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GUIDELINES

Consensus statement on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: Localized scleroderma, systemic sclerosis and overlap syndromes

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Abstract

The term 'sclerosing diseases of the skin' comprises specific dermatological entities, which have fibrotic changes of the skin in common. These diseases mostly manifest in different clinical subtypes according to cutaneous and extracutaneous involvement and can sometimes be difficult to distinguish from each other. The present consensus provides an update to the 2017 European Dermatology Forum Guidelines, focusing on characteristic clinical and histopathological features, diagnostic scores and the serum autoantibodies most useful for differential diagnosis. In addition, updated strategies for the first- and advanced-line therapy of sclerosing skin diseases are addressed in detail. Part 1 of this consensus provides clinicians with an overview of the diagnosis and treatment of localized scleroderma (morphea), and systemic sclerosis including overlap syndromes.

LOCALIZED SCLERODERMA (MORPHEA)

Epidemiology and pathogenesis

Localized scleroderma (LS) comprises a spectrum of sclerotic diseases that primarily affect the skin.[1] The incidence of LS ranges from 0.4 to 2.7 per 100,000 in adults and 0.3 to 3 per 100,000 in children.[1–5] The disease occurs 2.6 to 6 times more frequently in women than men.[2,6] Morphea, the most frequent subtype of LS usually appears in adults between 40 and 50 years of age, whereas linear subtypes primarily present in childhood between 2 and 14 years of age.[4,7] Other, rarer subtypes of LS have a peak incidence in the third and fourth decade of life.

Little is known about the potential triggers of the disease. LS has a multifactorial aetiology involving environmental factors, trauma and genetic predisposition leading to dysregulated immune and fibrotic pathways. Transition from LS to systemic sclerosis (SSc) does not occur, although coexistence has been reported.[8] Several reports of familiar clustering and coexistence of LS with autoimmune diseases (e.g. Hashimoto thyroiditis, alopecia areata, vitiligo and Type-1 diabetes), and genital lichen sclerosus suggest a possible genetic component.[5,9–11]

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Diagnostic procedures

Clinical presentation and physical examination

A classification of LS that considers the extent and depth of fibrosis comprises five main types: limited, generalized, linear, deep and mixed (Table 1). Eosinophilic fasciitis (Shulman syndrome) is a separate type belonging to the spectrum of LS. The clinical presentations of these types and subtypes differ in size, shape, colour and localization of the sclerotic lesions. Depending on the respective subtype, LS can also involve adjacent tissues such as the fat, fascia, muscle and bone, but not internal organs. An inspection of the anogenital region for possible concomitant genital lichen sclerosus[10,11] should be performed in patients with LS, especially in those with limited or generalized types.[9] In juvenile LS affecting the head (LS 'en coup de sabre' and/or progressive facial hemiatrophy [Parry–Romberg syndrome]) and in linear LS affecting the joints, screening for uveitis and arthritis should be performed, respectively. For paediatric patients, routine internal organ work-up is not recommended besides uveitis and CNS.

Clinical scores

The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) has become the standard tool to evaluate skin affection in LS. An additional new score to evaluate both cutaneous damage and extracutaneous involvement in LS and to document treatment response is called total morbidity score

TABLE 1 Classification according to the German guideline by Kreuter et al.[1] and clinical presentation of localized scleroderma/morphea.

Type of LS	Clinical presentation
Limited type	
Plaque morphea (classical plaque type)	• Oval-shaped lesions surrounded by an erythematous border (lilac ring) • In later stages, sclerotic in the centre with a whitish or ivory colour; old lesions may become atrophic and dyspigmented • May lead to hair loss and loss of the skin appendages • Predominantly located on the trunk
Guttate morphea	• Multiple yellowish or whitish, small sclerotic lesions with a shiny surface • Early inflammatory lesions may simply present as erythematous maculae • Predominantly located on the trunk
Atrophoderma idiopathica of Pierini and Pasini (superficial morphea)	• Symmetrical, single or multiple, sharply demarcated, hyperpigmented, non-indurated patches • Located on the trunk or extremities
Generalized type	
Generalized LS/morphea	• Four or more indurated plaques of more than 3 cm in diameter, involving two or more of seven anatomic sites (head–neck, each extremity, anterior trunk and posterior trunk) • Often distributed symmetrically and tend to coalesce
Disabling pansclerotic morphea	• Extensive involvement of the skin, fat tissue, fascia, muscle and bone • Fibrosis often results in severe contractures and poorly healing, large ulcerations and necroses • Usually manifests before the age of 14
Linear type	
Linear LS/morphea of the extremities	• Longitudinally arranged linear, band-like lesions that may follow the lines of Blaschko • May heal with residual hyperpigmentation or • May cause severe growth retardation, muscle atrophy, flexion contractures, myositis, arthritis and psychological disability
Linear LS/morphea 'en coup de sabre'	• Typically located on the frontoparietal region, ranging paramedian from the eyebrows into the hair-bearing scalp • May be accompanied by scarring alopecia, seizures, migraine, headache and eye involvement
Progressive facial hemiatrophy (Parry–Romberg syndrome)	• Progressive facial hemiatrophy with involvement of the subcutaneous tissue, muscle and bone, but usually not the skin • May result in severe facial asymmetry • Coincidence with linear LS 'en coup de sabre' in up to 40%
Deep type (deep morphea)	• Fibrotic process mainly affecting the deeper layers (subcutaneous fat tissue, fascia and underlying muscle) • Typically arranged symmetrically on the extremities
Mixed type	• Combined linear and plaque type, or linear and generalized LS; predominant in children
Eosinophilic fasciitis (Shulman syndrome)	• Rapid onset with symmetrical swelling of the skin • In later stages, indurated and fibrotic lesions with typical 'peau d'orange'-like appearance • Cutaneous veins might appear as depressed compared to the surrounding tissue ('negative vein sign') • Predominantly located on the extremities

Note: All types may present with overlapping features of other types (e.g. generalized types with linear or deep aspects).
Abbreviation: LS, localized scleroderma.

(TMS).[12] Patient's quality of life can be evaluated with the Dermatology Life Quality Index, Skindex-29 or the Hospital Anxiety and Depression Scale and the newly developed paediatric Localized Scleroderma Quality of Life Instrument (LoSQI).[13]

Histopathology

LS is a clinical diagnosis, and skin biopsies for histopathological evaluation should only be performed in atypical or unclear cases. Physicians should take care that the incisional biopsy is sufficiently deep, as some LS subtypes may primarily involve the subcutis or underlying fascia and muscle (e.g. eosinophilic fasciitis). In a large study conducted in 128 patients with eosinophilic fasciitis, eosinophilia and fibrosis were predictive factors of relapse, whereas oedema, relapse and fibrosis were predictive factors of sequelae.[14] By histopathology, it is neither possible to distinguish between LS and SSc, nor to differentiate among different LS subtypes.

Laboratory parameters

Specific serum markers for LS do not exist. However, routine laboratory parameters should be obtained in LS (especially before initiation of systemic treatment) and should include blood differential, clinical serum chemistry, blood sedimentation rate, C-reactive protein and antinuclear antibodies (ANAs). Abnormal blood findings are frequent especially in juvenile LS, with ANAs found in up to 40% of patients. The presence of ANAs is a risk factor for extracutaneous involvement (e.g. arthritis) and disease relapse.[5,15,16] In the active stage of generalized LS, blood eosinophilia may be observed.[17,18] In patients with linear LS of the extremities with concomitant joint involvement, increased levels of rheumatoid factor may be present and do sometimes correlate with the clinical degree of arthritis activity.[19,20] Additional diagnostics (e.g. screening for antibodies against extractable nuclear antigens) should only be performed to confirm or exclude SSc. Serological screening for *Borrelia burgdorferi* is not recommended in LS and should only be performed in clinically suspicious cases.

Imaging

Up to 50% of patients with head/face LS (e.g. 'en coup de sabre' and/or progressive facial hemiatrophy) suffer from neurological symptoms (e.g. migraine, headaches and eventually epilepsy).[12,16,21–26] Cranial magnetic resonance imaging (MRI) is recommended to detect potential subcortical calcifications or brain atrophy.[21,27–29] On the other hand, many patients are asymptomatic even if such abnormalities are seen. Accordingly, MRI of the brain is recommended at baseline in all cases of head/face LS or during the course of disease in case of new neurologic symptoms. Ophthalmologists or oral surgeons should be consulted and monitor disease course, as indicated. MRI and computed tomography (CT) studies might likewise be helpful for surgical planning (e.g. in LS 'en coup de sabre' type) or to detect muscle, joint or bone involvement, for instance in linear LS of the extremities.

Instrument-based outcome measures

A variety of instrument-based procedures have been reported in clinical trials on LS, for example, ultrasound scanning, cutometer, durometer, thermography, laser-Doppler-flowmetry and a computerized skin score. In most of the studies, these procedures were used as secondary outcome measures. Photo documentation of clinical lesions is advisable.

Differential diagnoses

A variety of differential diagnoses should be considered in LS.[22,30] A summary of differential diagnoses depending on the LS subtype and stage of disease is provided in Table 2. Early recognition of LS is important as late diagnosis results in longer disease activity and higher recurrence rates.[7,31,32] Typical facial (e.g. teleangiectases, beak-shaped nose and microstomia) and vascular (e.g. Raynaud's phenomenon, pitting scars and digital ulcers) features of SSc as well as highly specific serum antibodies (e.g. anti-centromere antibodies and anti-Scl-70 antibodies) are absent in LS.[29,33]

Treatment

Treatment options for LS can be divided into topical and systemic therapy as well as ultraviolet (UV) phototherapy. The extent and severity of LS should be taken into account before initiating the respective therapy. For example, topical and UV phototherapy are usually appropriate in limited types of LS that are restricted to the skin, whereas generalized, linear or deep types may require systemic treatment (Figure 1). In order to prevent persistent damage from linear types of juvenile LS, effective systemic therapy should be initiated in the active stage as early as possible. A treatment algorithm that incorporates the subtype, severity and extent of LS is provided in Figure 1. When evaluating the treatment efficacy, it should be taken into account that reduction of skin sclerosis starts 8–12 weeks after initiation of therapy, at the earliest. None of the below mentioned therapies are officially licensed in Europe for LS.

Topical therapy

Topical glucocorticoids are the mainstay of topical treatment in LS, although no well-performed studies exist.

TABLE 2 Differential diagnoses of localized scleroderma (morphea).[a]

LS subtype	Differential diagnoses
Limited LS (morphea) – initial inflammatory phase	• Atopic eczema • Lichen sclerosus[b] • Erythema chronicum migrans • Cutaneous mastocytosis • Granuloma annulare • Mycosis fungoides • Drug-related reactions • Chronic radiation dermatitis • Porokeratosis Mibelli • Drug-related reactions[254]
Limited LS (morphea) – late stage mainly with hyperpigmentation	• Post-inflammatory hyperpigmentation • Lichen planus actinicus • Café-au-lait spots • Erythema dyschromicum perstans
Limited LS (morphea) – late stage mainly with atrophy	• Acrodermatitis chronica atrophicans[b] • Lipodystrophy • Lichen sclerosus • Atrophic scarring
Limited LS (morphea) – late stage mainly with sclerosis	• Necrobiosis lipoidica • Pretibial myxoedema • Spontaneous keloid
Generalized LS	• Systemic sclerosis[b] • Mixed connective tissue disease • Pseudoscleroderma • Scleredema adultorum (Buschke's disease) • Scleromyxedema • Chronic graft-versus-host disease[b] • Nephrogenic systemic fibrosis[b,c] • Porphyria cutanea tarda
Linear LS, en coup de sabre and Parry–Romberg syndrome	• Panniculitis[b] • Lupus erythematosus profundus[b] • Progressive lipodystrophy • Localized lipodystrophy[d] • Focal dermal hypoplasia • Steroid atrophy

Abbreviation: LS, localized scleroderma.

[a]According to the German guideline for the diagnosis and treatment.

[b]The most relevant differential diagnoses are marked with an asterix.

[c]Also known as nephrogenic fibrosing dermopathy.

[d]For example, lipodystrophia centrifugalis abdominalis infantilis.

