SKIN INVOLVEMENT IN EARLY DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS – AN UNMET CLINICAL NEED

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ABSTRACT

Diffuse cutaneous systemic sclerosis (dcSSc) carries a high mortality due to early internal organ involvement. Therefore clinicians tend to focus on early diagnosis and treatment of potentially life-threatening cardiorespiratory and renal disease. However, it is the rapidly progressive painful, itchy skin tightening which characterises dcSSc that has the major impact on patients' quality of life, and for which there is currently no effective disease modifying treatment. In this review we shall describe the burden of skin disease in patients with dcSSc: this burden has only recently been fully recognised. We shall then outline advances in predicting 'progressors', including emerging molecular work from skin biopsies. Risk stratification for progressive skin disease is especially relevant now that haemopoetic stem cell transplantation is a treatment option, because this stratification will inform the balance of risk versus benefit for each patient. Measurement of skin disease remains a major challenge and we shall discuss the limitations of the modified Rodnan skin score (the current gold standard), citing recent clinical trials, and how new patient-reported and other potential outcome measures compare. Finally we shall outline best practice management of the skin disease of dcSSc including pathways for specialist referral.

KEY WORDS: Diffuse cutaneous systemic sclerosis, outcome measures, predictors, scleroderma, treatment

INTRODUCTION

There are two main subtypes of systemic sclerosis (SSc), as defined on the basis of the extent of the skin involvement ('scleroderma', which means 'hard skin'): diffuse cutaneous and limited cutaneous.[1] Diffuse cutaneous SSc (dcSSc) is the more 'feared' subtype because it is characterised by rapid progression and a high prevalence of early internal organ involvement (including lung, heart and kidney) which can be life-threatening. DcSSc is therefore associated with a high mortality,[2-4] with a five year survival rate in the order of 70%, and clinicians understandably tend to focus their attention on early identification and treatment of internal organ disease. However, on a day-to-day basis, in patients with early dcSSc it is the skin thickening which has most impact on quality of life by causing pain, intractable itch and functional limitation.

Skin involvement in early dcSSc is an important topic not only because of the impact of skin disease on the patient, but also because the skin is a very visible and accessible 'window' into the dcSSc disease process. Therefore examining the skin allows prediction and monitoring of disease progression and of treatment response. A review is timely because of (a) recent bench-marking of the burden of skin disease in patients with dcSSc (b) recent increased understanding of how to identify 'progressors' not only on the basis of clinical features but also through advances in molecular technologies applied to skin biopsies (c) the controversies surrounding how best to measure the extent and impact of skin disease, highlighted by recent clinical trials and (d) the need to promote best practice management of skin disease, as well as of internal organ disease.

The scope of this review is to give a comprehensive description of the clinical and scientific implications of skin involvement in dcSSc. First, we shall describe skin involvement, patterns of progression, and the associated clinical burden, including contractures and ulceration. Second, we shall outline how those patients whose skin disease progresses can now be predicted by considering different clinical features (including disease duration, extent of skin disease, and autoantibody status) and potentially by gene expression profiling of biopsied skin. Identifying progressors is especially relevant now that autologous haemopoetic stem cell transplantation (HSCT) is an option for patients

at high risk of progression, so that only those patients most in need are exposed to the procedure's potential toxicity (and mortality). Third, we shall discuss outcome measures of skin disease, specifically the modified Rodnan skin score (mRSS), but also patient reported outcome measures and non-invasive imaging techniques. Fourth, we shall describe best practice management, including general measures, immunosuppressant treatment, and HSCT, and also discussion on the controversial topic as to whether or not corticosteroids should be prescribed. We shall not discuss recent, ongoing and proposed studies of new targeted therapies (including biologic agents such as tocilizumab and rituximab) as these have been reviewed elsewhere.[5] However, we shall reinforce how patients with early dcSSc should, whenever possible, be recruited into clinical trials, to maximise the chances of identifying an effective disease modifying therapy for this currently incurable disease.

CLINICAL FEATURES AND BURDEN OF DISEASE

Clinical features

In patients with early dcSSc, skin involvement commences distally, usually first affecting the fingers which initially often become swollen and painful. This early oedematous phase is sometimes misdiagnosed as inflammatory arthritis, and can be associated with carpal tunnel syndrome, but over a few weeks the skin hardens and the diagnosis of SSc usually becomes obvious. It is a defining feature of the diffuse cutaneous subtype of SSc that skin involvement progresses (often rapidly) to proximal to the elbow or knee and/or involves the trunk. Conversely, in limited cutaneous SSc, skin involvement is confined to the extremities (distal to the elbows and knees) and to face and neck.[6]

During the early (inflammatory) phase of dcSSc, when the skin disease is progressing, the skin is often itchy and painful. Pigmentary change can occur[7,8] and can be distressing to patients, especially in those with darker skins. The skin tightening commonly leads to contractures, particularly fixed flexion deformities of the fingers[9] (Figure 1a) but also of the elbows and sometimes knees. Range of movement is often substantially reduced, for example at the shoulders or at the ankle, subtalar and mid-tarsal joints. The flexion contractures predispose to overlying ulcers (Figure 1b) which can be

refractory to treatment and which can lead to underlying osteomyelitis. Rarely the skin is so tightened that small superficial ulcers appear, unrelated to pressure points (Figure 1c).

