Management of cutaneous manifestations of systemic sclerosis: current approaches and emerging therapies

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Purpose of review
This review summarizes the most recent approaches in managing cutaneous involvement, one of the main clinical manifestations of systemic sclerosis (SSc). The following article is written for clinicians and researchers looking for optimizing patient care and exploring new therapies.

Recent findings
Recent studies have shown advancements in the management of cutaneous manifestations of SSc. While mycophenolate remains the first-line treatment, other immunosuppressive therapies targeting different pathways have shown promising results. B-cell depleting agents, such as Rituximab (RTX), are being increasingly utilized for cutaneous scleroderma with positive outcomes. Intravenous immunoglobulins (IVIG) have also demonstrated potential benefit for refractory cases with advanced skin fibrosis.
Moreover, emerging approaches such as autologous hematopoietic stem cell transplant (AHSCT) have been evaluated in clinical trials, with evidence suggesting its ability to reset the immune system and achieve remission in skin involvement in severe cases. Chimeric antigen receptor (CAR) T cell therapy is the most recent potential pathway to target refractory skin and systemic disease.

Summary
Management of cutaneous involvement in SSc remains challenging. The following study provides a comprehensive review of the most recent updates in treating cutaneous aspects (and associated complications) of SSc to help clinicians establish a more effective approach managing this condition.

Keywords
cutaneous scleroderma, immunosuppression, management, skin fibrosis, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disorder characterized by vasculopathy and fibrosis which affects the skin and internal organs [1]. Skin involvement is a hallmark feature that affects 95% of patients with SSc. It ranges from puffy fingers to skin hardening and thickening that vary in extent and severity. The extent of skin involvement divides SSc into its limited and diffuse cutaneous subtypes (Table 1). This classification helps determine the disease course with potential organ involvement, prognosis, and subsequently guides the treatment plan

PATHOPHYSIOLOGY OF CUTANEOUS SYSTEMIC SCLEROSIS

The pathophysiology of cutaneous SSc involves complex interplay between immune dysregulation, vascular involvement and fibrosis. Initial injury in the endothelium leads to endothelial dysfunction, likely driven by the immune activation. Recent data suggest that cytotoxic T lymphocytes in the skin are primarily driving the endothelial injury, apoptosis, and downstream activation of pro-fibrotic cytokines in early untreated patients with SSc [2]. Using systems biology (single cell RNA sequencing), there is robust interplay between the endothelial cells (with potential to transition into mesenchymal cells) and

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KEY POINTS

- Systemic sclerosis associated skin and musculoskeletal involvement often result in long-term disability that can be attenuated with medical and occupational therapy.
- Immunosuppressive should be considered in patients with early progressive diffuse cutaneous systemic sclerosis.
- Advanced cellular therapies (e.g. CAR-T cell therapy) are a novel emerging therapy that has provided promising results in recent case series.
- Hematopoietic stem cell transplant is highly effective for the treatment of advanced or refractory cases of systemic sclerosis but requires careful patient selection.

myofibroblasts, both contributing to the extracellular matrix deposition and drive pro-fibrotic signaling [3▪▪]. Early SSc skin involvement has a high prevalence of innate and adaptive immune signatures, whereas later skin tissue shows marked hyalinized collagen with little evidence of immune activation. In a US cohort, SSc patients with mean disease duration of 1.3 years had a high prevalence of M2 (96%) and M1 (94%) macrophage and CD8 T cell (65%), CD4 T cell (60%), and B cell (69%) signatures [4]. More details about pathogenesis of early skin fibrosis are published in a recent reviews [5].

Autoantibody formation

Antinuclear antibodies (ANAs) are the most prevalent antibodies, occurring in approximately 95% of cases. The presence of ANA, along with SSc-autoantibodies and nailfold capillaroscopy abnormalities in patients with Raynaud's phenomenon, is highly predictive of developing SSc.

Scleroderma-specific antibodies include anticentromere antibodies that have been associated with limited cutaneous systemic sclerosis (lcSSc). On the other hand, antitopoisomerase I antibodies (ATA) are strongly correlated with diffuse cutaneous systemic sclerosis (dcSSc), small and large joint contractures, and early digital ulceration. RNA polymerase antibodies have also been shown to be associated with accelerated skin progression with relationship with scleroderma renal crisis and significant small and large joint contractures [6].

