Systemic sclerosis in adults. Part II: Management and therapeutics

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Word count: (Limit = 3000)
Tables: 2
Figures: 2
References: 218

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Funding: No funding was received for this article

Keywords: Systemic sclerosis, digital ulcers, Raynaud's phenomenon, calcinocic cutis, treatment, management

Conflicts of interest:
RJ has no COI to declare
MN has received research grant support from Actelion, BMS, GSK, Janssen, UCB; and honoraria from Actelion, Boehringer Ingelheim, Janssen, Eli Lilly, Pfizer, UCB.
TK has received speaking fees from Actelion
CD reports personal fees or research grants to his institution from GlaxoSmithKline, Galapagos, Boehringer Ingelheim, Roche, CSL Behring, Corbus, Horizon, and Arxx Therapeutics outside the submitted work
AS has no COI to declare

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACR	American College of Rheumatologists
BAFF	B-cell activating factor
CCB	Calcium channel blocker(s)
CD	Cluster of differentiation
cGMP	Cyclic guanosine monophosphate
CRISS	Combined Response Index for Systemic Sclerosis
CT	Cutaneous telangiectasia
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
dcSSc	Diffuse cutaneous SSc
DM	Dermatomyositis
DU	Digital ulcer(s)
ENA	Extractable nuclear antigen
ERA	Endothelin receptor-1 antagonists
ET-1	Endothelin 1
EULAR	European league against rheumatism
EUSTAR	The European Scleroderma Trials and Research
FDA	Food and Drug Administration (US)
FVC	Forced vital capacity
GAVE	Gastric antral vascular ectasia
GABA	Gamma aminobutyric acid
GI/GIT	Gastrointestinal/Gastrointestinal Tract
GORD	Gastroesophageal reflux disease
HAQ-DI	Health Assessment Questionnaire-Disability Index
HLA	Human leukocyte antigen
HRCT	High-resolution computed tomography
HSCT	Haematopoietic stem cell transplant
IPL	Intense pulsed light
IL-X	Interleukin-X
ILD	Interstitial lung disease
IV	Intravenous
IVIg	Intravenous Immunoglobulins
JAK	Janus Kinase
lcSSC	Limited cutaneous systemic sclerosis
MDT	Multidisciplinary team
MMF	Mycophenolate mofetil
mRSS	modified Rodnan skin score
NSAID	Non-steroidal anti-inflammatory drugs
PAH	Pulmonary arterial hypertension
PDE5i	Phosphodiesterase 5 inhibitor
PDGF	Platelet-derived growth factor
PRO	Patient Reported Outcome
PUVA	Psoralen with Ultraviolet A
RCT	Randomised controlled trial
RP	Raynaud’s phenomenon
SRC	Scleroderma renal crisis
SSc	Systemic sclerosis
SSRI	Selective serotonin reuptake inhibitors
STAT4	Signal transducer and activator of transcription 4
TGF-β	Transforming growth factor beta
Th2	T Helper cell 2
UVA	Ultraviolet A

ABSTRACT

The management of systemic sclerosis (SSc) is complex, evolving and requires a multidisciplinary approach. At diagnosis and throughout the disease course, the skin can provide a window into overall SSc activity, thus clinical assessment and monitoring of skin involvement via the modified Rodnan Skin Score, patient reported outcomes and new global composite scores is vital. Patients should also be specifically screened for systemic manifestations at the time of diagnosis, and regularly thereafter.

Treatment of the many and varied cutaneous manifestations of SSc is challenging and occurs alongside treatment of systemic organ involvement. Immunomodulation is the mainstay of skin fibrosis treatment, while vasculopathy related manifestations (Raynaud's phenomenon, digital ulcers) and calcinosis, require specific and often multifaceted management approaches. Numerous targeted therapeutic options for SSc, including skin fibrosis, are emerging and include B-cell depletion, anti-IL-6, JAK and TGF-β inhibition.

The second article in this continuing medical education series discusses these key aspects of SSc assessment and treatment, with particular focus on skin involvement. It is vital that Dermatologists play a key role in the multidisciplinary approach to SSc management.

Section 1: Disease assessment and monitoring

Key points

- Validated outcome measures are vital clinical and research tools to allow for the standardised assessment of SSc disease activity, severity and treatment response.
- The skin can provide a window into overall disease activity and progression.
- The modified Rodnan Skin Score (mRSS) is a well-validated, routinely used clinical tool to measure and monitor the severity and extent of skin thickness in SSc.
- Patient reported outcomes are an important complementary measure to determine the impact of skin symptoms on patient's quality-of-life.
- The Combined Response Index for Systemic Sclerosis (CRISS) is a promising tool that allows for a comprehensive assessment of disease activity and burden.

Skin Scores

The skin can provide a window into overall systemic disease progression in SSc; with progression of skin fibrosis and/or cutaneous vasculopathy (such as telangiectases and digital ulcers), providing visible clues to possible progression of related changes systemically.

The modified Rodnan Skin Score (mRSS) is commonly used to measure and monitor the clinical severity and extent of cutaneous fibrosis (Figure 1). It evaluates skin thickness at 17 body sites, each of which receives a score between 0 and 3 (none (0; normal, the skin is soft and can be pinched between two fingers), mild (1), moderate (2), severe (3; the skin is immobile and does not pinch between two fingers)).[1] The specificity of sclerodactyly in SSc is reflected by the fingers and hands (proximal to the metacarpal-phalangeal joints) being scored as distinct body sites in the mRSS, thus strongly contributing to the overall score. Whilst the mRSS is well-validated and sensitive to change, its drawbacks include intra- and interobserver variability which necessitates regular training for standardisation.[2–5]

To date, other methods for quantifying skin thickness are not used routinely in clinical practice, but are increasingly discussed and studied. Histopathology is, of course, the gold standard, but its invasiveness and scarring make it unfavourable. A number of imaging techniques can be used, such as ultrasonography, magnetic resonance imaging and

computerised skin scoring.[6] Whilst reproducible, these methods are not standardised, can be expensive, are highly specialised and are not widely available.