Itch, often described as the most troublesome symptom, resolves when the early inflammatory phase subsides. In those patients who survive, the skin disease as assessed by the mRSS will generally plateau (usually within three to five years of onset),[10] and then the skin gradually softens and atrophies, to the extent that years later, there may no longer be any skin thickening. The contractures, however, persist and are usually irreversible (Figure 1d).[9]

Associated morbidity

Although it has long been recognised that the skin involvement in early dcSSc is painful, disabling, and disfiguring, it is only relatively recently that these elements of disease burden have been quantified. Although the main aim of the European Scleroderma Observational Study (ESOS),[11] which included 326 patients with early dcSSc from 19 countries (median disease duration from onset of skin thickening of 11.9 months) was to assess treatment outcome, ESOS also provided the opportunity to examine associations between severity of skin involvement and functional ability, as well as quality of life. Severity of skin involvement was measured by the mRSS. At the baseline visit, high mRSS was associated with high levels of disability (with 'grip' and 'activity' being most affected) as assessed by the Health Assessment Questionnaire disability index (HAQ-DI) (ρ=0.34, $p<0.0001$) and specifically with high levels of hand disability, as assessed by the Cochin Hand Function Scale (CHFS) (ρ=0.35, $p<0.0001$): fine finger movements were particularly affected.[12] High mRSS was also associated with severity of pain, as assessed on a 0-100 scale (ρ=0.17, p=0.002) and of fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score (ρ=-0.20, p=0.0005). Examining changes over 12 months, increases in the mRSS associated with worsening disability as measured by HAQ-DI (ρ=0.40, $p<0.0001$). In summary, ESOS demonstrated that the greater the degree of skin thickening, the greater the disability (with an emphasis on hand disability), pain, and fatigue, and that if skin thickening progresses then so too does disability.

The association between progression of skin thickening and worsening of disability in early dcSSc has since been confirmed in other studies: in a single centre retrospective study,[13] an increase in mRSS was associated with worsening disability as measured by HAQ-DI in that subgroup of patients with early dcSSc (ρ=0.36, p=0.004), and in a study of 154 patients from Canada with early dcSSc,[14] changes in mRSS correlated with changes in the HAQ-DI (r = 0.43 for 1 year data, r = 0.41 for 2 year data).

PREDICTORS FOR PROGRESSIVE SKIN INVOLVEMENT

Associates of extensive and/or progressive skin involvement

Amongst patients with early dcSSc, different trajectories of skin involvement have been described: skin score can progress (sometimes rapidly), stabilise or improve. We need to identify those patients with progressive skin involvement not only because this is painful and disabling as described in the previous section, but because extensive and/or progressive skin disease portends a poor outcome. Survival is reduced in patients with high skin scores.[15-17] A high 'skin thickness progression rate' (the mRSS at first visit divided by patient reported duration of skin thickening) has been shown to be a predictor of early mortality and of scleroderma renal crisis.[18] Reduced survival in 'progressors' amongst patients with dcSSc was also reported in an analysis of the European Scleroderma Trials and Research [EUSTAR] database: 78 'skin progressors' had lower survival (and more decline in lung function) compared to 943 'non-progressors'.[19] Conversely, a reduction in skin thickening is reassuring, being associated with improved survival[20] and reduced internal organ involvement.[21]

Predictors of progression

Accurate prediction of progressive skin involvement would allow clinicians to make informed decisions regarding whether or not to commence patients on potentially toxic treatments, usually an immunosuppressant but potentially (in highly selected patients) HSCT. Although treatment-related mortality of HSCT is much lower than previously, it remains a concern and so the procedure should

only be carried out in those at highest risk. Prediction of progressive skin disease is important also to clinical researchers when designing clinical trials of potential disease modifying therapies: inclusion and exclusion criteria should be selected to include 'progressors' rather than 'non-progressors', who are less likely to benefit from treatment. 'Progressors' are often defined as those experiencing a 5-unit and 25% increase in mRSS over 12 months.[22-24]

Tendon friction rubs are an indicator of disease that is very likely to progress.[25,26] Domsic et al. reported in 2011[18] that a positive anti-RNA polymerase III antibody was associated with rapid skin disease progression. In recent years, several studies have investigated predictors of progressive skin disease. Low mRSS, short disease duration and joint synovitis were found to be predictors of disease progression in an analysis from the EUSTAR database,[22] whereas a high baseline mRSS (and absence of friction rubs) predicted improvement.[27] On the basis of these results, Maurer et al[22] suggested that only patients with an mRSS of 22 or lower should be included into clinical trials of early dcSSc because patients with higher scores were unlikely to progress. This fairly stringent cut-off excludes many patients. An analysis of the ESOS cohort,[23] in whom mRSS was assessed 3-monthly (allowing detailed assessment of disease trajectory), demonstrated that patients with higher skin scores could reasonably be included into clinical trials if disease duration was short. The 66 progressors had shorter disease duration (median 8.1 vs. 12.6 months, p=0.001) and lower mRSS (median 19 vs 21 units, p=0.030) than the 227 non-progressors, with those patients who were anti-RNA polymerase III antibody positive going on to have the highest skin scores, and peaking earliest. Two predictive models were derived for progressive skin thickening[23]: the first included mRSS, duration of skin thickening and their interaction, the second additionally anti-RNA polymerase III positivity. Both were more accurate than a '22 mRSS' cut-off model and for a given skin score were more flexible, allowing a higher baseline skin score to be compensated by a shorter disease duration[23] (Table 1). Application of these models should maximise numbers of the most informative patients (progressors) to be included into clinical trials. Since then other studies have confirmed the role of skin score and disease duration as predictors of progression. A recent analysis from the Pittsburgh cohort[28] concluded that ideally only patients with a disease duration of less than 18 months should be included into

clinical trials. The findings underpinning Table 1 suggest that some flexibility in disease duration could be allowed with lower skin scores. Findings from the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS)[24] cohort suggested that an mRSS of 27 or less was predictive of progression, despite a mean disease duration of 2.4 $\pm$ 1.5 years (i.e. longer than in ESOS). Kuwana et al.[29] reported that disease duration of 12 months or less and an mRSS of 19 or less predicted progression (sensitivity 73.9%, specificity 81.1%), consistent with findings from ESOS (Table 1).