CLINICAL PRESENTATION

The cutaneous manifestations of SSc are variable and significantly affect disease severity and prognosis (Fig. 1). Skin thickening is the hallmark of SSc and can present as sclerodactyly, which is thickening and hardening of the skin that is limited to the fingers, lcSSc, and dcSSc [7▪].

Raynaud's phenomenon is one of the earliest and most prevalent manifestation of scleroderma. It is typically caused by loss of vasodilatory capacity within the digital arteries leading to vascular spasms in response to cold or stress. Additionally, endothelial dysfunction along with impaired fibrinolysis and activation of coagulation pathways play an important role in the pathogenesis of Raynaud's [8]. Chronic and/or severe Raynaud's can lead to digital ulceration, pitting scars, and gangrene in severe cases, significantly affecting the quality of life.

Other cutaneous manifestations may include telangiectasias, which are small, dilated blood vessels typically seen on the hands, face, and mucous

Table 1. Cutaneous scleroderma subtypes and their associated key features

Subtype	Key features
Limited cutaneous systemic sclerosis	Skin involvement: Limited to the face, distal aspects of limbs - upper extremities up to the arms, and lower extremities up to the knees Raynaud's phenomenon: Usually present for many years before the other symptoms Associated organ involvement: High risk (10–15%) of pulmonary hypertension, skin calcinosis, gastrointestinal involvement, and telangiectasias Renal involvement: Rarely affected Antibodies: Anticentromere antibody (ACA) positive in 50–60% of cases, while anti PM/Scl and anti-Scl-70 present in 5–10%
Diffuse cutaneous systemic sclerosis	Skin involvement: Involves distal and proximal aspects of the body, including upper arms, thighs, and torso Raynaud's phenomenon: Typically starts within one year of non-Raynaud's signs and symptoms, shortly before or followed by skin thickening Puffy fingers are the most common first non-Raynaud's sign or symptom Associated organ involvement: Higher risk of interstitial lung disease, renal disease, and myocardial involvement Antibodies: Anti-Scl-70 antibodies are positive in 15-30%, and anti- RNA-polymerase III antibodies in 15-30% of cases and varies based on geographic distribution