Therapy with moderate- to high-potency glucocorticoids should be performed in the active phase of disease, and their application should be restricted to a total of 3 months. Longer application of topical glucocorticoids should be given as an interval or proactive therapy (twice weekly at initially affected sites after remission). Topical calcipotriol should be considered for active inflammatory superficial types of LS with a low degree of sclerosis.[23,28,34,35] Tacrolimus 0.1% ointment might be an effective treatment option for active LS lesions.[30,36] No studies on pimecrolimus for LS are available. Several studies (including a prospective controlled multicentre study) have demonstrated efficacy of imiquimod in LS, with best results obtained for skin induration.[34–40] Intralesional interferon-γ did not prove effective in LS in a double-blinded, placebo-controlled trial.[41]

Systemic therapy

Systemic glucocorticoids

Systemic glucocorticoids (SG) are widely used agents in LS, particularly in linear, generalized and deep subtypes. SG are predominantly given as combination therapy, and only one study exists on SG as a monotherapy.[39,42] Systemic glucocorticoids are safe and effective in active lesions of LS, and should be considered in patients with severe disease, especially in those forms affecting extracutaneous structures (e.g. fat tissue, fascia, muscle and bone). Moreover, systemic glucocorticoids are the first-line treatment option in eosinophilic fasciitis.[40,43] Following relapse, an increase in glucocorticoids with or without addition of methotrexate is the most frequent option, leading to clinical improvement and glucocorticoid withdrawal.[14] Treatment should be planned over relatively long periods, as clinical effects are observed 3 months post-onset at the earliest.

Methotrexate

Methotrexate (MTX) is a well-known immunosuppressive agent that has been used in adults and children, with well-documented adverse effects. Among systemic treatments for LS, the best level of evidence exists for the use of MTX. MTX has been used in several retrospective and some non-controlled prospective studies, as well as in a large prospective multicentre trial.[41–51] Importantly, 28% of patients with juvenile LS experienced a relapse after treatment with MTX.[49,52] In 2012, the 'Childhood Arthritis and Rheumatology Research Alliance' (CARRA) recommended three different treatment regimens for juvenile LS: (1) MTX monotherapy, (2) pulsed MTX and methylprednisolone given intravenously and (3) pulsed MTX and prednisone given orally.[51,53] These recommendations have been incorporated in the treatment algorithm of this consensus (Figure 1).

Mycophenolate mofetil (MMF)

MMF inhibits the proliferation of lymphocytes, but also other mesenchymal cell types, including smooth muscle cells and fibroblasts.[50,54] In 2009, the first case series of seven methotrexate-resistant LS patients treated with MMF showed improvement of skin sclerosis and inflammation, as documented with infrared thermography and clinical scoring.[52,55] Since then, several retrospective cohort studies have confirmed the efficacy of MMF in LS, especially in children.[55–57] MMF is currently considered as second-line therapy if MTX has failed.[51,52]

Abatacept

Abatacept is a recombinant fusion protein licensed for rheumatoid arthritis and psoriatic arthritis in Europe, which is known to interfere with T-cell activation by binding to the CD80 and CD86 costimulatory molecules. It has shown efficacy in both cutaneous and musculoskeletal activity in LS patients that failed previous MTX and/or MMF treatment and glucocorticoids.[58] In a recent multicentre cohort study on abatacept for refractory juvenile LS,

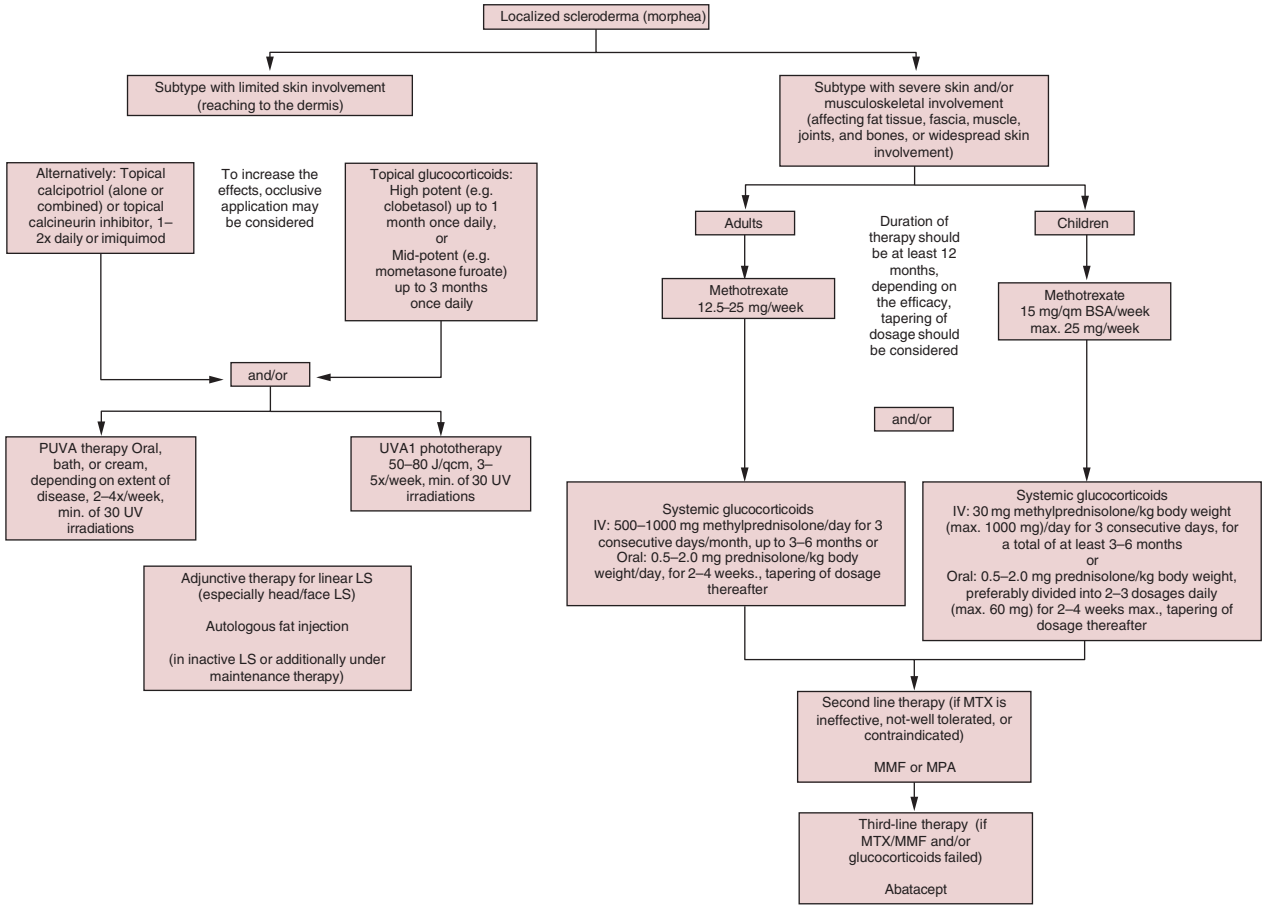


FIGURE 1 Treatment algorithm for localized scleroderma depending on the clinical subtype and extent of disease. In localized scleroderma subtypes with limited skin involvement that do not adequately respond to topical or phototherapy, systemic therapy should be considered. The dosages and treatment schedules on UVA1 phototherapy and PUVA might also be used in other sclerotic diseases (e.g. sclerotic skin in systemic sclerosis). Therapeutic approaches in Parry–Romberg syndrome (progressive facial hemiatrophy) are not included but mentioned in the text. MMF, mycophenolate mofetil; MPA, mycophenolic acid.

the majority (83% [$n = 18$] of patients) responded to treatment at 12 months, and response was sustained in 61% for 18 months. Abatacept might be considered as third-line option, alone or in combination with MTX, MMF or glucocorticoids.

Other immunosuppressive or immune modulating approaches

Numerous other systemics have been reported in LS, including tocilizumab, Janus kinase (JAK) inhibition, intravenous immunoglobulins rituximab, cyclosporine A, apremilast, azathioprine and infliximab.[53–55,59–65] These treatments should be reserved to single severe cases with contraindications or failure to standard therapy.

Autologous fat injection

Accumulating evidence indicates that autologous fat injections (AFI) can be used as effective adjunctive therapy in LS, especially for linear subtypes of the head and face. Apart from aesthetic improvement of contour irregularities, adipose stem cell transferred via AFI induce immunomodulatory and angiogenetic effects. Moreover, AFI has anti-fibrotic effects by limiting extracellular matrix proteins and increasing collagenase activity.[66–68] Although currently available studies are very promising, additional investigation is necessary to define the optimal timing and indications for AFI in LS.

Agents currently not recommended for the treatment of LS

Oral calcitriol and D-penicillamine have been reported in small case series of LS patients but cannot be recommended because of the low evidence level and problematic safety profile.[61–63,69–71] Penicillin has long been used for the treatment of LS because LS can manifest after an infection with borrelia. However, direct anti-fibrotic effects have so far not been demonstrated.

UV phototherapy

Phototherapy is a well-established treatment option for LS, especially for limited disease restricted to the skin.[69,72] The therapeutic mechanisms of different phototherapy modalities with their antifibrotic properties and components in various skin conditions, including sclerotic disorders, have been recently

reviewed comprehensively.[73] UV phototherapy induces interstitial matrix metalloproteinases and exerts anti-fibrotic and anti-inflammatory effects.[70–72,74–76] In addition, it leads to apoptosis of dermal T cells, depletion of Langerhans cells and to modulation of several pro-inflammatory cytokines.[69,72] As longer wavelengths in the UVA range (320–400 nm) penetrate deeper into the dermis than does UVB (280–320 nm), the majority of studies have focused on UVA1, broadband UVA or alternatively photochemotherapy. Comparative studies on the relative efficacy of phototherapies for LS are lacking except one small retrospective study that showed comparable response rates in morphea patients after oral PUVA and UVA1 phototherapy. The number of phototherapeutic exposures usually used in the treatment of LS is too low to induce any significant skin damage or skin cancer.[74,77]

Psoralen plus UVA (PUVA, photochemotherapy)

PUVA treatment was originally performed with oral application of 8-methoxypsoralen which frequently causes gastrointestinal disturbances such as nausea or vomiting. In order to avoid this common adverse effect of oral PUVA, several studies in LS employed bath-PUVA or cream-PUVA treatment.[75,76,78,79] PUVA phototherapy is usually performed two to three times weekly for a total of 30 irradiations. It is not recommended in children.

Broadband UVA

Three prospective studies have been published on the use of broadband UVA (320–400 nm) in LS.[77–82] The three dosages used (5, 10 and 20 J/cm^2 for 20 irradiations each) were similar in efficacy. Controlled studies comparing broadband UVA with other UV modalities are lacking.

UVA1 phototherapy

The most robust data for phototherapy in LS exist for UVA1, introduced in 1991.[80,83] Three different dosages of UVA1 can be distinguished: low-dose UVA1 (10–29 J/cm^2), medium-dose UVA1 (30–59 J/cm^2) and high-dose UVA1 (60–130 J/cm^2). The first prospective study on UVA1 phototherapy in LS demonstrated that high-dose UVA1 is highly effective, but low-dose UVA1 failed to show any substantial effects in LS.[82,84] By contrast, several prospective studies performed some years later showed that low- and medium-dose UVA1 are also effective.[23,34,81,83–91] So far, only one randomized controlled study compared low-dose UVA1, medium-dose UVA1 and narrowband UVB phototherapy in LS. All three UV regimens significantly improved the skin scores, with medium-dose UVA1 being significantly better than narrowband UVB.[89,92] Whether patients with darker skin respond less to UVA1 phototherapy is still a matter of debate.[90,91,93,94] Moreover, it has been shown that within 3 years, about 50% of patients treated with UVA1 experience recurrences after therapy.[95,96] In these cases, a second cycle of UVA1 phototherapy should be considered. UVA1 has recently been reported as adjuvant treatment in eosinophilic fasciitis.[97] UVA1 is usually performed three five times weekly for a minimum of 30 irradiations. Success with extracorporeal photopheresis has also been described in case reports.[93–95,98–101]

Narrowband UBV phototherapy

Narrowband UVB showed also clinical efficacy in localized scleroderma in studies, and case series and the British Photodermatology Group guidelines 2022 suggest considering it in patients when an alternative and more effective phototherapy or systemic therapy is not available or is contraindicated.[96,102]

Physiotherapy

Physiotherapy is an important component in the multimodal treatment concept for LS, especially for linear, generalized, deep and mixed types of LS. However, well-performed studies on physiotherapy in LS are lacking. Massage and lymphatic drainage are recommended as valuable treatments supporting systemic therapy in patients with sclerotic stage. Physiotherapy is indicated in all cases of joint contracture. In clinical practice, physiotherapy is usually performed once or twice a week for at least 3 months.