Gene expression profiling of skin biopsies may help to predict outcome. Higher 'fibroinflammatory' scores have been associated with higher skin scores (both mRSS and local at the biopsy site).[30] A recent study[31] suggested that gene expression profiles in forearm skin biopsies from patients with early dcSSc were associated with previous skin disease progression (higher Skin Thickness Progression Rate), but were not predictive of future progression. These findings contrast with those from a phase II trial of tocilizumab: here expressions of a limited number of fibrotic and inflammatory genes in forearm skin biopsies from placebo-treated patients were associated with mRSS progression[32]: these genes were not predictive of mRSS course in the study by Skaug et al.[31] Different skin gene expression subsets (inflammatory, fibroproliferative, and normal-like) have been described using a machine learning approach.[33] These gene expression subsets might help to explain variable response to immunomodulatory therapies. In a recent randomized controlled study of abatacept in dcSSc, patients with the inflammatory and normal-like subsets had a significant response to treatment while there was no significant treatment effect in the overall study population.[34] Recent studies have confirmed that skin gene expression profile is associated with disease duration as well as local/overall skin score. Specifically, patients with an inflammatory skin gene expression profile have a shorter disease duration and higher skin score.[31,35,36] At this point, it is unknown to what extent skin gene expression profiling can help predict response to treatment beyond the information provided by easily obtained clinical predictors such as disease duration, baseline skin score, or anti-RNA polymerase III positivity status. Recent work has suggested differences in gene expression and pathway enrichment

between major autoantibody subgroups in early dcSSc[37] that are likely to reflect both distinct and overlapping biological mechanisms determining progression and regression of skin disease at a patient level. Integration of local gene and protein expression may provide additional insights into local pathogenesis of skin fibrosis[38] as well as identify candidate biomarkers that could be used in patient stratification or assessment of outcome, building upon studies of the enhanced liver fibrosis (ELF) score.[39,40]

In summary, we now have a much better insight than 5 years ago into the factors predicting disease progression, with progress being made towards a stratified approach to therapy. As we continue to advance our knowledge, it will be possible to build upon the conceptual framework for skin score trajectory linked to biology of progression and regression outlined in Figure 2.

OUTCOME MEASURES

Reliable outcome measures which are sensitive to change are a prerequisite to monitor disease progression and treatment response. Over the years multiple different methods have been used to assess skin involvement.[41]

The mRSS (and PASTUL questionnaire)

Measurement of the extent of skin involvement is complex, and needs to take into account the surface area affected and the degree of involvement at the different body sites. The mRSS[42] has been fully validated as per OMERACT,[43] but presents challenges. Skin is assessed by palpation on a 0-3 scale at 17 sites (0 = uninvolved, 1 = mild involvement, 2= moderate involvement, 3 = so severely involved affected that the skin can hardly be moved). The score range is therefore 0-51 (although in practice, maximum observed scores are seldom above 40) with a minimally clinically important difference for improvement at 12 months, in the context of a clinical trial, of 5 units.[44]

It is well recognised that there is substantial inter-observer variability in this method of skin scoring,[45] although a recent study in which 10 rheumatologists assessed seven patients found high inter-observer

and intra-observer reliability of 0.81 and 0.94 respectively.[46] Concerns about inter-observer variability mean that when at all possible (and certainly in clinical trials) the same observer should perform the skin scoring in any given patient. One major contributor to inter-observer variability is that when scoring one particular area e.g. left forearm, some raters tend to 'maximise' (select a score based on the most severely affected area within the forearm), some choose a 'representative' score (select the score which seems more representative of the whole forearm), and some 'average'.[44,47] Another problem with the mRSS is that the skin is very difficult to assess in later stage disease,[48] because although the skin is then softening it can remain tethered, making it impossible to pinch. For example, in later stage disease the skin of the dorsum of the hand may appear atrophic and yet be tethered to the underlying tissues, with the result that some raters assign a score of 3 whereas others assign a score of zero. Standardised training may reduce variability in skin scoring.[49.50]

Without doubt the mRSS is useful in the outpatient clinic, because it is quick and easy to perform and will help the clinician decide whether or not to intensify or to begin withdrawing immunsuppressant treatment. It associates with patient-reported worsening of skin involvement.[51] But how useful is the mRSS as an outcome measure in clinical trials? For years the mRSS has tended to be the primary outcome in clinical trials of potential disease modifying therapies in patients with early dcSSc (Table 2), given that the degree of skin involvement reflects the 'overall' early dcSSc disease process. Several of these trials (Table 2)[34, 52-56] have failed to meet their primary end-point, despite signals of efficacy coming from secondary endpoints. For example, in the recent FocuSSed phase III randomised placebo-controlled trial (RCT) of tocilizumab,[53] patients did not improve significantly on active treatment in terms of mRSS, but there was a significant improvement in terms of lung function, and the United States Food and Drug Administration (FDA) has now approved the use of tocilizumab for SSc-related interstitial lung disease. And in the recent RCT of abatacept,[34] significant improvement on active treatment was demonstrated in terms of the HAQ-DI and of the American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (ACR CRISS), which is a composite measure including the mRSS)[57], but not in terms of the mRSS alone. Experience in these and other studies begs the question as to whether improvement was 'missed'

because of the limitations in mRSS scoring. However, because the mRSS is highly feasible for use in multicentre studies and 'makes sense', it is likely that it will continue to be used as an outcome measure, at least as a component of composite response indices which can also be used to monitor dcSSc disease progression (and which may include the HAQ-DI[58]).

Because the mRSS is 'hands on', this has implications for both clinical practice and clinical trials during the Covid-19 era, when patient visits to hospital are being minimised. Therefore patient's self-assessment of skin involvement, previously proposed[59.60] but up until now not widely applied, is an attractive option. An exciting development is the PASTUL (Patient self-Assessment of Skin Thickness in Upper Limb) questionnaire, a patient self-assessed skin score.[61] In an initial study of 104 patients with SSc, 78 (75%) of whom also had an mRSS performed, there was moderate correlation between PASTUL and both total mRSS (r = 0.56) and upper limb mRSS (0.58). PASTUL strongly correlated with results from the Scleroderma Skin Patient Reported Outcome (SSPRO)[62] discussed below. Once fully validated, PASTUL could be an important addition to clinical trials, bringing the possibility of more frequent skin scoring during trial treatment than has previously been possible (and in the patient's own home).