There are also tools available to measure skin hardness, including durometry and cutometry. Durometry is an easy-to-use option, with demonstrated reliability and accuracy in SSc; correlating well with mRSS, ultrasound-measured skin thickness and skin biopsies.[7–10] Unlike durometers, which evaluate skin hardness through resistance to indentation, cutometers assess skin hardness through resistance to controlled suction. Cutometer measurements correlate reasonably well with the mRSS,[11] and newer devices have been developed more recently to lessen the potential for interobserver technique variability.[11–13] As quantitative outcome measures, these tools are ideal as complementary outcome measures in the clinical trial setting, where reproducibility and consistency across multiple assessors is essential.[9]

Patient reported outcomes

Patient perception of the impact of skin manifestations on function and quality-of-life is an important consideration when evaluating treatment decisions, efficacy and disease progression. The mRSS scores correlate moderately with most patient reported outcomes (PROs),[14] PROs should be routinely used to complement objective clinical scores. The skin specific SSPRO is a well validated measure of the impact of skin manifestations on function and quality of life [REF Man et al 2017]. The Health Assessment Questionnaire-Disability Index (HAQ-DI) is often used in SSc. It contains a series of subjective questions related to patients' physical function and ability to perform certain tasks.[15] Baseline HAQ-DI scores have recently been shown to be a predictor of mortality in dcSSc thus emphasising the importance of this patient centred subjective measure.[16] To capture the multisystem effects of SSc, Steen and Medsger developed the Scleroderma Health Assessment Questionnaire (SHAQ), comprising of the HAQ-DI and 5 additional scleroderma-specific visual analogue scales.[15,17] A copy of these questionnaires can be found in the appendix of reference 15 (Johnson, *et al.*, 2005). The Dermatology Life Quality Index (DLQI) is not commonly used nor validated in SSc and has only been reported on in one study.[18,19] For a comprehensive overview of various PROs used in SSc, please see reference 19 (Almeida, *et al.*, 2015).

Composite measures

Composite scores considering the multisystemic and psychosocial impacts of SSc are being developed and undergoing validation. Physician and patient assessments are combined in the

Combined Response Index for Systemic Sclerosis (CRISS), which considers 5 core indices of disease (mRSS, Forced Vital Capacity (FVC), HAQ-DI, Patient Global assessment and Physician global assessment).[20] Examples of how to apply the CRISS to patients is given in Supplementary Tables 3-5 of reference 20 (Khanna, *et al.* 2016). Importantly, CRISS was developed based on an observational early-dcSSc patient cohort (disease duration less than 5 years) and it is demonstrated and intended for use in clinical trials.[21] The score has good content and face validity as well as sensitivity to change, and has been provisionally approved by the ACR.[20,22,23] Further validation and reliability testing based on external data is still required. Notably a modified version of the score (mCRS) has recently been externally validated.[24]

Systemic organ monitoring

Early screening for, and ongoing regular monitoring of systemic organ involvement is a crucial aspect of SSc management which improves patient outcomes and disease survival. Organ monitoring protocols are summarised in Table V, Part 1, of this CME series.

Section II: Treatment

OVERALL MANAGEMENT STRATEGY

As discussed in Part 1 of this CME series, SSc is a complex, multisystem disease with varied cutaneous features. A multidisciplinary approach is crucial for effective SSc management. Dermatologists must play a key role in early recognition, exclusion of SSc-mimics and overlap syndromes, disease monitoring and treatment of the heterogenous cutaneous SSc manifestations. Skin involvement can have significant psychosocial and functional impact which must be considered when making treatment decisions.

Overall, SSc management is challenging, but outcomes and survival in SSc has improved over the past four decades.[25] Current management strategies aim to dampen underlying immunological aberrancies, detect and treat complications, and prevent disease damage. Pathogenic and disease stratification studies continue to lead us closer to an ultimate goal of personalised and targeted therapeutic approaches. Enrolling patients into national and international SSc registries (e.g. EUSTAR) will contribute to improving disease understanding and management strategies.

MANAGEMENT OF DERMATOLOGIC MANIFESTATIONS

Skin fibrosis

Key points

- General measures including physiotherapy, massage and stretching exercises form an essential part of skin fibrosis management
- Conventional immunosuppression with mycophenolate mofetil (MMF) is considered first line treatment for skin and lung fibrosis; with the highest level evidence for improving skin scores and good tolerability.
- Newer therapies targeting molecules implicated in SSc pathogenesis include B-cell depletion therapy with rituximab; anti-IL6 therapy with tocilizumab; tyrosine kinase inhibition with nintedanib; and others.
- There are currently no targeted therapies approved for skin fibrosis in SSc. The tyrosine kinase inhibitor, nintedanib, was recently approved by the FDA for SSc related interstitial lung disease (SSc-ILD). Tocilizumab has shown a trend of benefit in clinical trials and may be helpful in some cases with severe skin involvement.

General measures

A non-pharmacologic approach coupled with comprehensive patient education is an important foundation for management of skin fibrosis in SSc. General management measures such as avoiding cold exposure, applying regular bland emollients and avoiding soaps, to keep the skin as moist and supple as possible, are important.

Sclerodactyly can have significant functional impact. Massage, heat, wax baths, regular stretching exercise, physiotherapy, splints and occupational therapy can all help to reduce the risk of mechanical injury and improve range of motion, whilst also empowering patients with daily activities to slowly improve their function. These therapies are safe and relatively easy to implement, although, high levels of evidence for their efficacy is lacking.[26] Specialist scleroderma centres often have allied health, specialist nursing and physician assistants who are well versed in assisting patients with techniques and day-to-day measures. Clinicians without access to such specialist services may assist patients' with accessing similar supports via online resource and/or patient support groups, through organisations such as the Scleroderma Foundation (USA), Scleroderma Canada, Scleroderma Raynauds United Kingdom (SRUK), Federation of European Scleroderma Association (FESCA) and Scleroderma Australia.

Topical treatments and phototherapy

Unlike in morphea and other conditions with localised sclerosis, topical corticosteroids and other topical agents do not play a major role in SSc skin fibrosis management. Occasionally in the context of significant inflammation and related pruritus, topical steroids may anecdotally be used to assist symptomatology.

Phototherapy is a supportive therapy in SSc. Ultraviolet A1 (UVA1) or UVA with topical (bath) or systemic psoralen (PUVA) may be beneficial in the early and late phase of SSc,[27] potentially improvement in skin fibrosis (and pruritus). If an experienced centre is available for the patient, phototherapy should be considered as an additional treatment.

Immunosuppression for skin fibrosis

Immunomodulation forms the cornerstone of SSc skin fibrosis management. Systemic corticosteroids have been used in SSc,[28,29] particularly during the initial oedematous phase.