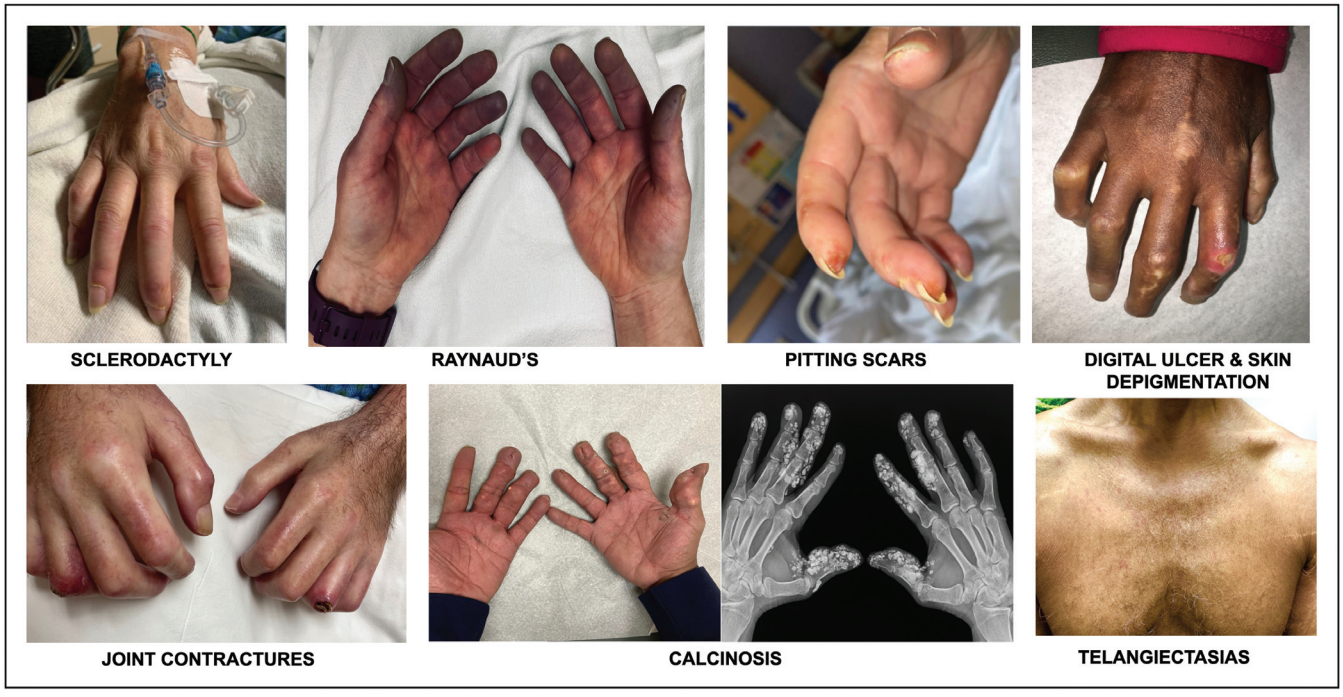

FIGURE 1. Cutaneous and musculoskeletal manifestations of systemic sclerosis .

membranes. Calcinosis is another manifestation of cutaneous scleroderma resulting from calcium salts deposits on the skin that can ulcerate and become infected. Additionally, traumatic ulcers are painful sores that can develop over the bone prominences as a result from skin breakdown and are associated with significant morbidity. Skin depigmentation, which gives the characteristic 'salt and pepper' appearance of the skin, results from melanocyte damage impairing their pigmentation pattern. Pruritus is another common feature caused by skin damage, inflammation, and vascular changes leading to itching and discomfort. Allodynia, which is characterized by skin sensitivity (feeling of sunburn), is often associated with nerve fiber damage and impaired innervation to the skin due to inflammation and fibrosis [9].

Joint contractures (both small and large joint involvement) can also result from severe skin thickening and fibrosis, leading to restricted joint mobility.

Fig. 1 shows pictures of different cutaneous manifestations of SSc.

MANAGEMENT OVERVIEW

The main goal of management of cutaneous manifestations of SSc is to minimize inflammation/immune deregulation, reduce the progression of skin fibrosis, prevent or reduce complications like digital ulcers and joint contractures, and subsequently improve the hand function and quality of life. It is a dual approach that balances immunosuppressive (disease-modifying) therapies to treat the underlying inflammation/ fibrosis axis and symptom control to address patient's concerns. Fig. 2 highlights the approach to cutaneous manifestations and Fig. 3 outlines the initial management approach for cutaneous SSc based on their initial symptoms and the duration of those symptoms.

A PRACTICAL APPROACH TO SKIN THICKENING

Localized scleroderma: phototherapy and laser therapy

Topical corticosteroids and topical tacrolimus have been historically prescribed by dermatologists for the treatment of localized areas of skin thickening [10]. Ultraviolet A1 (UVA-1) phototherapy applied to skin models of patients with scleroderma show upregulation of antifibrotic pathways and downregulation of pro-fibrotic pathways (e.g., TGF-ß) [11–13]. There are published studies showing efficacy in localized scleroderma of Psoralen + ultraviolet A (PUVA) with the greatest efficacy in early inflammatory lesions while UVA-1 excels in sclerotic skin lesions [14]. There are case reports in SSc where UVA1 treatment has been successful. However, many patients with SSc are treated with

