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GUIDELINES

European Dermatology Forum S1-guideline 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 guideline focuses on characteristic clinical and histopathological features, diagnostic scores and the serum autoantibodies most useful for differential diagnosis. In addition, current strategies in the first- and advanced-line therapy of sclerosing skin diseases are addressed in detail. Part 1 of this guideline provides clinicians with an overview of the diagnosis and treatment of localized scleroderma (morphea), and systemic sclerosis including overlap syndromes of systemic sclerosis with diseases of the rheumatological spectrum.

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Localized scleroderma (morphea)

Epidemiology and pathogenesis

Localized scleroderma (LS) comprises a spectrum of sclerotic diseases that primarily affect the skin. Depending on the respective subtype (Table 1), LS can also involve adjacent tissues such as the fat, fascia, muscle and bone, but not internal organs.[1] The incidence of LS ranges from 0.4 to 2.7 per 100 000 people.[2,3] The disease occurs 2.6–6 times more frequently in women than men.[4] 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.[5] 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. It has been hypothesized that certain stimuli, e.g. infections (particularly borrelia), trauma, radiation or drugs (bleomycin, vitamin K1 and L-5-hydroxytryptophan plus carbidopa, balicatib) might cause microvascular injuries and induce T-cell activation that subsequently result in a release of various adhesion molecules.[5] Upregulation of some of these adhesion molecules (e.g. vascular cell adhesion molecule-1 and intercellular adhesion molecule-1) might induce T-cell activation. This, in turn, activates the release of key pro-fibrotic mediators, such as transforming growth factor-beta (TGF-beta), platelet-derived growth factor, connective tissues growth factor, interleukin (IL)-4, IL-6 and IL-8, and certain chemokines.[6–11] Ultimately, and similarly to systemic sclerosis (SSc), activation of these pro-inflammatory and pro-fibrotic signals leads to excessive collagen production and decrease of matrix metalloproteinases responsible for collagen degradation.[12] However, transition from LS to SSc does not occur. Moreover, several reports of familiar clustering and coexistence of LS with autoimmune diseases (e.g. Hashimoto thyreoiditis, alopecia areata, vitiligo, type-1 diabetes) and genital lichen sclerosus suggest a possible genetic component.[13,14]

Diagnostic procedures

Clinical presentation and physical examination A German group of experts proposed a classification of LS that considers the extent and depth of fibrosis and comprises five main types and certain subtypes (Table 1). The authors consider eosinophilic fasciitis as a separate type within the spectrum of LS. The clinical presentations of each type or subtype are summarized in Table 1.

Clinical scores In 2009, the first validated skin score for LS called 'modified localized scleroderma skin severity index' (mLoSSI) was introduced. This score evaluates erythema, skin thickness and development of new skin lesions or lesional extension in 18 anatomical regions and has demonstrated a high inter-rater agreement.[18] The same group of researchers later introduced a score for skin damage in LS, called 'localized scleroderma skin damage index' (LoSDI).[19] Consequently, it was recommended to combine the LoSSI, LoSDI and the Physician's Global Assessment to measure both activity and damage in LS. These together compose the 'localized scleroderma cutaneous

Table 1 Classification according to the German guideline by Kreuter *et al.*[1] and clinical presentation of localized scleroderma/morphea. All types may present with overlapping features of other types (e.g. generalized types with linear or deep aspects)

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 anatomical sites (head-neck, each extremity, anterior trunk and posterior trunk)[15] • 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
Linear type	
Linear LS/morphea of the extremities	• Longitudinally arranged linear, band-like lesions that may follow the lines of Blaschko[16] • 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%[17]
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

LS, localized scleroderma.

assessment tool' (LoSCAT) that could become a standard tool to evaluate skin affection in LS. Patients' quality of live can be evaluated with the Dermatology Life Quality Index or the Hospital Anxiety and Depression Scale.

Histopathology Physicians should take care that the biopsy excision is sufficiently deep as some LS subtypes may primarily involve the subcutis or underlying fascia and muscle. By histopathology, it is neither possible to distinguish between LS and SSc nor to differentiate among different LS subtypes. Early inflammatory skin lesions of LS are characterized by thickened collagen bundles within the reticular dermis that run parallel to the skin surface, and by the presence of dense inflammatory infiltrates between the collagen bundles and around blood vessels and sweat glands. Lymphocytes predominate the inflammatory infiltrates, but plasma cells, histiocytes and eosinophilic

granulocytes might be present as well. The overlying epidermis might be either unaffected or thin and atrophic. In the late fibrotic stage, the lesional skin becomes relatively avascular, and often there is only little evidence of ongoing inflammation. Late lesions usually contain collagen fibres that are tightly packed and highly eosinophilic. Sweat glands are atrophic or absent. Collagen may replace fat cells in the subcutaneous tissue.[1,20]

Laboratory parameters Routine laboratory parameters should include blood differential and clinical serum chemistry including lactate dehydrogenase, creatine kinase (especially in case of suspected concomitant myositis), blood sedimentation rate and C-reactive protein. Abnormal blood findings are frequent in juvenile LS. In the active stage of generalized LS, blood eosinophilia may be observed.[21] 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.[22] Although certain autoantibodies (e.g. antinuclear, anti-single strand DNS, anti-histone, anti-topoisomerase II alpha, anti-small nuclear ribonucleoprotein and anti-matrix metalloproteinase antibodies) have been described in patients with LS,[23–28] routine screening for these antibodies is not recommended. Additional diagnostics (e.g. screening for antibodies against extractable nuclear antigens) should be only performed to confirm or exclude SSc. Likewise, blood screening for *Borrelia burgdorferi* is not generally recommended and should only be performed in clinically suspicious cases.

Imaging Patients with LS 'en coup de sabre' and/or progressive facial hemiatrophy often suffer from neurological symptoms (e.g. migraine, headaches and epilepsy).[29–31] Thus, cranial magnetic resonance imaging (MRI) should be considered to detect potential subcortical calcifications or brain atrophy.[23,32] On the other hand, many patients are asymptomatic even if such abnormalities are seen. Ophthalmologists or oral surgeons should be consulted, 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, e.g. 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.

Differential diagnoses

A variety of differential diagnoses should be considered in LS.[33] In daily routine, the physicians' pivotal challenge is to differentiate LS from SSc.[5] Typical facial (e.g. telangiectases, beak-shaped nose and microstomia) and vascular features (e.g. Raynaud's phenomenon, pitting scars and digital ulcers) of SSc as well as highly specific serum antibodies (e.g. anti-centromere antibodies and anti-Scl-70 antibodies) are absent in LS.[20] All differential diagnoses with respect to LS subtypes and stage of disease are summarized in Table 2.

Table 2 Differential diagnoses of localized scleroderma/morphea according to the German guideline for the diagnosis and treatment[1]

LS subtype	Differential diagnoses
Limited LS (morphea) – initial inflammatory phase	Lichen sclerosus† Erythema chronicum migrans Cutaneous mastocytosis Granuloma annulare Mycosis fungoides Drug-related reactions Chronic radiation dermatitis Porokeratosis Mibelli
Limited LS (morphea) – late stage mainly with hyperpigmentation	Postinflammatory hyperpigmentation Lichen planus actinicus Café-au-lait spots Erythema dyschromicum perstans
Limited LS (morphea) – late stage mainly with atrophy	Acrodermatitis chronica atrophicans† Lipodystrophy Lichen sclerosus Scarring
Limited LS (morphea) – late stage mainly with sclerosis	Necrobiosis lipoidica Pretibial myxedema
Generalized LS	Systemic sclerosis† Mixed connective tissue disease Pseudoscleroderma Scleredema adultorum (Buschke's disease) Scleromyxedema Chronic graft-vs.-host disease† Nephrogenic systemic fibrosis‡† Porphyria cutanea tarda
Linear LS, en coup de sabre	Panniculitis† Lupus erythematosus profundus† Progressive lipodystrophy Localized lipodystrophy§ Focal dermal hypoplasia Steroid atrophy

†The most relevant differential diagnoses.
‡Also known as nephrogenic fibrosing dermopathy.
§For example, lipodystrophia centrifugalis abdominalis infantilis.
LS, localized scleroderma.

Treatment

Although no causal treatment for LS exists, a variety of therapeutic options is available, especially for the active phase of disease. In general, treatment options for LS might 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

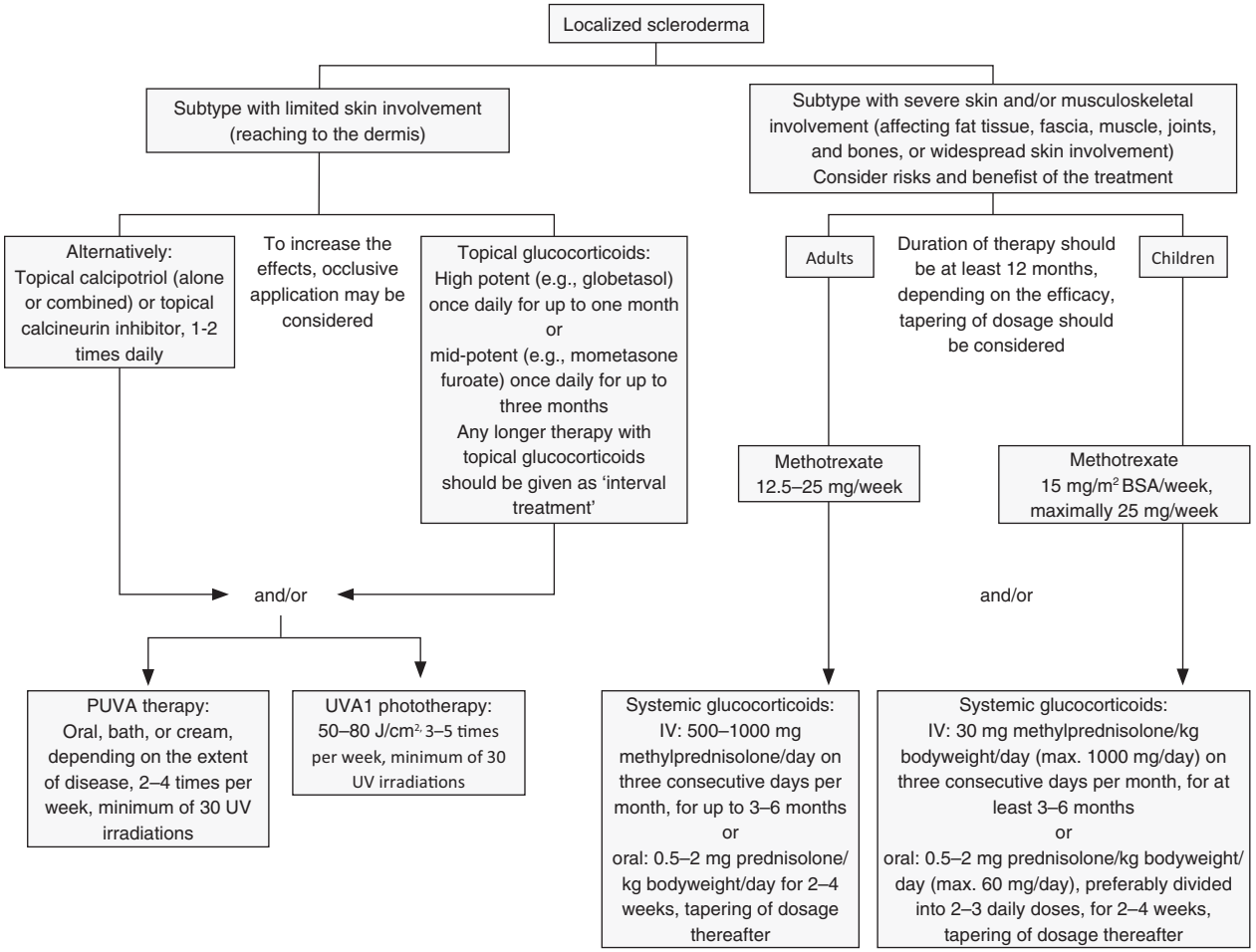


Figure 1 Treatment algorithm for localized scleroderma depending on the clinical subtype and extent of disease. BSA, body surface area; IV, intravenous; PUVA, psoralen plus ultraviolet A irradiation.

UV phototherapy are usually appropriate in limited types of LS that are restricted to the skin, whereas generalized, linear or deep types usually require systemic treatment. To prevent persistent damage from linear types of juvenile LS, effective systemic therapy should be initiated in the active stage as early as possible. Hereafter, all treatment options that have been reported for LS are summarized. A treatment algorithm that incorporates the subtype, severity and extent of LS is provided in Fig. 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 corticosteroids are the mainstay of topical treatment in LS, although no well-performed studies exist. Therapy with moderate- to high-potent corticosteroids 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 corticosteroids should be given as an interval therapy. To increase the efficacy, an application under occlusion might be considered. Intralesional steroid therapy might be performed in LS 'en coup de sabre', with injections into the active margin.