However, they are known to precipitate Scleroderma Renal Crisis (SRC) and are currently not recommended at high doses.[30]

Mycophenolate mofetil (MMF) is generally considered first line therapy for skin fibrosis in SSc. It has shown robust efficacy in improving SSc-related skin tightening. MMF (up to 3g/day) has shown efficacy in improving skin scores as well as SSc-ILD in a RCT (Scleroderma Lung Study II (SLS II)) and numerous previous case-series and open label studies.[31–34] In this and a previous study (SLS I), cyclophosphamide (up to 2mg/kg/day) also demonstrated significant improvement in skin fibrosis, as well as a modest effect on SSc-ILD, which, however, is lost on treatment discontinuation.[31,32,35,36]

Two randomised controlled trials (RCT) showed that methotrexate (15-25mg/week) improves skin scores in early dcSSc whilst offering no benefit for lung disease nor other organ manifestations.[21,37]

A prospective cohort study comparing efficacy of cyclophosphamide, MMF and methotrexate in early dcSSc showed no superiority of any one agent.[38] However, as mentioned, MMF is currently considered as the first-line treatment option for SSc skin fibrosis, including in those with concomitant SSc-ILD,[31,32,39] and its good safety profile, affordability and accessibility make it a favourable option overall.

Haematopoietic stem cell transplantation (HSCT)

Haematopoietic stem cell transplantation (HSCT) can significantly improve both skin and lung fibrosis in SSc (ASTIS, SCOT, ASSIST trials).[40–43] This bellicose approach is reserved for patients with severe rapidly progressive SSc refractory to other immunosuppression and at risk of poor outcomes.[44] Careful patient selection is crucial due to the significant treatment related toxicities and mortality which makes it an unfeasible option in many patients including those with advanced systemic manifestations.[43,45] Overall, there remains much debate amongst SSc experts regarding implementation of HSCT for rapidly progressive SSc and it is only performed at highly specialised centres.[46]

Emerging treatment options for skin fibrosis

Patients failing to respond to conventional immunosuppression or who cannot tolerate the aforementioned agents may benefit from newer, more pathogenesis-directed therapies. B-

cells and their dysregulation have been strongly implicated in the SSc fibrotic process.[47] B-cells directly induce pro-inflammatory (IL-6) and pro-fibrotic (TGF-β) gene expression as well as collagen secretion by dermal fibroblasts *in vitro*.[48] In mouse models of SSc, B-cells exhibit increased CD19 signalling with subsequent IL-6 and antibody overproduction[49] and their depletion has been shown to prevent skin fibrosis.[50] There is thus strong experimental evidence for the role of B-cells in SSc pathogenesis and their depletion or modulation is an attractive treatment objective. B-cell depletion therapy with Rituximab, an anti-CD20 antibody, has shown promising ability to significantly reduce mRSS and improve lung function in a small RCT as well as other larger collaborative EUSTAR studies.[51–59] Evidence of histological improvements (with a reduction in myofibroblast numbers and hyalinised collagen in the dermis) and serological improvements (with a reduction in IL-6 levels) have also been demonstrated.[53–55] A recent meta-analysis showed generally good tolerability, long-term improvement in mRSS and stabilisation of lung function.[60] Nonetheless, evidence of efficacy in large RCTs is lacking for rituximab and further studies are needed (see Table I).

Treatments targeting IL-6, a key pro-inflammatory and pro-fibrotic cytokine implicated in SSc pathogenesis, have anti-fibrotic effects in animal models of skin fibrosis.[61–63] IL-6 is frequently elevated in the serum of SSc patients, expressed by dermal fibroblasts and endothelial cells in dcSSc patients and associated with progressive skin fibrosis.[64] Tocilizumab, an anti-IL-6-antibody, has been studied in patients with dcSSc in the early inflammatory phase with skin progression and whilst there was a consistent trend of mRSS improvement this was not statistically significant compared to placebo in a phase II (FasSScinate) nor phase III (FocuSSced) RCT (see Table II).[65–67] Importantly however, there was a significant reduction in meaningful worsening of mRSS, FVC and CRISS scores in both studies (see Table II).[66] This of course raises the issue of selecting the most suitable and clinically meaningful end points in studies of SSc, which remains an ongoing challenge, as it does for other multi-organ complex diseases, such as systemic lupus erythematosus.

Recently, the tyrosine kinase inhibitor, nintedanib, became the first FDA approved targeted therapy for SSc-ILD after a positive phase III RCT (SENSCIS) which demonstrated significant improvement in the primary endpoint of FVC.[68] However significant treatment effect on mRSS was not demonstrated.[68]

The soluble guanylate cyclase stimulator, riociguat, has demonstrated anti-fibrotic and anti-inflammatory effects in mouse models.[69–71] Riociguat is now approved by the FDA for PAH,[72] and further studies are investigating its impact on fibrosis in SSc, including the phase II study (RISE-SSc) which demonstrated a trend towards statistically significant improvement in mRSS.[73]

These and other emerging targeted treatments for skin and lung fibrosis in SSc, such as anti-CTLA4 (abatacept), anti-IL13/4 (Romilkimab), TGF-β antibody (fresolimumab), cannabinoid receptor analogues (lenabasum) and JAK inhibitors (tofacitinib), are described in Table II and illustrated in Figure 2.

Vasculopathy

Key points

- Patient education around minimising cold exposure, preventing trauma and smoking cessation is important in the prevention and management of Raynaud's phenomenon (RP) and digital ulcers (DUs)
- Pharmacological management options include vasolidators and vasoactive medications; calcium channel blockers, phosphodiesterase type 5 inhibitors and prostanoids. Combination therapy is indicated for DU and recalcitrant RP.
- DU management is multifaceted and entails prevention, treatment of underlying RP, early recognition, ulcer classification, meticulous wound care, treating/preventing infections and adequate analgesia.
- Digital sympathectomy and botulinum toxin injections are non-pharmacological options for refractory RP and DUs, in specific cases.

Preventative general measures should always play a role in the management of peripheral vasculopathy in SSc. Patient education, with a focus on avoidance of triggering factors such exposure to cold, rapid temperature changes and emotional stress, minimising risk of trauma, encouraging and supporting smoking cessation, and avoiding exposure to vasoconstrictors such as caffeine, are all important. Smoking cessation should be strongly supported as smokers are more likely to experience severe digital vasculopathy requiring intravenous (IV) vasodilator therapy, surgical intervention and amputation.[74] Patient support groups and scleroderma nurse specialists can provide patients with access to tips and tools to help with this, such as; double lined gloves, silver socks, heat pads, the use of zinc oxide containing pastes to assist with pain and healing of fissures and wax baths.[75] Some low grade evidence supports the use of supplements including antioxidant vitamins C and E, gamolenic acid, ginko biloba, ginger and resveratrol (a natural phenol produced by certain plants, found in the skins of grapes, blueberries, raspberries and mulberries).[76–80]