Other outcome measures

The limitations of the mRSS have resulted in other outcome measures of skin involvement, and composite measures, being explored. These are attracting increasing interest for application in trials of early dcSSc. Here the main ones will be considered in turn:

Patient reported outcomes. The SSPRO developed by Man et al.[62] is an 18 item questionnaire assessing skin-related quality of life in patients with SSc. It is already being applied in clinical trials[56] and will most likely become widely adopted. The HAQ-DI (mentioned earlier), although not specific to the skin involvement of early dcSSc, captures much of the associated disability and has the advantage that most clinicians are familiar with it: several recent trials have included the HAQ-DI as an outcome measure.[34,52-56,63,64] Because itch can be a very prominent feature in early dcSSc, itch

assessment should also be considered, for example by the 5-D Itch scale,[65] which was included in the recent study of lenbasum.[56]

Non-invasive imaging methods. The two main contenders here are high frequency ultrasound and optical coherence tomography (OCT). Ultrasound reliably measures skin thickness, with several cross-sectional studies by different groups of investigators having been reported[66-69] and a very recent study advocating ultrasound as an outcome measure.[70] Ultrasound skin thickness (4-15 MHz linear probe) was recently shown to correlate well with histological skin thickness ($r = 0.6926$, $P = 0.009$) and with local (forearm) mRSS ($r = 0.7961$, $P = 0.001$) in 13 patients with SSc (9 of whom had dcSSc) who underwent forearm skin biopsies.[71] As the imaging resolution with newer ultrasound devices improves and ultrasound based elastography becomes available in clinical setting, additional studies are needed to assess the reliability and validity of these improved ultrasound-based skin thickness measurement modalities in SSc.[72] Moreover, accurate measurement by ultrasound requires training and is time-consuming if performed at multiple body sites, probably explaining why ultrasound has not been adopted as an outcome measure in later phase multicentre studies. This technical challenge will most likely apply also to OCT, which is another promising tool to assess skin thickness in early phase proof of concept studies. OCT essentially takes in vivo 'optical biopsy' images of the skin, similarly to ultrasound, but using light[73] to visualise skin structure. In this way epidermal thickness can be measured at high resolution (<10 μm). Very few studies have examined its use in patients with SSc.[74,75] While OCT can provide higher imaging resolution than ultrasound-based techniques, currently it has limited imaging depth which complicates assessment of lower layers of dermis in certain body areas with this imaging technique, underscoring the need for further development in this area. Polarisation-sensitive optical coherence tomography (Ps-OCT)[76] is an extension to OCT, measuring birefringence in addition to skin thickness (collagen is birefringent). Birefringence can be considered a measure of skin 'heterogeneity' and potentially therefore of fibrosis. Epidermal thickness measured by Ps-OCT correlated with histological thickness in a study including 10 patients with SSc and 10 healthy controls.[77] Larger, prospective studies examining change over time are required to validate both ultrasound and OCT as possible outcome measures.

Durometry. This measures skin hardness and although long advocated as a possible outcome measure in clinical trials of early dcSSc,[78] has not been 'taken up'. However, durometry has recently been revisited[79] and deserves further investigation including in longitudinal studies examining sensitivity to change. A durometer is hand-held, portable, and relatively easy to use, making it a potentially feasible additional outcome measure in multicentre studies.

Composite scores. At present there are no composite scores specifically of skin disease in patients with SSc. However, the ACR CRISS,[57,80] which is heavily weighted by the mRSS, has attracted considerable recent interest and is likely to become widely adopted in future RCTs in patients with dcSSc. Moreover, longitudinal skin gene expression levels of two skin transcripts, thrombospondin-1 (THBS1) and MS4A4A, were able to track longitudinal mRSS measurements.[81] However, there are currently no studies to show that changes in any skin transcripts correlate with how patients with dcSSc "feel, function, and survive" in order to establish them as surrogate outcome measures. Additional studies are needed to examine the utility of skin transcripts as clinically useful surrogate measures. Serum composite biomarkers have also been explored, including ELF and also novel proteomic markers that may be used as candidates to assess treatment response, but these are currently at a research level.[82] Recent work has suggested substantial heterogeneity in longitudinal relationship between serum markers, including ELF, and mRSS.[37]

In summary, current outcome measures are not ideal, but there are ongoing international efforts to improve on these through modification of existing tools and development of new measures, including (at least for early phase studies) non-invasive imaging techniques.

BEST PRACTICE MANAGEMENT

Although there is currently no cure for SSc (and for this reason it is imperative that whenever possible patients are recruited into clinical trials), there is no room for nihilism: much can be done to support patients through the worrying phase of early dcSSc. This includes symptomatic treatment for progressive skin disease and (in most patients) immunosuppression even though the evidence base in

favour of immunosuppression is weak. A small minority of patients will be candidates for HSCT. Despite the recent interest in nintedanib as a treatment for SSc-related interstitial lung disease, nintedanib has not been shown to improve skin score,[83] although SENSCIS was a trial investigating lung disease and not primarily a study of patients with early dcSSc.

