and ankles during motion is a significant predictor of developing diffuse SSc [1]. Before presenting the evidence for efficacy of the different agents in treatment of scleroderma skin disease, it is important to consider its relation to internal organ involvement in SSc patients and current methods of assessment that have shed insight onto the natural history of skin sclerosis in diffuse SSc.

Patients with early diffuse SSc tend to have worsening of their skin thickness over the first 1–3 years after disease onset. During this phase of skin thickening, patients develop internal organ involvement (Table 1). In addition, worsening skin thickness is a predictor of morbidity and mortality. Therefore, current efforts are directed in the early diagnosis of internal organ involvement and institute therapies. Fig. 1 summarises our current diagnostic approach in patients with SSc. After 1–3 years of worsening skin thickening, the skin tends to soften irrespective of treatment [2,3]. This has been noted both in clinical practice and randomised controlled trials (RCTs) of diffuse SSc [4]. Although softening of skin is associated with improved survival [5], this relationship between change in skin score and internal organ involvement is not straightforward, which questions its validity as a primary outcome in trials assessing treatment efficacy. With that background, the modified Rodnan skin score (MRSS), a measure of skin thickness has been used as the primary outcome measure in most of these trials, as it is feasible, reliable, valid and responsive to change in multicentre clinical trials[6] and is routinely performed in clinical practice at scleroderma centres. It assesses skin thickness in 17 body surface areas (face, chest, abdomen, and right and left fingers, hands, forearms, upper arms, thighs, lower legs and feet) [7]. Each area was assessed for thickness on a 0–3 scale (0 = normal, 1 = mild but definite thickening, 2 = moderate skin thickening and 3 = severe skin thickening). The total score (the sum of scores from all 17 body areas) ranges from 0 to 51; a score of $\geq$20 is associated with poor prognosis.

Although the MRSS is widely used as a clinical and research tool for the assessment of skin disease in SSc, there have been attempts to develop new tools and to correlate these novel approaches with skin score as well as structure and histology of skin, as observed on biopsy specimens. Assessment of biomechanical properties has shown promise including the assessment of skin elasticity using BTC-2000 suction device [8]. Similarly, it has been demonstrated that changes in skin score correlate well with durometer measurements [9]. The use of these devices may provide a simple way of assessing skin hardness while having the advantage of potentially less variability between observers and the development of a continuous variable rather than the categorical skin score.

Table 1
Diffuse vs. Limited Scleroderma -Distinguishing Features.

Diffuse	Limited
• ILD (severe in 15%)	• ILD (severe in 15%)
• Heart (severe in 10%)	• Minimal heart
• Pulmonary arterial hypertension (5-10%)	• Pulmonary arterial hypertension (10-15%)
• Kidney (10–15%)	• Minimal kidney
• Large joint contractures	• Concurrent Primary biliary cirrhosis (6-8%)
• Worse survival overall	

*ILD=interstitial lung disease

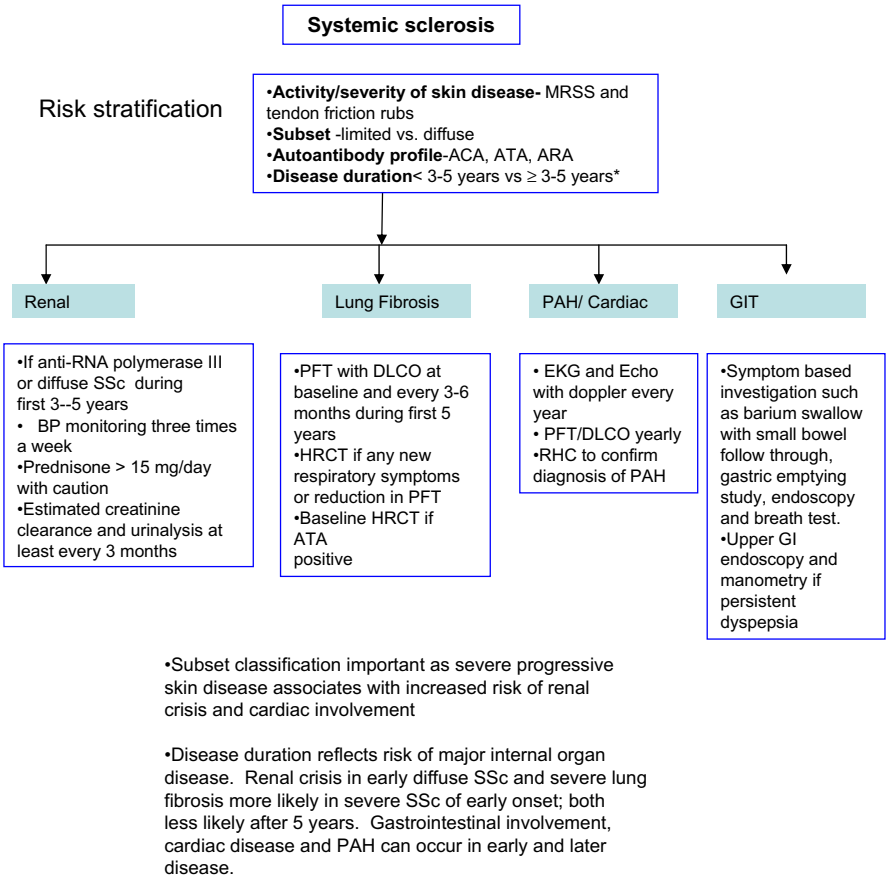


Fig. 1. Diagnostic approach in patients with systemic sclerosis.