Raynaud's phenomenon

<u>Pharmacological approach</u>

Evidence supports the use of vasodilators and vasoactive therapies to reduce the frequency and severity of RP attacks,[81] with calcium channel blockers (CCBs) considered first line (see Table I).[82–86] Trial data particularly supports implementation of non-cardioselective, dihydropirine CCBs (e.g. nifedipine and other agents ending in '-pine') to reduce the severity and frequency of RP attacks.[83] Primary RP seems more responsive than SSc-RP and higher doses of CCBs are likely to be more effective.[83] Notably, the UK consensus pathway lists diltiazem (a non-dihydropiridine, cardioselective CCB) together with nifedipine and amlodipine as a CCB option despite very few studies reporting on its efficacy.[85,87]

Second line options, which are usually used in addition to CCBs, include phosphodiesterase type 5 inhibitors (PDE5i e.g. sildenafil)[86,88,89] and prostanoids (e.g. iloprost).[86] PDE5i improve digital blood flow in SSc by preventing degradation of cyclic GMP with subsequent vasodilation[90] and have shown efficacy in secondary RP.[91] Intravenous iloprost is typically reserved for severe RP, resistant to oral therapy or complicated by DU (see below).[39,86] Prostanoids work through vasodilation as well as inhibiting platelet aggregation and vascular smooth muscle proliferation.[92,93] The effects usually last for 4-8 weeks and therefore may need to be repeated throughout the year, depending on the situation. Variations in iloprost administration regimens exist,[39,94] but generally no more than 2mg/kg/min is administered over 1-5 days, with other therapies continued.

Third and fourth line options include selective serotonin reuptake inhibitors (SSRIs),[95] anti-platelets,[96] anti-coagulants,[97] alpha-blockers[98] and statins.[99,100] The evidence for these options is less robust and further studies are required to establish their role in RP management.[82,84,101] A single study reported fluoxetine (an SSRI) to be superior to nifedipine and to significantly reduce the severity and frequency of primary RP attacks whilst only a modest improvement was seen in secondary RP.[95] Fluoxetine is thus considered by experts as a potential treatment option in patients in whom a blood pressure lowering agent is contraindicated. A number of small, short-term studies have reported conflicting results on the efficacy of ACE inhibitors (captopril, enalapril) in RP.[102–106] Meanwhile two studies have reported losartan (an angiotensin-II receptor antagonist) reduces the severity and frequency of RP, with one showing a reduction specifically in SSc patients, however, this effect was only statistically significant in primary RP patients.[106–108] Larger, longer-term studies are required to provide conclusive evidence for these agents.

Topical vasodilators containing nitroglycerin or benzyl nicotinate can be used for subjective, intermittent and temporary relief of RP symptoms, however, there is little evidence to specifically support this approach.

In refractory RP, cases associated with progressive DU or critical digital ischaemia (see below), a combination of these vasodilatory and vasoactive therapies is often indicated. Of course, in such cases, the beneficial treatment effects must be balanced with adverse effects such as hypotension, headaches and peripheral oedema.[109]

Procedural options

In specific cases of severe RP, not responding to pharmacological therapies and potentially associated with DU and/or critical digital ischaemia, alternative options can be considered. Botulinum toxin injections promote local arterial vasodilation and a small number of retrospective studies (including both primary and secondary RP patients) report improvements in symptoms with variable objective change in blood flow.[82,110,111] No significant improvement in doppler imaging blood flow was found in a placebo controlled, randomised trial with 40 SSc-RP patients.[112] Therefore, conclusive evidence for botulinum toxin is currently lacking. Meanwhile there are favourable reports for digital sympathectomy, which through disruption of sympathetic input to the digital vessel smooth muscles causes vasodilation.[82,111,113,114] One study reported 24 of 26 hands experiencing pain resolution or improvement after digital sympathectomy, with the vast majority of surveyed patients wishing they had had the procedure sooner.[113] This approach could be particularly beneficial early in digital ischaemia to prevent complications such as digital ulcers, but is curretnyl rarely employed.

Digital Ulcers

Assessment

The early recognition and thorough assessment of DUs are important aspects of management. Digital ulcer assessment should ideally include characterisation and classification of size, location, ulcer bed, exudate, ulcer depth, perilesional skin and pain.[115] Meticulous wound care is required to minimise further damage and tissue loss and prevent or treat secondary infection. [85,116,117] Dressings should be tailored to wound character and reviewed regularly

throughout the healing process. Any contributory causes e.g. underlying large-vessel disease, vasculitis or prothrombotic coagulopathy (such as cryoglobulinemia) should be identified early and treated.[116] Patients may report significant ischaemia-related or ulcer-related pain which should be managed with sufficient analgesia, including topical (such as lidocaine),[118] and systemic, often opioid, analgesia.

Pharmacological approach

Vasculopathy associated DUs usually require a step wise therapeutic approach, often with a combination of vasodilatory and vasoactive medications including CCBs (nifedipine/diltiazem), PDE5i (sildenafil), prostanoids (IV iloprost) +/- endothelin receptor-1 antagonists (ERA; bosentan). For a systematic guide to medication selection and use in DUs please refer to the UK best practice consensus pathway available in reference 85 (Hughes, *et al*., 2015).[85] Figure 3 of these guidelines provides a clear DU management approach[85] and the implementation of these treatments is supported by the recently updated EULAR SSc treatment recommendations.[86]

Most of these therapies for DUs, are supported by medium to high level evidence (see Table 1).[81] PDE5i in particular reduce new DU development and are potentially associated with improved DU healing.[119,120] They are commonly used first line alone or in combination with CCBs in early DUs.[81,85,88] For DUs resistant to oral therapies or in cases of critical ischaemia, IV prostanoids (iloprost) can be used and have been shown to improve DU healing and reduce new DU formation in RCTs.[121–123] Meanwhile, oral prostanoids have not proven to reduce the number of new DUs.[119]

Endothelin-1 receptor antagonists work by inhibiting vasoconstriction, smooth muscle and fibroblast proliferation.[119] Bosentan, a dual ERA, is licenced for treatment of PAH and prevention of recurrent DUs in Europe. It requires regular monitoring of blood counts and liver function.[116] RCTs have shown it reduces the number of new DUs whilst not changing healing of existing DUs.[124,125] The same efficacy was not found in an RCT studying macitentan,[126] another dual ERA, while two small studies showed a reduction in new DUs using ambrisentan, a selective ET_A ERA.[127,128] Some studies suggest ERAs can be combined with PDE5i in severe cases of refractory DUs, but this would require close monitoring for adverse effects.[129,130] Combination IV iloprost and bosentan can reduce progression of microvascular damage in SSc after 1-2 years of combination therapy.[131,132]

Up to a third of patients with SSc have refractory DUs.[133] Other pharmacological options include antiplatelets and anticoagulants,[96,97] ACE inhibitors,[101] and statins.[99] Notably, B-cell depletion therapy (rituximab) and anti-IL6 (tocilizumab), when used for SSc-ILD management, have also demonstrated positive impact on DU healing and clearance in a few cases.[134,135]

Alternative therapies for refractory DUs are under investigation, including hyperbaric oxygen, negative pressure therapy, acoustic pressure wound healing and intermittent compression.[136–138] Topical therapies for DUs include Vitamin E gel,[139] topical digital iontophoresis of 16reprostinil,[91] high temperature sauna,[140] and PUVA,[141] but systematic studies supporting their use are lacking.