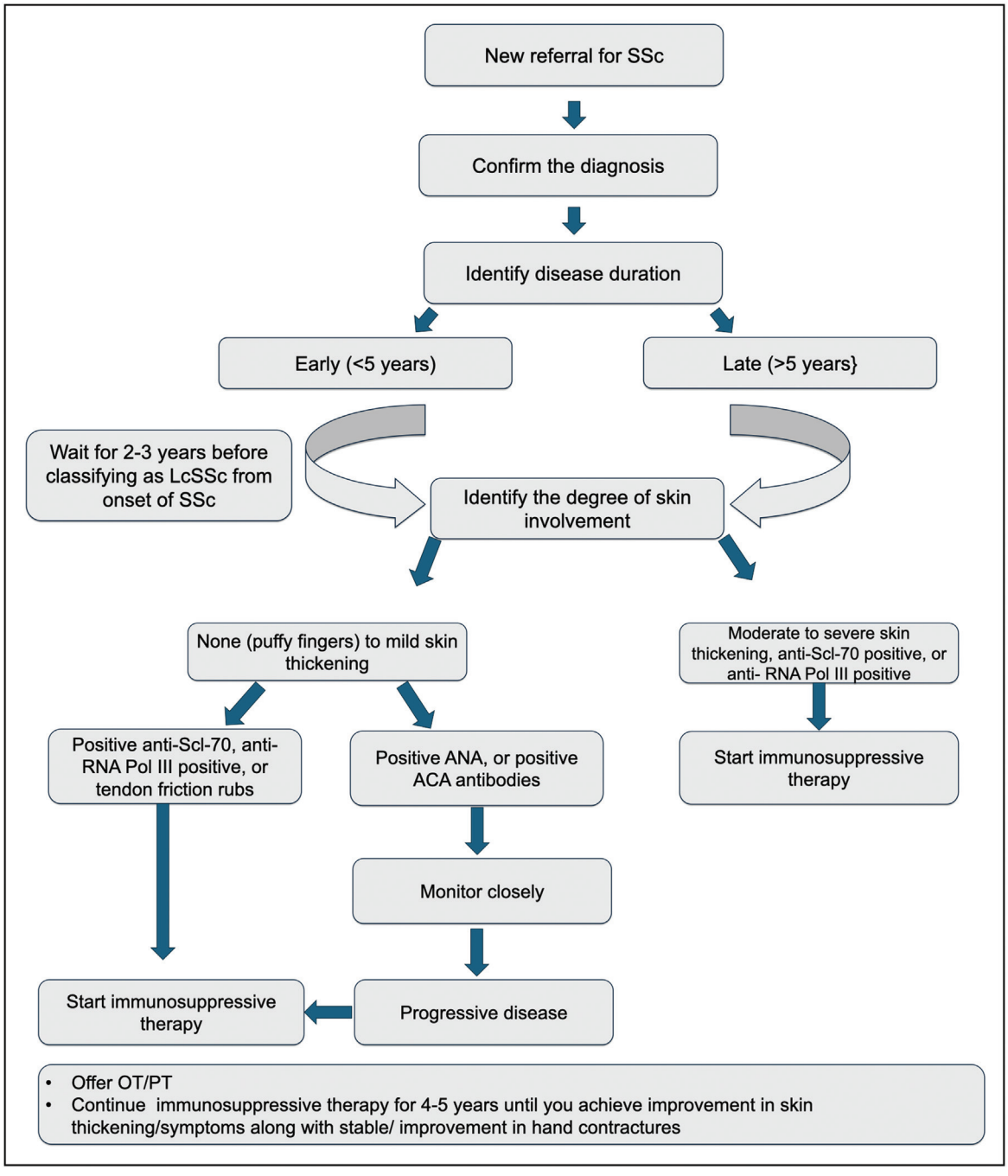

FIGURE 2. Summary of how to approach patients with cutaneous scleroderma. ACA, anti-centromere antibodies; ANA, antinuclear antibodies; lcSSc, limited cutaneous systemic sclerosis; OT, occupational therapy; PT, physical therapy; SSc, systemic sclerosis.

immunosuppressive therapy, due to systemic nature of the disease, and not with UVA1 treatment.

Fractional ablative carbon dioxide laser (FAL) has been used to decrease skin fibrosis and improve skin elasticity in patients with morphea. FAL has been reported to be effective in observational studies and to be superior to low dose UVA-1 phototherapy in one clinical trial, although it is not widely utilized in United States [15,16]. FAL has also been evaluated with and without the use of topical methotrexate (MTX) [17]. Lastly, an open-label RCT utilized pulsed dye laser for the treatment of telangiectasias in the head and neck with favorable results [18▪]. Patients should be referred to dermatology for phototherapy or laser therapy evaluation when feasible. Immunosuppressive therapies, as described below,