High-frequency ultrasound provides a tool to measure skin thickness and has been shown to reflect skin score [10] while providing potential information about the biochemical composition of skin and the degree of oedema. These tools are likely to be more applicable to clinical trials than for routine practice.

Bottom line

The extent of skin involvement differentiates limited versus diffuse SSc. MRSS continues to be primary outcome measure to assess skin involvement in clinical trials and practice but disease duration needs to be considered when interpreting change in MRSS in diffuse SSc. Worsening skin thickness is a predictor of morbidity and mortality.

Renal involvement in rapidly progressive SSc

The pattern of kidney manifestations in SSc may be divided into scleroderma renal crisis (SRC), chronic kidney disease and inflammatory renal pathology. However, SRC is the most important renal

complication in SSc and occurs in 10–15% of patients with diffuse SSc and very rarely (1–2%) in limited SSc [11]. The mortality among patients with SRC remains high despite the early treatment with angiotensin-converting enzyme (ACE) inhibitors [12], and clear evidence that ACEi therapy has a dramatically beneficial effect on early death rate. The typical features of SRC comprise new onset of significant systemic hypertension (>150/85 mmHg) and decreased renal function (≥30% reduction in calculated glomerular filtration rate (eGFR)). In approximately 20% of the patients, the diagnosis of SRC precedes the diagnosis of SSc; therefore, early identification of SSc is highly important [11]. Other clinical features of SRC include either non-specific systemic symptoms (headaches, fever, malaise and exertional breathlessness) or signs and symptoms suggestive of end-organ damage (hypertensive retinopathy and encephalopathy, pulmonary oedema and acute renal failure). Arrhythmia, myocarditis and pericarditis, if present, may indicate poorer prognoses. Microangiopathic haemolytic anaemia (MAHA) and thrombocytopaenia are common, estimated to be 60% and 50%, respectively, but coagulopathy is rare [13]. Urinalysis commonly demonstrates non-nephrotic range proteinuria and haematuria, with granular casts evident on microscopy. Risk factors that may predict development of SRC have been identified. Patients with early diffuse SSc are at greatest risk with the estimated median duration of SSc at SRC diagnosis being only 8 months. Rapidly progressive skin thickening and TFRs represent other independent risk factors. An estimated 66% of SRCs develop within a year of diagnosis of SSc [11]. SRC has been linked to corticosteroid therapy; many patients had received corticosteroids prior to presentation. A recent history of high-dose corticosteroid use (e.g., prednisolone or equivalent at >15 mg day^{-1}) may precede SRC diagnosis[13] and studies suggest that even low doses of corticosteroids may be associated with SRC [14]. Although there is no evidence of a causal effect, this observation necessitates extreme caution in using corticosteroids in diffuse SSc. The incidence of extensive skin and renal disease are also significantly higher in patients with SSc-specific anti-RNA polymerase antibodies (I and III) [15], which were present in 59% of SRC patients in one cohort [10]. This represents the single strongest clinical association of any scleroderma-specific autoantibody. Commercial anti-RNA polymerase antibodies III ELISA methods are now available, which makes identification of these antibodies simpler.

Bottom line

Consider anti-RNA polymerase antibodies III in all patients with diffuse SSc. Encourage 3 times per week blood pressure monitoring at home in early diffuse SSc (first 3 years). Moderate-to-high dose prednisone (>15 mg day^{-1}) should be used with caution and ACE inhibitors should be instituted immediately after the diagnosis of renal crisis. Role of ACE inhibitors for prevention of SRC is not clear.

Interstitial pulmonary fibrosis

The commonest forms of interstitial lung disease in SSc are histologically classified as usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). Investigation and assessment of interstitial lung disease in SSc focusses on early detection, severity assessment and determination of progression that is best performed by regular pulmonary function tests (PFTs). High-resolution computed tomography (HRCT) imaging remains the most valuable tool for detection of early lung fibrosis [16]. Interstitial lung disease (ILD) develops insidiously and generally progresses to fibrosis. The majority of decline in lung function occurs in a small (15%) of patients and in those, the majority decline during the first 4 years of disease. Because lung fibrosis is irreversible, early diagnosis is vital. The most common initial symptoms are breathlessness, especially on exertion, and a dry cough. Chest pain is infrequent and haemoptysis rare; either one suggests the presence of additional pathology. On physical examination, the most frequent finding is bilateral inspiratory crackles at the lung bases. Radiographic features consist of reticulonodular shadowing, usually symmetrical and most marked at the lung bases. However, because the chest radiograph is an insensitive indicator of early pulmonary fibrosis, it should be used only as an initial screen or to exclude infection or aspiration. Mildly symptomatic SSc patients often have normal chest radiographs despite interstitial lung disease, and PFTs are more discriminatory. The single-breath diffusion capacity (DLCO) is abnormal in over 70% of patients with diffuse SSc, including asymptomatic patients with no complaints and an unremarkable chest radiograph [17].