Topical calcipotriol 0.005% should be considered for active inflammatory superficial types of LS with a low degree of sclerosis. This treatment should be performed twice daily (under occlusion) for a minimum of 3 months.[34,35]

Tacrolimus 0.1% ointment might be an effective treatment option for active LS lesions. A recent double-blinded, placebo (petroleum emollient)-controlled pilot study has shown that topical tacrolimus significantly improves LS in terms of changes in surface area, erythema and induration, as assessed by clinical and durometer scores.[36] So far, studies on pimecrolimus for LS are missing.

The topical immune response modifier imiquimod has been reported to significantly improve abnormal pigmentation, sclerosis and erythema in LS[37–39] but cannot be recommended for LS until more valid data are available. Intralesional interferon gamma did not prove effective in LS in a double-blinded, placebo-controlled trial.[40]

Systemic therapy *Systemic corticosteroids.* Systemic corticosteroids are widely used agents in LS, particularly in linear, generalized and deep subtypes. In the only published uncontrolled study on 17 patients with LS where a dosage of 0.5–1.0 mg prednisone equivalent per kg bodyweight and day was used, a marked improvement was noticed in nearly all of the patients.[41] However, about one-third of patients experienced recurrences after finishing therapy. Systemic corticosteroids 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 corticosteroids are the first-line treatment option in eosinophilic fasciitis.[42] When planning the treatment, one should keep in mind that clinical effects are sometimes seen 3 months after onset at the earliest.

Methotrexate. Methotrexate is a well-known immunosuppressive agent that has been used in adults and children with well-documented side-effects. Among systemic treatments for LS, best evidence exists for the use of methotrexate. In a placebo-controlled study, 70 children with active LS were randomized to receive methotrexate orally (15 mg/m^2, maximum: 20 mg; $n = 46$) or placebo ($n = 24$). Oral prednisone (1 mg/kg/day, maximum: 50 mg) was added in both arms for 3 months. In both arms, a reduction of the computerized clinical scores was observed within the first 6 months. However, at month 12, a significant decrease of the clinical score as well as target lesion temperature in infrared thermography was only observed in the methotrexate group.[43] In three non-controlled prospective studies (24 adults and 10 children in total), a combination of high-dosage intravenous methylprednisolone and methotrexate (adults: 15 mg/week; children: 0.3 mg/kg/week) was used. All adults and nine of the ten children experienced a significant improvement under therapy, as assessed by a (non-validated) clinical score and ultrasound scanning.[44–46] Likewise, in four retrospective studies (52 patients with methotrexate monotherapy and 67 patients with a combination of methotrexate and systemic corticosteroids), a clinical improvement was observed in 97% of patients.[47–50] However, 28% of patients with juvenile LS experienced a relapse after treatment with methotrexate.[51] In 2012, the 'Childhood Arthritis and Rheumatology Research Alliance' (CARRA) recommended three different treatment regimens for juvenile LS: (i) methotrexate monotherapy, (ii) pulsed methotrexate and methylprednisolone given intravenously and (iii) pulsed methotrexate and prednisone given orally.[52] These recommendations have been incorporated in the treatment algorithm of this guideline (Fig. 1).

Mycophenolate mofetil. *In vitro* studies have shown that mycophenolate mofetil (MMF) inhibits the proliferation of lymphocytes, but also of other mesenchymal cell types, including smooth muscle cells and fibroblasts.[53] In 2009, a case series of seven methotrexate-resistant LS patients treated with MMF has shown improvement of skin sclerosis and inflammation, as documented with infrared thermography and clinical scoring.[54] Consequently, MMF should be considered as a second-line therapy if methotrexate has failed.[52]

Miscellaneous. Numerous other systemics have been reported in cases of LS, including cyclosporine A, azathioprine, chloroquine and hydroxychloroquine, phenytoin, colchicine, retinoids, intravenous immunoglobulins (IVIg), abatacept, infliximab, rituximab or imatinib.[55–59] These treatments should be reserved to single severe cases with contraindications or failure to standard therapy.

Agents currently not recommended for the treatment of LS. Oral calcitriol failed to achieve any significant improvement in comparison with placebo.[60] D-penicillamine has been reported as effective in small case series of LS patients,[61,62] but cannot be recommended because of the low evidence level and the problematic safety profile. Penicillin has long been used for the treatment of LS because the disease can manifest after an infection with borrelia. However, direct anti-fibrotic effects have so far not been demonstrated.

UV phototherapy Within the last two decades, the vast majority of clinical studies on LS came from the field of photodermatology.[63] One of the rationales for using UV phototherapy in sclerotic skin diseases is the fact that UV can induce interstitial matrix metalloproteinases and thus exerts anti-fibrotic and anti-inflammatory effects.[64–66] In addition, UV phototherapy leads to apoptosis of dermal T cells, depletion of Langerhans cells and modulation of several pro-inflammatory cytokines.[63] As longer wavelengths in the UVA range (320–400 nm) penetrate deeper into the dermis than does UVB (280–320 nm), most studies have focused on UVA. However, as the penetration is not deep enough to affect layers beyond dermis such as fat tissue, fascia, muscle and bone, UV phototherapy may not be effective in LS subtypes with involvement of these deep structures. The dosages and duration of UVA irradiation used in the treatment of sclerotic

skin diseases are most likely too low to induce any significant skin damage or skin cancer.[67]

PUVA phototherapy. To avoid the well-known side-effects of oral application of 8-methoxypsoralen, PUVA in LS was mainly applied as bath-PUVA phototherapy. In a retrospective study published in 2013, 28 patients were treated with three-times-weekly bath-PUVA and experienced complete clearance of all lesions in 39%, clinical improvement in 50% and no response in 10% of patients.[68] Similar encouraging results were reported from four patients treated with cream-PUVA phototherapy.[69] PUVA phototherapy is usually performed 2–3 times weekly for a total of 30 irradiations.

Broadband UVA. Three prospective studies have been published on the use of broadband UVA (320–400 nm) in LS.[70–72] Among these, the largest study included 63 patients.[72] The three dosages used (5, 10 and 20 J/cm² for 20 irradiations each) were similar in efficacy. Controlled studies comparing broadband UVA with other UV modalities are lacking.

UVA1 phototherapy. In the area of phototherapy, the most robust data exist for UVA1. Three different dosages of UVA1 can be distinguished: low-dose UVA1 (10–29 J/cm²), medium-dose UVA1 (30–59 J/cm²) and high-dose UVA1 (60–130 J/cm²). All regimens have been used in LS, and the first report was published in 1991.[73] 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.[74] By contrast, several prospective studies performed some years later showed that low- and medium-dose UVA1 are effective as well.[34,75–81] So far, only one randomized controlled study compared low- and medium-dose UVA1, and narrow-band UVB phototherapy in a collective of 64 LS patients. All three UV regimens significantly improved the skin scores, with medium-dose UVA1 being significantly better than narrow-band UVB.[82] Whether patients with darker skin respond less to UVA1 phototherapy is still a matter of debate.[83,84] Moreover, it has been shown that within 3 years after therapy, about 50% of patients treated with UVA1 experience recurrences.[85] In these cases, a second cycle of UVA1 phototherapy should be considered. UVA1 is usually performed 3–5 times weekly for a minimum of 30 irradiations. Success with extracorporeal photopheresis has also been described in case reports.[86–89]

Physiotherapy Studies on physiotherapy in LS are lacking. Nevertheless, physiotherapy is an important component in the multimodal treatment concept for LS, especially for linear, generalized, deep and mixed types of LS. It should not be performed in the active, inflammatory stage of disease. Massage and lymphatic drainage can be added to systemic therapy in patients with sclerotic stage. 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 to adjust leg length inequality can be considered in consultation with an experienced paediatric orthopaedist. Plastic-surgical interventions might be considered for cosmetic reasons in linear LS 'en coup de sabre' or progressive facial hemiatrophy. It is important that surgical interventions are only considered in the inactive stage of disease to keep down the risk for reactivations.

Clinical course and prognosis

So far, only limited data are available on the long-term clinical course of LS. A recent retrospective analysis including 344 patients with adult or juvenile LS from the Netherlands demonstrated that about one quarter of the patients experienced a reactivation of disease. Univariate analysis demonstrated that the age at onset of disease was a risk factor for recurrent disease; relapses occurred significantly more often in paediatric (27%) compared to adult (17%) LS patients. Moreover, disease subtype was another risk factor; 37% of patients with linear LS of the limbs (either solitary or as part of mixed type of LS) experienced a relapse, whereas recurrences in the other subtypes occurred less frequently (17%). The two most frequent subtypes in adults (morphea/plaque type and generalized LS) had recurrence rates of 16% and 25%, respectively. Importantly, this study also showed that disease relapses can occur after years of quiescent disease; the median time between disease remission and first recurrence was 26 months in juvenile and 27 months in adult LS, respectively.[90] In the study of Saxton-Daniels *et al.* regarding long-term outcome of paediatric cases, 89% of the paediatric onset cases developed new or expanded lesion over time. Time to recurrence of activity ranged from 6 to 18 years from initial disease onset.[91] The clinical course of disease is often more severe in juvenile linear LS as compared to adult linear LS. It may lead to considerable atrophy of the skin, fat tissue, fascia and muscle resulting in functional, physical and mental disability. Moreover, 30–50% of patients with linear LS experience osteoarticular complications on the affected extremity.[92–94]

Recommendations

- Patients with LS should be evaluated for possible concurrent rheumatic and autoimmune diseases. 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 and serum chemistry. Routine screening for antinuclear antibodies (ANA) and borrelia is not recommended. Screening for antibodies against extractable nuclear antigens should be only performed to confirm or exclude SSc (if clinically relevant).
- Among the clinical scores for LS, the most robust data exist for the validated LoSCAT. Photodocumentation of clinical lesions is advisable.
- 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 and fat tissue. If eosinophilic fasciitis is suspected, deep biopsy must include the fascia as well.
- 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.
- In patients with linear LS 'en coup de sabre' or progressive facial hemiatrophy, neurological examination and MRI of the skull should be performed to exclude an affection of the brain. MRI and CT might be helpful for surgical planning and to detect muscle or bone involvement.
- In juvenile LS affecting the head (LS 'en coup de sabre' or progressive facial hemiatrophy), and in linear LS affecting the joints, screening for uveitis and arthritis should be performed.
- Routine systemic workup is not recommended in LS.
- Topical glucocorticosteroids can be used in the active stage of patients with limited types of LS (high-potent corticosteroids for up to 4 weeks, mid-potent corticosteroids for up to 12 weeks). To increase the efficacy, an occlusive application can be considered. Longer treatment should be performed as interval therapy. Alternatively, topical calcipotriol or topical calcineurin inhibitors can be used. If the lesions do not adequately respond to topical- or phototherapy, systemic therapy should be considered.
- Methotrexate is the current first-line treatment for subtypes of LS with severe skin affection or musculoskeletal involvement. Duration of methotrexate 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 corticosteroids should be performed if contraindications are absent, especially in severe cases (linear or deep LS) or in cases with extracutaneous involvement. Alternatively, MMF should be considered in cases with failure or contraindications to methotrexate.
- First choice phototherapy for limited types of LS is medium-dose UVA1. Alternatively, bath-PUVA or cream-PUVA phototherapy can be considered.
- 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, especially those with linear or mixed types of LS, are particularly affected by recurrent disease. In these patients, a multidisciplinary approach is necessary because of the high rate of extracutaneous involvement (e.g. dermatologist and rheumatologist).