Procedural options

Surgery is a last resort for patients with refractory DUs, severe pain, osteomyelitis or for removal of necrotic or underlying calcinotic material. Botulinum toxin injections[110,142,143] and digital periarterial sympathectomy[144–146] can prevent and heal DUs and reduce pain. Other surgical options include debridement (of necrotic or calcified material), amputation (if gangrenous) and more recently, autologous fat grafting is being explored.[147,148] Critical digital ischaemia or gangrene is a medical emergency and requires emergency assessment and treatment.

Telangiectasia

Cutaneous telangiectasia are classically associated with ACA positive SSc, and are a visible clinical indicator of other microvascular involvement. Telangiectases can be of significant cosmetic concern for many patients and may warrant treatment for this reason. Current treatment options include skin camouflage including green tinted camouflage makeup, fine wire diathermy for limited small lesions and laser (i.e. potassium titanyl phosphate or flashlamp pulsed dye laser) or intense pulsed light therapy (see Table I).[149]

Calcinosis cutis

Key Points

- There is a lack of high level evidence for the treatment in calcinosis cutis, with very few RCTs and no specific treatment guidelines
- Improving digital circulation and avoiding trauma play a role in prevention
- Sodium thiosulphate (topical or intralesional) may be efficacious

General and pharmacological management

There is an urgent need for controlled studies to guide the management of calcinosis cutis (CC). Treating RP, keeping hands warm and avoiding trauma are important preventative measures. Small retrospective, prospective and case studies have reported varied success with diverse treatments for CC in SSc, which are described below in brief (see also Table I).

Warfarin (1mg/day) has been studied across 6 adult SSc patients with CC.[150–152] Two patients experienced a partial and subsequent complete response[143] whilst the others had no improvement. Retrospective studies of diltiazem across 28 patients with CC (12 with SSc) reported no complete responders.[154–157] Meanwhile, B-cell depletion therapy, specifically rituximab, for adults with CC has shown conflicting efficacy across different studies.[157–161] A study of 3 SSc patients with CC reported 100% response rate with rituximab[158] whilst another study with 6 SSc patients reported no complete responsers.[160] True efficacy is unclear given the small number of patients (27 across all studies, including 18 with SSc), therefore further, larger, controlled studies are necessary.

Suspected to be due to its anti-inflammatory effects and chelation of calcium, minocycline (50-100mg/day) led to a partial response in 9 of 12 patients (9 SSc patients) with CC across two studies.[156,162] Side effects included nausea, dizziness and discolouration of calcium deposits.[162] Colchicine is also thought to reduce inflammation secondary to calcinosis but has shown variable efficacy across 16 patients (number with SSc unspecified), with only 4 partial and one complete responser.[156,157,163]

Topical, intralesional and intravenous sodium thiosulfate (STS) has been tried for CC with variable success.[164–170] Topical application to superficial lesions and/or as an adjunct for refractory ulcers associated with CC is an attractive option as it is well-tolerated.[165,170] Twice daily application of 25% STS compounded in zinc oxide for up to 12 months was found to be

effective in 19 of 25 patients (15 SSc patients) with CC in a recent case series.[170] Side effects include skin irritation and pain.

Additional treatments have been reported in CC associated with dermatomyositis (DM), but not in SSc, including bisphosphonates,[156,171,172] intravenous Immunoglobulins (IVIg),[157,173–175] cyclophosphamide,[176] low frequency ultrasound,[156] anti-CTLA4 therapy,[177] (abatacept) and TNF-α inhibition (infliximab) [157,178,179] (see Table I).

Procedural options

Surgical removal of calcified deposits should be considered only in specific suitable cases which are refractory to pharmacological therapy and/or due to intractable pain. Studies on surgical management of CC have reported high rates of partial responders.[156,180] However, there is a possibility of damaging surrounding healthy tissue, inducing post-operative worsening ischaemia through neurovascular damage, poor wound healing and skin necrosis, thus ultimately leading to worse pain and/or functional impairment.[181]

Physical interventions such as CO_2 laser and extra-corporeal shock wave lithotripsy (ESWT) have also been tried for CC. CO_2 laser lead to 5 partial responders in a case series (of 6 total SSc patients) and one complete responder in a case report.[182,183] Small studies of ESWT reported a partial response in a cumulative 7 SSc patients and an analgesic effect of the therapy.[184–186] A study of iontophoresis of acetic acid plus ultrasound was ineffective for CC in three SSc participants.

Pruritus

Pruritis is common in SSc, with 43% of patients being symptomatic at some stage during their disease.[187] Pruritus is associated with active SSc, indicating the need for treatment of the systemic condition, and its presence also suggests a greater risk of more severe skin and GIT involvement.[187] SSc-associated pruritus can be very troubling for patients and should not be overlooked as a symptom which can have significant patient impact. Dermatologists should play an active role in its treatment. It is also important to exclude other secondary causes of itch in these patients, and treat accordingly.

For symptomatic relief, all patients experiencing SSc related pruritus should use regular emollients, non-soap cleansers, avoid overheating and irritants. Studies have reported elevated levels of histamine in SSc patients, particularly dcSSc.[188] Therefore, antihistamines are a common first line treatment but are often ineffective (see Table I). Phototherapy, including PUVA, has limited specific evidence for pruritus in SSc, but may be tried in suitable patients, with concurrent lessening of skin fibrosis and inflammation.[189,190] Montelukast, a leukotriene receptor antagonist, is another option which aims to reduce inflammatory irritation of nerve fibres.[191] Neuroactive nerve-stabilising anti-pruritic agents such as gabapentin, pregabalin, amitriptyline and doxepin tend to be anecdotally more efficacious. Interestingly, low dose oral naltrexone, an opioid receptor antagonist, has demonstrated efficacy in small studies of SSc-pruritus and can be considered in the treatment armamentarium for those with treatment resistant and debilitating itch.[192,193] However, larger controlled studies are required to establish the role of naltrexone for routine management of SSc-pruritus. Dysregulation of the endocannabinoid system has also been linked to pruritus in scleroderma.[194] A phase II RCT found an oral cannabinoid receptor type 2 (CB2) agonist, Lenabasum, was safe and resulted in a significant improvement in itch scores, likely due to reduction in expression of inflammation-related genes.[195] Topical cannabinoid modulators (e.g. palmitoylethanolamine containing cream) have shown efficacy in other conditions with pruritus but not yet been specifically reported on in SSc.[196]