A reduction in DLCO is the earliest detected abnormality in SSc patients who go on to develop ILD. The combination of normal lung volumes but reduced gas transfer in the face of normal chest imaging is suggestive of pulmonary vascular disease [18].

The application of HRCT has been of immense value for the definition and assessment of diffuse lung diseases and has revealed the character and distribution of fine structural abnormalities not visible on chest radiographs [19]. Pleural disease and mediastinal lymphadenopathy may also be identified. It is important to perform HRCT in both prone and supine positions, particularly in patients with early SSc, to exclude the contribution of gravity to the radiographic appearances from vascular and interstitial pooling in the dependent areas. In addition to identifying early disease, HRCT can be used to quantify the extent and delineate the pattern of lung abnormality. Recently published data from a well-characterised cohort of cases of SSc-associated lung fibrosis has used threshold analysis to determine the association between extent of disease on a formally scored HRCT and outcome. This has led to the development of a simple staging algorithm that uses simple lung function variables and rapid evaluation of HRCT to discriminate a mild form of extensive lung fibrosis [20]. Those in the mild group require close observation but not necessarily intervention with currently available immunosuppressive agents (see below). In the future, it is likely that markers of epithelial damage such as DTPA clearance or serum KL-6 will also be useful in stratifying cases of lung fibrosis in SSc and determining the likelihood of progression although bronchoalveolar lavage does not appear to add to information from lung function or HRCT [21].

Bottom line

PFT with DLCO should be performed at baseline and every 3–6 months during first 4 years of onset of disease, irrespective of limited or diffuse SSc. HRCT of lungs is a useful tool to characterise fibrosis as recent studies showed a positive association of degree of baseline lung fibrosis and subsequent decline in forced vital capacity (FVC)% predicted and mortality. Bronchoalveolar lavage is not useful in clinical care.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH), defined as an elevation in the mean pulmonary artery pressure >25 mmHg at rest with normal pulmonary capillary wedge pressure (PCWP) on right heart catheterisation, occurs in both limited and diffuse cutaneous forms of SSc, and has major mortality. The outcome in SSc-associated pulmonary hypertension is considerably worse than that of idiopathic pulmonary hypertension [22]. This may reflect co-morbidity or differences in underlying pathogenetic mechanisms. In SSc, PAH due to intrinsic fibroproliferative abnormalities in the pulmonary vasculature, pathologically indistinguishable from idiopathic PAH, is most common, with a prevalence of approximately 10–15%. It is important to consider that left-heart disease, diastolic dysfunction, severe systemic hypertension and pulmonary hypertension in association with pulmonary interstitial fibrosis may also occur in SSc. However, PAH in SSc also occurs in the context of pulmonary fibrosis, and typical histological appearance of PAH can be found in lung biopsies from SSc patients with lung fibrosis. Indeed, it has been suggested that it is co-existent vasculopathy that determines outcome and survival in many cases of SSc-associated pulmonary fibrosis [23]. Although considered a late complication, recent data show PAH is associated with both early and late SSc [24].

PAH may remain asymptomatic until quite advanced. The initial symptoms include exertional breathlessness, and less often chest pain or syncope. In patients with SSc, PAH is typically discovered during regular monitoring with PFT, Doppler echocardiography and electrocardiography (ECG) examinations. An isolated reduction in DLCO with preservation of lung volumes (FVC)/DLCO ratio> 1.4–1.6 is suggestive of PAH [18]. Definitive diagnosis requires exclusion of thrombo-embolic disease by ventilation:perfusion lung scan, spiral CT scan or pulmonary angiography and haemodynamic demonstration of a mean pulmonary artery pressure >25 mmHg at rest. There is a strong correlation between peak pulmonary artery pressure estimated by Doppler echocardiography and direct measurements at right-heart catheterisation, except when pulmonary artery pressures are in the 30–50 mmHg range [25]. Cardiac catheterisation is essential because it allows the recognition of

pulmonary venous hypertension and the precise determination of pulmonary vascular resistance, cardiac output (cardiac index) and pulmonary artery pressures. Serum levels of the N-terminal pro-brain natriuretic peptide (NT-Pro-BNP) may be helpful for screening and monitoring PAH. The levels of serum BNP correlate with survival in patients with SSc-associated PAH [26]. Treatment options for PAH in SSc are discussed below, together with the results of recent RCTs that have included cases of PAH–SSc.

Bottom line

A high index of suspicion is required in SSc. Echocardiogram with Doppler is a good screening tool but associated with false negative (in early PAH) and false positive (in pulmonary fibrosis) rates. BNP or N-TPro-BNP is a useful biomarker. Isolated decline in DLCO $<$ 55% and/or FVC/DLCO% ratio of $>$1.4–1.6 is a specific predictor of PAH. RHC is required to confirm the diagnosis.