Systemic sclerosis

Epidemiology and pathogenesis

SSc is a heterogeneous, chronic autoimmune disorder leading to fibrosis of the skin and many internal organs.[95] Its incidence is 0.3–2.8 per 100 000 per year with female predominance (3 : 1). A positive family history increases the relative risk by 12-fold compared to the population without genetic predisposition. Cellular and humoral immune reactions (cytokines, adhesion molecules, growth factors) are centrally involved in the pathogenesis

of SSc. Apart from autoimmunity, various infections such as cytomegalovirus, parvovirus B19, human papilloma virus and toxoplasmosis as well as environmental toxins have been implicated as causes of SSc.[96]

Diagnostic procedures

Clinical presentation and physical examination The diagnosis of SSc/systemic scleroderma is challenging due to the heterogeneity of disease manifestations and disease course. In 1980, the American College of Rheumatology (ACR) published preliminary criteria for the classification of patients with established disease.[97] A subclassification, developed by LeRoy *et al.*,[98] has been the most widely used classification system in clinical practice and forms the basis for many registries worldwide (Table 3).[99–101]

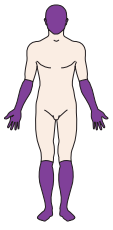
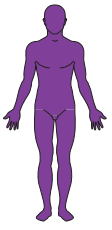
It has been widely accepted that the so called 'CREST syndrome' and 'systemic sclerosis sine scleroderma' can be seen as a part of the disease spectrum of the limited cutaneous form of SSc.[102] For patients with very early disease (also referred to as very early/early SSc, pre-SSc or undifferentiated connective tissue disease), there are no generally accepted diagnostic criteria.[103] Among these cases, only two-thirds of those patients who present with Raynaud's phenomenon, nail fold capillaroscopic changes and/or SSc-specific antibodies (anti-centromere, anti-topoisomerase-1) will develop definite SSc after 5 years, and almost 80% develop SSc in the long term. In contrast, those who have neither scleroderma pattern on capillaroscopy nor SSc-specific antibodies in serum mostly do not develop SSc (1.8% during long-term follow-up).[104]

Skin manifestations. Raynaud's phenomenon is present in more than 90% of patients. It typically affects the hands, 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.[105] At the onset of the disease, particularly in the diffuse form, patients tend to have swollen fingers and hands over extended time periods (so called 'puffy hands'). Sclerotic changes follow later on, finally leading to dermatogenic contractures and sclerodactyly, perioral plication and microstomia and mask-like facial stiffness. They are possibly accompanied by additional symptoms such as hair loss, diminished sweating, hyperpigmentation, depigmentation or severe pruritus. In later disease stages, internal organ involvement may progress, while skin fibrosis of the trunk and proximal extremities will diminish. Among patients with SSc, 15–25% have active digital ulcerations, and 35% have digital ulcerations or had them in the past, although this number varies considerably between centres and studies.[106–109] Ulcers that occur on the fingertip are thought to be exclusively due to ischaemia, whereas ulcers over the extensor surfaces of the proximal and distal interphalangeal joints are usually due to a combination of poor perfusion, stretched fibrotic skin and trauma. Digital ulcers may be complicated by secondary infection, osteomyelitis, acro-osteolysis or gangrene.[110] 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.

Musculoskeletal disorder. Arthralgia and musculoskeletal pain are among the most frequent complaints in SSc and may lead to secondary fibromyalgia.[111] 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. Inflammatory arthritis can occur in up to 10% of patients and raises the suspicion of the presence of an SSc-rheumatoid arthritis overlap syndrome.

Pulmonary manifestations. Interstitial lung disease affects up to 65% of SSc patients to varying degrees. The typical presentation is a predominantly bibasilar pattern which most often corresponds to a non-specific interstitial pneumonitis.[112] The sensitivity of high-resolution CT is superior when compared with lung function testing.[113] Lung function testing should include spirometry, body plethysmography and the diffusing capacity of lung for carbon monoxide (DLCO; corrected for haemoglobin). Pulmonary arterial hypertension occurs in about 15% of patients and

Table 3 Subclassification of systemic sclerosis according to LeRoy *et al.* (1988)[98]

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 positive	

develops particularly in patients with long disease duration and anti-centromere antibodies in serum. All SSc patients should be evaluated for possible pulmonary arterial hypertension in line with current recommendations and referred for specialist management. Annual screening on symptoms (unexplained or progressive dyspnoea, syncope, signs of right-heart failure) and by echocardiography are strongly recommended in all SSc patients.

Gastrointestinal manifestations. The gastrointestinal tract is frequently involved, with 80% of patients having oesophageal involvement and 40–70% having involvement of the stomach, and small and large intestine.[100,114] In long-standing disease (>10 years), upper gastrointestinal involvement occurs in nearly all patients and may include Barrett's oesophagus as a late sequel of reflux disease, and telangiectasia on the mucosa as a potential source of occult intestinal bleeding.[115]

Cardiovascular manifestations. 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. These may lead to diagnostic uncertainty.[116]

Renal disorder. Chronic renal involvement in SSc is associated with a slowly progressive obliterative vasculopathy. Acute renal crisis is a serious and potentially fatal SSc complication. It occurs most likely in patients with the progressive diffuse form with a disease duration of <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.[117]

In 2013, the ACR and the European League Against Rheumatism (EULAR) published new diagnosis criteria (Table 4). However, they were primarily developed for clinical research purposes. Moreover, they cannot be applied to patients without skin involvement of the hands or to patients with scleroderma-like disorders.[118]

Capillaroscopy Capillaroscopy (e.g. by use of nail fold videocapillaroscope, stereomicroscope or dermatoscope) is a well-established, non-invasive technique for the identification of changes in the nail fold capillaries that differentiate primary Raynaud's phenomenon from SSc.[119]

Clinical score The best and validated tool to measure the progress of the skin sclerosis is the modified Rodnan skin score (mRSS). The mRSS is evaluated by manual palpation at 17 different anatomical areas. The skin score is 0, 1, 2 and 3 for uninvolved skin, mild thickening, moderate thickening and severe thickening, respectively. Subsequently, the sum over all anatomical areas will be used as the total skin score. The mRSS is feasible, is 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.[120]

Laboratory parameters Autoantibodies targeting characteristic nuclear antigens are one of the hallmarks of SSc. The frequency of detection of ANA in SSc patients in a recent study approached 95%,[101] which corresponds well with ANA frequencies of between 85% and 99% reported in other literature. In this study, 86.6% of the ANA-positive patients had antibodies specific for SSc, 96.4% of which were detecting five antigens [i.e. centromere, topoisomerase-1, RNA polymerase III, exosomal ribonuclear protein (PM/Scl) and uridine-rich small nuclear ribonuclear protein (U1-snRNP)] (Table 5). It is generally well accepted that the SSc-specific antibodies described in Table 5 are largely mutually exclusive. Coincidences in individual patients do occur but are rare.

Organ-oriented diagnostic workup As a baseline assessment, a broad range of clinical, laboratory and radiographic examinations is indicated to explore the patients' general and organ status thoroughly. The diagnostic procedures recommended are summarized in Table 6. At least annual, lifelong 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.

Table 4 American College of Rheumatology/European League against Rheumatism 2013 criteria for classification of systemic sclerosis (adapted from van den Hoogen *et al.*)[118]

Item	Subitems	Score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	–	9
Skin thickening of the fingers	Puffy fingers Sclerodactyly (distal to MCP but proximal to PIP)	2 4
Fingertip lesions	Digital tip ulcers Finger tip pitting scars	2 3
Telangiectasia	–	2
Abnormal nail fold capillaries	–	2
Pulmonary changes	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	–	3
SSc-related autoantibodies in serum‡	Anti-centromere Anti-topoisomerase-1 (anti-scl 70) Anti-RNA polymerase III	3

†Do not add up the scores for subitems, count the highest score that applies for each item. A total score ≥9 indicates systemic sclerosis (SSc).
‡Any of the antibodies listed as subitems.
MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joints.

The annual workup should include a thorough clinical investigation including the mRSS and the following diagnostic measures: lung function test with body plethysmography including DLCO, blood pressure, electrocardiography, echocardiography, erythrocyte sedimentation rate/C-reactive protein, complete blood count, clinical chemistry (liver function, creatinine, urea) and urinary protein.

Differential diagnoses

LS, scleromyxedema, nephrogenic systemic fibrosis, scleredema and SSc overlap syndromes should be taken into consideration. To distinguish primary from secondary Raynaud's phenomenon, nail fold capillaroscopy and the analysis of autoantibodies are required. Contributory causes such as vasculitis, thromboangiitis or arteriosclerotic vascular disease should be excluded (e.g. by Allen test or fist closure test). Lesions due to calcinosis cutis should be distinguished from superficial ulceration, yet they are a possible risk factor for digital ulcers. The histological and ultrastructural type of myositis can be determined by muscle biopsy.

Treatment

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. The present guideline 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. Many of the recommendations given below are described in more detail in the 'Consensus best practice recommendations for scleroderma' developed by UK Scleroderma Study Group.[121]

Therapy for skin involvement *Treatment of Raynaud's phenomenon.* Avoidance of cold exposure is paramount. Heated gloves, shoes and pockets are usual measures. Furthermore, paraffin baths, heated seed pillows, therapy balls and physical therapy are recommended.[122] Smoking should be stopped. Beta-blocker treatment should be substituted, if feasible.

These lifestyle measures should be supported by pharmacologic therapy. First-line therapy consists of calcium antagonists such as nifedipine or amlodipine. Large meta-analyses revealed that calcium antagonists reduce the severity and frequency of Raynaud's attacks.[123] The dosage should be increased carefully. Recent controlled studies indicated that phosphodiesterase-5 (PDE-5) inhibitors (i.e. sildenafil, vardenafil) may also be effective in the treatment of Raynaud's phenomenon by reducing the severity and frequency of attacks.[124–126] However, these drugs have not been licensed for this indication. Selective serotonin reuptake inhibitors, such as fluoxetine, have shown benefit in some patients.[127] Angiotensin converting enzyme (ACE) inhibitors or angiotensin-receptor antagonists may also be considered.[128] Improvement of severe Raynaud's phenomenon has been demonstrated following intravenously administered iloprost.[129,130] A dosage of 0.5–2 ng/kg/min for 3–6 h on at least five (up to 14) consecutive days at monthly intervals is generally

Table 5 Autoantibodies potentially detectable in systemic sclerosis

Antigens targeted by autoantibodies	Associated condition
SSc-specific antibodies	
Centromere	Pulmonary arterial hypertension
Topoisomerase-1 (Scl-70)	Digital ulcerations, interstitial lung disease, skin fibrosis
RNA polymerase III	Renal crisis, skin fibrosis, paraneoplasia
PM/Scl (exosomal ribonucleoprotein)	Myositis, interstitial lung disease
Uridine-rich small nuclear ribonucleoprotein (U1-snRNP)	Joint involvement
SSc-associated antibodies	
Ro, La (extractable nuclear antigens)	Parotis (Sjögren's syndrome)
Cyclic citrullinated peptide (CCP)	Arthritis
Fc portion of IgG (rheumatoid factor)	Arthritis
Mitochondrial antigen M2	Primary biliary cirrhosis

Table 6 Organ-oriented baseline diagnostic workup in systemic sclerosis

Organ system	Diagnostic procedures
General	Medical history†, physical examination†, complete blood count†, clinical chemistry†, CRP/erythrocyte sedimentation rate†, autoantibody testing (Table 5)
Skin	Modified Rodnan skin score†, X-ray in case of calcinosis cutis
Musculoskeletal	Clinical examination, creatine kinase, anti-CCP, rheumatoid factor; in case of myositis, magnetic resonance imaging and muscle biopsy
Gastrointestinal	Upper gastrointestinal tract endoscopy
Lung	High-resolution computed tomography, pulmonary function with body plethysmography (forced vital capacity, DLCO/SB)†
Heart	Electrocardiography†, echocardiography†
Kidneys	Blood pressure† (preferably self-monitoring in high-risk patients‡), serum creatinine†, urinary protein†

†Examinations are likewise recommended for the annual diagnostic workup.
‡For example, patients positive for RNA polymerase III antibodies in serum.
CRP, C-reactive protein; Anti-CCP, antibodies targeting cyclic citrullinated peptide; DLCO/SB, diffusing capacity of lung for carbon monoxide per single breath method.