Here we describe best practice management of skin thickening in early dcSSc, summarised in Figure 3. Decisions on treatment (particularly choice of immunosuppressant) will be influenced by presence or absence of other SSc 'complications', for example concomitant myositis or interstitial lung disease.[84]

Early recognition

Diagnosis of early dcSSc is often made very late, [85] leading to delays in identification and early treatment of (for example) internal organ involvement, and in patient education. The key point here is raising awareness. Any patient with new onset of skin thickening which could indicate early dcSSc should be referred to a specialist centre, especially if the skin thickening has rapidly progressed. Although most patients with early dcSSc describe Raynaud's phenomenon, this may develop only after the skin thickening, and so the 'red flag' of Raynaud's phenomenon[86] does not always apply (in contrast to the situation in lcSSc, when the onset of Raynaud's phenomenon usually precedes the diagnosis of Sc by many years.[6]

General measures

The four main aspects here are analgesia, treatment of itch, physiotherapy and occupational therapy. But also to be included are consideration of clinical psychology input and intravenous (IV) iloprost infusions.

Analgesia. The pain of skin disease in early dcSSc is often insufficiently recognised, yet it has a major impact on quality of life. Among the 326 patients recruited into ESOS[12] the mean and median scores for the sHAQ pain scale (0-100, 100 most disabled) were 32.9/100 (SD 26.9) and 29.0/100 (IQR 8.7-52.7), and the greater the skin thickening, the greater the pain ($p = 0.17$, $P = 0.002$). If contractures

and ulcers develop then these further compound the pain. Adequate analgesia is therefore a key aspect of management, as well as treatment of digital ulceration. There may be a neurogenic component to the pain,[87] and therefore treatment with gabapentin or pregabalin could be considered. Some patients will benefit from referral to a pain management clinic.

Management of itch. In the authors' experience this is very difficult. Antihistamines can be tried but seldom seem helpful. Some patients find 1% menthol in aqueous cream of benefit. Anecdotally, low dose prednisolone can relieve itch. Prednisolone is, however, a risk factor for scleroderma renal crisis as discussed below.

Physiotherapy and occupational therapy. There has been very little research examining the role of physiotherapy and occupational therapy in early dcSS but these 'make sense'. Anecdotally, patients benefit from stretching exercises to maintain range of movement, and many enjoy hydrotherapy. A recent study including 34 patients with dcSSc, but with unspecified disease duration, suggested benefit from hand exercises.[88] Ideally all patients with early dcSSc should be assessed by an occupational therapist as almost all patients have significant functional disability including (and as discussed above) impairment of hand function. 'Remote' occupational therapy via an App[89] could be a way forward at least in some patients.

Clinical psychology input. Patients with early dcSSc report feeling overwhelmed by their disease, with loss of control. This relates in large part to the disability, pain and fatigue which are directly or indirectly related to skin disease. Clinical psychology referral should be considered.

Immunosuppressant therapy

Both the British Society for Rheumatology (BSR)/British Health Professionals in Rheumatology (BHPR)[90] and the European League Against Rheumatism (EULAR)[91] recommend immunosuppressant therapy for the skin disease of SSc. The BSR/BHPR guidelines suggest mycophenolate mofetil, methotrexate or cyclophosphamide, whereas EULAR has methotrexate as the favoured option. There have been few clinical trials of immunosuppressants specifically examining the skin disease primarily in early dcSSc: two of methotrexate, [92,93] none of mycophenolate (despite

several early retrospective and prospective observational studies suggesting benefit[94-96]) and none of cyclophosphamide. Given the challenges of clinical trials in early dcSSc, especially trials of immunosuppressive therapies which are now out of patent, ESOS[11] set out to examine the relative effectiveness of commonly used immunosuppressants in patients with early dcSSc. The chosen treatment options in this observational study were methotrexate (oral or subcutaneous at a target dose of 20 to 25 mg weekly), mycophenolate mofetil (MMF, target dose 1g twice daily), cyclophosphamide (IV or oral) or no immunosuppressant. There was a trend in favour of immunosuppression: after 12 months, mRSS fell in all groups but more so in the immunosuppressant groups: for methotrexate (n= 65) -4.0 units (-5.2 to -2.7), for MMF (n= 118) -4.1 (-5.3 to -2.9), for cyclophosphamide (n=87) -3.3 (-4.9 to -1.7) and for no immunosuppressant (n=56) -2.2 (-4.0 to -0.3) (p value for between-group differences=0.346). The conclusion from ESOS was that immunosuppression conferred benefit, but that this benefit was modest. Improvements in mRSS in patients with dcSSc were also found in Scleroderma Lung Study I (with cyclophosphamide compared to placebo) and in Scleroderma Lung Study II (with cyclophosphamide and mycophenolate mofetil, compared to patients treated with placebo in Scleroderma Lung Study 1) at 12, 18 and 24 months ($p < 0.05$)[97] : these were not studies specifically of early dcSSc. Further support for the use of MMF includes from an Australian observational study, [98] and the report of 5 patients with recurrence of progressive skin involvement following either discontinuation or dose reduction of MMF.[99]

Corticosteroids

The use of corticosteroids in early dcSSc is highly controversial,[100] and clinicians have different views: some prescribe them and others do not, evidenced by 44% of patients being recruited into ESOS having been prescribed corticosteroids.[11] Anecdotally, corticosteroids can relieve symptoms during the early inflammatory phase of skin thickening in patients with early dcSSc, reducing itch (as mentioned earlier) and pain, and potentially preventing contracture. However, corticosteroids, especially when used in high dose, are a risk factor for renal crisis.[101-103] This is a major concern because patients with early dcSSc and progressive skin disease are already at high risk of renal crisis especially when anti-RNA polymerase III antibody positive.[104,105] Whether or not corticosteroids

should be prescribed in patients with early dcSSc is a question currently being addressed in a randomised placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03708718).[64]

Intravenous iloprost

Intravenous iloprost is widely used in the treatment of SSc-related digital vasculopathy but may have other beneficial effects, and has been shown to downregulate connective tissue growth factor. [106] In the authors' experience, it can help heal the superficial ulcers which can occur in patients with very tightened skin (Figure 1c), the assumption being that there may be an ischaemic element to these ulcers.