Cardiac involvement

Cardiac involvement is a major factor determining mortality in SSc. As with other complications, it is associated particularly with rapidly progressive diffuse SSc but current limitations in detection and diagnosis mean that the precise frequency of significant cardiac involvement in SSc has been difficult to ascertain [27]. Moreover, one potential consequence of cardiac involvement is reduction in the ability to cope well with the intercurrent haemodynamic of cardiac stress such as that due to electrolyte disturbance, fluid shift or acidosis so that these other complications become much more severe. In contrast to myocardial involvement, abnormalities of the pericardium are relatively easy to detect by virtue of the formation of a pericardial effusion. Up to 35% of SSc patients are found to have haemodynamically insignificant effusions. Larger effusions are less frequent. Pericardial effusions in SSc are often associated with complications such as PAH and SRC, where they may precede the onset of renal failure.

Myocardial involvement may be due to myocardial ischaemia, fibrosis and myocarditis. Potential mechanisms for ischaemic damage include coronary arterial vasospasm, small vessel disease and occlusive coronary artery disease. However, histological examination of the coronary arteries in SSc has not shown excess fibromuscular hypertrophy. Moreover, the frequency of angiographically proven coronary artery disease does not appear to be increased[28] although recent data showed increased asymptomatic coronary calcium, especially in patients with limited SSc than in age- and sex-matched controls [29]. An association between cardiac mortality and myositis has been demonstrated in SSc, raising the possibility of associated myocarditis. Myocarditis may explain the frequent occurrence of exudative pericardial effusions in SSc, endocardial lesions found on histology and ECG evidence of conducting tissue damage. Although, at present, there are few published data suggesting low-grade myocarditis leading to diastolic dysfunction and the other cardiac abnormalities in SSc, we have described excess of troponin T release [27]. An attractive hypothesis is that low-grade intermittent myocardial inflammation causes subtle myocardial damage in the first few years when the disease process is most active, leading to mild fibrosis with diastolic dysfunction in later stages. Gated magnetic resonance imaging (MRI) may be a useful tool for detecting myocardial fibrosis, and for quantitation of abnormal contraction or relaxation [30]. The frequent occurrence of diffuse interfascicular fibrosis in SSc may be challenging to detect by current imaging methods. Tissue Doppler studies and cardiac MRI, together with more advanced echocardiographic methods, are likely to be valuable in defining abnormalities in SSc cardiac structure and function; but, at present, the definition of clinically important abnormalities is more challenging. Post-mortem studies consistently point to discrepancy between cardiac involvement and clinical and imaging abnormalities.

Gastrointestinal manifestations

The gastrointestinal tract (GIT) is the most commonly involved internal organ system (approximately 90%) in SSc, and gastro-oesophageal manifestations are the most frequent [31]. Despite major

morbidity, only a minority of cases have life-threatening complications. Severe involvement of the small intestine typically occurs in patients with established SSc. At its most severe, small intestinal involvement leads to recurrent episodes of intestinal pseudo-obstruction due to ileus with dilated small bowel loops. Small bowel bacterial overgrowth complicating hypomotility results in recurrent diarrhoea and bloating, and in more severe cases leads to malabsorption, weight loss, malnutrition and cachexia. The classic symptoms are change in bowel pattern, with frequent loose, floating, foul-smelling stools and abdominal distension. Management of advanced bowel disease includes rotating antibiotics, stimulation of intestinal motility with prokinetic agents, such as erythromycin or domperidone, and supplemental alimentation. In the short term, nocturnal feeding to maintain nutrition and a nasogastric or nasojejunal feeding tube may be effective. Longer-term nutritional supplementation requires percutaneous jejunostomy, or gastroscopy if stomach emptying is not delayed. When malnutrition is the major problem, intermittent parenteral hyperalimentation may be required [32]. Recent European League against Rheumatism/EULAR Scleroderma Trials and Research Group (EULAR/EUSTAR) guidelines recommend PPI should be used for the prevention of SSc-related gastro-oesophageal reflux disease (GERD), oesophageal ulcers and strictures; prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc.); and when malabsorption is caused by bacterial overgrowth, rotating antibiotics may be useful [33].

Bottom line

GIT involvement in SSc is very common and has a major impact on the quality of life. A proactive approach is suggested. The cornerstones of GIT examination are imaging studies and laboratory tests; physical examination of the GIT system yields little information [34]. For motility disorders, a barium contrast study is the preferred radiographic procedure, and for assessment of mucosal disease, endoscopy is the preferred test. Body weight or body mass index (BMI) should be collected in patients with SSc.

Autoantibodies in assessment of SSc

The role of autoantibodies in SSc is still unclear, although there is a growing body of evidence that antibodies are potential markers of organ-based complications that impact on disease outcome. Easier assays and more systematic evaluation offers real potential in risk stratification of SSc cases since most patients can be defined by their serological profile at initial presentation [35]. The three most frequent SSc-associated antibodies – anti-centromere antibodies (ACAs), anti-topoisomerase (ATA) and anti-RNA polymerase III antibodies (ARAs) are found in over 50% of patients with the disease. They are highly specific and generally mutually exclusive. Strong associations between antibody type and pattern of organ complications and survival in SSc patients exist and it is now widely accepted that autoantibodies are stronger predictors of disease outcome and organ involvement than of disease subset, making antibody testing essential for disease assessment. Due to the specific organ disease associations, autoantibodies can be used also as predictors of survival in SSc patients. For example, ATA-positive subjects have been demonstrated to have significantly higher mortality than other autoantibodies, which is related to the strong association with interstitial lung disease. Antibodies associated with features of overlap syndromes, such as anti-Pm/Scl, anti-U1RNP and anti-Ku generally predict milder disease.