Surgical therapy

Surgical therapy is predominantly indicated in linear types of LS. In linear LS of the limbs, epiphysiodesis of the healthy extremity in order to adjust leg length inequality can be considered in consultation with an experienced paediatric orthopaedist, but it is best to prevent it with effective immunomodulatory treatment using the therapeutic window. Plastic surgical interventions might be considered for cosmetic reasons in inactive linear LS 'en coup de sabre' (excision of the sclerotic scalp area and hair transplantation in alopecic areas) or facial hemiatrophy (autologous fat grafting). To prevent possible psychological damage, plastic surgical interventions can also be considered in the active phase of disease.

Parry–Romberg syndrome (progressive facial hemiatrophy) involves also the bone and demonstrates neurological, vascular and soft tissue damage. It is often highly resistant to systemic anti-inflammatory therapy. Therefore autologous fat injections (see above) has been applied and more recently, surgical intervention is suggested as first-line therapy for active Parry–Romberg syndrome, which may prevent progressive bone deformities and secondary neurocutaneous symptoms in children or young adults.[103–105]

Clinical course and prognosis

Although still limited data are available on the long-term clinical course, standard therapy results in complete remission of most patients with LS, especially in cases with limited skin involvement. Nevertheless, relapses of LS following

treatment have been reported in 25%–50% of patients.[16,56,106] Age at onset and extracutaneous involvement of disease is the most important risk factor for recurrent disease, and relapses occurred significantly more often in paediatric (27%) compared to adult (17%) patients with LS.[32] Disease subtype (generalized or mixed type of LS) as well as ANA positivity are other risk factors for recurrences.[31,106] Importantly, disease relapses can occur after years of quiescent disease, with recurrence of activity reported ranging from 6 to 18 years.[99,100,107] Moreover, 30%–50% of patients with linear LS experience osteoarticular complications on the affected extremity.[32,101,107–110] In such patients, a multidisciplinary approach is necessary (e.g. dermatologist, orthopaedist and rheumatologist).

Recommendations

- Patients with localized scleroderma should be evaluated for possible rheumatic and autoimmune diseases. These patients should be referred to a rheumatologist and an ophthalmologist, for example, to exclude an autoimmune uveitis and arthritis and by screening for ANA (see below). To exclude concomitant genital lichen sclerosus, an inspection of the anogenital region should be performed in patients with LS, especially in those with limited or generalized types.
- Blood screening should be performed in patients with LS prior to systemic therapy. It should include blood differential, serum chemistry and antinuclear antibodies. Routine screening for Borrelia is not recommended. Screening for antibodies against extractable nuclear antigens should be only performed to confirm or exclude SSc (if clinically relevant).
- A biopsy should be considered in case of inconclusive clinical presentation. If deep, generalized or linear types of LS are suspected, a deep biopsy should be performed that includes subcutaneous tissue. If eosinophilic fasciitis is suspected, deep biopsy must include the fascia as well.
- In patients with linear LS 'en coup de sabre' or progressive facial hemiatrophy, neurological examination and MRI of the skull should be performed at baseline to exclude an affection of the brain. Moreover, MRI should be performed during the course of disease only in case of new neurologic symptoms. MRI and CT might be helpful for surgical planning and to detect muscle or bone involvement.
- Ultrasound scanning, cutometer, durometer, thermography, laser-Doppler-flowmetry or the computerized skin score can be considered to evaluate disease activity and clinical course of LS over time.
- The most robust data for clinical scores exist for the validated LoSCAT, which should therefore be used for LS to assess disease severity and progression.
- In juvenile LS affecting the head (LS 'en coup de sabre' or progressive facial hemiatrophy) and linear LS affecting the joints, screening for uveitis and arthritis should be performed, respectively. For paediatric patients, routine internal organ work-up is not recommended besides uveitis and CNS.
- High potency topical glucocorticoids (Class 3 and 4) can be used in the active stage of patients with limited types of LS, in children as bridging therapy for methotrexate. Longer treatment should be performed as interval therapy. In selective cases, topical calcipotriol, topical calcineurin inhibitors, or imiquimod can be used. If the lesions do not adequately respond to topical or phototherapy, systemic therapy should be considered.
- MTX is the current first-line treatment for subtypes of LS with skin affection which crosses joints, causes cosmetic changes or has musculoskeletal involvement. Duration of MTX therapy should be at least 12 months, and a reduction of dosage can be considered after first signs of clinical improvement.
- In the active stage of disease, concomitant treatment with systemic glucocorticoids should be performed if contraindications are absent, especially in severe cases (linear or deep LS) or in cases with extracutaneous involvement. MMF is considered as second-line treatment in cases with failure or contraindications to methotrexate. Abatacept and/or tocilizumab alone, or in combination with MTX, MMF or glucocorticoids can be considered as third-line treatment option.
- Autologous fat injections can be used as effective adjunctive therapy in LS, especially for linear subtypes of the head and face.
- First choice phototherapy for limited types of LS is medium-dose UVA1. Alternatively, bath-PUVA, oral PUVA or cream-PUVA phototherapy can be considered in adult patients.
- Physiotherapy and manual therapy should be added to topical and systemic therapy in all types of LS that result in restrictions of motion. Massage and lymphatic drainage should be concomitantly performed in sclerotic types of LS.
- Functionally indicated surgical interventions should be performed in the inactive stage of disease and concern patients with linear LS. Plastic-surgical procedures can be considered for linear LS 'en coup de sabre' and progressive facial hemiatrophy.
- Clinical-follow-up visits (at least once a year) should be performed in LS with high risk for recurrences after successful treatment. Children with LS, especially those with generalized or mixed types, patients with ANAs and patients with a delay in starting adequate treatment are particularly affected by recurrent disease.

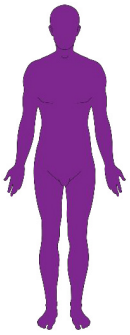
SYSTEMIC SCLEROSIS

Introduction

The term systemic sclerosis is often used interchangeably with systemic scleroderma. The diagnosis and treatment of SSc is challenging due to the heterogeneity of disease

TABLE 3 Subclassification of LeRoy et al.[117]

Limited form	Diffuse form
• Acral sclerosis • Skin involvement of the extremities distal to the elbow and knee joints • Possible involvement of the face • Long duration of Raynaud's phenomenon • Late pulmonary arterial hypertension • Often anti-centromere positive	• Progressive systemic sclerosis • Rapid involvement of the trunk, face and extremities • Lung fibrosis • Early onset of Raynaud's phenomenon (within 1 year of skin changes) • Often anti-topoisomerase-1 (scl 70)-positive



manifestations and disease course. Diagnosis and care should, at least in part, be in the hands of specialists who have daily exposure to the disease and have access to modern diagnostic procedures (e.g. high-resolution computed tomography [HRCT], MRI, body plethysmography, echocardiography, gastroscopy, spirometry and nailfold capillaroscopy) and to a laboratory with expertise in autoimmune serology. In order to provide optimal care, cooperation with different subspecialties (e.g. rheumatology, dermatology, gastroenterology, pulmonary medicine, cardiology and nephrology) is necessary due to the nature of the disease, which affects several organ systems.

Systematic baseline and longitudinal assessments to define the complications are mandatory. Multidisciplinary care for patients with early progressive disease should be provided in a setting where the outpatient facilities also have access to hospital beds, in order to ensure timely and appropriate treatment for patients presenting with exacerbation of their disease. In these specialized facilities, access to physical therapy should be available.

Evidence-based recommendations for the treatment of SSc were published by the European League against Rheumatism Scleroderma Trials and Research (EUSTAR) study group in 2009 and updated in 2015,[111,112] where many of the recommendations given below are described in more detail. In addition, for a more detailed description, the reader is referred to the 'Consensus best practice recommendations for scleroderma' developed by UK Scleroderma Study Group.[113] These have also been summarized in a treatment guideline prepared using the NICE accredited BSR-BHPR process.[114]

The present consensus has been prepared bearing in mind that healthcare systems differ considerably between countries in Europe. The recommendations, as presented here, may be influenced, among others, by hospitalization rules, the availability of outpatient facilities and financial reimbursement of specific procedures and therapies.

Clinical manifestation and classification

SSc is a heterogeneous, chronic autoimmune disorder, leading to fibrosis of the skin and many internal organs.[115] In 1980, the American College of Rheumatology published preliminary criteria for the classification of patients with established disease.[116] A subclassification, developed by LeRoy et al.,[117] has been the most widely used classification system in clinical practice, and forms the basis for many registries worldwide (Table 3). In this classification, diffuse cutaneous SSc (dcSSc) is defined as a progressive form with an early onset of Raynaud's phenomenon, usually within 1 year of the onset of skin changes. This subset is characterized by rapid involvement of trunk, face, proximal and distal extremities and frequently, anti-topoisomerase-1 antibodies (anti-topo-1 and anti-Scl-70) are present.[118–120]

Limited cutaneous SSc (lcSSc) is defined by skin affection of the extremities distal to the elbow and knee joints. Around 50%–70% of these patients have anti-centromere antibodies (ACA).[118–120] It has been widely accepted that 'CREST syndrome' and 'systemic sclerosis sine scleroderma' can be seen as part of the disease spectrum of the limited cutaneous form of SSc.[121]

In 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published new classification criteria (Table 4).[122] The classification incorporates diagnostic measures, such as antinuclear antibodies and capillaroscopy, which have not been included before. However, when applying these new classification criteria, it should be kept in mind that they were developed primarily for clinical research purposes and cannot be applied to patients without skin involvement of the hands, or to patients with scleroderma-like disorders.

For patients with very early disease (also referred to as very early/early SSc, pre-SSc or undifferentiated connective tissue disease), there are no generally accepted criteria.[123,124] In these cases, it should be considered that two-thirds of patients with Raynaud's phenomenon, nailfold capillaroscopic changes and/or SSc-specific antibodies (ACA, anti-topo-1) will develop definite SSc after 5 years.[125] Nevertheless, almost 80% of these patients develop SSc in the long term. In addition, patients without a scleroderma pattern on capillaroscopy, nor presence of SSc-specific antibodies, do not develop SSc (1.8% during long-term follow-up).[125] Subsequently, capillaroscopy and SSc-specific antibodies seem to be good prognostic predictors for the disease. Therefore, it is recommended that

TABLE 4 American College of Rheumatology/European League against Rheumatism 2013 criteria for classification of systemic sclerosis.[122]

Item	Sub-item(s)	Weight/score[a]
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	–	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anti-centromere, anti-topoisomerase-1 [anti-topo-1, anti-Scl-70], anti-RNA polymerase III) (maximum score is 3)	Anti-centromere	3
	Anti-topoisomerase-1	
	Anti-RNA polymerase III	

Abbreviation: SSc, systemic sclerosis.

[a]Score ≥ 9 is classified as SSc.

patients with suspected early SSc are referred to centres that are experienced in SSc diagnosis and care.

Diagnostic procedures

Antinuclear antibodies

Autoantibodies targeting characteristic nuclear antigens are one of the hallmarks of SSc. The frequency of detection of antinuclear antibodies (ANA) in SSc patients in a recent study approached 95%,[120] which corresponds well with ANA frequencies of between 85% and 99% reported in the literature. In this study, 86.6% of the ANA-positive patients had SSc-specific antibodies, 96.4% of which were detecting five antigens (i.e. ACA, anti-topo-1, anti-RNA polymerase III, anti-PM/Scl and anti-U1-RNP) (Table 5). It is generally well accepted that the SSc-specific antibodies described above are largely mutually exclusive. Coincidences in individual patients do occur but are rare. An outcome-based classification system for SSc has recently been proposed, which reflects current approaches to case stratification in clinical practice.[126]

For a more detailed description of autoantibodies linked to overlap syndromes, please see Section – Systemic Sclerosis Overlap Syndromes.

Capillaroscopy

Capillaroscopy (e.g. videocapillaroscope, stereomicroscope or dermatoscope) is a well-established, non-invasive technique for the identification of changes in the nailfold capillary that differentiate primary Raynaud's phenomenon from SSc. For a detailed review the reader is referred to the article by Cutolo and Smith.[127]

A variety of scoring systems have been proposed, and automated analysis platforms are also being developed that could underpin in future use of this methodology in clinical practice.

TABLE 5 Autoantibodies in systemic sclerosis.

Antibodies	Organ involvement
SSc-specific autoantibodies	
Centromere	Pulmonary arterial hypertension
Topoisomerase-1 (Scl-70)	Digital ulcerations, interstitial lung disease, skin fibrosis
RNA polymerase III	Renal crisis, skin fibrosis and paraneoplasia
PM/Scl	Myositis, interstitial lung disease
U1-RNP	Joints
SSc-associated antibodies	
Ro, La	Parotis (Sjögren syndrome)
CCP	Rheumatoid arthritis
Rheumatoid factor	Rheumatoid arthritis
Mitochondrial (M2)	Liver (primary biliary cirrhosis)

Abbreviations: CCP, cyclic citrullinated peptide; SSc, systemic sclerosis.