Table 7 Overview of therapeutic options for skin manifestations of systemic sclerosis

	Raynaud's phenomenon (adapted from Herrick *et al.*)[105]	Digital ulcerations (adapted from Riemekasten *et al.*)[133]	Skin fibrosis†	Calcinosis cutis†
General measures and physical therapy	Cessation of smoking, avoidance/discontinuation of beta-blocker therapy, protection from cold exposure (heated gloves, shoes and pockets) and from trauma			
	Paraffin baths, heated seed pillows, therapy balls, vasodilatory physical therapy	Wound care, vasodilatory physical therapy	Skin care, lymph drainage, physiotherapy	Skin care
First-line drugs or phototherapy	Calcium channel blocker	Vasodilators, analgesics, antibiotics for infected ulcers	Mild SF: Phototherapy‡ Inflammatory or progressive SF: MTX, MMF, cyclophosphamide ± phototherapy/ECP‡	Carbon dioxide laser
Second-line therapy	PDE-5 inhibitor, SSRI, ACE inhibitor or angiotensin-receptor antagonist ± ASS or clopidogrel; cyclic treatment with iloprost i.v.§ for severe RP	Cyclic treatment with iloprost i.v.§	MTX, MMF, cyclophosphamide ± phototherapy/ ECP‡ until stable disease or regression	–
Advanced-line therapy	–	Repeat iloprost treatment; PDE-5 inhibitor, bosentan	–	–
Option in severe and refractory cases	Palmar sympathectomy ± botulinum toxin injection	Palmar sympathectomy ± botulinum toxin injection; may require amputation	Consider autologous haematopoietic stem cell transplantation[154,155]	Surgical excision of symptomatic lesions

†Treatment algorithm proposed by the authors. References are given in the text.
‡UVA1, PUVA or bath-PUVA; Extracorporeal photopheresis may be used as a second-line or adjuvant treatment in early progressive disease.[149]
§0.5–2 ng/kg/min over 3–6 h on at least five (up to 14) consecutive days at monthly intervals.
ACE, angiotensin converting enzyme; ASS, acetylsalicylic acid; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MTX, methotrexate; RP, Raynaud's phenomenon; SF, skin fibrosis; PDE-5 inhibitor, phosphodiesterase-5 inhibitor (sildenafil, vardenafil); SSRI, serotonin reuptake inhibitor (e.g. fluoxetine).

recommended.[131,132] The most frequent side-effects of iloprost are headaches, low blood pressure and flushing. To minimize these side-effects, a slow daily increase of the dosage, depending on the individual patient's condition, is necessary.[132] Digital (palmar) sympathectomy (with or without botulinum toxin injection) may be considered in severe and/or refractory cases (Table 7).[128]

Treatment of digital ulceration. Avoidance of cold exposure, cessation of smoking and the avoidance of beta-blocker treatment are accompanying measures. Infections, especially those that affect deep adjacent structures, should be treated with antibiotics in order to prevent osteomyelitis and to avoid amputation.[133,134] If possible, the antibiotic therapy should be combined with vasodilatory agents 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.[134] 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 thorough cleaning and disinfection with sodium chloride, antiseptics or other wound cleansing solutions. Two randomized controlled trials demonstrated that intravenous iloprost is effective in healing digital ulcers in SSc.[131,132] A recent meta-analysis of several randomized controlled trials indicated that PDE-5 inhibitors foster the healing of digital ulcers[135] and can, therefore, be recommended 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).[136–138] A significant reduction in the number of new ulcers was shown, particularly in patients with multiple ulcers. Side-effects of bosentan include possible liver toxicity, teratogenicity and reduced effectiveness of oral contraceptive pills through interference with the cytochrome P450 enzyme system.[131,135] However, bosentan does not affect the healing of existing digital ulcers. Digital (palmar) sympathectomy (with or without botulinum toxin injection) may be considered in severe and/or refractory cases (Table 7).[128]

Treatment of skin fibrosis. Therapy for skin sclerosis should be guided by the phase of the fibrotic process (early vs. late

phase), the disease activity and the progression of the fibrosis. There is currently no approved treatment for skin 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. Small open controlled trials suggest that manual lymphatic drainage may improve hand function in SSc.[139] In the early phase with limited or localized skin involvement, UVA1 or bath-PUVA or oral 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.[140–143] However, controlled studies are still lacking. Pruritus often occurs in fibrotic skin and may respond to standard therapy and phototherapy. However, longer treatment durations may be needed. Photopheresis (extracorporeal photochemotherapy) has shown promise in several uncontrolled and controlled studies for skin manifestations of SSc.[88,144–148] According to the 2014 European Dermatology Forum guidelines on photopheresis,[149] photopheresis should be used in SSc on the basis of its safety profile as a second-line or adjuvant therapy in mono- or combination treatment of the skin, but not organ, involvement. It is recommended that it should be applied in early progressive disease, preferably of less than 2-year duration. For more details, the reader is referred to the guideline.[149]

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.[150,151] A dosage of 10–15 mg per week for 6–12 months is generally recommended, but higher dosages may be considered. The use of MMF is recommended by the EULAR Scleroderma Trials and Research (EUSTAR) study group as a second-line therapy following methotrexate. The recommended standard dosage varies at about 1–2 g per day for at least 12 months.[131,152] An improvement of skin sclerosis was demonstrated for cyclophosphamide in the scleroderma lung study.[131,153] The use of cyclophosphamide is recommended after failure of methotrexate and MMF due to high rates of side-effects.[152] As renewed deterioration of the skin score 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 Table 7.

The systemic use of glucocorticoids, which is considered a standard therapy for most autoimmune diseases, does not play a role in the therapy of fibrosis in patients with SSc.[131] More importantly, it is well known that glucocorticoids at a dose of >15 mg are associated with a higher incidence of renal crisis.[117]

Treatment of calcinosis cutis. Various therapeutic strategies have been investigated, but there is currently no evidence of an effective therapy for calcinosis cutis. Ectopic calcifications, or calcinosis that compromise blood circulation or cause other symptoms, may be either removed surgically or by the use of carbon dioxide laser. Surgical excision seems to be the best option after failure of conservative treatment attempts. However, surgery should only be performed in cases of urgent medical indication.[156–158]

Treatment of telangiectasia. Telangiectasia may appear in the face, the hands (even on the palms) and the mucosa of patients with SSc.[159,160] Laser (i.e. potassium titanyl phosphate or flashlamp pulsed dye laser) or intense pulsed light therapy is the treatment of choice to remove telangiectasias.[159,161] Cosmetics are often used to cover the affected area.

Therapy for musculoskeletal involvement For detailed treatment recommendations, the reader is referred to the section about systemic sclerosis overlap syndromes.

Therapy for pulmonary involvement *Treatment of lung fibrosis.* Interstitial lung disease 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 forced vital capacity can ensue. Progressive lung fibrosis is recognized as a major cause of mortality.[112] It is therefore crucial to identify patients at risk for interstitial lung disease and to identify patients with significant deterioration of lung function, as measured by a reduction in forced vital capacity (>5% in 6 months or >10% in 1 year) or DLCO (>15% in 1 year). Patients with interstitial lung disease should be considered for early treatment, when the disease is active and the damage is still largely reversible. Another component of therapy should be adequate treatment of reflux disease, as this may prevent progression of interstitial lung disease.[162] The best available data exist for cyclophosphamide, which showed a modest, statistically significant benefit in a randomized, controlled, double-blinded trial on both lung and skin fibrosis.[153] 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 by the use of azathioprine or MMF.[152] Two randomized controlled trials and a number of uncontrolled studies have shown that autologous haematopoietic stem cell transplantation (HSCT) improves lung function and skin fibrosis compared with

standard immunosuppressive treatment.[154,163] Transplantation can result in rapid (over months) and sustained improvement of mRSS and forced vital capacity. However, in the first year, a significantly increased mortality was observed in the transplantation arm.[154] Thus, 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. They have dramatically changed the therapy of pulmonary arterial hypertension. Diagnosis and therapy of pulmonary arterial hypertension belong in the hands of an experienced cardiologist/pulmonologist with special expertise in right-heart disease. 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 (refer to the 2015 guidelines of the European Society of Cardiology).[164]

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 histamine receptor (H2)-blockers and antacids in addition to appropriate lifestyle changes.[131,165] Telangiectasia and gastric antral venous ectasia may occur and cause gastrointestinal bleeding which should be treated by endoscopic coagulation. Prokinetic dopamine agonists may be used for dysphagia and reflux (e.g. metoclopramide, octreotide).[166] Bacterial overgrowth and fungal infections (e.g. candida esophagitis) can be managed by intermittent antimicrobial therapy and antimycotics.[167] Anti-diarrhoeal 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.[115]

Therapy for renal involvement Prompt recognition of scleroderma renal crisis and initiation of therapy with an ACE inhibitor offers the best opportunity for a good outcome. Other antihypertensive agents may be considered for managing refractory hypertension in conjunction with ACE inhibitors in scleroderma renal crisis.

The treatments for organ involvement in systemic sclerosis are summarized in Table 8.

Clinical course and prognosis

The chronic and unpredictable course of the disease implies regular at least annual follow-up of patients. 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 telangiectasia, 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.[168] Similarly, erectile dysfunction in male patients is markedly underdiagnosed and undertreated.[169] Furthermore, involvement of the masticatory organ may be significant and lead to remarkable deterioration of life quality. Likewise, sicca syndrome, gingivitis, tooth decay and osteolysis/necrosis all contribute to a deterioration of oral health-related quality of life.

Table 8 Therapy of internal organ involvement in systemic sclerosis

Organ	Treatment
Lung involvement	
Interstitial lung disease (lung fibrosis)	Cyclophosphamide†, HSCT for selected cases
Pulmonary arterial hypertension	Prostanoids, endothelin receptor antagonist, phosphodiesterase-5 inhibitor, soluble guanylate cyclase stimulator (riociguat)
Gastrointestinal tract involvement	
Reflux disease	Proton pump inhibitors, H2 blockers, antacids
Dysphagia and reflux	Prokinetics (metoclopramide, octreotide)
Bacterial overgrowth and fungal infection	Antibacterial and antimycotic agents
Diarrhoea or constipation	Loperamide or laxatives
Malnutrition	Parenteral nutrition
Bleeding from gastrointestinal telangiectasias or antral venous ectasias	Endoscopic coagulation
Renal disease, renal crisis	ACE inhibitor ± additional antihypertensive agents

†Some authors recommend to continue immunosuppression after 6 or 12 pulses of cyclophosphamide by the use of MMF or azathioprine.[152]
ACE, angiotensin converting enzyme; H2, histamine receptor 2; HSCT, haematopoietic stem cell transplantation.

Recommendations

- 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 and to a laboratory with expertise in autoimmune serology (Tables 5 and 6). This applies especially to patients with suspected early SSc.
- 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. Multidisciplinary care for patients with early progressive disease should be provided in a setting where the outpatient facilities also have access to physical therapy and hospital beds in order to ensure timely and appropriate diagnosis and treatment for patients presenting with exacerbation of their disease.
- Capillaroscopy and SSc-specific antibodies seem to be good prognostic predictors for the disease.
- At least annual, lifelong, 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.[164]
- Particularly in patients with an increased risk for renal crisis (progressive diffuse disease, anti-RNA polymerase III antibodies), regular control of blood pressure (at least twice weekly/home monitoring) is recommended. Urinary protein excretion has been determined in several studies as a major independent risk factor for mortality.[170]
- Glucocorticoids in higher doses exceeding 15 mg prednisone equivalents should be avoided due to their long-term side-effects and association with renal crisis.[117]
- Modern comprehensive disease management should also consider the associated physical and psychological consequences.

Systemic sclerosis overlap syndromes

Epidemiology and pathogenesis

SSc 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.[171–173] Epidemiologic studies report divergent frequencies (incidence and prevalence rates have not been reported yet) of overlap subgroups, ranging between 9% and 38% of SSc patients.[171,172,174,175] The most common autoimmune diseases overlapping with SSc are polymyositis or dermatomyositis (~43% of SSc patients), rheumatoid arthritis (~32%), Sjögren's syndrome (~17%) and systemic lupus erythematosus (~8%).[174] A recent meta-analysis has revealed that the mean age at diagnosis of patients with SSc overlap syndromes was 47.6 ± 2.6 years, and that it was found more often in European patients than in patients from North America.[176] The question of why some patients develop only one connective tissue disease and other patients have a combination of clinical features of different diseases has not yet been answered. A common or overlapping genetic susceptibility possibly plays an important role.[176,177] Koumakis *et al.*[177] reported that a gene located in the *TNFAIP3* region is associated with a higher risk of developing SSc polyautoimmunity.

Diagnostic procedures

Clinical presentation and physical examination Most SSc overlap syndromes appear to encompass a subtype of SSc similar to limited cutaneous SSc, but with more frequent involvement of the musculoskeletal system than in limited or diffuse cutaneous SSc, and with an apparently earlier onset of lung fibrosis or heart involvement.[174,175] Raynaud's phenomenon is also a very common feature.[173] Digital ulcerations and calcinosis cutis can also be observed in patients with SSc overlap syndromes.[175,178] The other cutaneous and extracutaneous features depend on the overlapping connective tissue disease. Involvement of the gastrointestinal tract is probably the most common internal organ system involved (approximately 50–60%).[114,175] Lung fibrosis, pulmonary arterial hypertension and myocardial involvement are less frequent than in patients with diffuse SSc, but similarly (pulmonary arterial hypertension) or significantly more frequent than in limited forms of SSc.[175] The skin- and organ-oriented diagnostic methods used in patients with SSc are described in detail in the SSc section.