OVERVIEW OF SYSTEMIC SSc MANIFESTATION MANAGEMENT

Key points

- Multidisciplinary care is required to manage the diverse systemic manifestations of SSc
- It is important for dermatologists to have a broad understanding of individual organ manifestations and their treatment, as part of the MDT care team

A comprehensive review of systemic SSc manifestation management is beyond the scope of this CME article. Early screening, treatment and monitoring for progression of organ based manifestations is essential and improves mortality (see Table V, Part 1 of this CME). A multidisciplinary approach is vital, and for each organ system involved, specialist care is indicated.

Respiratory

SSc-ILD

Immunosuppressive therapies for cutaneous fibrosis are often also effective for management of SSc-ILD (with the exception of methotrexate), emphasising the shared underlying pathogenesis of these manifestations. Mycophoenolate mofetil and/or cyclophosphamide are considered first line treatment options for SSc-ILD.[86,197] Autologous HSCT and lung transplantation are reserved for severe or progressive cases.[197–199] Importantly, nintedanib, a small molecule tyrosine kinase inhibitor, has recently been FDA approved for SSc-ILD, after positive findings in the Phase III SENSCIS study.[68]

PAH

High-quality evidence supports the use of PDE5i, ERAs and sGC analogue Riociguat in SSC-related PAH (see Table II).[86,197] Continuous intravenous epoprostenol and other prostacyclin analogues can be used in refractory cases as well as lung/heart transplantation.[86,197]

Cardiac

Standard treatments for ischaemic heart disease, valvular disease, arrhythmias, diastolic and/or systolic dysfunction is indicated, which includes ACE inhibitors, diuretics and implantable defibrillators.[197] Myocarditis and pericarditis may respond to immunosuppression with MMF or corticosteroids, NSAIDs and/or colchicine are additional options for the latter condition.[86,197] Interventions such as pericardiocentesis for pericardial effusion and/or creation of a pericardial window in cases of tamponade may be indicated.

Renal

ACE inhibitors should be used to manage SRC, however, their role in SRC prevention is not established.[86] Frequent at home blood pressure monitoring is important for those at increased risk of SRC.

Gastrointestinal

Gastrointestinal (GI) complications can be particularly challenging and are managed through symptom directed therapies. Proton pump inhibitors, H2-blockers and antacids are used for

GORD. Prokinetic agents are indicated for GI dysmotility and associated bloating or pseudo-obstruction (e.g. metoclopramide, domperidone). In cases of oesophageal strictures, patients may require endoscopic dilatation. Small bowel bacterial overgrowth (SIBO) can be treated with various protocols of rotating antibiotics, such as ciprofloxacin, norflaxacin, amoxicillin and metronidazole.[86] GAVE management involves correction of anaemia, iron supplementation and, in some cases, endoscopic treatment with argon plasma photo-coagulation or with radiofrequency ablation.[200] Chronic severe malabsorption related malnutrition should be prevented and initially addressed with oral supplementation, including pancreatic enzymes and fat soluble vitamins, however, in severe end stage cases of refractory weight loss, total parenteral nutrition or percutaneous jejunostomy may be required.[84,197]

SUMMARY

The early diagnosis, assessment and initiation of disease modifying treatments is vital in the management of SSc. Continued regular reassessment for the development and/or progression of systemic and cutaneous complications remains vital and allows ongoing prompt therapeutic adjustments. Cutaneous fibrosis and its impact on patient quality-of-life can and should be monitored using validated outcome measures, most especially the mRSS.

The skin manifestations of SSc are vast and associated with a high degree of morbidity. Management is therefore equally multifaceted, complex and requires a thoughtful systematic multidisciplinary approach. Treatment of skin fibrosis often overlaps with SSc-ILD, with mycophenolate mofetil currently remaining first line, but targeted therapies on the horizon. Overall, effective SSc management requires a multi-disciplinary and collaborative team. In many cases, the skin provides a window to systemic progression in SSc, allowing dermatologists to ultimately contribute to early diagnosis, treatment initiation, effective disease monitoring and hence, improved patient outcomes.

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Table I: Studied Scleroderma therapies and their level of evidence

Treatment	Level of evidence
Skin fibrosis	
Emollients	III
Systemic corticosteroids	III
Mycophenolate Mofetil	III
Methotrexate	IIb
Cyclophosphamide	III
Rituximab	III
HSCT	IIa
Raynaud's Phenomenon	
Calcium channel blockers	Ia
Phosphodiesterase type 5 inhibitors	IIa
Intravenous iloprost	Ia
Selective serotonin reuptake inhibitors	III
ACE inhibitors	IV
Angiotensin II receptor antagonists	Ib
Alpha-blockers	III
Statins	III
Digital sympathectomy +/- botulinum toxin	III
Digital ulcers	
Calcium channel blockers	I
Phosphodiesterase type 5 inhibitors	I
Intravenous iloprost	Ia
Statins	II
Digital sympathectomy +/- botulinum toxin	III
Bosentan	Ia
Aspirin	IV
Calcinosis	
Warfarin	Ib - not recommended
Minocycline	IV
Diltiazem	IV (SSc/DM)
B-cell depletion therapy (Rituximab)	IV (SSc/DM)
Topical/intralesional sodium thiosulfate	IV (SSc/DM)
Intravenous sodium thiosulfate	IV – not recommended
Colchicine	IV (SSc/DM)
Surgical excision/physical therapies	IV (SSc/DM)
CO_2 laser	IV (SSc/DM)
Low frequency Ultrasound	IV (SSc/DM)
ESWT	IV(SSc/DM)
Iontophoresis of acetic acid + Ultrasound	IIB (SSc/DM) - ineffective)
IV-Ig	IV (DM)
Bisphosphonates	IV (DM)
Anti-TNFα (Infliximab)	IV (DM)
Anti-CTLA4 (Abatacept)	IV (DM)
Cyclophosphamide	IV (DM)
Telangiectasia	
IPL	III

Laser	III
Cosmetic camouflage	III
Pruritus	
Emollients	III
Anti-histamines	III
PUVA	IV
Low dose oral naltrexone	IV
Cannabinoid receptor modulator (Lenabasum)	Ib