Organ involvement and diagnostic work-up

Raynaud's phenomenon

Raynaud's phenomenon is characterized by a vasospasm resulting in blanching, cyanosis and then reactive hyperaemia

(triphasic). Raynaud's phenomenon is present in more than 90% of patients. It typically affects the hands and less commonly the feet, but may also involve the tongue, ears, and nose. Cold exposure is the usual trigger, but emotional stress may evoke the same symptoms.

Primary Raynaud's phenomenon is mainly caused by functional disturbances, whereas in secondary Raynaud's phenomenon in the context of SSc, there is also involvement of structural alterations in digital arteries. These combined changes are major causes for the formation of ulcers. To distinguish primary from secondary Raynaud's phenomenon, nailfold capillaroscopy and the analysis of autoantibodies are required. Additional laboratory and radiologic examinations may become necessary to exclude other factors that could contribute to the symptoms of Raynaud's phenomenon.[128]

It has been shown that when there are additional laboratory or clinical features of connective tissue disease in the presence of Raynaud's phenomenon, there is an increased risk of development of systemic sclerosis or a related disorder. This has been formalized in research studies that define criteria for very early diagnosis of systemic sclerosis (VEDOSS). This has helped to define progression and early diagnosis of cases at high risk of developing SSc.[129]

Skin fibrosis

At the onset of the disease, particularly in the diffuse form, patients tend to have swollen fingers and hands over extended periods of time, so called 'puffy hands'. Sclerotic changes follow later on, finally leading to disabling contractures and sclerodactyly. Perioral plication and microstomia are typical features of the face, as is a mask-like stiffness.

The best and validated tool to measure the progress of the skin sclerosis is the modified Rodnan Skin Score (mRSS). At 17 different anatomical locations, the skin score is evaluated by manual palpation. The skin score is 0 for uninvolved skin, 1 for mild thickening, 2 for moderate thickening and 3 for severe thickening. Subsequently, the sum is used as the total skin score. The mRSS is feasible, reliable and has been validated for initial and follow-up skin evaluation. The administration of this simple method requires some experience, and a careful teaching process is warranted.[130] Other assessment methods such as ultrasound, MRI or durometry have been used in a research setting but are not validated for clinical practice and have not outperformed mRSS in clinical trials.

Skin involvement and its rate of progression are thought to reflect the severity of internal organ involvement. However, in later disease stages, internal organ involvement may progress, while skin fibrosis of the trunk and proximal extremities will diminish.

Fibrosis may be accompanied by additional symptoms such as hair loss, diminished sweating, hyperpigmentation, depigmentation or severe pruritus.

Digital ulceration

Among patients with SSc, 15%–25% have active digital ulceration (DU) and 35% have or have had DUs in the past, although this number varies considerably between centres and studies.[131–134] Analysis of registry data indicates that the extent of skin sclerosis, male sex, presence of pulmonary arterial hypertension, involvement of the oesophagus, presence of anti-topo-1 (but not anti-centromere) antibodies, early age at onset of Raynaud's phenomenon and elevated erythrocyte sedimentation rate could be independent risk factors.[131,133] History of DU when patients first present has been shown to predict the occurrence of DUs at follow-up, and is associated with cardiovascular worsening and decreased survival.[135]

Ulcers over the extensor surfaces of the proximal and distal interphalangeal joints have a mixed aetiology. They are usually due to a combination of poor perfusion, stretched fibrotic skin and trauma. DUs are complicated by secondary infection, osteomyelitis, gangrene and amputation. Acro-osteolysis may further complicate wound healing. Recurring ulcers lead to chronic use of pain relievers and antibiotics, and eventually to hospitalization either for treatment of active DUs or for surgery (amputation).[136]

Contributory causes, such as coexisting large vessel disease, should be excluded by clinical assessment (including Allen's test) or imaging such as magnetic resonance angiography. In addition, differential diagnoses such as vasculitis, thrombangitis or arteriosclerotic vascular disease should be ruled out. Calcinosis cutis should be distinguished from superficial ulceration, but is a possible risk factor for DU particularly in fingertips.

Calcinosis cutis

Calcinosis cutis is marked by subcutaneous calcium carbonate deposits, which appear in all subtypes of SSc and most frequently on the acral parts of the body. They may induce superficial erosions and cause intense pain for the patient. Calcinosis cutis is an important consideration when assessing DUs and can be excluded via X-ray of the affected body parts.

Musculoskeletal system

Arthralgia and musculoskeletal pain are among the most frequent complaints in SSc and may lead to secondary fibromyalgia. Tendon friction rubs are a typical sign of an inflammatory, progressive form of the disease. Muscle weakness and a varying increase in serum creatine kinase levels are quite common and can indicate the presence of an SSc-myositis overlap syndrome (i.e. overlap myositis syndrome, anti-synthetase syndrome mixed connective tissue disease). In these cases, magnetic resonance imaging and a muscle biopsy to determine the type of myositis should be considered.

Inflammatory arthritis can occur in up to 10% of patients and raises the suspicion of the presence of an SSc overlap syndrome (SSc-rheumatoid arthritis). In these cases, rheumatoid factors and anti-cyclic citrullinated peptide (CCP) antibodies (ACPA) (Table 5) should be determined and a rheumatologic work-up initiated. A more detailed description of the diagnosis and treatment can be found in Section – Systemic Sclerosis Overlap Syndromes.

Pulmonary involvement

Interstitial lung disease. Interstitial lung disease (ILD) affects up to 65% of SSc patients to varying degrees. The typical presentation is a predominantly bibasilar pattern. While some patients develop a rapid decline of forced vital capacity (FVC) within the first 3 years, others may remain remarkably stable or may even experience improvement.[137] In early disease, inflammatory alveolitis may precede and/or accompany interstitial fibrosis, leading to loss of pulmonary function, as evidenced by decreased diffusing capacity of the lungs for carbon monoxide (DLCO) and decreased FVC in more severe cases. Most often ILD corresponds to a non-specific interstitial pneumonitis.

Most patients will present with symptoms such as dyspnoea, a dry cough and reduced exercise tolerance. Chest X-ray can be useful but is a relatively insensitive method for the detection of ILD and is no longer recommended at time of first diagnosis. Chest HRCT has a markedly higher diagnostic sensitivity and is the recommended diagnostic tool to determine the extent and distribution of ILD. The sensitivity of HRCT is superior when compared with lung function testing (LFT).[138] LFT should include spirometry, body plethysmography and decrease in transfer factor (DLCO; corrected for haemoglobin). LFT should be performed every 6 months, or more frequently if the patient is developing a loss in FVC and/or a DLCO.

Pulmonary hypertension. Pulmonary arterial hypertension (PAH) occurs in about 15% of patients and develops particularly in patients with long disease duration and anti-centromere antibodies. PAH is associated with significant mortality and is among the most common causes of death in SSc.[139] All SSc patients should be evaluated for possible PAH in line with current recommendations and referred for specialist management. Annual screening of symptoms (unexplained or progressive dyspnoea, syncope and signs of right heart failure) and by echocardiography are strongly recommended in all SSc patients[111] and are part of the current recommendations of cardiologic and pulmonary societies (see 2015 Guidelines of the European Society of Cardiology[140]).

Recent pooled data analysis of trials and registries have demonstrated substantially improved outcomes and survival due to better care and treatment of the patients. As well as supporting use of currently available agents in SSc-PAH, the approach and benefit from combination therapies provides a template for advancing practical management of SSc in other clinical domains.

Gastrointestinal involvement

The gastrointestinal tract is frequently involved, with 80% of patients having oesophageal involvement and 40%–70% having involvement of the stomach, small intestine and large intestine.[119,141] In longstanding disease (i.e. >10 years), upper gastrointestinal involvement occurs in nearly all patients. The most common symptoms are heartburn, oesophageal dysfunction in the upper gastrointestinal tract, diarrhoea due to bacterial overgrowth and faecal incontinence in the distal tract. Barrett's oesophagus is a late sequel of reflux disease and requires surveillance according to the respective guidelines.[142]

Rarely, telangiectasias may also be present on the mucosa, representing a potential source of occult intestinal bleeding. The standard diagnostic procedure for this is endoscopy.

Cardiac involvement

The nature and severity of cardiac disease depends on the extent of myocardial fibrosis, and on the extent to which concurrent fibrosis of the lung and thickening and fibrosis of the small pulmonary arteries place an additional burden on the circulation. Myocarditis and pericarditis can be observed in a subset of patients and may lead to diagnostic uncertainty. Risk factors for cardiac involvement are diffuse disease, particularly with rapid progression, and signs of inflammation such as tendon friction rubs. Patchy myocardial fibrosis contributes to diastolic dysfunction and to a diminished left ventricular ejection fraction.

Arrhythmias are quite common in SSc. In patients with the diffuse form of SSc, severe forms of arrhythmias are considered an important source of mortality.[143] As regular electrocardiogram is relatively insensitive, there should be a low threshold to use Holter monitoring.

Renal involvement

Acute kidney injury associated with microangiopathic haemolytic anaemia (MAHA) and accelerated phase hypertension is a serious and potentially fatal SSc complication (scleroderma renal crisis; SRC). It is most likely to occur in patients with the progressive, diffuse form of the disease, with a disease duration of less than 4 years. The presence of anti-RNA polymerase III antibodies is considered a particular risk factor and is detected in about one-third of cases.[144] Thus, regular control of blood pressure (at least twice weekly/home monitoring) is recommended to detect acute renal involvement early on. Glucocorticoids in doses exceeding 15 mg of prednisone equivalents should be avoided, due to their long-term adverse effects and their possible association with renal crisis.[144]

In a small subset of patients, normotensive acute renal crisis will develop. In these cases, patients often present with signs of thrombotic microangiopathy. Chronic renal involvement in SSc is associated with a slowly progressive obliterative vasculopathy. Urinary protein excretion has been determined in several studies as a major independent risk factor for mortality.[145] Therefore, urinary protein excretion should be determined at least annually.

Consensus criteria for classification and diagnosis of SRC are being developed and validated.[146] In addition, there is the need for better management of chronic kidney disease (CKD) in the context of SSc; more efficient biomarkers and treatment options are also being developed.

TABLE 6 Organ-oriented baseline work-up.

Organ system	Diagnostic procedures
General	• History and physical examination • ESR/CRP • Blood count • Clinical chemistry • Autoantibody testing
Skin	• Modified Rodnan Skin Score
Musculoskeletal	• Clinical exam • Creatine kinase • Anti-CCP • Rheumatoid factor
Gastrointestinal	• Upper gastrointestinal endoscopy
Lung	• High-resolution computed tomography • Lung function (FVC, DCOc/SB)
Heart	• Electrocardiogram • Echocardiography
Kidneys	• Blood pressure (weekly self-monitoring in high-risk patients [anti-RNA polymerase III+]) • Creatinine • Urinary protein

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DLCOc/SB, diffusing capacity of the lungs for carbon monoxide per single breath; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; RNA, ribonucleic acid.

TABLE 7 Organ-oriented recommended annual work-up.

Organ system	Diagnostic procedures
General	• History and physical examination • ESR/CRP • Blood count • Clinical chemistry
Skin	• Modified Rodnan Skin Score
Lung	• Lung function (FVC, DCOc/SB)
Heart	• Electrocardiogram • Echocardiography
Kidneys	• Blood pressure (weekly self-monitoring in high-risk patients [anti-RNA polymerase III+]) • Creatinine • Urinary protein

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DLCOc/SB, diffusing capacity of the lungs for carbon monoxide per single breath; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; RNA, ribonucleic acid.

General recommendation for a regular diagnostic work-up in patients with SSc

After an initial baseline assessment (Table 6), at least annual, life-long, follow-up of patients is recommended due to the chronic nature of the disease. In patients with progressive disease, corresponding with disease activity, patients should be followed more frequently. The annual work-up should include a thorough clinical investigation including mRSS and the following diagnostic measures: lung function test with plethysmography including DLCO, blood pressure, electrocardiography, echocardiography, erythrocyte sedimentation rate/C-reactive protein, complete blood count, clinical chemistry (liver function, creatinine and urea) and urinary protein.

Particularly in patients with an increased risk for renal crisis (progressive diffuse disease, anti-RNA polymerase III antibodies), frequent blood pressure measurements are recommended (preferably home monitoring) (Table 7).

Treatment

Therapy for skin involvement

Treatment of Raynaud's phenomenon

Avoidance of cold exposure and the constant protection against cold is paramount. Heated gloves, shoes and pockets are usual measures. Furthermore, paraffin baths, heated seed pillows, therapy balls and physical therapy are recommended.[147] Smoking should be stopped, and beta-blocker treatment should be substituted, if feasible.