SSc-myositis overlap syndrome Limited cutaneous SSc together with symmetrical proximal muscle weakness, muscle pain and/or muscle atrophy with intact reflexes and sensitivity are the typical clinical features.[171,174,175] Patients may develop myositis before or simultaneously with SSc, or later in the course of already established SSc. Some patients may show cutaneous symptoms of dermatomyositis.[171] Serologic tests usually show an elevation of serum creatine kinase (≥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.[114,179–181] As these patients have a higher risk of developing diffuse interstitial myocardial fibrosis which may lead to systolic and diastolic dysfunctions, cardiac arrhythmia, paroxysmal tachycardia, incomplete or complete right-heart blocks or heart insufficiency, regular electrocardiograms (or Holter monitoring) and echocardiography are required.[172] The frequency of lung and gastrointestinal involvement varies among studies, ranging between 32.0% and 78.1%.[172]

SSc-Sjögren's overlap syndrome Patients with SSc-Sjögren's overlap syndrome show a limited form of skin involvement and a very low frequency of lung involvement.[171] Due to a reduced glandular function, they suffer from dry mouth (xerostomia)

and dry eyes (xerophthalmia). In addition, these patients also typically show anti-Ro and anti-La antibodies, often together with anti-centromere antibodies. Specific diagnostics include functional tests for ocular and oral sicca symptoms, together with a glandular biopsy (to detect lymphocytic infiltration).[182]

SSc-rheumatoid arthritis overlap syndrome 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-cyclic citrullinated peptide (CCP) antibodies in the serum of affected patients. X-ray, ultrasound of affected joints, as well as MRI can be helpful tools to identify inflammation areas and damage of joints.[114] However, it is often very difficult to distinguish between SSc patients with mild, sero-negative arthralgia and those with the significant arthritis associated with SSc-rheumatoid arthritis overlap syndrome.

Table 9 Autoantibodies possibly associated with SSc overlap syndromes

SSc overlap syndrome	Antigens targeted by autoantibodies
MCTD	U1-snRNP (specific), found in 75–90% of MCTD patients[185,187]
SSc-myositis	PM/Scl (specific), Ku†, U1- or U3-snRNP, Scl-70, Jo1, Ro, RNA polymerase III, RuvBL1/2[188,189]
SSc-rheumatoid arthritis	Rheumatoid factor (high titres in 60–72%), CCP (64%), Scl-70, centromere[172,174]
SSc-Sjögren's syndrome	Centromere, Ro, La[172,174]
SSc-SLE	dsDNA, Scl-70; centromere and PM/Scl in single cases[172]
SSc-antiphospholipid syndrome‡	Lupus anticoagulant, cardiolipid, β2-glycoprotein-1[171]
SSc-sarcoidosis‡	–
SSc-PBC‡	Centromere, mitochondria

†Anti-Ku antibodies recognize a protein required for DNA replication and are characteristic for patients suffering from muscle involvement and severe interstitial lung disease.[190]
‡Rare SSc overlap syndromes.[171]
SSc, systemic sclerosis; SLE, systemic lupus erythematosus; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; MCTD, mixed connective tissue disease; PBC, autoimmune hepatitis/primary biliary cirrhosis.

SSc-systemic lupus erythematodes overlap syndrome This subtype is associated with a higher risk of developing polyserositis, pancreatitis, avascular bone necrosis, lung involvement, lupus glomerulonephritis, skin rashes and leukoencephalopathy.[171] 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.[114,183] It may be necessary to perform a kidney biopsy to distinguish between renal failures due to lupus nephritis or scleroderma renal crisis.[183,184]

SSc-antiphospholipid syndrome Apart from autoantibodies characteristic for antiphospholipid syndrome (Table 9), this rare condition may be associated with severe ischaemia, pulmonary arterial hypertonia, digital loss and thromboembolism.[171]

SSc-autoimmune hepatitis/primary biliary cirrhosis This rare subtype is mostly associated with limited cutaneous SSc and often clinically silent. Anti-mitochondrial antibodies, elevation of cholestatic enzymes as well as hyperglobulinemia are possible.[171]

SSc-sarcoidosis The very rare SSc-sarcoidosis overlap syndrome usually presents with elevated temperature, weight loss

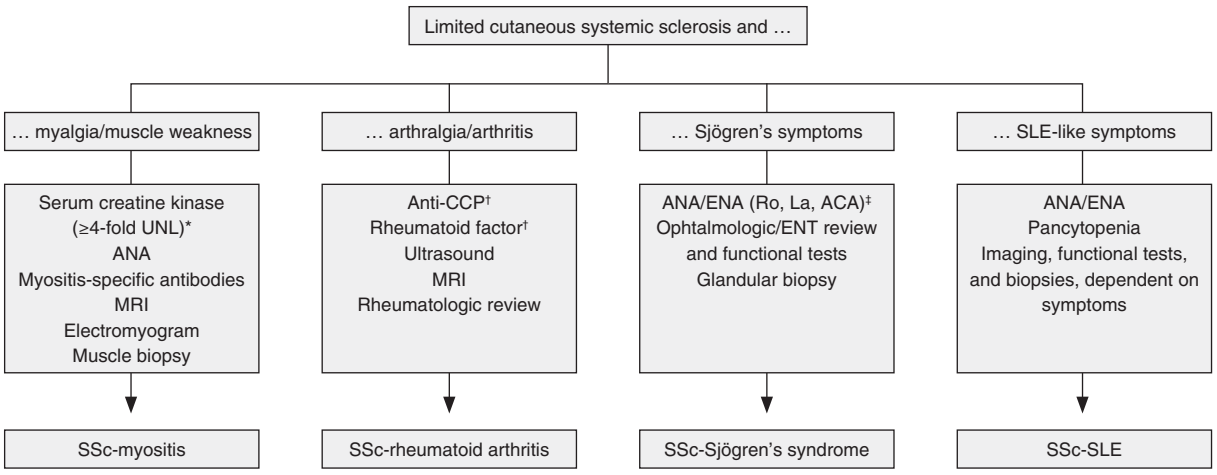


Figure 2 Flow chart for diagnostic procedures in patients with different SSc overlap syndromes. *Exclude other reason for creatine kinase elevation (drugs, toxins, thyroid dysfunction). †Some patients may be negative for rheumatoid factor and/or anti-CCP. ‡Rule out hepatitis C virus positivity, vasculitis and internal organ manifestation. ANA, antinuclear antibodies; Anti-CCP, anti-cyclic citrullinated peptide antibodies; ENA, extractable nuclear antigen; ENT, ear, nose, throat; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; UNL, upper normal limit.

and bihilary adenopathy. Lung and lymph node biopsy is necessary to define the condition.[171]

Mixed connective tissue disease Patients with mixed connective tissue disease (MCTD) present a range of clinical symptoms usually found in patients with myositis, systemic lupus erythematodes (SLE), inflammatory arthritis and SSc. Typical for MCTD are puffy fingers (50%), polyarthritis (65%), Raynaud's phenomenon (53%), sclerodactyly (35%), muscle involvement (80–90%; elevation of serum creatine kinase levels) and oesophageal involvement.[185,186] The occurrence of high antinuclear antibody titres together with high levels of U1-snRNP antibodies helps to differentiate MCTD from other connective tissue diseases.[186] Cardiovascular and lung involvement are less frequent, but are major contributors to poor outcome.[185]

Treatment

There have been major advances in treating many of the organ-specific complications of SSc and overlapping diseases (see also Table 8 in the SSc section).

Agents predominantly used to treat SSc overlap syndromes *Systemic glucocorticoids.* Systemic glucocorticoids can be used for musculoskeletal involvement together with other immunosuppressive agents.[172]

Methotrexate. Methotrexate is still the treatment of choice in patients with SSc-myositis and SSc-rheumatoid arthritis overlap syndromes.[191,192]

Mycophenolate mofetil. Mycophenolate mofetil (MMF) is a well-tolerated immunosuppressive agent, which is recommended as long-term therapy in scleroderma. It has been successfully applied in several overlap syndromes.

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

Cyclophosphamide. Cyclophosphamide is often used for lung involvement in patients with SSc,[193] and also in SSc-myositis overlap syndrome or in SSc-SLE overlap syndrome with lupus nephritis. Cyclophosphamide should be used for musculoskeletal involvement as a second-line immunosuppressive therapy when other treatments (methotrexate, MMF) have failed or when they cannot be used due to specific side-effects. As in other autoimmune diseases, it can be used as intravenous pulse or oral treatment.

Bioimmunomodulatory agents. Limited information is available for the use of IVIg, rituximab and anti-tumour necrosis factor (TNF) agents in the treatment of SSc overlap syndromes.

Therapeutic approaches Figure 3 shows the first- and advanced-line therapeutic approaches for the most frequent SSc overlap syndromes.[118,171,194–199] In patients with MCTD, the inflammatory features (elevated temperature, serositis, pleuritis, myositis and arthritis) usually respond well to systemic glucocorticoid treatment, while symptoms, such as sclerotic skin changes and cardiopulmonary involvement need immunosuppressive/cytotoxic drugs.[186,200] The most frequently used drugs

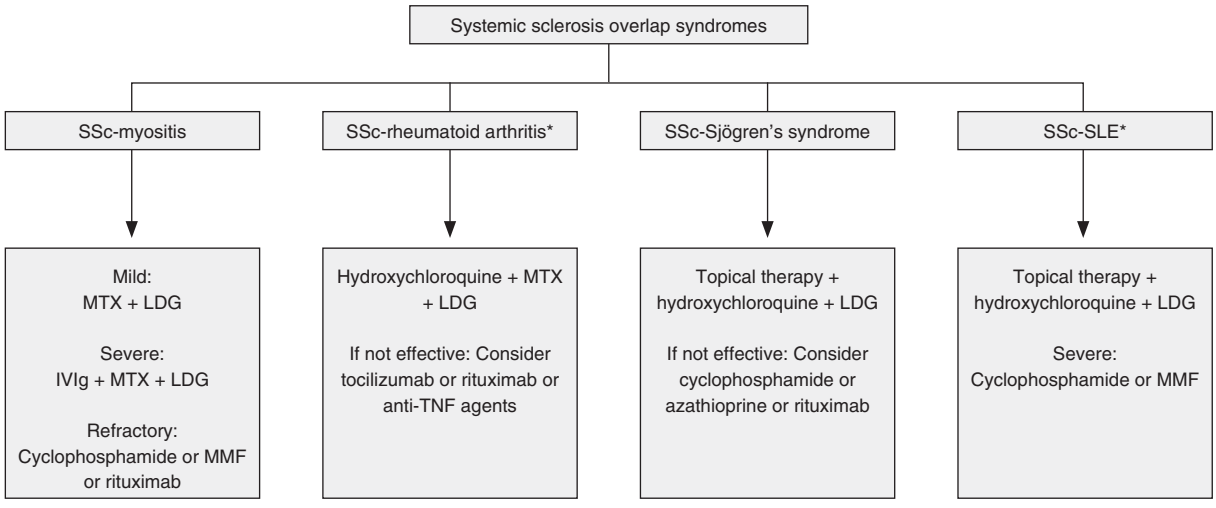


Figure 3 Flow chart for therapeutic options for different SSc overlap syndromes. *For detailed information, refer to the respective ACR/EULAR guidelines. IVIg, intravenous immunoglobulin; LDG, low-dose glucocorticoids; MTX, methotrexate; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TNF, tumour necrosis factor.

are hydroxychloroquine, methotrexate and cyclophosphamide, depending on the severity of the disease.[186]

Clinical course and prognosis

The prognosis of SSc overlap syndromes is highly dependent on the involvement of vital organs, as described above for patients with exclusive SSc. Balbir-Gurman *et al.*[171] reported that the overall mortality in their SSc overlap cohort did not differ from other SSc patients.

Recommendations

- Overlap syndromes of SSc with autoimmune diseases can be distinguished by certain clinical and laboratory characteristics.
- It is recommended to follow the diagnosis and treatment guidance in Table 9 and Figures 2 and 3.
- Corticosteroid doses higher than 15 mg prednisone equivalent per day should not be given in patients with a higher risk for renal crisis.[117]
- Methotrexate should not be used in case of alveolitis.
- Bioimmunomodulatory agents such as tocilizumab, rituximab and anti-TNF agents should be used with caution in the context of serious infections, tuberculosis and fibrosis.
- In patients with SSc-Sjögren's overlap syndrome, clinical features such as xerostomia and xerophthalmia can usually be improved by using mouth rinse, saliva substitutes and artificial teardrops, respectively.
- Patients with SSc-SLE overlap syndrome require additional UV skin protection.
- As the treatment of lupus nephritis differs from scleroderma-associated renal failure (cyclophosphamide vs. vasoactive treatment with ACE inhibitors and iloprost), a kidney biopsy may be helpful to distinguish between these two entities.
- Pulmonary and gastrointestinal complications require treatment as described in Table 8.
- Patients with MCTD usually respond well to systemic glucocorticoid and immunosuppressive therapy with classical agents (e.g. hydroxychloroquine, methotrexate and cyclophosphamide).[186,200]

References

1 Kreuter A, Krieg T, Worm M *et al.* AWMF Guideline no. 013/066. Diagnosis and therapy of circumscribed scleroderma. *J Dtsch Dermatol Ges* 2009; **7**(Suppl 6): 1–14.