Table II: Emerging treatments for skin fibrosis in systemic sclerosis

Target	Medication name	Rationale for implementation	Studies	p-values for endpoint data from placebo-co		
				mRSS	FVC	HAQ-DI o SHAQ
CD20	Rituximab	B cells strongly implicated in SSc pathogenesis (see text)	Has shown promising ability to significantly reduce mRSS and improve lung function in a small RCT as well as other larger collaborative EUSTAR studies.[51–59] A recent meta-analysis showed generally good tolerability, long-term improvement in mRSS and stabilisation of lung function.[60] Nonetheless, evidence of efficacy in large RCTs is lacking for rituximab and further studies are needed.	0.06[51] (small RCT) 0.03[57] (Case-control analysis) 0.029[58] (Comparative study, at 5 years)	0.002[51] (small RCT) 0.02[57] (Case-control analysis) 0.013[58] (Comparative study, at 7 years)	NS[51] (small RCT Not reporte Not reporte
Anti-B-cell activating factor (BAFF)-antibody	Belimumab	BAFF is a key cytokine for B-cell activation and increased in the serum and skin of SSc patients.[201]	Phase II trial (NCT01670565) comparing belimumab with placebo on background of MMF treatment showed reduction in mRSS (albeit not statistically significant) and was well tolerated. Decrease in B-cell signalling and profibrotic genes was demonstrated.[202]	0.41	0.27	0.04
Combination of B cell depleting agents (anti-CD20 antibody, anti-BAFF antibody)	Rituximab + Belimumab + MMF	B cells strongly implicated in SSc pathogenesis (see text).	Ongoing phase II study combining dcSSc patients on MMF with either rituximab + belimumab or placebo and assessing safety and change in CRISS (NCT03844061).	NA		

Small molecule tyrosine kinase inhibitor	Nintedanib	Block signalling pathways with downstream transcription factors implicated in vasculopathy and fibrosis (e.g. PDGF and VEGF)	Phase III study (SENSCIS, NCT02597933) did not show significant treatment effect on mRSS.[68] Recently approved by FDA for SSc-ILD.	0.58	0.035	NA
IL-6	Tocilizumab	Anti-Il-6 treatments have been shown to have anti-fibrotic effects in animal models of skin fibrosis.[61–63] IL-6 is frequently elevated in the serum of SSc patients, expressed by dermal fibroblasts and endothelial cells in dcSSc patients and associated with skin fibrosis progression.[64]	A phase II (FaSScinate) and phase III (FocuSSED) study in dcSSc patients in the early inflammatory phase with skin progression found a trend toward mRSS improvement.[65–67]	0.06 (FaSScinate) 0.1 (FocuSSed)	0.03 (FaSScinate) 0.002 (FocuSSed)	0.53 (FaSScinat NS (FocuSSe
Anti-CTLA4	Abatacept	CTLA4 is required for T cell co-stimulation and activation.	Phase II trial (ASSET, NCT02161406) showed a numerically greater but not statistically significant improvement in adjusted mRSS in early dcSSc compared with placebo after 1 year.[203]	0.28	0.11	0.005
sGC analogue/ stimulator	Riociguat	sGC triggers signalling cascades which regulate vascular tone and remodelling.[69] sGC attenuates TGF-β signalling in animal models and in vitro studies thus having anti-proliferative, anti-inflammatory and anti-fibrotic effects.[69–71]	A small phase II RCT (RISE-SSc, NCT02283762) in early dcSSc found a trend towards but not statistically significant improvement in mRSS. Found potential efficacy for ILD, DUs and RP.[73] Approved for treatment of PAH after showing efficacy in the phase III Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (PATENT-1) study, which included a subgroup with PAH-SSc.[72]	0.08 (RISE-SSc)	NS (RISE-SSc)	NS (RISE-SS

Anti-TGF-β antibody	Fresolimumab	Directly target the key cytokine involved in fibrosis	Phase I open-label study in patients with early dcSSc showed an improvement in mRSS, a reduction in TGF-β related gene expression and decline in dermal myofibroblast infiltration.[204]	Not applicable		
Anti-TGF-β	Pirfenidone	Reduce fibroblast proliferation, inhibit TGF-β	Open-label Phase II study in SSc-ILD showed acceptable safety and tolerability.[205] An ongoing phase II trial (SLS III) combing pirfenidone with MMF for SSc-ILD will also assess skin fibrosis as a secondary endpoint (NCT03221257).	NA		
Anti-IL-4/IL-13 antibody	Romilkimab	Th2 cytokines have been associated with fibrosis in animal studies.[206]	A phase II study (NCT02921971) in early dcSSc patients with background immunosuppressive therapy found a statistically significant decrease in mRSS with efficacy seen in the most severe disease group as well as those in early disease stages.[207]	0.03	0.10	0.4
Cannabinoid receptor type 2 (CB2) agonist	Lenabasum	CB2 agonists reduce expression of pro-inflammatory and pro-fibrotic genes.[208]	A phase II study (JBT-101-SSc, NCT02465437) in dcSSc patients found lenabasum was safe, well tolerated and there was a trend towards improvement in mRSS and reduction in itch.[209] An ongoing phase III study (RESOLVE-1, NCT03398837) will provide further insights into the safety and efficacy.	0.085	NS	0.03
Pan-peroxisome proliferator-activated receptor (PPAR) agonist.	Lanifibranor	Though to antagonise TGF-β pro-fibrotic signalling pathways. PPAR-gamma agonists ameliorated dermal fibrosis in	Phase II proof of concept trial (FASST, NCT02503644) found no significant improvement in mRSS, complete results awaited.[212]	NS	NS	NA

		vitro and in mouse models of SSc.[210] Lanifibranor prevented lung fibrosis in animal models.[211]				
JAK-inhibitor	Tofacitinib	Prevents pro-inflammatory and pro-fibrotic signalling via JAK/STAT pathway. Tofacitinib prevented bleomycin induced fibrosis in mouse model and reduced skin fibrosis in TSK1/+ mice.[213,214]	Phase I/II study (TOFA-SSc, NCT03274076) of tofacitinib at 5mg twice daily with background MMF or MTX was well tolerated and showed trends in improvement for mRSS and CRISS scores.[215]	0.42	NA	0.35
Anti-CD30	Brentuximab	Target activated immune cells.	Ongoing phase I/II dose esclataion study (BRAVOs, NCT03222492) assessing safety and tolerability in dSSc patients on background immunosuppression.	NA		
Micro reinjection of autologous adipose tissue stromal cells	Human adipose-derived stromal cells (ADSCs) and Adipose tissue-derived stromal vascular fraction (SVF)	Reduce localised handicap caused by skin fibrosis.	Previous case series demonstrated a subjective and objective reduction in skin tightening on the face[216] and another reported reduction in finger oedema and improvement in hand function.[217] A small open label study using autologous stromal bascular fraction of adipose tissue on fingers of SSc patients (NCT01813279) reported an improvement in finger oedema, hand disability, pain, RP and quality of life.[218] Ongoing prospective study (FACE, NCT02206672) assessing efficacy of micrografting on facial handicap in SSc patients.	Not applicable		

NA, data not available. ‘Not applicable’ indicates not a placebo controlled trial.