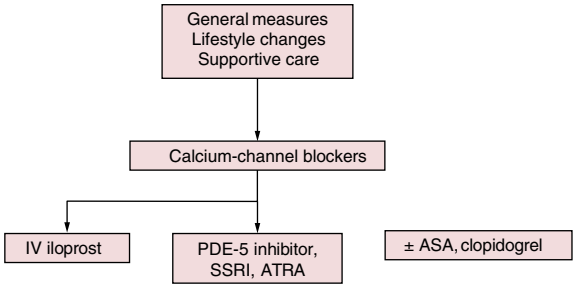


FIGURE 2 Flowchart for management of Raynaud's phenomenon. Adapted from Herrick.[128] ASA, acetylsalicylic acid; ATRA, angiotensin receptor antagonist; IV, intravenous; PDE, phosphodiesterase; SSRI, selective serotonin reuptake inhibitor.

These lifestyle measures should be supported by pharmacologic therapy (Figure 2). First-line therapy consists of calcium antagonists such as nifedipine or amlodipine. Large meta-analyses have revealed that calcium antagonists reduce the severity and frequency of Raynaud's attacks. The dosage should be increased carefully. Controlled studies indicated that PDE-5 inhibitors (i.e. sildenafil and vardenafil) may also be effective in the treatment of Raynaud's phenomenon, by reducing the severity and frequency of attacks.[148–150] Selective serotonin reuptake inhibitors, such as fluoxetine, have shown benefit in some patients,[151] and angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor antagonists may also be considered.[152]

An improvement of severe Raynaud's phenomenon has been demonstrated following intravenously administered iloprost, as described under digital ulcer treatment (below).[153,154]

Digital (palmar) sympathectomy (with or without botulinum toxin injection) may be considered in severe and/or refractory cases.

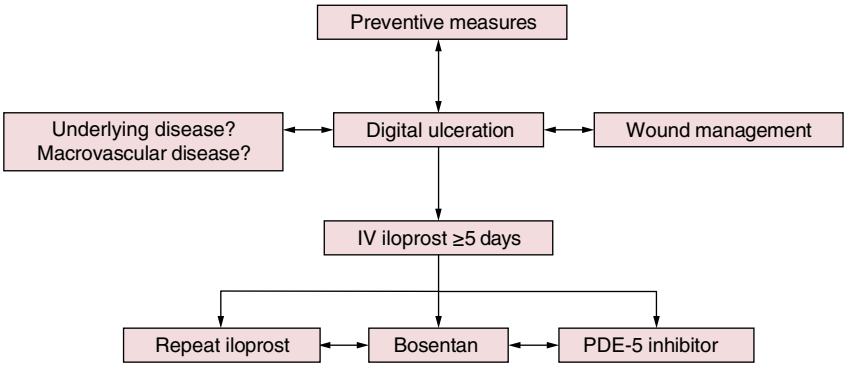


FIGURE 3 Flowchart for management of digital ulcerations. Adapted from Riemekasten et al.[155] IV, intravenous; PDE, phosphodiesterase.

Treatment of digital ulceration

Avoidance of cold exposure and cessation of smoking are accompanying measures. Beta-blocker treatment should be substituted, if feasible. A modified algorithm as published by Riemekasten et al.[155] is shown in Figure 3.

Infections, especially those that affect deep adjacent structures, should be treated with antibiotics in order to prevent osteomyelitis and avoid amputation.[156] If possible, the antibiotic therapy should be combined with a vasodilatory therapy to improve perfusion of the involved area. Sufficient analgesic therapy is recommended to improve quality of life and to reduce pain-induced vasoconstriction. Adequate wound care and regular clinical inspection are mandatory, to prevent infections, gangrene or necrosis.[156] In the case of dry, superficial ulcers, non-occlusive wound care is recommended. The use of a protective wound dressing (i.e. alginate) is advised when deep ulcers are present, in order to protect the wound from sources of infection and to support granulation. Wound care includes a thorough cleaning and disinfection of the wound with sodium chloride, antiseptics or wound cleansing solutions.

Two randomized controlled trials demonstrated that intravenous iloprost is efficacious in healing digital ulcers in SSc; it should be administered at a dosage of 0.5–2 ng/kg per minute for 3–6 h for at least 5 consecutive days.[111,157] The recommended treatment duration varies between 3 and 14 days and is in part influenced by restrictions in the respective national healthcare system.[157] The most frequent adverse effects are headaches, low blood pressure, and cutaneous flushing. To minimize these adverse effects, a slow daily increase of the dosage, depending on the individual patient's condition, is necessary.[157]

A meta-analysis of several randomized controlled trials indicated that PDE-5 inhibitors improve healing of digital ulcers.[158] Therefore, PDE-5 inhibitors can be considered for the treatment of active digital ulcers.

Bosentan is a non-selective endothelin receptor antagonist that demonstrated efficacy in the prevention of digital ulcers in two randomized and controlled studies (RAPIDS-1 and -2) in SSc patients.[159–161] A significant reduction in the number of new ulcers was revealed, particularly in patients with multiple ulcers. Adverse effects consist of possible liver toxicity, teratogenicity and reduced effectiveness of oral contraceptive pills through interference with the cytochrome P450 system.[111,158] Bosentan does not affect healing of active DUs. Subgroup analysis of a prospective trial of sildenafil suggested additional benefit from combination of bosentan with sildenafil that may be analogous to treatment of pulmonary arterial hypertension.[162]

Digital (palmar) sympathectomy (with or without botulinum toxin injection) may be considered in severe and/or refractory cases, though long-term efficacy has not yet been demonstrated.[152]

Treatment of skin fibrosis

Therapy for skin sclerosis should be guided by the phase of the fibrotic process (early phase vs. late phase), the disease activity, and the progression of the fibrosis. General measures include skin protection from cold and trauma, skin care with moisturizing creams, lymph drainage and active physiotherapy for the prevention of contractures. These general measures may suffice in mild, non-progressing forms of fibrosis.

In the early phase with limited skin involvement, UVA1 or photochemotherapy (PUVA) should be considered. Similarly, to the successful treatment of LS with UVA modalities, a number of uncontrolled studies have indicated a beneficial effect on fibrosis in SSc.[163–165] However, controlled studies are still lacking. Pruritus often occurs in fibrotic skin and may respond to standard therapy and phototherapy. For further details, the reader is referred to Figure 1, however, longer treatment durations may be needed.

Photopheresis (extracorporeal photochemotherapy) has shown promise in a few controlled studies,[166–168] but at present it is still controversially discussed. For more details,

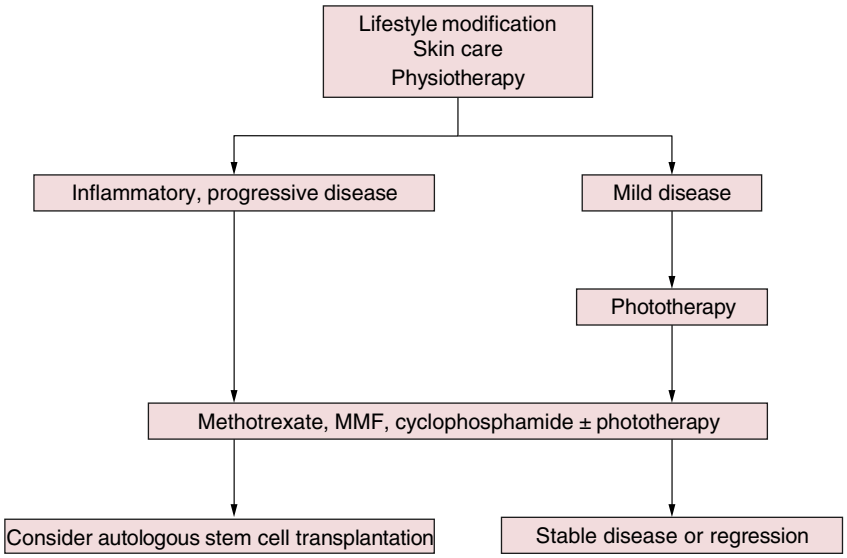


FIGURE 4 Flowchart for therapy of skin fibrosis. MMF, mycophenolate mofetil.

the reader is referred to the recently updated 2020 EDF guideline.[169]

The systemic use of glucocorticoids, which is considered a standard therapy for most autoimmune diseases, plays no role in the therapy of fibrosis in patients with SSc.[111] More importantly, it is well known that glucocorticoids in a dose of >15 mg are associated with a higher incidence of renal crisis.[144]

The best data for systemic therapy of progressive skin fibrosis are available for methotrexate. In two randomized, controlled studies it was shown that methotrexate decreased skin fibrosis in early diffuse SSc. Positive effects on other organs such as the lung could not be shown.[170,171] A dosage of 10–15 mg per week for 6–12 months is generally recommended. Higher dosages may be considered. The use of MMF is recommended by the EUSTAR study group as second-line therapy following methotrexate.[111,172] The recommended standard dosage varies at about 1–2 g per day for at least 12 months.[111,172] This approach was shown to be well tolerated and equivalent to MTX for overall outcome of skin in a large prospective observational study and can be used in patients with ILD or musculoskeletal involvement.[173] Many experts now consider MMF the most appropriate first-line systemic immunosuppressive treatment for SSc skin and ILD in cases without prominent overlap arthritis or myositis.

An improvement of skin sclerosis was demonstrated for cyclophosphamide in the scleroderma lung study.[111,174] The use of cyclophosphamide is recommended after failure of methotrexate and MMF due to high rates of adverse effects.[172] As renewed deterioration of mRSS and lung involvement were observed during follow-up in the scleroderma lung study, a continuation of immunosuppression with MMF or azathioprine after cyclophosphamide therapy is recommended by some experts. An algorithm for the treatment of SSc skin fibrosis is shown in Figure 4.

High dose combination immunosuppression and autologous haematopoietic stem cell rescue ('stem cell transplant') can result in a dramatic decrease in mRSS and has emerged as an important treatment option for some patients that may benefit skin fibrosis.[175] However, despite well conducted trials[176,177] showing superiority over intravenous cyclophosphamide, there remains uncertainty about when and who to treat with this powerful therapeutic approach.[178]

Treatment of calcinosis cutis

Various therapeutic strategies have been investigated for calcinosis cutis, but few have been shown as efficacious. The most promising data are for sodium thiosulfate. In a recent case series, topical sodium thiosulfate was shown to reduce the size of lesions <2 mm. Reduction in the size of larger lesion through intralesional injections is also thought to be possible by experts.[179,180]

Ectopic calcifications or calcinosis that compromise blood circulation or cause symptoms may be removed surgically or by the use of carbon dioxide laser. Surgical excision seems to be the best option after failure of conservative treatment attempts and sodium thiosulfate therapy. However, surgery should only be performed in cases of urgent medical indication.[181–183]

Treatment of telangiectasias

Telangiectasia may appear in the face, the hands (even on the palms), and the mucosa of patients with SSc.[184,185] Laser (i.e. potassium titanyl phosphate or flashlamp pulsed dye laser) or intense pulsed light therapy is the treatment of choice to remove telangiectasias.[184,186] Cosmetics are often used to cover the affected area.

Therapy for musculoskeletal involvement

For detailed treatment recommendations, the reader is referred to Section – Systemic Sclerosis Overlap Syndromes.

Therapy for pulmonary involvement

Treatment of lung fibrosis

ILD in many patients is relatively mild and has a low rate of progression. However, particularly in patients with progressive diffuse disease, a severe reduction in FVC can ensue and the progressive lung fibrosis is recognized as a major cause of mortality.[137] It is therefore crucial to identify patients with risk for ILD and to identify patients with a significant progression as measured by a reduction of FVC (>5% in 6 months or >10% in 1 year) or DLCO (>15% in 1 year). Patients with ILD should be considered for early treatment, when the disease is active and the damage is not yet irreversible. Another component of therapy should be adequate treatment of reflux disease, as this may prevent progression of ILD.[187]

There are now licensed therapies for SSc-ILD including nintedanib[188] and tocilizumab (currently only approved by FDA in USA).[189] Although both drugs appear to slow progression of decline in lung function in SSc, the trials recruited very different populations and so cannot be directly compared. It is possible that tocilizumab is most effective in early-stage lung fibrosis.[189]

The best available data exist for cyclophosphamide, which showed a modest, statistically significant benefit in a randomized, controlled, double-blind trial on both lung and skin fibrosis.[174] As the follow-up data of this trial indicated a renewed progression of fibrosis, several groups recommend the prolongation of immunosuppression after 6 or 12 pulses of cyclophosphamide with the use of azathioprine or MMF.[172]

There are now data supporting use of MMF alone as a treatment for SSc lung fibrosis including data from a comparative trial suggesting similar efficacy to oral cyclophosphamide, and from the SENSCIS trial of nintedanib patients treated with MMF showed less decline in lung function that those on placebo.[188] Interestingly, numerical benefit from combination treatment with immunosuppression was also shown in analysis of the SENSCIS clinical trial.[190]

Based on the results of a randomized, double-blind, double-dummy and Phase 2b trial to assess the superiority of rituximab compared with cyclophosphamide in individuals with connective tissue disease-associated interstitial lung disease (CTD-ILD), rituximab should be considered as a therapeutic alternative to cyclophosphamide.[191]

Two randomized controlled trials (RCTs), one open-label, randomized phase 2 trial and a number of uncontrolled studies have shown that autologous haematopoietic stem cell transplantation improves lung function compared with standard immunosuppressive treatment.[176,177] Transplantation can result in rapid (over months) and sustained improvement of mRSS and FVC. However, in the first year of one RCT, a significantly increased mortality was observed in the transplantation arm.[176] Careful selection of SSc patients for transplantation is mandatory.