2 Peterson LS, Nelson AM, Su WP, Mason T, O'Fallon WM, Gabriel SE. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960–1993. *J Rheumatol* 1997; **24**: 73–80.

3 Murray KJ, Laxer RM. Scleroderma in children and adolescents. *Rheum Dis Clin North Am* 2002; **28**: 603–624.

4 Silman A, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol* 1988; **27**: 286–290.

5 Fett N, Werth VP. Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol* 2011; **64**: 217–228.

6 Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. *FASEB J* 2004; **18**: 816–827.

7 Higley H, Persichitte K, Chu S, Waegell W, Vancheeswaran R, Black C. Immunocytochemical localization and serologic detection of transforming growth factor beta 1. Association with type I procollagen and inflammatory cell markers in diffuse and limited systemic sclerosis, morphea, and Raynaud's phenomenon. *Arthritis Rheum* 1994; **37**: 278–288.

8 Ihn H, Sato S, Fujimoto M, Kikuchi K, Takehara K. Demonstration of interleukin-2, interleukin-4 and interleukin-6 in sera from patients with localized scleroderma. *Arch Dermatol Res* 1995; **287**: 193–197.

9 Kreuter A, Hyun J, Skrygan M *et al.* Ultraviolet al-induced downregulation of human beta-defensins and interleukin-6 and interleukin-8 correlates with clinical improvement in localized scleroderma. *Br J Dermatol* 2006; **155**: 600–607.

10 Yamamoto T. Chemokines and chemokine receptors in scleroderma. *Int Arch Allergy Immunol* 2006; **140**: 345–356.

11 Gambichler T, Skrygan M, Labanski AA, Kolios AG, Altmeyer P, Kreuter A. Significantly increased CCL5/RANTES and CCR7 mRNA levels in localized scleroderma. *Regul Pept* 2011; **170**: 4–6.

12 Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest* 2007; **117**: 557–567.

13 Zulian F, Athreya BH, Laxer R *et al.* Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology (Oxford)* 2006; **45**: 614–620.

14 Kreuter A, Kryvosheyeva Y, Terras S *et al.* Association of autoimmune diseases with lichen sclerosus in 532 male and female patients. *Acta Derm Venereol* 2013; **93**: 238–241.

15 Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; **18**: 606–613.

16 Weibel L, Harper JI. Linear morphoea follows Blaschko's lines. *Br J Dermatol* 2008; **159**: 175–181.

17 Orozco-Covarrubias L, Guzman-Meza A, Ridaura-Sanz C, Carrasco Daza D, Sosa-de-Martinez C, Ruiz-Maldonado R. Scleroderma 'en coup de sabre' and progressive facial hemiatrophy. Is it possible to differentiate them? *J Eur Acad Dermatol Venereol* 2002; **16**: 361–366.

18 Arkachaisri T, Vilaiyuk S, Li S *et al.* The localized scleroderma skin severity index and physician global assessment of disease activity: a work in progress toward development of localized scleroderma outcome measures. *J Rheumatol* 2009; **36**: 2819–2829.

19 Arkachaisri T, Vilaiyuk S, Torok KS, Medsger TA Jr. Development and initial validation of the localized scleroderma skin damage index and physician global assessment of disease damage: a proof-of-concept study. *Rheumatology (Oxford)* 2010; **49**: 373–381.

20 Krieg T, Takehara K. Skin disease: a cardinal feature of systemic sclerosis. *Rheumatology (Oxford)* 2009; **48**(Suppl 3): iii14–iii18.

21 Arkachaisri T, Fertig N, Pino S, Medsger TA Jr. Serum autoantibodies and their clinical associations in patients with childhood- and adult-onset linear scleroderma. A single-center study. *J Rheumatol* 2008; **35**: 2439–2444.

22 Sato S, Fujimoto M, Kikuchi K, Ihn H, Tamaki K, Takehara K. Soluble CD4 and CD8 in serum from patients with localized scleroderma. *Arch Dermatol Res* 1996; **288**: 358–362.

23 Christen-Zaech S, Hakim MD, Afsar FS, Paller AS. Pediatric morphea (localized scleroderma): review of 136 patients. *J Am Acad Dermatol* 2008; **59**: 385–396.

24 Leitenberger JJ, Cayce RL, Haley RW, Adams-Huet B, Bergstresser PR, Jacobe HT. Distinct autoimmune syndromes in morphea: a review of 245 adult and pediatric cases. *Arch Dermatol* 2009; **145**: 545–550.
25 Takehara K, Sato S. Localized scleroderma is an autoimmune disorder. *Rheumatology (Oxford)* 2005; **44**: 274–279.
26 Hayakawa I, Hasegawa M, Takehara K, Sato S. Anti-DNA topoisomerase IIalpha autoantibodies in localized scleroderma. *Arthritis Rheum* 2004; **50**: 227–232.
27 Tomimura S, Ogawa F, Iwata Y *et al.* Autoantibodies against matrix metalloproteinase-1 in patients with localized scleroderma. *J Dermatol Sci* 2008; **52**: 47–54.
28 Yimane K, Ihn H, Kubo M, Asano Y, Yazawa N, Tamaki K. Anti-U3 snRNP antibodies in localised scleroderma. *Ann Rheum Dis* 2001; **60**: 1157–1158.
29 Tollefson MM, Witman PM. En coup de sabre morphea and Parry-Romberg syndrome: a retrospective review of 54 patients. *J Am Acad Dermatol* 2007; **56**: 257–263.
30 Holland KE, Steffes B, Nocton JJ, Schwabe MJ, Jacobson RD, Drolet BA. Linear scleroderma en coup de sabre with associated neurologic abnormalities. *Pediatrics* 2006; **117**: e132–e136.
31 Stone J. Parry-Romberg syndrome: a global survey of 205 patients using the Internet. *Neurology* 2003; **61**: 674–676.
32 Sommer A, Gambichler T, Bacharach-Buhles M, von Rothenburg T, Altmeyer P, Kreuter A. Clinical and serological characteristics of progressive facial hemiatrophy: a case series of 12 patients. *J Am Acad Dermatol* 2006; **54**: 227–233.
33 Chung L, Lin J, Furst DE, Fiorentino D. Systemic and localized scleroderma. *Clin Dermatol* 2006; **24**: 374–392.
34 Kreuter A, Gambichler T, Avermaete A *et al.* Combined treatment with calcipotriol ointment and low-dose ultraviolet al phototherapy in childhood morphea. *Pediatr Dermatol* 2001; **18**: 241–245.
35 Cunningham BB, Landells ID, Langman C, Sailer DE, Paller AS. Topical calcipotriene for morphea/linear scleroderma. *J Am Acad Dermatol* 1998; **39**: 211–215.
36 Kroft EB, Groeneveld TJ, Seyger MM, de Jong EM. Efficacy of topical tacrolimus 0.1% in active plaque morphea: randomized, double-blind, emollient-controlled pilot study. *Am J Clin Dermatol* 2009; **10**: 181–187.
37 Dytoc M, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphoea. *Br J Dermatol* 2005; **153**: 815–820.
38 Campione E, Paternò EJ, Diluvio L, Orlandi A, Bianchi L, Chimenti S. Localized morphea treated with imiquimod 5% and dermoscopic assessment of effectiveness. *J Dermatolog Treat* 2009; **20**: 10–13.
39 Pope E, Doria AS, Theriault M, Mohanta A, Laxer RM. Topical imiquimod 5% cream for pediatric plaque morphea: a prospective, multiple-baseline, open-label pilot study. *Dermatology* 2011; **223**: 363–369.
40 Hunzelmann N, Anders S, Fierlbeck G *et al.* Double-blind, placebo-controlled study of intralesional interferon gamma for the treatment of localized scleroderma. *J Am Acad Dermatol* 1997; **36**: 433–435.
41 Joly P, Bamberger N, Crickx B, Belaich S. Treatment of severe forms of localized scleroderma with oral corticosteroids: follow-up study on 17 patients. *Arch Dermatol* 1994; **130**: 663–664.
42 Michet CJ Jr, Doyle JA, Ginsburg WW. Eosinophilic fasciitis: report of 15 cases. *Mayo Clin Proc* 1981; **56**: 27–34.
43 Zulian F, Martini G, Vallongo C *et al.* Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2011; **63**: 1998–2006.
44 Seyger MM, van den Hoogen FH, de Boo T, de Jong EM. Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol* 1998; **39**: 220–225.
45 Kreuter A, Gambichler T, Breuckmann F *et al.* Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. *Arch Dermatol* 2005; **141**: 847–852.
46 Uziel Y, Feldman BM, Krafchik BR, Yeung RS, Laxer RM. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; **136**: 91–95.
47 Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol* 2006; **155**: 1013–1020.
48 Fitch PG, Rettig P, Burnham JM *et al.* Treatment of pediatric localized scleroderma with methotrexate. *J Rheumatol* 2006; **33**: 609–614.
49 Cox D, O'Regan G, Collins S, Byrne A, Irvine A, Watson R. Juvenile localised scleroderma: a retrospective review of response to systemic treatment. *Ir J Med Sci* 2008; **177**: 343–346.
50 Kroft EB, Creemers MC, van den Hoogen FH, Boezeman JB, de Jong EM. Effectiveness, side-effects and period of remission after treatment with methotrexate in localized scleroderma and related sclerotic skin diseases: an inception cohort study. *Br J Dermatol* 2009; **160**: 1075–1082.
51 Mirsky L, Chakkittakandiyil A, Laxer RM, O'Brien C, Pope E. Relapse after systemic treatment in paediatric morphoea. *Br J Dermatol* 2012; **166**: 443–445.
52 Li SC, Torok KS, Pope E *et al.* Development of consensus treatment plans for juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. *Arthritis Care Res (Hoboken)* 2012; **64**: 1175–1185.
53 Roos N, Poulalhon N, Farge D, Madelaine I, Mauviel A, Verrecchia F. In vitro evidence for a direct anti-fibrotic role of the immunosuppressive drug mycophenolate mofetil. *J Pharmacol Exp Ther* 2007; **321**: 583–589.
54 Martini G, Ramanan AV, Falcini F, Girschick H, Goldsmith DP, Zulian F. Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. *Rheumatology (Oxford)* 2009; **48**: 1410–1413.
55 Chimenti MS, Teoli M, Di Stefani A, Giunta A, Esposito M, Perricone R. Resolution with rituximab of localized scleroderma occurring during etanercept treatment in a patient with rheumatoid arthritis. *Eur J Dermatol* 2013; **23**: 273–274.
56 Diab M, Coloe JR, Magro C, Bechtel MA. Treatment of recalcitrant generalized morphea with infliximab. *Arch Dermatol* 2010; **146**: 601–604.
57 Moinzadeh P, Krieg T, Hunzelmann N. Imatinib treatment of generalized localized scleroderma (morphea). *J Am Acad Dermatol* 2010; **63**: 102–104.
58 Stausbøl-Grøn B, Olesen AB, Deleuran B, Deleuran MS. Abatacept is a promising treatment for patients with disseminated morphea profunda: presentation of two cases. *Acta Derm Venereol* 2011; **91**: 686–688.
59 Peter RU, Ruzicka T, Eckert F. Low-dose cyclosporine A in the treatment of disabling morphea. *Arch Dermatol* 1991; **127**: 1420–1421.
60 Hulshof MM, Bouwes Bavinck JN, Bergman W *et al.* Double-blind, placebo-controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. *J Am Acad Dermatol* 2000; **43**: 1017–1023.
61 Falanga V, Medsger TA Jr. D-penicillamine in the treatment of localized scleroderma. *Arch Dermatol* 1990; **126**: 609–612.
62 Clements PJ, Furst DE, Wong WK *et al.* High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999; **42**: 1194–1203.
63 Gambichler T, Terras S, Kreuter A. Treatment regimens, protocols, dosage, and indications for UVA1 phototherapy: facts and controversies. *Clin Dermatol* 2013; **31**: 438–454.
64 Stein B, Rahmsdorf HJ, Steffen A, Litfin M, Herrlich P. UV-induced DNA damage is an intermediate step in UV-induced expression of human immunodeficiency virus type 1, collagenase, c-fos, and metallothionein. *Mol Cell Biol* 1989; **9**: 5169–5181.