Autologous haemopoetic stem cell transplantation

HSCT should be considered in highly selected patients with rapidly progressive dcSSc. In all three trials which provided the evidence base for this recommendation (ASSIST,[107] ASTIS[108] and SCOT[109]), those patients undergoing HSCT demonstrated benefit in terms of mRSS compared to those patients treated with cyclophosphamde, although mRSS was not the primary endpoint (mRSS was, however, part of the composite primary endpoint in the ASSIST study[107]). Improvement in mRSS was also reported in a prospective 'real-world' study of 80 patients.[110] The treatment related mortality of HSCT in the SCOT study was 3% at 54 months and 6% at 72 months[109] and therefore lower than previously reported,[111] most likely reflecting careful patient selection and adjustments to the transplant regime. A key question which is currently being addressed[112] is whether HSCT should be recommended as an 'upfront' therapy as opposed to being reserved for patients not responding to immunosuppressant therapies. These are difficult decisions which will be informed by the stratified medicine approach referred to earlier, and by ensuring that individualised care is tailored to the patients' needs and expectations.[113]

CONCLUSIONS

The last five years have provided new insights into the most visible and most characteristic manifestation of early dcSSc - skin thickening (sclerodema) - which is often rapidly progressive.

Importantly, we now recognise the disease burden of skin disease with its very significant impact on quality of life: previously this was often overlooked. We are now in a good position to predict which patients develop rapid progression of skin thickening, thus allowing early intervention with immunosuppressive therapies or with HSCT and/or inclusion into clinical trials. The challenges of monitoring skin disease, both in the clinic and in the setting of clinical trials, are now better understood, and research is ongoing. Better outcome measures (and improved identification of 'progressors') will maximise the efficiency of future clinical trials of the many promising new targeted therapies. Pending identification of a safe and effective treatment, clinicians should not forget current best practice guidelines which can provide at the very least some symptomatic relief from painful, disabling skin disease.

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Table 1 – Rules for selecting progressive patients according to two selected models. From Herrick et al. Ann.Rheum. Dis. 2018.[23]

Table 2 – Recent examples of studies in which mRSS was an outcome measure (usually the primary outcome)

Study	Key inclusion criteria[a]		Primary end-point	Comment
	mRSS	Disease duration (months)		
Tocilizumab vs placebo phase II (FaSScinate) [52]	15-40	≤ 60	Change in mRSS at 24 weeks (not met)	No significant improvement in mRSS on tocilizumab. although trend in favour, and less decline in FVC
Tocilizumab vs placebo phase III (FocuSSed)[53]	10-35	≤ 60	Change in mRSS at 48 weeks (not met)	No significant improvement in mRSS on tocilizumab. Changes in FVC (significant) in favour of tocilizumab.
Abatacept vs placebo[34]	≥10 ≤ 35 or ≥15 ≤ 45	≤ 18 >18 ≤ 36	Change in mRSS at 12 months (not met)	No significant improvement in mRSS on abatacept (although there was for the inflammatory and normal-like gene expression subsets), but significant improvement in HAQ-DI and ACR CRISS on abatacept.
Riociguat vs placebo[54]	10-22	≤18	Change in mRSS at 52 weeks (not met)	No significant improvement in mRSS on riociguat
Romilkimab vs placebo[55]	10-35	<36	Change in mRSS at 24 weeks (met)	mRSS improved more on romilkimab

				than on placebo
Lenabasum vs placebo[56]	Proximal or truncal involvement or ≥16 (or ≥12 with increase ≥ 5 in previous 6 months)	≤ 36 >36 ≤72	No single primary efficacy outcome, but outcomes included change in mRSS	No significant improvement in mRSS on lenabasum, but trend in favour. Other measures significantly improved including SSPRO and itch score

a. For full details, see full publications

ACR CRISS: American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (ACR CRISS)

FVC: Forced vital capacity

SSPRO: Scleroderma Skin Patient Reported Outcome

LEGENDS TO FIGURES

1. Skin involvement in dcSSc: (a) Flexion contractures of the fingers in early dcSSc (b) Flexion contractures associated with ulceration (c) Superficial cutaneous ulceration in early dcSSc (d) Late stage disease with persisting contracture (note the scar from carpal tunnel decompression, performed soon after onset of symptoms of dcSSc).

2. Conceptual framework for skin score trajectory linked to biology of progression and regression. Cohort studies suggest differences in skin score change over time for SSc that are summarised into groups with higher peak score and greater regression over time. Conceptually this is likely to reflect interplay between the drivers of progression and fibrosis and the counteracting effect of the mechanisms determining spontaneous regression that is a hallmark of normal skin wound healing. It is likely that molecular and cellular determinants of these processes interact and underly the distinct patterns of skin disease and may also determine the development and severity of internal organ complications in SSc.[16, 23, 37]

3. The approach to management of skin disease in patients with early dcSSc.

KEY POINTS

1. Much of the pain and disability of early diffuse cutaneous systemic sclerosis (dcSSc) is due to skin thickening (scleroderma) which can be rapidly progressive, commencing distally then extending proximally.