Treatment of pulmonary arterial hypertension

Drugs targeting different aspects of vascular pathology have become available in recent years and have dramatically changed therapy of PAH. The diagnosis and therapy of PAH belong in the hands of experienced cardiologists/pulmonologists with specialist expertise. The primary task of the dermatologist taking care of an SSc patient will be to initiate regular (i.e. at least annual) echocardiography and to have a high clinical suspicion for this complication (see 6th World Symposium recommendations[192] and guidelines of the European Society of Cardiology[140]).

Therapy for gastrointestinal involvement

Standard treatment for gastrointestinal reflux disease and the prevention of oesophageal ulcers and strictures is proton pump inhibitors (i.e. pantoprazole 40 mg/day). The majority of patients require maintenance therapy. Second-line options are H_2-blockers and antacids, in addition to appropriate lifestyle changes.[111,193]

Telangiectasias may occur and cause gastrointestinal bleeding (i.e. gastric antral venous ectasia), which should be treated by endoscopic coagulation.

Prokinetic dopamine agonists may be used for dysphagia and reflux (e.g. metoclopramide, octreotide).[194] Bacterial overgrowth and fungal infections (e.g. candida esophagitis) can be managed by intermittent antimicrobial therapy and antimycotics.[195] Anti-diarrheal agents (e.g. loperamide) or laxatives may be used for the symptomatic management of diarrhoea or constipation that often alternate as clinical problems. Parenteral nutrition should be considered for patients with severe weight loss refractory to enteral supplementation. For a more detailed overview, the reader is referred to the consensus best practice pathway of the UK scleroderma study group.[142]

Therapy for renal involvement

Acute renal crisis was the major cause of death before the advent of ACE inhibitor therapy. Prompt recognition of scleroderma renal crisis and initiation of therapy with an ACE inhibitor offers the best opportunity for a good outcome. Other anti-hypertensive agents may be considered for managing refractory arterial hypertension in conjunction with an ACE inhibitor in scleroderma renal crisis.

TABLE 8 Therapy of internal organ involvement.

Organ involvement	Diagnostic procedures
Gastrointestinal	• Proton pump inhibitor, H2 blockers, antacids • Prokinetics (metoclopramide, octreotide) • Antibiotics (bacterial overgrowth) • Laxatives, loperamide • Parenteral nutrition
Kidney	• Prostanoids • Endothelin receptor antagonist, PDE-5 inhibitor, riociguat
Lung	
Pulmonary arterial hypertension	• Prostanoids • Endothelin receptor antagonist, PDE-5 inhibitor, riociguat
Interstitial lung disease	• Cyclophosphamide • Haematopoietic stem cell transplantation

Abbreviation: PDE, phosphodiesterase.

General recommendations for disease management

In order to tailor treatment to the individual patient, it is important to determine disease subset, organ involvement and disease activity. In recent years, the organ-based approach has brought forward significant pharmacologic advancements, changing remarkably the prognosis and life quality of patient subgroups (Table 8).

Multidisciplinary care of SSc patients should aim beyond the treatment of classic organ involvement. Quality of life is increasingly acknowledged in clinical studies and has to be addressed. The psychosocial well-being of SSc patients is often severely affected by the impression of disfigurement (e.g. from telangiectasias, microstomia and contractures), and patients should be appropriately counselled. This also applies to the treatment of chronic pain and depression/anxiety. It has been shown that pain is an important indicator of sexual dysfunction among women with SSc.[196] Similarly, erectile dysfunction in male patients is markedly underdiagnosed and undertreated.[197] Involvement of the masticatory organ may be significant and lead to remarkable deterioration of life quality. Sicca syndrome, gingivitis, tooth decay and osteolysis/necrosis all contribute to a deterioration of oral health-related quality of life. Adjunctive therapy such as physiotherapy and respiratory therapy should be considered early in the course of organ involvement. Small open controlled trials suggest that manual lymphatic drainage may improve hand function in SSc.

Recommendations

- Modern comprehensive interdisciplinary disease management in SSc patients should be directed at the underlying disease process and the resulting organ complications and should also consider the associated physical and psychological consequences.
- Patients should be accurately diagnosed and all cases with diffuse skin disease should be offered systemic immunosuppression such as MMF or MTX.
- Baseline assessment in all cases of SSc should include assessment of organ-based complications including lung fibrosis.
- Evidence based treatment is available for ILD including immunosuppression and approved therapies such as nintedanib.
- Digital vasculopathy should be treated with vasodilators including PDE5 inhibitors, and bosentan for digital ulcers and intravenous iloprost in severe cases.
- Management of pulmonary arterial hypertension should follow expert recommendations using combination therapies and risk stratification scores to optimize outcome.
- Management should be holistic and multidisciplinary and involve expert centres as appropriate for organ-based and symptomatic treatment.

SYSTEMIC SCLEROSIS OVERLAP SYNDROMES

Introduction

Systemic sclerosis overlap syndrome is a term used to describe a very heterogeneous group of patients with features of different connective tissue diseases, combined with clinical signs of SSc.[198–202] To date, no firm classification criteria for SSc overlap syndromes has been established. Musculoskeletal involvement, or features of other rheumatic diseases, are significantly greater in these patients than usually found in general SSc patients.[203,204] These other autoimmune disorders are classified depending on internationally accepted classification systems.[205–209]

Whether mixed connective tissue disease (MCTD) is an additional entity, or part of the overlap syndromes, is still a topic of discussion among experts. MCTD is clinically well characterized with specific circulating autoantibodies (U1-RNP). However, in this review it is considered to represent a subset of SSc overlap syndromes.

Most SSc overlap syndromes appear to encompass a subtype of SSc similar to limited cutaneous SSc (lcSSc), but with more frequent involvement of the musculoskeletal system than in lcSSc or diffuse cutaneous (dcSSc), and an earlier onset of lung fibrosis or heart involvement.[204,210]

Epidemiology

SSc overlap syndromes represent the third major subgroup of SSc, and epidemiologic studies report divergent frequencies (incidence and prevalence rates are not reported yet) of overlap

TABLE 9 Frequencies of different systemic sclerosis overlap syndromes.[200]

SSc overlap syndrome	Frequency of syndrome	Total
SSc (number of patients)	118,[255] 719,[256] 1483,[141] 165,[198] 1700,[203] 2425[221]	6610[200]
SSc overlap syndrome	32.2%,[255] 38%,[256] 10.9%,[141] 24.2%,[198] 20%,[203] 9.2%[221]	16.2%[200]
SSc-polymyositis or SSc-dermatomyositis	5.3%,[255] 47.5%,[198] 42.8%,[203] 60.1%[221]	44.6%[200]
SSc-Sjögren's syndrome	26.3%,[255] 18%,[256] 42.5%,[198] 16.8%[203]	18.5%[200]
SSc-rheumatoid arthritis	8%,[255] 21.1%,[256] 15.4%,[198] 32%,[203] 6.2%[221]	19.3%[200]

Abbreviation: SSc, systemic sclerosis.

subgroups, ranging between 6% and 38% (Table 9).[198,199,201–204] The most common SSc overlap syndromes are SSc and myositis (polymyositis or dermatomyositis), SSc and rheumatoid arthritis, SSc and Sjögren's and SSc and systemic lupus erythematosus (SLE) overlap syndromes.[203] Pakozdi et al.[203] reported recently that 20% of SSc patients attending the Centre for Rheumatology at the Royal Free Hospital (London, UK) had features overlapping with other rheumatologic diseases. Of these, 43% overlapped with polymyositis/dermatomyositis, 8% with SLE, 17% with Sjögren's syndrome and 32% with rheumatoid arthritis. The German Network for Systemic Scleroderma (DNSS) reported that 10% of the registered patients suffered from SSc overlap syndromes.[204]

The mean age at diagnosis of patients with SSc overlap syndromes varies, depending on the cohort, between 47.6 years (SD 2.6) and 62.5 years (SD 14.5), and has been diagnosed more frequently in European patients than in patients from North America.[201,211] Patients diagnosed as classic MCTD were significantly younger (38.4 years; $p < 0.0001$) than other SSc overlap syndromes.[202] Patients with SSc-overlap syndromes including MCTD were more frequently female (76%–86%) and were more likely to have limited skin involvement than patients with SSc only.[202,212]

Balbir-Gurman and Braun-Moscovici[198] reported that the overall mortality in their SSc overlap cohort did not differ from other SSc patients. In comparison, Fairley et al.[202] reported that patients suffering from MCTD and SSc overlap syndromes had a lower mortality after ILD/PAH diagnosis than patients with only SSc diagnosis. Depending on different geographical regions/centres, a wide range of frequencies of SSc overlap syndromes have been reported (Table 9).

Pathogenesis

To date, the pathogenesis of SSc overlap syndromes remains unclear. The question of why some patients develop only one connective tissue disease and other patients have a combination of clinical features of different rheumatic diseases has not yet been answered. Probably a common or overlapping genetic susceptibility may play an important role. Genetic studies have shown the existence of some susceptibility genes, which predispose patients to multiple autoimmune diseases.[211] Koumakis et al. reported that a regulatory gene located in the TNFAIP3 region is associated with a higher risk of developing SSc polyautoimmunity.[211,213] Acosta-Herrera et al.[214] similarly reported a number of immune-related genes that predispose patients to a higher risk of developing different connective tissue diseases, including HLA-DRB1, PTPN22, STAT4 and TNFAIP3.

Clinical manifestations

Clinical features of SSc overlap syndrome are very heterogeneous. Patients usually present with skin sclerosis typical of lcSSc, although organ manifestations clearly separate these patients as a distinct subset.[204] A German study showed that patients suffering from SSc overlap syndromes developed an involvement of the musculoskeletal system significantly earlier and more often than patients with dcSSc and lcSSc. In addition, they developed lung fibrosis and heart involvement significantly earlier and more often than lcSSc patients, but still less frequently and later than dcSSc patients.[204] A further study also showed a relationship between the age at disease onset and symptoms. The musculoskeletal manifestations developed in elderly SSc overlap patients (>60 years) less often compared with the younger group (<40 years).[215]

Therefore, identification of these patients is essential for clarifying prognosis and facilitating therapeutic options. The clinical signs include both cutaneous and extracutaneous features, depending on the overlapping connective tissue disease (CTD) and often overlap between the different overlapping forms, especially regarding vasculopathy, gastrointestinal and cardiopulmonary involvement.

For more details on the following conditions, please refer to Section – Systemic sclerosis.