Controlled studies recently reported for systemic sclerosis

Overall

High-dose immunosuppressive therapy (HDIT) and autologous haematopoietic stem cell transplantation (HSCT)

Patients with severe SSc have been evaluated using HSCT. The underlying hypothesis is that upfront intensive immunosuppression would ablate immune responses driving disease activity, and the infused haematopoietic progenitors, depleted *in vitro* of disease-causing mature lymphoid elements (using CD34-selection), may then be able to generate a new non-autoreactive immune system [36].

Inclusion criteria included: ≤65 years, early (≤4 years), diffuse SSc and significant visceral organ involvement, including progressive pulmonary disease with a decrease of at least 15% in FVC or DLCO in the previous 6 months, with any skin involvement [36,37]. The eligibility criteria selected patients with a mortality risk from SSc of approximately 50% at 5 years with conventional treatment. Of the 34 patients, 27 survived 1 year. Of these, 17 patients had sustained responses at a median follow-up of 4 (range, 1–8 years) years with stabilisation of their FVC and DLCO. There were 12 deaths during the study (transplantationrelated, eight; SSc related, four). The estimated progression-free survival was 64% at 5 years.

Based on these and other preliminary findings, a multicentre, randomised trial of CYC versus HSCT in Europe is underway: Autologous Stem cell Transplantation in Scleroderma (ASTIS). As of July 2008, 122 patients have been randomised in 25 centres from 10 countries and allocated to either high-dose immunoablation followed by autologous stem cell transplantation or cyclophosphamide pulse therapy (http://www.astistrial.com/ASTISnews.HTM accessed 17 August 2009). All patients were enrolled because of severe SSc with extensive skin thickening and involvement of heart, lung or kidneys.

Another National Institutes of Health (NIH)-sponsored study (Scleroderma: Cyclophosphamide or Transplant (SCOT; www.sclerodermatrial.org)) will randomise 113 patients to either HSCT or CYC (57 randomised as of 18 August 2009) with a primary composite end point (death, organ failure, change FVC, Scleroderma Health Assessment Questionnaire (SHAQ) and MRSS) at 54 months after randomisation. Patients with early diffuse SSc (≤5 years) and lung or renal involvement are eligible to participate.

Bottom line. HDIT and autologous HSCT is an option for patients with early diffuse SSc with progressive pulmonary fibrosis and/or renal involvement. Patients should be referred to ASTIS or SCOT studies to assess the efficacy and safety of HSCT versus high-dose monthly CYC.

Skin

The diffuse SSc condition is a subset of SSc in which more rapid change in skin involvement occurs, making it more feasible to study in relatively short clinical trials. It is for this reason that diffuse SSc has been the focus of investigation in many clinical trials [38,39]. As described before, MRSS, a measure of skin thickness has been used as the primary outcome measure in most of these trials [6]. Recent studies have assessed different biological agents for the treatment of skin thickness.

Anti-transforming growth factor (TGFβ1) antibody

A human recombinant neutralising TGFβ1 antibody was tested in a multicentre phase I/II trial [40]. The study recruited patients with early diffuse SSc (<18 months; mean disease duration of 6–9 months) and was designed as a safety study. Patients were randomly assigned to the placebo group or to one of three TGFβ1 antibody treatment groups: 10 mg kg^{-1}, 5 mg kg^{-1} and 0.5 mg kg^{-1}. Infusions were given on day 0 and weeks 6, 12 and 18. There were four deaths in the TGFβ1 antibody group and no deaths in the placebo group. All deaths in the study were attributed to the progression of SSc. There were no differences in the TGFβ1 antibody versus placebo in the MRSS or in changes in either the FVC or DLCO.

Tyrosine kinase inhibitors

Imatinib mesylate (Gleevec) is currently approved for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours. Imatinib mesylate is a small molecule tyrosine kinase inhibitor that binds to the c-abl and blocks efficiently its tyrosine kinase activity; c-abl is an important downstream signalling molecule of TGFb [41,42]. In addition, imatinib mesylate interferes with PDGF signalling by blocking the tyrosine kinase activity of PDGF receptors. In the tight skin 1 mouse model and bleomycin-induced dermal fibrosis, imatinib prevented fibrosis and induced regression of established fibrosis. In another proof-of-concept study, two patients with early diffuse SSc had a clinical improvement in MRSS and the immunohistochemical analyses of skin biopsy specimens demonstrated reductions of phosphorylated PDGFR-beta and Abl with imatinib therapy. Recently reported preliminary outcome from a number of prospective pilot

studies suggests that imatinib treatment in SSc is generally tolerated but there is no unequivocal message of significant efficacy.