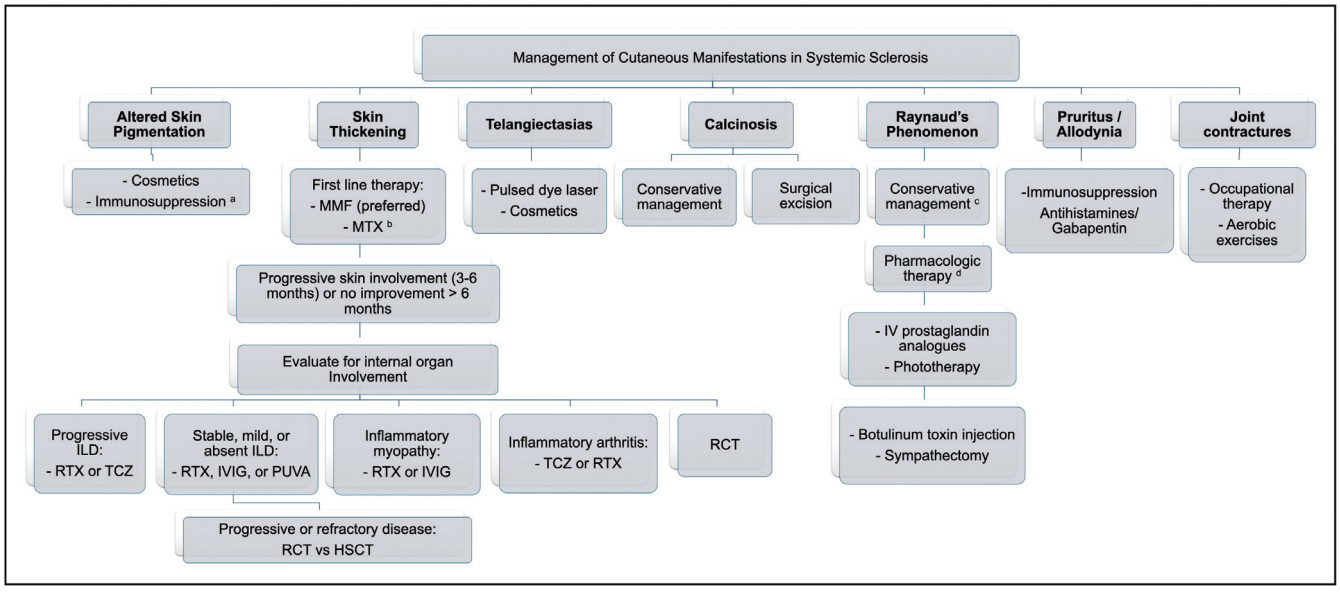

FIGURE 3. Suggested treatment algorithm for cutaneous manifestations of systemic sclerosis. A. Assure the patients that pigmentation changes will improve with compliance over the years. B. Preferred in the absence of ILD and presence of inflammatory arthritis. C. Avoiding cold objects and weather, wearing gloves with hand warmers, abstaining from smoking, stopping drugs that promote vasoconstriction. D. Calcium channel blockers, phosphodiesterase-5 inhibitors, endothelin-1 receptor antagonists. HSCT, hematopoietic stem cell transplant; ILD, interstitial lung disease; IV, intravenous.IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; MTX, methotrexate; RCT, randomized clinical trial; RTX, rituximab; TCZ, tocilizumab.

are prescribed for large, involved areas with significant disability, and/or deep morphea (morphea profunda).

In our practice, in conjunction with our dermatologists, we prescribe topical corticosteroids and tacrolimus for the treatment of local lesions. In addition, for those who have widespread disease or treatment resistant disease we prescribe UVA therapy for at least 3 to 6 months to see a beneficial effect. Patients should be referred to dermatology for phototherapy or laser therapy evaluation when feasible.

Early diffuse skin thickening: mycophenolate mofetil versus methotrexate

The immunomodulatory therapies that are discussed below have shown benefit on the treatment of other manifestations of SSc and can be considered for skin and musculoskeletal involvement in patients with SSc.

The two most used therapies for early and progressive skin thickening in patients with SSc are methotrexate (MTX) and mycophenolate mofetil (MMF).

MMF is commonly used for the treatment of SSc. The active metabolite of MMF is mycophenolic acid, which reversibly impairs lymphocyte proliferation and can modulate fibroblast biology [19]. Different case series and secondary analyses from the Scleroderma Lung Study (SLS) II showed that MMF was beneficial in improving skin involvement, as assessed by the modified Rodnan skin score and most utilized therapy in the US for early SSc with progressive skin involvement [20].

MTX is known to act as a competitive inhibitor of the enzyme dihydrofolate reductase, leading to a reduction of folinic acid levels and pyrimidine synthesis [21]. At low doses, MTX has shown to increase intracellular and extracellular levels of adenosine, which modifies the activity of immune cells and fibroblasts [22]. Two small randomized clinical trials (RCTs) studied the use of MTX in SSc [23,24]. The largest study included 71 patients with dcSSc and less than 3 years of diagnosis with skin involvement. At 12 months, mRSS was -4.3 in the MTX group versus (vs) 1.8 in the placebo group ($P < 0.009$) [23]. Both trials used lower doses of MTX (15 mg weekly) compared to the higher target dose of 25 mg weekly that is now used. MTX remains a commonly prescribed medication for the treatment of skin involvement and can be considered first line in patients with concurrent inflammatory arthritis. There are also geographic variations, based on the costs and availability of these medications. In a recent international trial focused on early dcSSc, MMF was most prescribed therapy followed by MTX [25].