Raynaud's phenomenon

Raynaud's phenomenon is a very common feature in patients with SSc overlap syndromes.[200] Some SSc overlap patients also develop digital ulcerations, but this occurs significantly less frequently compared with lcSSc and dcSSc patients.[204]

Skin sclerosis

The skin sclerosis in patients with SSc overlap syndromes can be generalized, similar to the diffuse form of SSc. More

frequently, however, it is only located below the elbow and knee joints, similar to the limited form of SSc.[202–204]

Calcinosis cutis

Calcinosis cutis is observed in patients with SSc overlap syndromes and, depending on the subset, can be very severe. It is associated with longer disease duration, positive anticentromere and anti-PM/Scl antibodies, and occurs usually over pressure points (acral or next to joints).[216]

Gastrointestinal involvement

As in SSc, the involvement of the gastrointestinal tract is probably the most common internal organ system involved (approx. 50%–60% of patients).[141,204]

Lung fibrosis and myocardial involvement

Lung fibrosis and myocardial involvement are significantly less frequent than in patients with diffuse SSc, but significantly more frequent than in limited forms of SSc.[204]

Pulmonary arterial hypertension

PAH occurs less frequently in patients with SSc overlap syndromes than in patients with dcSSc, but similarly to those with the limited form of SSc.[202,204]

Clinical characteristics of systemic sclerosis overlap syndromes

Systemic sclerosis and myositis

Myositis is the most frequent systemic involvement in patients with SSc overlap syndromes. In some SSc patients, muscle weakness, pain and atrophy result from disuse secondary to joint contractures, dermatogenous contractures or chronic disease. However, significantly more patients with SSc overlap syndromes present with myositis, characterized by proximal muscle weakness with no loss of reflexes or sensitivity, myalgia, increased creatinine kinase serum levels and later atrophy of muscles. Patients suffering from SSc-myositis overlap syndrome may develop myositis simultaneously, before or in already established SSc.[198]

Some patients may show cutaneous symptoms of dermatomyositis. The limited extent of skin thickening is still the most frequent form in patients with SSc overlap syndromes.[198,203,204] Recent studies have shown that an increased proportion of patients also develop lung fibrosis,[204,217] which is in line with a high percentage (up to 30%) of ILD in patients with dermatomyositis. Patients with SSc-myositis overlap syndromes have a higher risk of developing a diffuse interstitial myocardial fibrosis, which may lead to diastolic dysfunctions as well as restricted contractibility of the myocardium. These patients typically present symptoms, such as cardiac arrhythmia, paroxysmal tachycardia, incomplete or complete right-heart blocks, finally leading to heart insufficiency. The frequency of lung and gastrointestinal involvement varies among studies, ranging between 32.0% and 78.1%.[199]

Patients suffering from the SSc-myositis overlap syndrome (except those with antibody to PM/Scl) have a worse prognosis due to an increased risk of myocardial involvement compared with patients with only SSc.[217–219] In those patients heart monitoring should be undertaken regularly.[219] SSc-myositis overlap syndromes may be associated with specific autoantibodies, including PM/Scl, anti-Ku, anti-U1RNP, anti-U2RNP and anti-U5snRNP (Table 10).[198,220] Patients, carrying the antibody to PM/Scl are usually younger, have limited skin involvement and suffer from arthritis and a benign course of ILD. They also have a better survival.[221] Positive antibodies against Ku are more characteristic for patients suffering from muscle involvement as well as severe ILD (Table 10).[222]

TABLE 10 Autoantibodies with systemic sclerosis overlap syndromes.

SSc overlap syndrome	Autoantibodies
MCTD	• Anti-U1snRNP (specific), found in MCTD patients[231,258]
SSc-myositis	• Anti-PM/Scl (specific)[221] • Anti-Ku, -U1RNP, -Scl70, -Jo1, -Ro/SSA, -U3RNP, -RNA-polymerase have also been reported[200] • Anti-RuvBL1/2 antibody is a new SSc-related antibody, associated with muscle involvement and diffuse skin thickening[257]
SSc-rheumatoid arthritis	• High titres of RF (60%–72%), anti-CCP (prevalence of 64%)[200] • Anti-CCP more frequent in patients with rheumatoid arthritis features in SSc patients[203] • Anti-Scl-70 and anti-ACA antibodies have been reported[203]
SSc-Sjögren's syndrome	• Anti-Ro/SSA and -La/SSB have been reported[200,203] • Clearly more often associated with anti-ACA[200,203]
SSc-SLE	• Anti-dsDNA together with anti-Scl70 antibodies have been reported[200] • Also, single cases with anti-ACA and -PM/Scl have been reported[200]

Abbreviations: ACA, anti-centromere antibodies; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; MCTD, mixed connective tissue disease; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SSA, Sjörgren's-syndrome-related antigen A autoantibodies; SSc, systemic sclerosis.

Systemic sclerosis and rheumatoid arthritis

Joint involvement is reported to be the second most frequent manifestation in patients with musculoskeletal involvement and overlap syndromes.[203] These patients may present with typical clinical symptoms (usually limited skin involvement, morning stiffness and arthritis), together with high titres of anti-cyclic citrullinated peptides (CCP) and/or higher rheumatoid factors (SSc-RA overlap syndrome). One recent study confirmed, that anti-citrullinated proteins (CCP/ACPA) are important to identify patients with a more severe joint disease in SSc-RA overlap patients. Furthermore, they suggested that anti-CarP antibodies could be a relevant biomarker for skin fibrosis and lung involvement.[223] However, it is often very difficult to distinguish between SSc patients with mild, sero-negative arthralgia and the significant arthritis associated with SSc-RA overlap syndrome.

Systemic sclerosis and systemic lupus erythematosus

This subtype is a very rare condition.[224] Patients often have a fatal course of the disease due to a higher risk of developing polyserositis, pancreatitis, avascular bone necrosis, PAH, lung involvement, lupus glomerulonephritis, skin rashes and leukoencephalopathy.[198] It is also difficult to distinguish whether the patient suffers from a lupus-nephritis or a scleroderma renal crisis. Depending on the reason for renal failure, patients need a different therapeutic strategy to improve renal function. Alharbi et al. reported that patients with SSc-SLE were younger at disease onset, suffered more frequently from PAH and showed less frequently SSc associated skin manifestations.[225] SLE-associated skin lesions can be a major aesthetic disturbing factor, because of the predilection for the face. These patients usually have a combination of SSc-associated antibodies and anti-double-stranded DNA antibodies.

Systemic sclerosis and Sjögren's syndrome

This SSc overlap syndrome was first described in 1965 by Bloch et al.[226] Xerostomia and xerophthalmia are very common in patients suffering from SSc (68%–83%), but only 14%–20% of SSc patients fulfil the criteria of Sjögren's syndrome,[227] making the diagnosis of SSc/SS overlap syndromes challenging.[228] It is defined by a lymphocytic infiltration of the salivary glands. Patients with SSc-SS overlap syndrome show a limited form of skin involvement (83.6% vs. 16.4%) and a very low frequency of lung involvement.[198,229] Compared with patients with SS or SSc alone, SSc-SS patients are more likely to have another autoimmune disorder and other autoantibodies.[229] Antibodies against Ro are very likely in SSc-SS overlap syndromes, often together with ACAs.[203] Patients suffering from this type of overlap syndrome showed a higher mortality rate; the underlying cause remained unclear.[201]

Mixed connective tissue disease

Mixed connective tissue disease (MCTD) was first described by Sharp et al.[230] These patients present clinical symptoms typically found in patients with myositis, SLE, inflammatory arthritis (RA) and SSc. Typical for this condition are puffy fingers (50%), polyarthritis (65%), Raynaud's phenomenon (53%), sclerodactyly (35%), muscle involvement and oesophageal involvement,[231,232] and the occurrence of high antinuclear antibody titres with high levels of U1snRNP antibodies, which help to differentiate MCTD from other connective tissue diseases. Arthralgia occurs in approximately 60% of patients, and muscle disease is present in 80%–90% of cases with proximal muscle involvement and elevation of serum creatine kinase levels.[232] Pulmonary involvement (lung fibrosis and PAH) is less frequent, but is a major contributor to a poor outcome/prognosis.[231] PAH is associated with a 56% 10-year survival. ILD, pericarditis, thrombocytopenia, and anti-Sm antibodies are risk factors for PAH in MCTD.[233] SSc may also occur together with other organ-specific autoimmune diseases, such as autoimmune hepatitis/primary biliary cholangitis, autoimmune thyroiditis, sarcoidosis and antiphospholipid syndrome (Table 11).

Diagnostic procedures

Muscle involvement (myositis/myopathy)

Typical clinical symptoms include a symmetrical proximal muscle weakness, muscle pain and/or muscle atrophy

TABLE 11 Rare cases of systemic overlap syndromes.[198]

SSc overlap syndrome with	Definition
Antiphospholipid syndrome	• Incidence varies between 7% and 13%[198] • Presence of lupus anticoagulant, anti-cardiolipid or anti-β2-glycoprotein-1 antibodies has been reported in SSc patients,[198] and has been associated with severe ischemia, PAH, digital loss, thromboembolism
Sarcoidosis	• Very rare variant of SSc overlap syndrome • Elevated temperature and weight loss have been shown in SSc sarcoidosis and overlap syndromes • Lung and lymph node biopsy are necessary to diagnose the disease[198]
Primary biliary cirrhosis	• Prevalence ranges between 7% and 15% • Mostly associated with lcSSc • Positive ACA reveals a higher risk for lcSSc • Often clinically silent, but anti-mitochondrial antibodies, elevation of cholestatic enzymes, as well as hyperglobulinemia are possible[198]

Abbreviations: ACA, anti-centromere antibodies; lcSSc, limited cutaneous systemic sclerosis; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

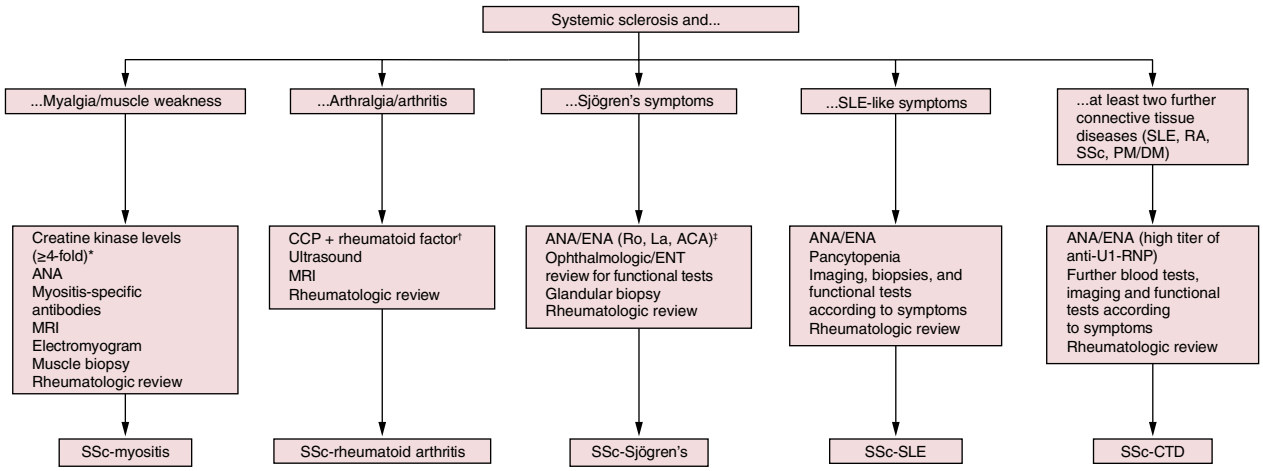


FIGURE 5 Flowchart for diagnostic procedures in patients with different systemic sclerosis overlap syndromes. *Exclude other reason for creatine kinase elevation (drugs, toxins, thyroid dysfunction).†Some patients may be rheumatoid factor-negative and/or anti-CCP-negative. ‡Rule out hepatitis C virus positivity, vasculitis, internal organ manifestation. ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide; ENA, extractable nuclear antigen; ENT, ear nose throat; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus.

with intact reflexes and sensitivity. Serologic tests usually show an elevation of serum creatine phosphokinase (≥4-fold) and acute phase parameters in blood (e.g. C-reactive protein and erythrocyte sedimentation rate). An electromyography, MRI and muscle biopsy will help to identify affected muscles and help to exclude other disease entities (Figure 5).[141,205,206,234]

Sjögren's symptoms

Due to a reduced glandular function, patients with SSc-Sjögren's overlap syndrome suffer from dry mouth (xerostomia) dry eyes (xerophthalmia) and genital dryness. In addition, these patients also typically show anti-Ro and anti-La antibodies, often together with anti-centromere antibodies. Further diagnostics include functional tests for ocular and oral sicca symptoms, together with a glandular biopsy.[235]

Joint involvement

A rheumatologic examination is essential to identify rheumatoid arthritis. Joint involvement can be due to dermatogenous contractures or inflammation. It is recommended to examine the rheumatoid factor and anti-CCP antibodies in the serum of affected patients. X-ray, ultrasound of affected joints, as well as MRI scans can be helpful tools to identify inflammation and damage of the joints.[141]

Kidney involvement

Creatinine clearance, urine analysis to control proteinuria and haematuria, as well as regular blood pressure tests are necessary for the early identification of renal involvement.[141,236] In patients with SSc-SLE overlap syndromes it may be necessary to perform a kidney biopsy to distinguish between renal failures due to lupus nephritis[237] (see also the ACR/EULAR guidelines on SLE) or scleroderma renal crisis[236] (see also Section – Systemic sclerosis).[236] For more details on diagnostic procedures and SSc-associated organ manifestations/complications see Section – Systemic sclerosis.