Recombinant human relaxin

Relaxin is a naturally occurring protein with anti-fibrotic properties: it down-regulates collagen production and increase collagen degradation [43]. A phase II RCT suggested that relaxin was safe and clinically effective in improving skin disease and functional disability [44]. To replicate this finding, subjects with diffuse SSc (disease duration of $\leq$5 years) were enrolled in an RCT evaluating the safety, efficacy and dose-response effect of continuous subcutaneously infused recombinant human relaxin [45]. A total of 231 patients were randomised in the 24-week study to receive either relaxin (25 $\mu g\ kg^{-1}\ day^{-1}$, 10 $\mu g\ kg^{-1}\ day^{-1}$) or placebo in a 2:1:2 ratio for 24 weeks. The primary outcome measure, the MRSS, was similar between the three groups at baseline and at weeks 4, 12 and 24 ($p = NS$). Secondary outcome such as functional disability was similar in all three groups and the FVC significantly decreased in the relaxin groups ($p < 0.04$). The discontinuation of relaxin (both doses) at week 24 led to statistically significant declines in creatinine clearance and serious renal adverse events (defined as either doubling of baseline serum creatinine, renal crisis or grade 3 or 4 hypertension), which were seen in seven patients who had received relaxin therapy but in none who had received placebo ($p = 0.04$). With a renewed interest in relaxin for management of heart failure, pre-eclampsia, or induction of labour, patients may require close follow-up after they cease relaxin therapy.

Oral bovine type I collagen. This phase III RCT assessed the efficacy and safety of oral bovine type I collagen (500 $\mu g\ day^{-1}$) versus placebo [46]. The premise was that oral collagen will induce immune tolerance and will lead to improvement in skin thickness as assessed by MRSS. This trial randomised 168 diffuse SSc patients with baseline disease duration of up to 10 years. The results showed no statistically significant difference in the change in the skin score at month 12 or 15 in the two groups. However, in a subanalysis of the available data at month 15, the CI-treated group of patients with late-phase diffuse SSc (>3–10 years) experienced a significant reduction in the MRSS compared with that in the placebo-treated patients with late-phase diffuse SSc (change in MRSS at month 15; $p = 0.0063$). The authors postulated that immune-mediated fibrosis in the early phase of the disease may be less susceptible to modulation by CI than are those in the late phase of the disease. A future study is being planned to assess the late-phase diffuse SSc.

Other therapies. Investigators have recently assessed infliximab and rituximab in open-labelled trials without much clinically beneficial effect on MRSS. Rapamycin was compared to methotrexate in a single blind trial and was shown to have similar efficacy and toxicity.

Bottom line. Two randomised controlled trials have shown that low-dose methotrexate (MTX) is more effective than placebo in patients with active SSc in improving skin thickness. Based on these studies, recent EULAR/EUSTAR guidelines recommend considering the use of MTX in the treatment of skin manifestations in early diffuse SSc [33]. Oral cyclophosphamide improved skin thickness in diffuse SSc patients participating in SLS. Other drugs (such as tryosine kinase inhibitors) should be considered investigational at this time.

Lung

Interstitial lung disease (ILD)

Cyclophosphamide. The Scleroderma Lung Study (SLS) was the first RCT to demonstrate the effectiveness of cyclophosphamide in improving lung function (FVC% predicted), relative to placebo, at the end of the 1-year treatment period [47]. Although the physiologic benefits of cyclophosphamide compared with placebo were modest (2.53% improvement in % predicted FVC at 12 months; $p < 0.03$), these results were supported by parallel findings of improvement in patient-reported outcomes, including

breathlessness, function (HAQ-DI) and some health-related quality-of-life measures [48], as well as skin thickness scores. Moreover, extent of fibrosis on the 'baseline' HRCT scan was a significant predictor of worsening FVC in the placebo group and of response to cyclophosphamide [49]. By contrast, BAL cellularity at baseline was not a predictor of response [21].

After 1 year of therapy, patients were followed for an additional year with the premise that 1 year of treatment with cyclophosphamide would be sufficient to prevent further disease progression without the need for ongoing immunosuppressive therapy. During the year following cessation of randomised treatment in the SLS, the beneficial effects of cyclophosphamide (compared with placebo) on lung function (FVC) continued to increase for an additional 6 months [49]. After 18 months, the beneficial effects of the preceding treatment with cyclophosphamide waned so that by the end of the 2-year period, lung function in the two treatment groups was essentially the same [49]. During the 2-year follow-up, cyclophosphamide was associated with greater adverse events related to microscopic haematuria and leucopaenia. However, in all other adverse events, including serious adverse events and death, there were no significant differences.

In an alternative approach, cyclophosphamide was administered by intravenous infusion monthly for 6 months (to minimise the risk of haemorrhagic cystitis associated with the oral route) followed by azathioprine, compared with placebo infusions followed by oral placebo, in 45 patients with active systemic sclerosis-interstitial lung disease (SSc-ILD) [50]. The results showed a trend toward a favourable outcome in the actively treated group ($p = 0.08$) while minimising the toxicity of cyclophosphamide.

Tyrosine kinase inhibitors

In an *in vitro* model of bleomycin-induced pulmonary fibrosis, c-Abl inhibition by imatinib prevented TGF-beta induced extracellular matrix gene expression, transformation and proliferation of fibroblasts [42]. There is an ongoing study assessing safety and efficacy of open-label imitinab in patients with SSc-ILD wherein the inclusion/exclusion criteria are similar to those of SLS (Clinical Trial Registration Number: NCT00512902). Preliminary data from an ongoing open-label study suggests some stabilisation of pulmonary function (Khanna D EULAR 2009). However, a high proportion of patients dropped out due to adverse events. A trial has also been designed to study dasatinib, a second-generation tyrosine kinase inhibitor that also inhibits src-kinase, which plays an important role in extracellular matrix protein in dermal fibroblasts[51] in SSc-ILD (Clinical Trial Registration Number: NCT00764309).