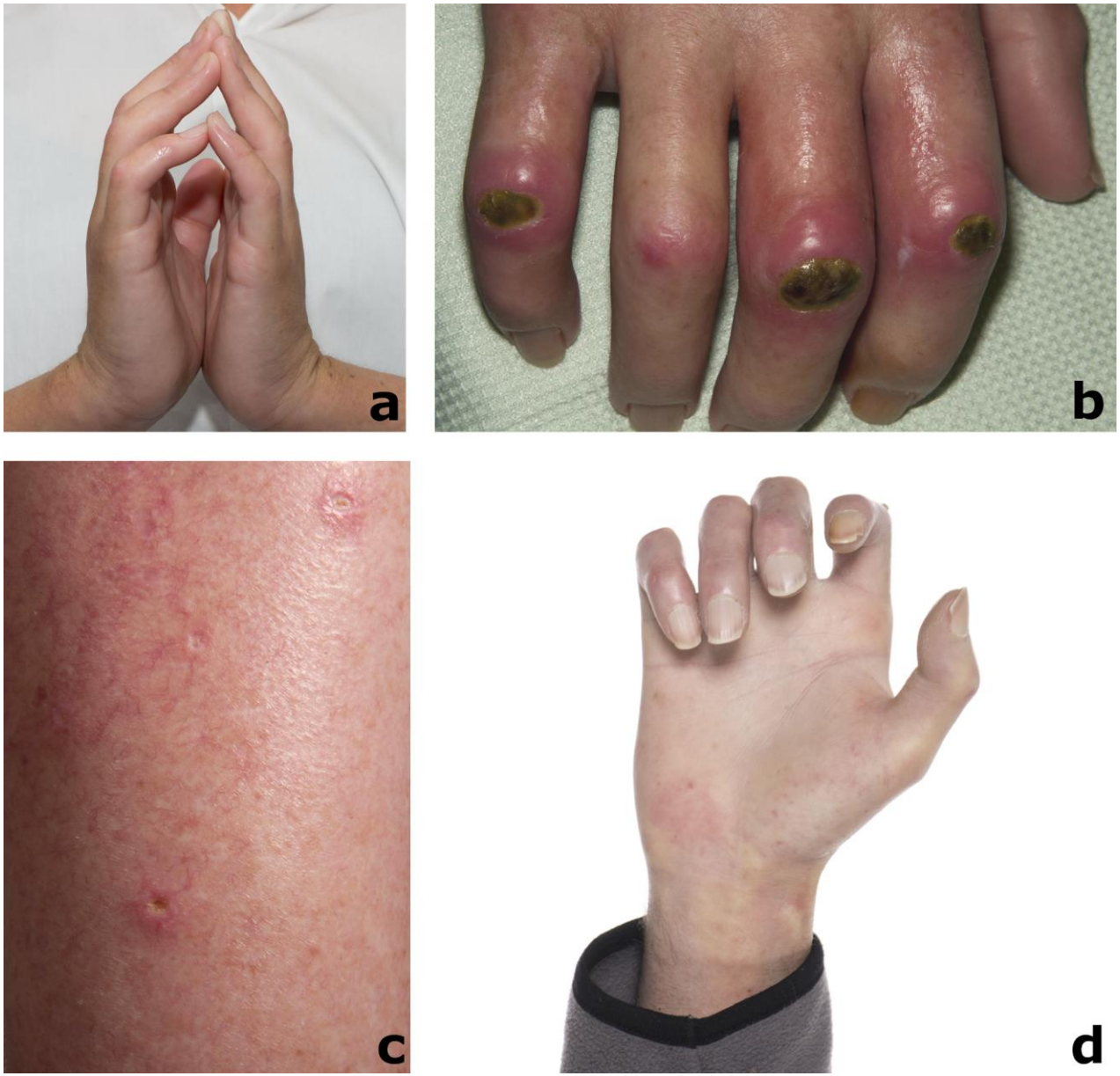
2. 'Progressors' in terms of skin disease can now be identified by considering disease duration, extent of skin disease, autoantibody status and (potentially) gene expression profiling of biopsied skin.

3. Improved ability to predict progressive skin disease will inform selection of patients for haemopoetic stem cell transplantation, as well as more targeted inclusion of patients into clinical trials.

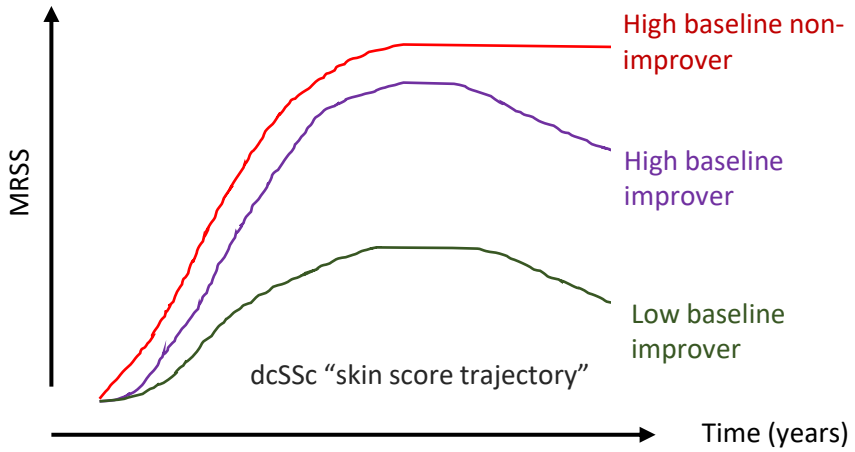
4. Limitations of the modified Rodnan skin score (mRSS) are driving development of other outcome measures of skin disease: including patient reported outcome measures, non-invasive imaging methods, and composite scores.

5. Best practice management of early dcSSc includes early referral to a specialist centre, pain management, multidisciplinary input, immunosuppressive therapy, and when at all possible inclusion into a clinical trial.