Treatment

There have been major advances in treating many of the organ-specific complications of SSc and overlapping diseases (see also Section – Systemic sclerosis). Fairley et al.[202] reported the treatment differences within their Australian scleroderma cohort between SSc patients, patients with SSc-overlap syndromes and MCTD. SSc overlap and MCTD patients were significantly more often treated with immunosuppressive agents, such as prednisolone, hydroxychloroquine and methotrexate, compared to SSc only patients.[202]

Systemic glucocorticoids

Systemic glucocorticoids can be used for musculoskeletal involvement together with other immunosuppressive agents.

The use of high-dose glucocorticoids should be used with caution due to the increased risk of renal crisis in SSc patients with diffuse extent of skin involvement.[199]

Methotrexate

Methotrexate is the treatment of choice in patients with SSc-myositis and SSc-RA overlap syndromes.[238–240] The European League Against Rheumatism recommended that methotrexate may be considered as first line treatment option for skin involvement in early diffuse SSc, but there is still a lack of evidence for efficacy in ILD, therefore it should be used only in patients without ILD.[111,202] However, more recently, MTX is often replaced by MMF.

Mycophenolate mofetil

MMF is a preferred treatment option for skin thickening and particularly for those suffering from ILD.[111,240,241] Furthermore it is considered for those with progressive skin disease who are unable to tolerate methotrexate.[240]

Azathioprine

This immunosuppressive agent is usually well tolerated and has been used successfully in patients with MCTD as well as patients with SSc-SLE overlap. However, compared with MMF, adverse effects seem to be more pronounced and the response to the therapy limited.

Cyclophosphamide

Cyclophosphamide is often used for lung involvement in patients with SSc,[242] and also SSc-myositis overlap or SSc-SLE overlap syndromes, in case of lupus nephritis. Cyclophosphamide should be used for musculoskeletal involvement as a second-line immunosuppressive therapy after other treatments (methotrexate, MMF) have failed or cannot be used due to defined adverse effects. As in other autoimmune diseases, it can be used as intravenous pulse or oral treatment.

Immunosuppressive or immunomodulatory agents

Only limited information is available for the use of intravenous immunoglobulin (IVIg),[240] rituximab,[240] abatacept,[240] nintedanib, tocilizumab,[240,243,244] pirfenidone and anti-tumour necrosis factor (TNF) agents in the treatment of overlap syndromes.

Therapeutic approaches

Systemic sclerosis and myositis

In this group of patients, treatment is mainly directed against muscle inflammation, alveolitis and skin sclerosis (Figure 6). Glucocorticoid therapy (not in patients with a higher risk for renal crisis; see Section – Systemic sclerosis), methotrexate (not in case of alveolitis), azathioprine, IVIg, cyclophosphamide and rituximab (in patients with uncontrolled myositis)

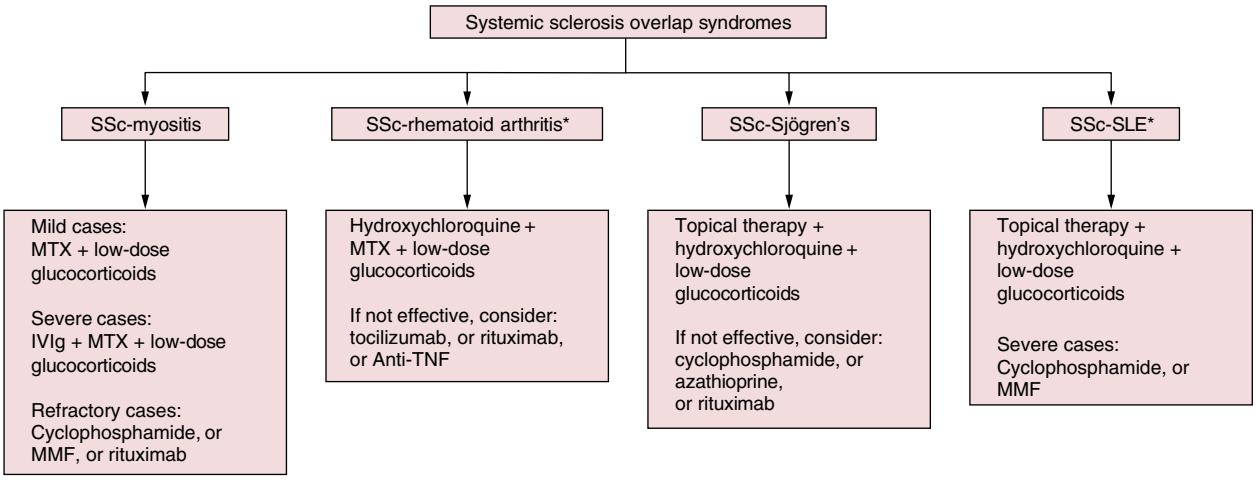


FIGURE 6 Flowchart for therapeutic options for different systemic sclerosis overlap syndromes. *For detailed information, see the ACR/EULAR guidelines. IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TNF, tumour necrosis factor.

may be helpful agents. Histological evidence of muscle inflammation is associated with good response to glucocorticoid therapy.[245]

Agents of choice in mild cases are methotrexate together with low-dose glucocorticoids. In severe cases, IVIg can be added, allowing a reduction of glucocorticoids dose.[246] In patients with a refractory course of the disease, cyclophosphamide (also known to improve skin and lung involvement), MMF (also known to improve skin thickening and lung involvement) or rituximab (also known to improve skin and lung involvement) can be tried to improve clinical symptoms.[198,240,247–249]

Systemic sclerosis and rheumatoid arthritis

These patients are usually treated with hydroxychloroquine, possibly together with methotrexate and low-dose glucocorticoids. If this therapeutic strategy is not effective, tocilizumab, rituximab as well as anti-TNF agents should be considered. All of these treatments must be used with caution, in the context of serious infections, (e.g. tuberculosis). For further details see Section – Systemic sclerosis and ACR/EULAR guidelines on rheumatoid arthritis.[122,240,243]

Systemic sclerosis and systemic lupus erythematosus

Treatment in patients with cutaneous lesions due to SLE should start with topical glucocorticoid therapy, together with UV skin protection. The topical treatment can be combined with hydroxychloroquine together with low-dose glucocorticoids. In severe cases, cyclophosphamide or MMF can be initiated. The treatment of renal involvement differs between a lupus- and a scleroderma-associated renal failure (cyclophosphamide vs. vasoactive treatment with ACE inhibitors and iloprost). For further details see Section – Systemic sclerosis and EULAR/ACR guidelines on rheumatoid arthritis.[122]

Mixed connective tissue disease

Patients with MCTD usually respond well to systemic glucocorticoid and immunosuppressive therapy with several classical agents. However, some long-term studies have shown that a group of patients with MCTD develop more severe organ manifestations and need a more aggressive therapeutic strategy. Inflammatory features (elevated temperature, serositis, pleuritis, myositis and arthritis) respond well to glucocorticoid treatment, while symptoms, such as sclerotic skin changes and cardiopulmonary involvement need immunosuppressive/cytotoxic drugs.[232,250] The most frequently used drugs are hydroxychloroquine, methotrexate and cyclophosphamide, depending on the severity of the disease.[202,232]

Systemic sclerosis and Sjögren's overlap syndrome

Clinical features such as the xerostomia can usually be improved by using various antiseptic mouth rinse and saliva substitutes. Xerophthalmia can be improved by using artificial tear drops.[251] This topical treatment should be combined with hydroxychloroquine and low-dose glucocorticoids. In severe cases, cyclophosphamide, azathioprine or rituximab have shown to be effective in open-label studies.[252] For further details see Section – Systemic sclerosis and guidelines for Sjögren's syndrome.[253]

Recommendations

- Systemic sclerosis overlap syndromes represent a heterogeneous group of patients with features of other connective tissue diseases combined with clinical signs of SSc.
- All patients have to be regularly monitored for organ complications including myositis, arthritis, lung, heart and GI involvement.
- Circulating autoantibodies have to be characterized to allow a better diagnosis of the subsets.
- Therapeutic approaches have to be adapted according to the specific organs involved.
- Check general medication and included drug-induced scleroderma-like symptoms.

Methods

The current consensus statement on diagnosis and treatment of sclerosing diseases of the skin was developed through discussion with a panel of 30 international experts in dermatology, rheumatology and related fields in an iterative process. Multiple rounds of emails were shared to gather individual opinions and recommendations on the topic in question, allowing participants to review and revise their responses until a consensus was reached.

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CONFLICT OF INTEREST STATEMENT

Prof. Dr. Robert Knobler received consultancy fees from Therakos/Mallinckrodt and Actelion. Dr. M. Geroldinger-Simić, PhD, received fees for lectures from Janssen and for attending meetings from Astra Zeneca. Prof. Dr. Alexander Kreuter received fees for lectures and manuscript preparation from Actelion and had advisory board membership with Sanofi Pasteur, Merck Sharp & Dohme and AbbVie. Prof. Dr. Nicolas Hunzelmann received lecture fees from Boehringer and Janssen. Dr. Pia Moinzadeh received lecture fees from Boehringer Ingelheim and received a research grant, consulting honoraria, fees for lectures and participation in review activities from Actelion. Prof. Dr. Franco Rongioletti received research grants from Abbvie and Almirall. Prof. Dr. Christopher Denton received research grants from Actelion, Roche and CSL Behring, and consulting fees from Actelion, Glaxo Smith Kline, Bayer and Roche. Prof. M. Cutolo received research grants from Boehringer-Ingelheim and Horizon. V. Smith has received grant/research support to her institution from the Research Foundation Flanders, Belgian Fund for Scientific Research in Rheumatic Diseases, Janssen-Cilag and Boehringer-Ingelheim; consulting fees from Boehringer-Ingelheim (payments made to self and institution) and Janssen-Cilag (payments made to institution); support for attending meetings and/or travel from Boehringer Ingelheim (payments made to institution). I. Foeldvari has received research grants from Joachim Herz Stiftung and consultancy fees from Eli Lilly, Pfizer, MEDAC, AMGEM and Novartis. Dr. Ahmad Jalili received research grants, consultancy honoraria and fees for lectures and participation in review activities from AbbVie, Almirall, Amgen, Bayer, BioMed, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galderma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Merz Pharma, Novartis, Pfizer, Sanofi, Sandoz and UCB Pharma. Dr. K. Kofoed has received fees for lectures from Eli Lily, Astra Zeneca, Abbvie, Bristol-Myers Squibb, LEO Pharma, Astra Zeneca, Orifarm and Boehringer Ingelheim and fees for consulting from Eli Lilly, Pfizer and Janssen. Prof. Dr. Cord Sunderkötter has received consulting fees from Boehringer Ingelheim, Biotest AG and Janssen Cilag; payment for lectures from Boehringer Ingelheim, Biotest AG and Janssen Cilag; and support for attending meetings from Boehringer Ingelheim and Pfizer. Prof, Dr. Adrian Tanew has received consulting honoraria or lecture fees from Amgen, Incyte, mibe GesmbH and Pelpharam. Prof. Dr. Peter Wolf has received research grants, speaker and/or consulting honoraria, and/or travel refunds from Actavis, Amgen GmbH, Almirall, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Merck Sharp & Dohme, Therakos/Mallinckrodt, Roche, Sandoz, Sanofi, Pfizer and UCB. M. Worm has received of honoraria and/or consultation fees by the following companies: Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, DBV Technologies S.A, Aimmune Therapeutics UK Limited, Regeneron Pharmaceuticals, Inc, Leo Pharma GmbH, Boehringer Ingelheim Pharma GmbH &Co.KG, ALK-Abelló Arzneimittel GmbH, Lilly Deutschland GmbH, Kymab Limited, Amgen GmbH, Abbvie Deutschland GmbH & Co. KG, Pfizer Pharma GmbH, Mylan Germany GmbH (A Viatris Company), AstraZeneca GmbH, Lilly Deutschland GmbH and GlaxoSmithKline GmbH & Co. KG. L. Rudnicka has had an advisory board membership with Pfizer, Sandoz, Sanofi, L'Oreal and has provided medical lectures for Leo Pharma, L'Oréal, UCB and Pierre-Fabre. ICMJE Disclosure of Interest form was used to collect conflicts of interest. Prof. Dr. Thomas Krieg, Prof. Dr. Luc Mouthon, Prof. Armando Gabrielli, M. Bagot, Ass. Prof. Dr. A. B. Olesen, Prof. Veli-Matti Kähäri, S. Kárpáti, Prof. Malgorzata Olszewska, Assoc. Prof. Dr. Jaana Panelius, Pietro Quaglino, Prof. Dr. Julien Seneschal, M. Sticherling and A. Skrok report no conflicts of interest.

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ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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