Bottom line. Cyclophosphamide therapy results in stabilisation of lung fibrosis and the effect lasts for an additional 6 months. The improvement in lung physiology is associated with improvement in patient-reported outcomes. EULAR/EUSTAR guidelines recommend cyclophosphamide for treatment of SSc-ILD despite its known toxicity. Mycophenolate mofetil[52] and rituximab are investigational therapies at this time and require further studies.

Pulmonary artery hypertension

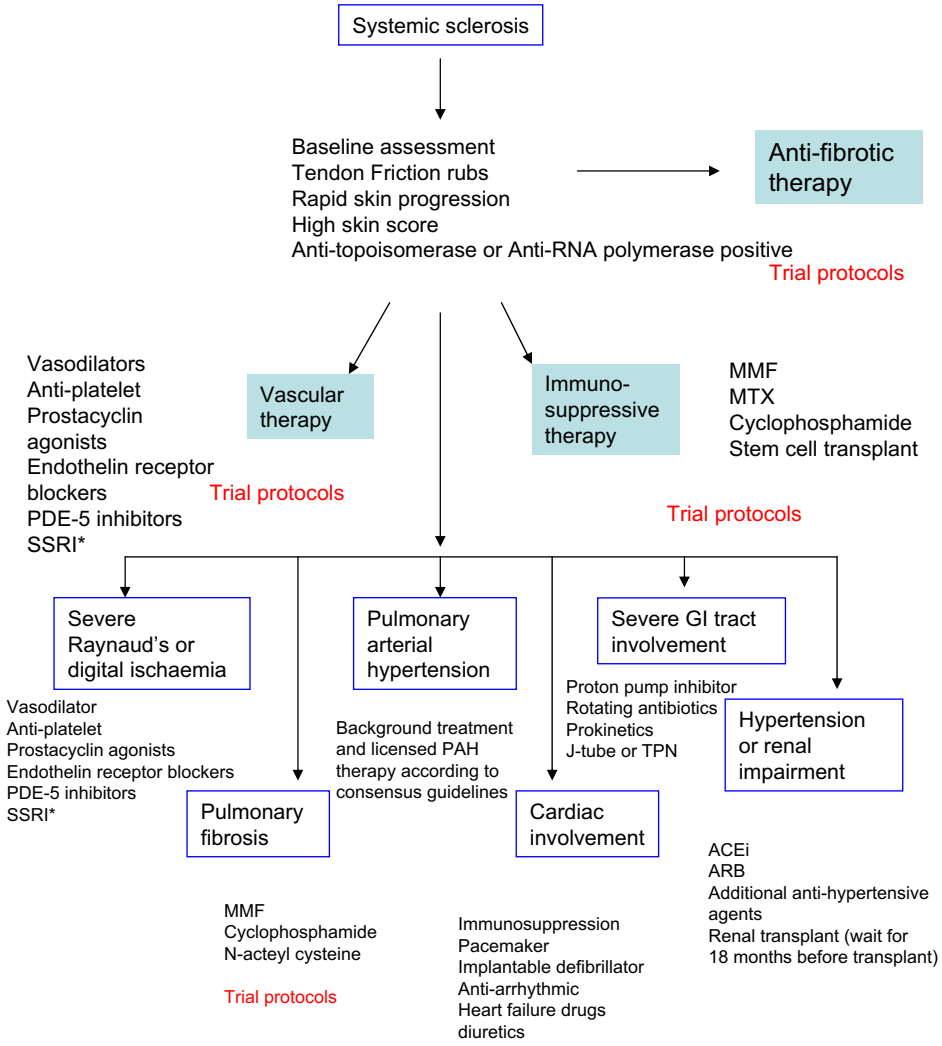
PAH is a progressive disease that leads to increased pulmonary vascular resistance, compromised vasoreactivity and eventual right-heart failure and death. Due to the overlap in the pathophysiology and specific therapeutic interventions, the 2008 Dana Point meeting has classified idiopathic, familial and CTD (including SSc) under the umbrella of PAH. There are eight FDA approved therapy for PAH in US. These include two endothelin-1 receptor blockers (bosentan (Tracleer®])and ambrisentan (Letaris®)), two phosphodiesterase-5 inhibitors (sildenafil (Revatio®) and tadalifil (Revatio®), and prostacyclin derivatives (epoprostenol (Flolan ®], treprostinil (Remodulin ®]).

Management of rapidly progressive SSc

The current understanding of the diverse patterns of disease that fall within the spectrum of scleroderma and specifically within the subgroup of systemic sclerosis necessitates a systematic approach to case assessment and management. This needs to address important issues around the likelihood of progression and the detection and appropriate treatment of organ-based complications

such as PAH and interstitial lung fibrosis as well as SSc. The emerging evidence base that underpins current therapy provides support for active treatment in all cases that are severe or progressive. A global approach to management is summarised in the clinical algorithm shown in Fig. 2. All patients should be considered for ongoing clinical trials. This approach should be considered in the context of more detailed discussion of disease assessment and treatment that is included in this article. Treatment for rapidly progressive SSc is based on skin, heart, lung, renal, GIT or vascular involvement.