Beyond skin thickening: managing patients with multiorgan involvement

Rituximab

Rituximab (RTX) is chimeric mAB that targets the CD20 receptor on B cells and eradicates them [26▪]. RTX has been studied in SSc with a specific interest in the treatment of SSc-ILD [27▪,28▪▪,29]. The DESIRES trial evaluated RTX vs. placebo measuring change in mRSS as the primary endpoint. Twenty-eight patients received RTX 375 mg/m^2 weekly for 4 consecutive weeks or placebo. At 24 weeks, mRSS was significantly lower in the rituximab group than in the placebo group (−6.30 vs. 2.14; [95% CI − 11.00 to − 5.88]; $P < 0.0001$) and led to approval of RTX in Japan [30]. An open-label extension ran from week 24 to week 48 that showed improvement in mRSS for patients in the rituximab-rituximab group and in the placebo-rituximab group [31]. In an open-label trial comparing RTX vs. monthly pulse cyclophosphamide (CYC) therapy in early dcSSc and ILD, RTX was associated with a favorable impact on mRSS vs. CYC. RTX is an appropriate and effective second-line therapy for SSc patients who do not respond to MMF/MTX and also for those with underlying ILD, inflammatory arthritis, and/or inflammatory myopathy when present.

Tocilizumab

Tocilizumab (TCZ) is an anti-interleukin-6 (IL-6) receptor mAb and its use for the treatment of skin disease remains controversial. The efficacy of TCZ in patients with an early diagnosis of SSc (< 5 years) was evaluated in two multicenter, double-blinded RCTs: the phase two faSScinate and the phase three focuSSced trials. The primary endpoint was the difference in mean change from baseline in mRSS at 24 weeks in the faSScinate trial and at 48 weeks in the focuSSced trial. Neither trial met its primary endpoint, however greater numerical improvement in mRSS was observed in the TCZ group [32,33]. The clear benefits in pulmonary function tests in patients with SSc-ILD in the TCZ group lead to the FDA approval of TCZ for the treatment of SSc. TCZ can be considered as second line therapy in patients especially in those with ILD, inflammatory arthritis, and elevated inflammatory markers are present.

Intravenous immunoglobulins

Intravenous immunoglobulins (IVIGs) are an immunomodulatory therapy that has been shown to prevent skin and dermal thickening, decrease pro-inflammatory cytokine response, and reduce inflammatory skin infiltrates in experimental mice models with SSc [34]. Only one RCT has been published evaluating the difference in mRSS in SSc patients who received a single course IVIG (2 g/kg) vs. placebo and no difference was found at 12 weeks [35]. A recent large retrospective multicenter study in 78 patients with SSc found a statistically significant improvement from baseline mRSS with the use of IVIG (15 ± 12.4 to 13 ± 12.5 [$P = 0.015$]) [36]. A systematic literature review on the use of IVIG in SSc evaluated 11 studies from which eight yielded positive results favoring IVIG, especially in patient's refractory to immunosuppressive therapies [37▪]. In our practice, we utilize IVIG for progressive skin involvement where first (and sometimes second-line therapies) are ineffective, those with significant side effect profile with immunosuppressive therapies, active disease such as tendon friction rubs, and patients with inflammatory myopathy.

Stem cell transplantation

Autologous hematopoietic stem cell transplantation (AHSCT) has been studied for SSc in the ASSIST (2011), ASTIS (2014), and SCOT (2018) trials and is the most effective treatment for skin disease at present. Patients enrolled in the ASSIST and ASTIS trials received nonmyeloablative therapy plus AHSCT or intravenous (i.v.) cyclophosphamide [38,39]. At 1 year, mean mRSS went from 28 to 15 in the ASSIST AHSCT group and increased in the placebo group ($P = 0.0004$) [38]. The 2-year follow up of ASTIS trial showed mRSS change of - 19.9 in the AHSCT group vs. − 8.8 in the placebo group ($P < 0.001$) [39].