Figures: please see Powerpoint

CME QUESTIONS

45-year-old Jenny is a new patient in your practice. She has rapidly expanding pruritic sclerosis on her arms, chest and abdomen. She also reports dry eyes and mouth and tight skin around her fingers. On questioning she admits to reduced exercise tolerance in the last 6 months which she attributed to being unfit. After conducting the appropriate examination and investigations you diagnose dcSSc. You urgently refer her for lung function studies. Based on the available evidence, how would you treat her skin manifestations?

a) Start with topical tacrolimus twice daily to affected areas
b) Start methotrexate in combination with systemic steroids
c) Start mycophenolate mofetil, regular emollients and trial an anti-histamine
d) Await pulmonary function testing results with the plan to start her on nintedanib if there is evidence of pulmonary involvement
e) Advise her to use regular emollients, non-soap cleansers, avoid overheating and skin irritants

Despite your treatment, Jenny's skin and pulmonary manifestations progress. She would like to enter into a clinical trial using a new experimental medication which she read about online. Which of the following outcome measures is unlikely to be included to evaluate treatment efficacy in this trial?

a) Modified Rodnan Skin Score
b) ACA and anti-Scl70 titre
c) The Dermatology Life Quality Index (DLQI)
d) Forced Vital Capacity
e) B and C

Mr Smith comes to see you for a review. He has had Raynaud's phenomenon (RP) for many years and you recently diagnosed him with lcSSc. He is avoiding the cold, keeping warm, has regular wax baths but is still struggling with painful RP. He is otherwise well with no systemic symptoms. He is a type 2 diabetic for which he takes metformin but has no other medication. His heart rate today is 77 bpm, blood pressure 138/79mmHg, SpO_2 97% on room air. What would be your next step in management?
You can assume you have excluded other contributory causes to his RP.

a) Commence him on sustained release nifedipine, advise him about possible symptoms of low blood pressure
b) Commence him on an ACE inhibitor, given he is a diabetic this will be cardioprotective as well as help with his RP
c) Admit him for an IV prostanoid infusion
d) Commence him on sildenafil (a PDE5i)
e) Given he hasn't responded to general measures, he is likely to have complications, you organise referral for a digital sympathectomy

Your next patient has been suffering with recurrent digital ulceration. Despite adherence to general measures and optimisation of her oral therapy (PDE5i plus CCB) she continues to have painful, cold fingers and has now developed yet another ulcer on her left index fingertip. She now has 4 active ulcers. What would be the best next step in management?
Hint: use figure 3 from the Consensus best practice pathway of the UK Scleroderma Study

Group to guide your decision.

a) Optimise wound care and analgesia, organise to review her again next week to ensure there are no signs of infection
b) Switch to a different CCB and remind her of the importance to quit smoking
c) Continue current management, advise her she must wear gloves all day
d) Organise an IV prostanoid infusion, assess for infection including osteomyelitis and treat accordingly
e) Start her on a statin or aspirin

Which of the following is not a target of an emerging treatment option in SSc:

A) TGF-β
B) IFN-y
C) IL-6
D) IL-4/IL-13
E) Soluble Guanyl Cyclase (sGC)

Figure 1: The modified Rodnan Scoring Scale (mRSS) considers the degree and severity of cutaneous fibrosis in 17 anatomical sites.

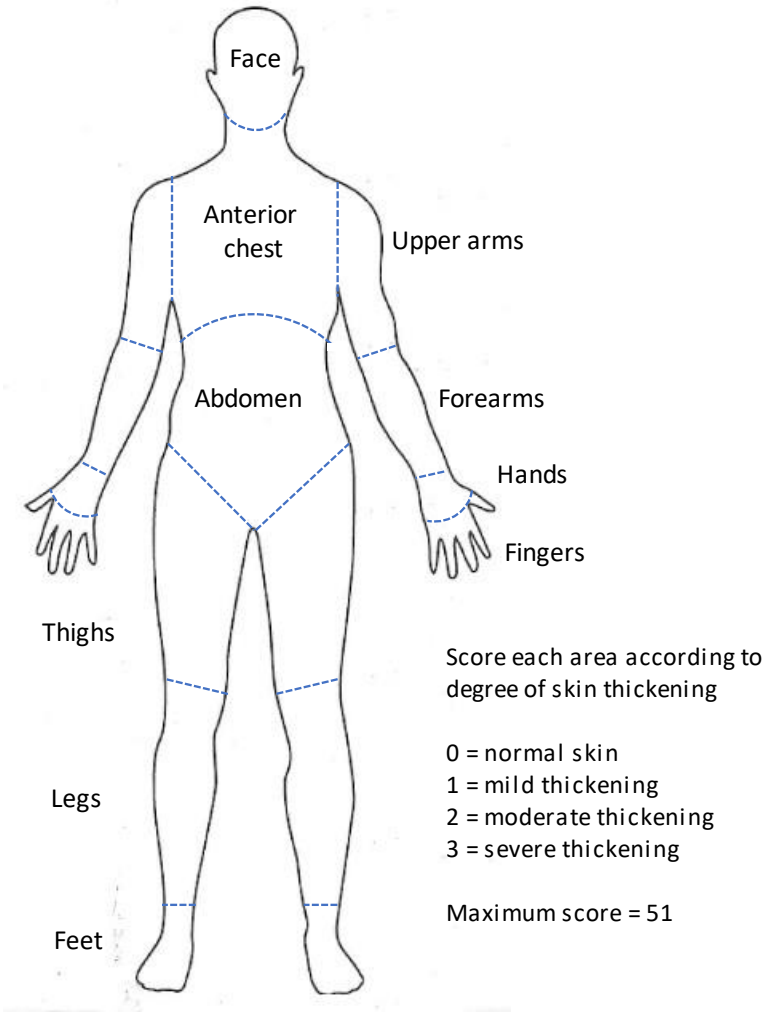

Figure 3: Illustration of emerging SSc therapies and their targets