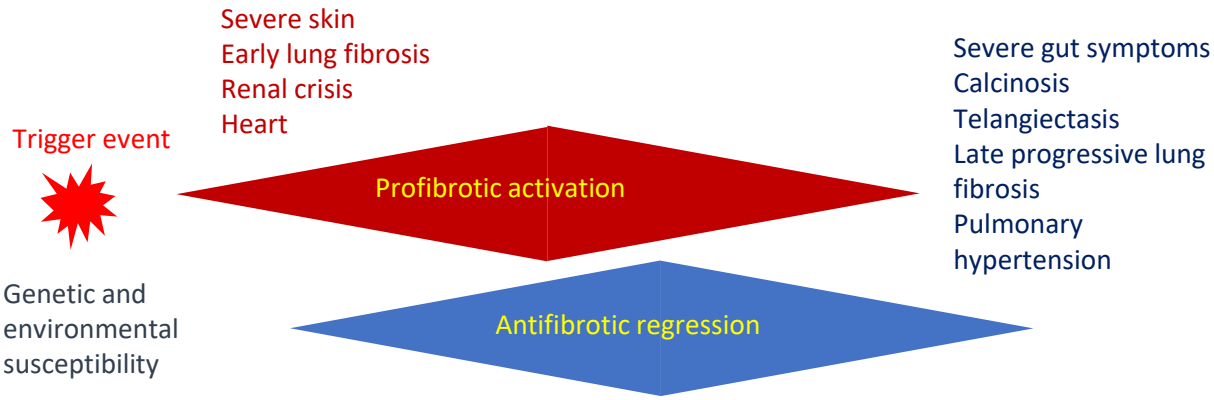
Figure 1



A conceptual framework for skin score and clinical diversity in diffuse cutaneous systemic sclerosis

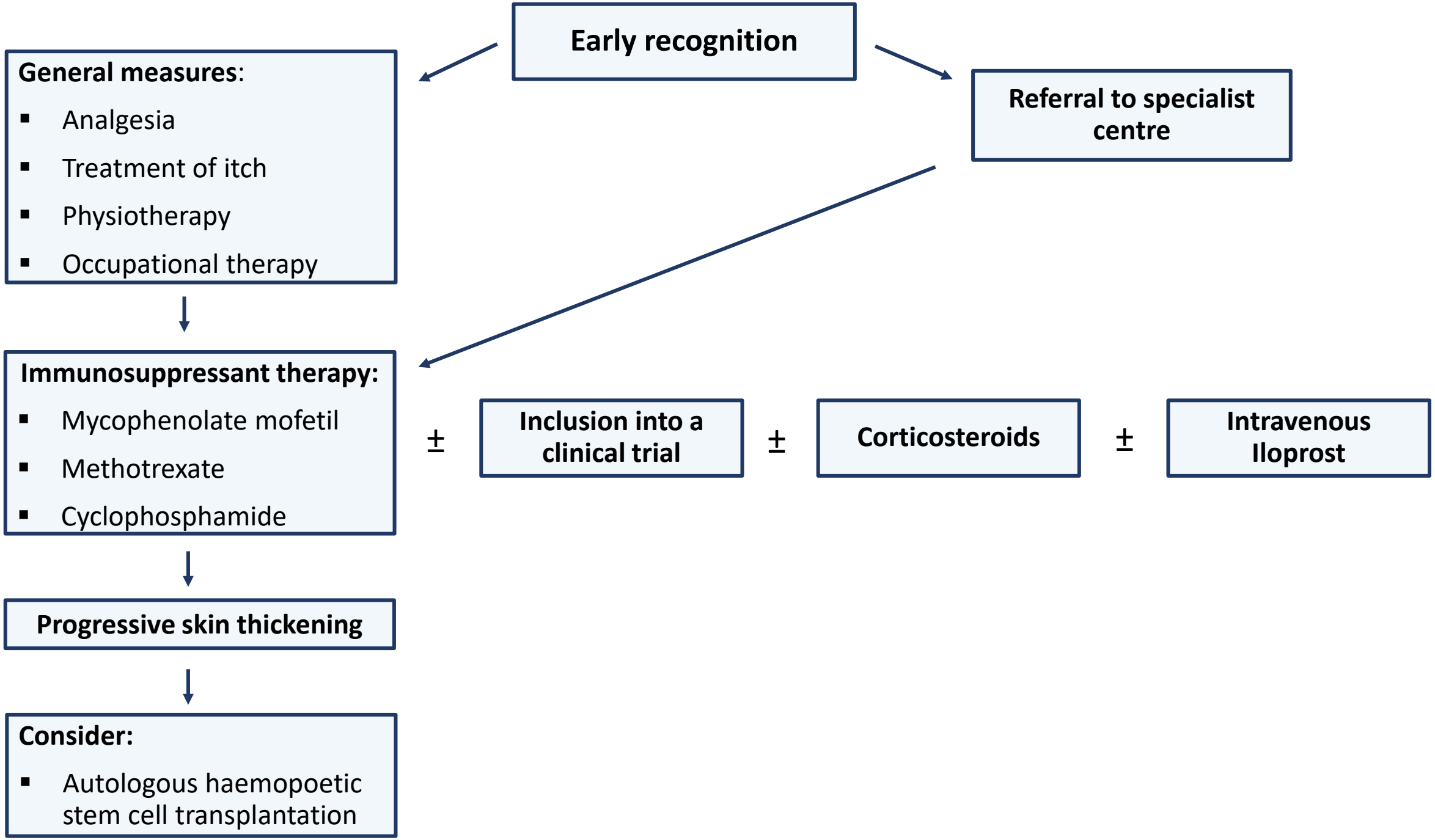


	Biological process	Clinical association
High baseline non-improver	High activation Low regression Persistent drivers	Increased mortality
High baseline improver	High activation high regression	More frequently associated with anti-RNA polymerase III autoantibody
Low baseline improver	Medium activation Medium regression	Lower risk of organ based complications



Overlapping TGFβ regulated tissue repair processes determine progression and regression of skin fibrosis analogous to would healing

Balance between profibrotic activation and antifibrotic regression determines skin score trajectory and disease phenotype including risk of organ based disease


Early recognition
General measures:
Analgesia
Treatment of itch
Physiotherapy
Occupational therapy
Referral to specialist centre
Immunosuppressant therapy:
Mycophenolate mofetil
Methotrexate
Cyclophosphamide
±
Inclusion into a clinical trial
±
Corticosteroids
±
Intravenous Iloprost
Progressive skin thickening
Consider:
Autologous haemopoetic stem cell transplantation