Patients in the SCOT trial received myeloablative therapy followed by AHSCT or CYC for 12 months, mRSS improved in the majority of patients in the AHSCT arm (86%) and only in 49% of patients in the CYC arm [40]. AHSCT, although very effective, is reserved for patients with severe skin disease with progressive internal organ involvement (usually ILD) and those who are refractory to immunosuppressive therapy given its significant morbidity.

Emerging therapies: a glance into the future and the role of clinical trials

There are multiple ongoing trials targeting proinflammatory and profibrotic cytokines and chemokines in SSc to stabilize and improve skin involvement that are recently published [41▪]. At our center, trials are considered as part of the treatment algorithm as no treatment is currently FDA approved for cutaneous manifestations of SSc.

In addition, cellular therapies, including chimeric antigen receptor (CAR) T-cell therapy targeting CD19, have shown preliminary but promising

data for patients with moderate to severe cutaneous and extra-cutaneous manifestations of SSc [42▪▪, 43▪▪,44]. More data are needed, including larger trials, and consideration for patients with significant skin involvement with or without ILD and internal organ involvement.

PRURITUS AND DRY SKIN

Pruritus is a bothersome and common symptom in early progressive SSc. There is neuropathic component with possible compression of small nerve fibers by thickened and/or dense collagen contributes to the pruritic skin. Conservative measures to decrease pruritus include taking showers shorter than 10 min, showering with lukewarm water, utilizing moisturizing skin lotion, and liberal frequent application of emollients. Oral antihistamines are first-line of treatment and low-dose gabapentin can be used if conservative measures fail to improve the symptoms, especially with associated allodynia. Ultimately, addressing skin thickening will be the most effective way to achieve symptom control.

JOINT CONTRACTURES

Joint contractures are common in both lcSSc and dcSSc. Small joint contractures are due to progressive skin thickening and resulting tendon shortening and usually in those who are ATA positive [45].

Other cause of joint contracture includes inflammatory arthritis. Large joint contractures are associated with dcSSc and higher mortality. Occupational and physical therapy are somewhat effective in preventing further progression, although effects wane off once therapy is stopped [46]. In 2023, EULAR released nonpharmacologic recommendations for patients with systemic lupus erythematosus and SSc and emphasized orofacial, hand, aerobic, and resistance exercises with the aim to decrease microstomia, improve hand function, and decrease disability [47▪,48].

MICROSTOMIA

Microstomia is decreased in mouth aperture due to loss of fat and fibrosis around the perioral area. Education and regular exercises may help prevent or stabilize microstomia. Immunosuppressive therapies seem to be ineffective in preventing development of microstomia. FAL and other phototherapies have shown benefits by improving limited mouth opening in patients with SSc [49]. Finally, autologous fat grafting and hyaluronidase are a promising option for patients with microstomia and microcheilia [50,51,52▪].

CALCINOSIS CUTIS

Calcinosis is commonly seen in later part of SSc. No medical treatments are widely accepted. Large or bothersome deposits can be treated with surgical excision [53,54]. Other therapies used include laser therapy, IVIG, RTX, minocycline, diltiazem, among others but provide mixed effects [55▪]. However, there is no definitive or effective therapy for this manifestation.

RAYNAUD'S PHENOMENON AND DIGITAL ULCERS

Nonpharmacological interventions for Raynaud's phenomenon such as avoiding cold objects and weather, wearing gloves with hand warmers, abstaining from smoking, or vasoconstrictive substances are the first steps in management. The appearance of digital ulcers indicates severe Raynaud's phenomenon leading to ischemia and can be treated with oral dihydropyridine calcium channel blockers or phosphodiesterase-5 inhibitors, followed by endothelin-1 receptor antagonists [56,57▪, 58,59]. If there is concern for worsening or rapid digital ischemia, the patient should be hospitalized for infectious and thrombotic investigation and prompt i.v. prostacyclin analogue administration [60]. Other strategies such as botulinum toxin injections and sympathectomy are available for refractory cases.

CONCLUSION

The cutaneous manifestations of SSc remain a common and yet complicated feature of the disease that warrant a comprehensive approach in terms of diagnosis and management. Current management is driven by symptoms and signs but lacks disease-modifying effects. Advances in immunosuppressive therapies have provided variable options to treat, stabilize, and prevent disease progression. Natural softening of skin complicates the assessment of therapeutic response of available therapies. Understanding the pathophysiology of the disease is critical for appropriate and timely management that will improve patient outcomes.

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