65 Scharffetter K, Wlaschek M, Hogg A *et al.* UVA irradiation induces collagenase in human dermal fibroblasts in vitro and in vivo. *Arch Dermatol Res* 1991; **283**: 506–511.
66 Breuckmann F, Gambichler T, Altmeyer P, Kreuter A. UVA/UVA1 phototherapy and PUVA photochemotherapy in connective tissue diseases and related disorders: a research based review. *BMC Dermatol* 2004; **4**: 11.
67 Dawe RS. There are no safe exposure limits for phototherapy. *Br J Dermatol* 2010; **163**: 209–210.
68 Pavlotsky F, Sakka N, Lozinski A, Barzilai A. Bath psoralen-UVA photochemotherapy for localized scleroderma: experience from a single institute. *Photodermatol Photoimmunol Photomed* 2013; **29**: 247–252.
69 Grundmann-Kollmann M, Ochsendorf F, Zollner TM *et al.* PUVA-cream photochemotherapy for the treatment of localized scleroderma. *J Am Acad Dermatol* 2000; **43**: 675–678.
70 El-Mofty M, Zaher H, Bosseila M, Yousef R, Saad B. Low-dose broadband UVA in morphea using a new method for evaluation. *Photodermatol Photoimmunol Photomed* 2000; **16**: 43–49.
71 El-Mofty M, Mostafa W, Esmat S *et al.* Suggested mechanisms of action of UVA phototherapy in morphea: a molecular study. *Photodermatol Photoimmunol Photomed* 2004; **20**: 93–100.
72 El-Mofty M, Mostafa W, El-Darouty M *et al.* Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. *Photodermatol Photoimmunol Photomed* 2004; **20**: 148–156.
73 Kerscher M, Dirschka T, Volkenandt M. Treatment of localised scleroderma by UVA1 phototherapy. *Lancet* 1995; **346**: 1166.
74 Stege H, Berneburg M, Humke S *et al.* High-dose UVA1 radiation therapy for localized scleroderma. *J Am Acad Dermatol* 1997; **36**: 938–944.
75 Kerscher M, Volkenandt M, Gruss C *et al.* Low-dose UVA phototherapy for treatment of localized scleroderma. *J Am Acad Dermatol* 1998; **38**: 21–26.
76 Camacho NR, Sanchez JE, Martin RF, Gonzalez JR, Sanchez JL. Medium-dose UVA1 phototherapy in localized scleroderma and its effect in CD34-positive dendritic cells. *J Am Acad Dermatol* 2001; **45**: 697–699.
77 de Rie MA, Enomoto DN, de Vries HJ, Bos JD. Evaluation of medium-dose UVA1 phototherapy in localized scleroderma with the cutometer and fast Fourier transform method. *Dermatology* 2003; **207**: 298–301.
78 Tuchinda C, Kerr HA, Taylor CR *et al.* UVA1 phototherapy for cutaneous diseases: an experience of 92 cases in the United States. *Photodermatol Photoimmunol Photomed* 2006; **22**: 247–253.
79 Sator PG, Radakovic S, Schulmeister K, Honigsmann H, Tanew A. Medium-dose is more effective than low-dose ultraviolet al phototherapy for localized scleroderma as shown by 20-MHz ultrasound assessment. *J Am Acad Dermatol* 2009; **60**: 786–791.
80 Andres C, Kollmar A, Mempel M, Hein R, Ring J, Eberlein B. Successful ultraviolet al phototherapy in the treatment of localized scleroderma: a retrospective and prospective study. *Br J Dermatol* 2010; **162**: 445–447.
81 Su O, Onsun N, Onay HK *et al.* Effectiveness of medium-dose ultraviolet al phototherapy in localized scleroderma. *Int J Dermatol* 2011; **50**: 1006–1013.
82 Kreuter A, Hyun J, Stucker M, Sommer A, Altmeyer P, Gambichler T. A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. *J Am Acad Dermatol* 2006; **54**: 440–447.
83 Wang F, Garza LA, Cho S *et al.* Effect of increased pigmentation on the antifibrotic response of human skin to UV-A1 phototherapy. *Arch Dermatol* 2008; **144**: 851–858.
84 Jacobe HT, Cayce R, Nguyen J. UVA1 phototherapy is effective in darker skin: a review of 101 patients of Fitzpatrick skin types I-V. *Br J Dermatol* 2008; **159**: 691–696.
85 Vasquez R, Jabbar A, Khan F, Buethe D, Ahn C, Jacobe H. Recurrence of morphea after successful ultraviolet al phototherapy: a cohort study. *J Am Acad Dermatol* 2014; **70**: 481–488.
86 Cribier B, Faradji T, Le Coz C, Oberling F, Grosshans E. Extracorporeal photochemotherapy in systemic sclerosis and severe morphea. *Dermatology* 1995; **191**: 25–31.
87 Schlaak M, Friedlein H, Kauer F, Renner R, Rogalski C, Simon JC. Successful therapy of a patient with therapy recalcitrant generalized bullous scleroderma by extracorporeal photopheresis and mycophenolate mofetil. *J Eur Acad Dermatol Venereol* 2008; **22**: 631–633.
88 Neustadter JH, Samarin F, Carlson KR, Girardi M. Extracorporeal photochemotherapy for generalized deep morphea. *Arch Dermatol* 2009; **145**: 127–130.
89 Pileri A, Raone B, Raboni R, Giudice V, Patrizi A. Generalized morphea successfully treated with extracorporeal photochemotherapy (ECP). *Dermatol Online J* 2014; **20**: 21258.
90 Mertens JS, Seyger MM, Kievit W *et al.* Disease recurrence in localized scleroderma: a retrospective analysis of 344 patients with paediatric- or adult-onset disease. *Br J Dermatol* 2015; **172**: 722–728.
91 Saxton-Daniels S, Jacobe HT. An evaluation of long-term outcomes in adults with pediatric-onset morphea. *Arch Dermatol* 2010; **146**: 1044–1045.
92 Uziel Y, Krafchik BR, Silverman ED, Thorner PS, Laxer RM. Localized scleroderma in childhood: a report of 30 cases. *Semin Arthritis Rheum* 1994; **23**: 328–334.
93 Marzano AV, Menni S, Parodi A *et al.* Localized scleroderma in adults and children. Clinical and laboratory investigations on 239 cases. *Eur J Dermatol* 2003; **13**: 171–176.
94 Zulian F, Vallongo C, Woo P *et al.* Localized scleroderma in childhood is not just a skin disease. *Arthritis Rheum* 2005; **52**: 2873–2881.
95 Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med* 2009; **360**: 1989–2003.
96 Sticherling M. Systemic sclerosis – dermatological aspects. Part 1: pathogenesis, epidemiology, clinical findings. *J Dtsch Dermatol Ges* 2012; **10**: 705–718.
97 Masi AT, Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; **23**: 581–590.
98 LeRoy EC, Black C, Fleischmajer R *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; **15**: 202–205.
99 Mayes MD, Lacey JV Jr, Beebe-Dimmer J *et al.* Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003; **48**: 2246–2255.
100 Walker UA, Tyndall A, Czirják L *et al.* Clinical risk assessment of organ manifestations in systemic sclerosis – a report from the EULAR Scleroderma Trials and Research (EUSTAR) group data base. *Ann Rheum Dis* 2007; **66**: 754–763.
101 Mierau R, Moinzadeh P, Riemekasten G *et al.* Frequency of disease-associated and other nuclear autoantibodies in patients of the German network for systemic scleroderma: correlation with characteristic clinical features. *Arthritis Res Ther* 2011; **13**: R172.
102 Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. *Arthritis Rheum* 2000; **43**: 444–451.
103 Valentini G. Undifferentiated connective tissue disease at risk for systemic sclerosis (SSc) (so far referred to as very early/early SSc or pre-SSc). *Autoimmun Rev* 2015; **14**: 210–213.
104 Koenig M, Joyal F, Fritzler MJ *et al.* Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. *Arthritis Rheum* 2008; **58**: 3902–3912.
105 Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. *Nat Rev Rheumatol* 2012; **8**: 469–479.
106 Khimdas S, Harding S, Bonner A *et al.* Associations with digital ulcers in a large cohort of systemic sclerosis: results from the

Canadian Scleroderma Research Group registry. *Arthritis Care Res* 2011; **63**: 142–149.
107 Mouthon L, Mestre-Stanislas C, Bérezné A *et al.* Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. *Ann Rheum Dis* 2010; **69**: 214–217.
108 Sunderkoetter C, Herrgott I, Brückner C *et al.* Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. *Br J Dermatol* 2009; **160**: 835–843.
109 Ennis H, Vail A, Wragg E *et al.* A prospective study of systemic sclerosis-related digital ulcers: prevalence, location, and functional impact. *Scand J Rheumatol* 2013; **42**: 483–486.
110 Hachulla E, Clerson P, Launay D *et al.* Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. *J Rheumatol* 2007; **34**: 2423–2430.
111 Clements P. Management of musculoskeletal involvement in systemic sclerosis. *Curr Treatm Opt Rheumatol* 2016; **2**: 61–68.
112 Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. *Eur Respir Rev* 2013; **22**: 6–19.
113 Hoffmann-Vold AM, Aaløkken TM, Lund MB *et al.* Predictive value of serial HRCT analyses and concurrent lung function tests in systemic sclerosis. *Arthritis Rheumatol* 2015; **67**: 2205–2212.
114 Hunzelmann N, Genth E, Krieg T *et al.* The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. *Rheumatology* 2008; **47**: 1185–1192.
115 Hansi N, Thoua N, Carulli M *et al.* Consensus Best Practice pathway of the UK Scleroderma Study Group: gastrointestinal manifestations of systemic sclerosis. *Clin Exp Rheumatol* 2014; **32**(Suppl 86): S214–S221.
116 Vacca A, Meune C, Gordon J *et al.* Scleroderma Clinical Trial Consortium Cardiac Subcommittee. Cardiac arrhythmias and conduction defects in systemic sclerosis. *Rheumatology* 2014; **53**: 1172–1177.
117 Mouthon L, Bussone G, Berezné A, Noël LH, Guillevin L. Scleroderma renal crisis. *J Rheumatol* 2014; **41**: 1040–1048.
118 van den Hoogen F, Khanna D, Fransen J *et al.* 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013; **72**: 1747–1755.
119 Cutolo M, Sulli A, Smith V. How to perform and interpret capillaroscopy. *Best Pract Res Clin Rheumatol* 2013; **27**: 237–248.
120 Czirják L, Foeldvari I, Müller-Ladner U. Skin involvement in systemic sclerosis. *Rheumatology* 2008; **47**(Suppl 5): v44–v45.
121 UK Scleroderma Study Group. Consensus best practice recommendations for scleroderma. [WWW document] URL http://www.sclerodermа-royalfree.org.uk/UKSSG.html (last accessed: 09 February 2017).
122 Sticherling M. Systemic sclerosis – focus on dermatological aspects. Part 2: diagnostics, therapy. *J Dtsch Dermatol Ges* 2012; **10**: 783–791.
123 Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum* 2001; **44**: 1841–1847.
124 Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; **112**: 2980–2985.
125 Caglayan E, Huntgeburth M, Karasch T *et al.* Phosphodiesterase type 5 inhibition is a novel therapeutic option in Raynaud disease. *Arch Intern Med* 2006; **166**: 231–233.
126 Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis* 2013; **72**: 1696–1699.
127 Coleiro B, Marshall SE, Denton CP *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology* 2001; **40**: 1038–1043.
128 Hughes M, Ong VH, Anderson ME *et al.* Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. *Rheumatology* 2015; **54**: 2015–2024.
129 Wigley FM, Wise RA, Seibold JR *et al.* Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med* 1994; **120**: 199–206.
130 Pope J, Fenlon D, Thompson A *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000; (2): CD000953.
131 Kowal-Bielecka O, Landewé R, Avouac J *et al.* EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009; **68**: 620–628.
132 Bali G, Aberer E. Iloprost therapy in systemic sclerosis. *Hautarzt* 2003; **54**: 845–851.
133 Riemekasten G, Hoffmann U, Sunderkötter C, Weiss N. Kuhn A; angiologisch-dermatologisch-rheumatologische DU-Expertenboard. Management of digital ulcers in patients with systemic sclerosis. *Dtsch Med Wochenschr* 2012; **137**: 34–40.
134 Herrick AL. Contemporary management of Raynaud's phenomenon and digital ischaemic complications. *Curr Opin Rheumatol* 2011; **23**: 555–561.
135 Tingey T, Shu J, Smuczek J, Pope J. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. *Arthritis Care Res* 2013; **65**: 1460–1471.
136 Korn JH, Mayes M, Matucci Cerinic M *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; **50**: 3985–3993.
137 Seibold JR, Denton CP, Furst DE. Bosentan prevents occurrence but does not speed healing of digital ulcers in patients with systemic sclerosis (SSc). *Arthritis Rheum* 2005; **52**(Suppl 9): 552.
138 Matucci-Cerinic M, Denton CP, Furst DE *et al.* Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2011; **70**: 32–38.
139 Maddali Bongi S, Del Rosso A, Passalacqua M, Miccio S, Cerinic MM. Manual lymph drainage improving upper extremity edema and hand function in patients with systemic sclerosis in edematous phase. *Arthritis Care Res (Hoboken)* 2011; **63**: 1134–1141.
140 Morita A, Sakakibara S, Sakakibara N, Yamauchi R, Tsuji T. Successful treatment of systemic sclerosis with topical PUVA. *J Rheumatol* 1995; **22**: 2361–2365.
141 Kreuter A, Breuckmann F, Uhle A *et al.* Low-dose UVA1 phototherapy in systemic sclerosis: effects on acrosclerosis. *J Am Acad Dermatol* 2004; **50**: 740–747.
142 Connolly KL, Griffith JL, McEvoy M, Lim HW. Ultraviolet al phototherapy beyond morphea: experience in 83 patients. *Photodermatol Photoimmunol Photomed* 2015; **31**: 289–295.
143 Hofer A, Soyer HP. Oral psoralen-UV-A for systemic scleroderma. *Arch Dermatol* 1999; **135**: 603–604.
144 Rook AH, Freundlich B, Jegasothy BV *et al.* Treatment of systemic sclerosis with extracorporeal photochemotherapy. Results of a multicenter trial. *Arch Dermatol* 1992; **128**: 337–346.
145 Knobler RM, French LE, Kim Y *et al.* A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *J Am Acad Dermatol* 2006; **54**: 793–799.
146 Enomoto DN, Mekkes JR, Bossuyt PM *et al.* Treatment of patients with systemic sclerosis with extracorporeal photochemotherapy (photopheresis). *J Am Acad Dermatol* 1999; **41**: 915–922.
147 Muellegger RR, Hofer A, Salmhofer W, Soyer HP, Kerl H, Wolf P. Extended extracorporeal photochemotherapy with extracorporeal administration of 8-methoxypsoralen in systemic sclerosis. An Austrian single-center study. *Photodermatol Photoimmunol Photomed* 2000; **16**: 216–223.
148 Papp G, Horvath IF, Barath S *et al.* Immunomodulatory effects of extracorporeal photochemotherapy in systemic sclerosis. *Clin Immunol* 2012; **142**: 150–159.