For skin, first-line treatment varies according to local experience and practice but our recommendation is that all cases should be enrolled into clinical trial protocols where possible. Otherwise, we recommend initial treatment with immunosuppressive agents and would recommend MTX at



ACEi = angiotensin converting enzyme inhibitors, ARB= angiotensin receptor blocker, PDE-5=phosphodiesterase-5 inhibitor, MMF=mycophenolate mofetil, MTX= methotrexate, TPN= total parenteral nutrition

*Selective serotonin reuptake inhibitors

Fig. 2. Algorithm for treatment of severe progressive systemic sclerosis.

doses up to 25 mg (oral or subcutaneous) every week with folic acid or treatment with oral mycophenolate mofetil with a target dose of at least 2 g daily. If improvement is not seen within 3–6 months, then we would consider switching between these agents or use of low-dose pulse intravenous CYC. We have used monthly intravenous immunoglobulin (IVIG) with success, especially in patients with myopathy or inflammatory myositis and some success with anti-thymocyte globulin has been reported, although longer-term benefit over less intensive treatment regimens is not clear [53].

For ILD, we recommend treatment with pulse CYC at doses of 500–750 mg m^{-2} every month. Moderate- to high-dose prednisone has not shown to be effective in treatment of ILD and we discourage this especially due to risk of renal crisis with prednisone. FVC should be assessed every 3–4 months and a decline of $>10\%$ is considered a clinically meaningful decline and should lead to change in therapy. Other choices include mycophenolate mofetil and azathioprine.

For cardiac involvement, the precise management is less clear than for skin and lung. Based upon baseline investigations, there should be medical treatment of haemodynamically significant arrhythmias or pericardial effusion (although uncommon – see text above). Our current practice is to use echocardiography to define systolic cardiac function and consider immunosuppressant with pulse CYC if there is impaired left ventricular (LV) function (left ventricular ejection fraction (LVEF) $<50\%$). In addition, if there are documented tachyarrhythmias or conduction defects, implantable defibrillator or pacemaker devices may be considered. Cardiac MRI is increasingly used to assess patients with suspected myocardial involvement in SSc, as discussed above. The place of this, together with serum markers such as troponin, remains to be established.

For renal involvement, diagnosis of renal crisis should lead to initiation of ACE-inhibitor with a goal to normalise blood pressure (BP). If inadequate BP control is achieved, add calcium-channel blocker and/or furosemide. Patients should be dialysed, if needed. If on dialysis, wait 18 months before considering a renal transplant.

In GIT involvement, the most common cause of continuing weight loss is malabsorption syndrome related to small bowel bacterial overgrowth and gastroparesis. Treatment with rotating antibiotics and prokinetics is necessary. In resistant cases, daily subcutaneous octreotide (50 mg 2–3 times a day) may be helpful. In addition, some patients may need percutaneous gastric or jejunal feeding or parenteral nutrition.

For severe Raynaud's phenomenon (cold blue finger) and digital necrosis, we initiate intravenous iloprost or another prostacyclin in the hospital setting. PDE-5 inhibitors may be used in addition to prostacyclin therapy. We have also used anti-platelet therapy and performed angiogram if we suspect vasculitis/thrombo-embolic event. Bosentan reduced new digital ulcer formation in two large controlled trials and may be considered for preventative therapy, and is a licensed therapy in the European Union. It is probably most appropriate in those cases with severe ongoing digital ulcer disease [54].

Concluding comments

As can be seen in this review, there have been substantial recent advances in the field of SSc in terms of disease assessment and therapy. This has included a greater appreciation of the strengths and limitations of current assessment techniques and a growing appreciation of the clinical diversity of SSc and heterogeneity in terms of disease progression. Thus, it is clear that in those cases that are at highest risk of life-threatening complications or progression, an aggressive approach to treatment is mandatory. This may well include high-intensity immunosuppression and in the future, the use of biological agents that target key pathogenic mediators or pathways. It is also clear that some cases of SSc follow a more benign or slowly progressive course; vigilant monitoring with timely intervention to tackle organ-based complication such as pulmonary arterial hypertension or scleroderma renal crisis is the cornerstone of managing these cases. Therefore, the immediate challenges for clinicians treating cases of SSc include identification of the most progressive cases as well as better definition of the clinical benefit from intervention both within formal clinical trials and also from careful observation of well-characterised clinical cohorts. Survival has improved in SSc but there is still scope for progress and this includes attention to the substantial disease burden beyond those complications that are immediately life threatening.

Clinical practice points

☐ Treatment of early SSc requires risk stratification.

☐ Rapidly progressive scleroderma requires frequent physician visits and screening tests to evaluate for internal organ involvement.

☐ Effective treatments are available for rapidly progressive skin disease, interstitial lung disease and pulmonary hypertension, if diagnosed early.

☐ Patients should be referred to Scleroderma Centres to participate in multiple ongoing clinical trials.

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