149 Knobler R, Berlin G, Calzavara-Pinton P *et al.* Guidelines on the use of extracorporeal photopheresis. *J Eur Acad Dermatol Venereol* 2014; **28** (Suppl 1): 1–37.
150 van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996; **35**: 364–372.
151 Pope JE, Bellamy N, Seibold JR *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; **44**: 1351–1358.
152 Walker KM, Pope J, participating members of the Scleroderma Clinical Trials Consortium (SCTC), Canadian Scleroderma Research Group (CSRG). Treatment of systemic sclerosis complications: what to use when first-line treatment fails – a consensus of systemic sclerosis experts. *Semin Arthritis Rheum* 2012; **42**: 42–55.
153 Tashkin DP, Elashoff R, Clements PJ *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354**: 2655–2666.
154 van Laar JM, Farge D, Sont JK *et al.* Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014; **311**: 2490–2498.
155 Del Papa N, Onida F, Zaccara E *et al.* Autologous hematopoietic stem cell transplantation has better outcomes than conventional therapies in patients with rapidly progressive systemic sclerosis. *Bone Marrow Transplant* 2017; **52**: 53–58.
156 Balin SJ, Wetter DA, Andersen LK, Davis MD. Calcinosis cutis occurring in association with autoimmune connective tissue disease: the Mayo Clinic experience with 78 patients, 1996–2009. *Arch Dermatol* 2012; **148**: 455–462.
157 Wu JJ, Metz BJ. Calcinosis cutis of juvenile dermatomyositis treated with incision and drainage. *Dermatol Surg* 2008; **34**: 575–577.
158 Saddic N, Miller JJ, Miller OF 3rd, Clarke JT. Surgical debridement of painful fingertip calcinosis cutis in CREST syndrome. *Arch Dermatol* 2009; **145**: 212–213.
159 Murray AK, Moore TL, Richards H, Ennis H, Griffiths CE, Herrick AL. Pilot study of intense pulsed light for the treatment of systemic sclerosis-related telangiectases. *Br J Dermatol* 2012; **167**: 563–569.
160 Halachmi S, Gabari O, Cohen S, Koren R, Amitai DB, Lapidoth M. Telangiectasis in CREST syndrome and systemic sclerosis: correlation of clinical and pathological features with response to pulsed dye laser treatment. *Lasers Med Sci* 2014; **29**: 137–140.
161 Dinsdale G, Murray A, Moore T *et al.* A comparison of intense pulsed light and laser treatment of telangiectases in patients with systemic sclerosis: a within-subject randomized trial. *Rheumatology* 2014; **53**: 1422–1430.
162 Lee JS, Collard HR, Anstrom KJ *et al.* Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomized controlled trials. *Lancet Respir Med* 2013; **1**: 369–376.
163 Burt RK, Shah SJ, Dill K *et al.* Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* 2011; **378**: 498–506.
164 Galiè N, Humbert M, Vachiery JL *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev Esp Cardiol (Engl Ed)* 2016; **69**: 177.
165 Ntoumazios SK, Voulgari PV, Potsis K, Koutis E, Tsifetaki N, Assimakopoulos DA. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. *Semin Arthritis Rheum* 2006; **36**: 173–181.
166 Nikou GC, Toumpanakis C, Katsiari C, Charalambopoulos D, Sfikakis PP. Treatment of small intestinal disease in systemic sclerosis with octreotide: a prospective study in seven patients. *J Clin Rheumatol* 2007; **13**: 119–123.
167 Frech TM, Khann D, Maranian P, Frech EJ, Sawitzke AD, Murtaugh MA. Probiotics for the treatment of systemic sclerosis-associated gastrointestinal bloating/distention. *Clin Exp Rheumatol* 2011; **29**(2 Suppl 65): S22–S25.
168 Knafo R, Haythornthwaite JA, Heinberg L, Wigley FM, Thombs BD. The association of body image dissatisfaction and pain with reduced sexual function in women with systemic sclerosis. *Rheumatology* 2011; **50**: 1125–1130.
169 Foocharoen C, Tyndall A, Hachulla E *et al.* Erectile dysfunction is frequent in systemic sclerosis and associated with severe disease: a study of the EULAR Scleroderma Trial and Research group. *Arthritis Res Ther* 2012; **14**: R37.
170 Fransen J, Popa-Diaconu D, Hesselstrand R *et al.* Clinical prediction of 5-year survival in systemic sclerosis: validation of a simple prognostic model in EUSTAR centres. *Ann Rheum Dis* 2011; **70**: 1788–1792.
171 Balbir-Gurman A, Braun-Moscovici Y. Scleroderma overlap syndrome. *Isr Med Assoc J* 2011; **13**: 14–20.
172 Iaccarino L, Gatto M, Bettio S *et al.* Overlap connective tissue disease syndromes. *Autoimmun Rev* 2013; **12**: 363–373.
173 Jury EC, D'Cruz D, Morrow WJ. Autoantibodies and overlap syndromes in autoimmune rheumatic disease. *J Clin Pathol* 2001; **54**: 340–347.
174 Pakozdi A, Nihtyanova S, Moinzadeh P, Ong VH, Black CM, Denton CP. Clinical and serological hallmarks of systemic sclerosis overlap syndromes. *J Rheumatol* 2011; **38**: 2406–2409.
175 Moinzadeh P, Aberer E, Ahmadi-Simab K *et al.* Disease progression in systemic sclerosis-overlap syndrome is significantly different from limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2015; **74**: 730–737.
176 Elhai M, Avouac J, Kahan A, Allanore Y. Systemic sclerosis at the crossroad of polyautoimmunity. *Autoimmun Rev* 2013; **12**: 1052–1057.
177 Koumakis E, Dieude P, Avouac J, Kahan A, Allanore Y. Familial autoimmunity in systemic sclerosis – results of a French-based case-control family study. *J Rheumatol* 2012; **39**: 532–538.
178 Valenzuela A, Chung L. Calcinosis: pathophysiology and management. *Curr Opin Rheumatol* 2015; **27**: 542–548.
179 Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975; **292**: 403–407.
180 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; **292**: 344–347.
181 Akesson A, Fiori G, Krieg T, van den Hoogen FH, Seibold JR. Assessment of skin, joint, tendon and muscle involvement. *Clin Exp Rheumatol* 2003; **21**(3 Suppl 29): S5–S8.
182 Santiago ML, Seisdedos MR, Garcia Salinas RN, Catalan Pellet A, Villalon L, Secco A. Usefulness of antibodies and minor salivary gland biopsy in the study of sicca sindrome in daily clinical practice. *Reumatol Clin* 2015; **11**: 156–160.
183 Steen VD, Mayes MD, Merkel PA. Assessment of kidney involvement. *Clin Exp Rheumatol* 2003; **21**(3 Suppl 29): S29–S31.
184 Kistler AD. Lupusnephritis. *Ther Umsch* 2015; **72**: 171–177.
185 Tani C, Carli L, Vagnani S *et al.* The diagnosis and classification of mixed connective tissue disease. *J Autoimmun* 2014; **48–49**: 46–49.
186 Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: an overview of clinical manifestations, diagnosis and treatment. *Best Pract Res Clin Rheumatol* 2012; **26**: 61–72.
187 Habets WJ, de Rooij DJ, Salden MH *et al.* Antibodies against distinct nuclear matrix proteins are characteristic for mixed connective tissue disease. *Clin Exp Immunol* 1983; **54**: 265–276.
188 Koschik RW 2nd, Fertig N, Lucas MR, Domsic RT, Medsger TA Jr. Anti-PM-Scl antibody in patients with systemic sclerosis. *Clin Exp Rheumatol* 2012; **30**(2 Suppl 71): S12–S16.
189 Kaji K, Fertig N, Medsger TA Jr *et al.* Autoantibodies to RuvBL1 and RuvBL2: a novel systemic sclerosis-related antibody associated with diffuse cutaneous and skeletal muscle involvement. *Arthritis Care Res* 2014; **66**: 575–584.

190 Rigolet A, Musset L, Dubourg O *et al.* Inflammatory myopathies with anti-Ku antibodies: a prognosis dependent on associated lung disease. *Medicine (Baltimore)* 2012; **91**: 95–102.
191 Fendler C, Braun J. Use of methotrexate in inflammatory myopathies. *Clin Exp Rheumatol* 2010; **28**(5 Suppl 61): S164–S167.
192 Kowal-Bielecka O, Distler O. Use of methotrexate in patients with scleroderma and mixed connective tissue disease. *Clin Exp Rheumatol* 2010; **28**(5 Suppl 61): S160–S163.
193 Walker KM, Pope J. Expert agreement on EULAR/EUSTAR recommendations for the management of systemic sclerosis. *J Rheumatol* 2011; **38**: 1326–1328.
194 Levy Y, Amital H, Langevitz P *et al.* Intravenous immunoglobulin modulates cutaneous involvement and reduces skin fibrosis in systemic sclerosis: an open-label study. *Arthritis Rheum* 2004; **50**: 1005–1007.
195 Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 2005; **52**: 601–607.
196 Mok CC, Ho LY, To CH. Rituximab for refractory polymyositis: an open-label prospective study. *J Rheumatol* 2007; **34**: 1864–1868.
197 Feltsan T, Stanko P, Mracna J. Sjogren's syndrome in present. *Bratisl Lek Listy* 2012; **113**: 514–516.
198 Carubbi F, Cipriani P, Marrelli A *et al.* Efficacy and safety of rituximab treatment in early primary Sjogren's syndrome: a prospective, multicenter, follow-up study. *Arthritis Res Ther* 2013; **15**: R172.
199 Vitali C, Bootsma H, Bowman SJ *et al.* Classification criteria for Sjögren's syndrome: we actually need to definitively resolve the long debate on the issue. *Ann Rheum Dis* 2013; **72**: 476–478.
200 Lundberg IE. The prognosis of mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; **31**: 535–547, vii–viii.

