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REVIEW

Systemic sclerosis and localized scleroderma—current concepts and novel targets for therapy

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Abstract Systemic sclerosis (SSc) is a chronic autoimmune disease with a high morbidity and mortality. Skin and organ fibrosis are key manifestations of SSc, for which no generally accepted therapy is available. Thus, there is a high unmet need for novel anti-fibrotic therapeutic strategies in SSc. At the same time, important progress has been made in the identification and characterization of potential molecular targets in fibrotic diseases over the recent years. In this review, we have selected four targeted therapies, which are tested in clinical trials in SSc, for in depths discussion of their preclinical characterization. Soluble guanylate cyclase (sGC) stimulators such as riociguat might target both vascular remodeling and tissue fibrosis. Blockade of interleukin-6 might be particularly promising for early inflammatory stages of SSc. Inhibition of serotonin receptor 2b signaling links platelet activation to tissue fibrosis. Targeting simultaneously multiple key molecules with the multityrosine kinase-inhibitor nintedanib might be a promising approach in complex fibrotic diseases such as SSc, in which many partially independent pathways are activated. Herein, we also give a state of the art overview of the current classification, clinical presentation, diagnostic approach, and treatment options of localized scleroderma. Finally, we discuss whether the novel targeted therapies currently tested in SSc could be used for localized scleroderma.

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Systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune disease with both fibrotic and microvascular manifestations. Other than localized scleroderma (LS), skin fibrosis of SSc always involves the fingers usually in a symmetric distribution at disease onset and can progress from there to more proximal parts of the body depending on the subtype of SSc. Accordingly; skin thickening sparing the fingers has been defined as an exclusion criterion for SSc in the new ACR/EULAR classification criteria [1]. SSc is thus in most cases easily distinguishable from the localized forms of scleroderma just by past medical history and clinical examination. In addition, SSc frequently involves internal organs such as the lungs, heart and the gastrointestinal tract which significantly contribute to morbidity and reduced quality of life in these patients.

SSc is accepted by agencies as an orphan disease. Prevalence ranges from 0.7/100,000 to 53/100,000 depending on demographics and country, with higher numbers in the USA than in Europe or Japan. SSc has an increased mortality compared to the general population, and the standardized mortality ratio is approximately 2.7. Cumulative survival from diagnosis has been estimated at 74.9 % at 5 years and 62.5 % at 10 years [2]. Indeed, SSc has one of the highest mortality rates among the rheumatic diseases, and pulmonary manifestations are the main cause of death [3].

At the same time, the available anti-fibrotic treatments are limited. The EULAR/EUSTAR treatment recommendations are listing only two medications as anti-fibrotic therapies in SSc. This includes methotrexate which “might be considered”

for the treatment of skin fibrosis in SSc based on two randomized controlled clinical trials showing borderline efficacy on skin fibrosis [4]. Similarly, cyclophosphamide "should be considered" for the treatment of SSc-interstitial lung disease (SSc-ILD), with two randomized controlled clinical trials showing statistically significant or borderline efficacy, but of questionable clinical importance. These recommendations from 2009 are currently being updated [5]. However, the only addition as an anti-fibrotic or disease modifying therapy in the updated recommendations has been hematopoietic stem cell transplantation (HSCT). HSCT showed convincing efficacy in two randomized controlled clinical trials on event-free survival compared to cyclophosphamide, but at the cost of a treatment-related mortality as high as 10 % in the first year. It is therefore only recommended for treatment of highly selected patients with rapidly progressive SSc at risk of organ failure [5].

The high disease burden with increased mortality and morbidity together with the lack of generally accepted anti-fibrotic treatments defines a high unmet need for novel therapeutic strategies in SSc. This has been paralleled by a rapid development in the characterization of molecular key pathways in SSc and other fibrotic diseases over the last years. This progress was supported by an availability of an increasing number of animal models of SSc, which cover different aspects of the disease. Animal models have been used for both improved understanding of disease processes as well as for proof of concepts studies for certain targeted therapies [6].

General considerations for the development of targeted therapies in SSc

Modern drug development consists of the identification of potential targets for therapy, preclinical characterization by both in vitro and animal studies, clinical testing in smaller proof of concept clinical trials including dose-ranging and toxicity studies, and finally, proof of efficacy in larger adequately powered randomized controlled clinical trials. Opposite to common perception, less than 1/3 of expenses are spent on preclinical development, while the majority of financial losses are made in the last two steps of drug development by producing negative clinical trials [7]. Therefore, it is of key importance to develop general concepts for preclinical drug development with the overall aim of a better prediction of successful clinical trials. This is particularly true for diseases such as SSc for which a larger number of advanced clinical trials could not show anti-fibrotic efficacy. Some of these concepts have been recently reviewed in detail [8]. One of the key messages from these concepts is the proof of target activation in humans. Rheumatic diseases in general, and SSc particularly, show a wide clinical heterogeneity, which is reflected in similarly heterogeneous molecular expression patterns. For example, even extremely well characterized pro-fibrotic key pathways like TGF-β or PDGF show very different activation states in the individual patient depending on the disease subtype, the stage of the disease, the organ of interest, and possibly many other yet not identified factors. Notably, in a patient with low or absent activation of these pathways, targeted therapies of PDGF and TGF-β pathways are very unlikely to be efficient. This concept calls for personalized medicine approaches in heterogeneous rheumatic diseases such as SSc, as it has been increasingly established in oncology [9]. Similarly, animal models showing much higher activation levels of the targeted pathway than the human disease likely overestimate the therapeutic potential and should be interpreted with caution.

Novel targeted therapies on the horizon

The identification and characterization of "druggable" molecular targets has been one of the breakthrough findings in fibrosis research in recent years. While in the past, unspecific immunosuppressive agents that were used for other rheumatic diseases such as rheumatoid arthritis were applied to SSc with little success, the novel approaches are based on the identification of specific pro-fibrotic key players and the availability of specific therapeutic modifiers. We have selected four of these novel molecular targets for in-depth discussion in this review based on their translation into large controlled clinical trials. It has to be emphasized that this selection is by far not exhaustive, and that a larger number of additional promising targets are currently tested in proof of concept clinical trials. Together with new developments in clinical trial design, these novel targeted therapies hold the promise that efficient anti-fibrotic therapies might become available in SSc [10].

Soluble guanylate cyclase stimulators

Soluble guanylate cyclase (sGC) stimulators are causing a nitric oxide (NO)-independent, direct stimulation of sGC leading to an increased production of cyclic guanosine monophosphate (cGMP) [11]. Because NO is the physiological ligand of sGCs, other therapeutic principles include direct application of NO or NO donating drugs. However, this has the disadvantage of rapid development of tolerance and unspecific effects of NO. For example, NO can induce oxidative stress, which has been identified as one of the pathophysiological pathways in fibroblast activation [12]. Oxidation of sGC also makes the enzyme unresponsive to NO and might thereby contribute to tolerance. Thus, direct stimulation of sGC appears to be a more attractive approach.

sGC is well known for its role in the regulation of vascular tone and vascular remodeling. Vascular remodeling is one of the key characteristics of pulmonary arterial hypertension (PAH), which affects approximately 10 % of patients with

SSc. Accordingly, the sGC activator riociguat has been shown in large randomized controlled clinical trials to be effective in patients with different forms of PH including patients with SSc-related PAH [13]. Riociguat has been recently approved by agencies for therapy of PAH in the USA, EU, Switzerland, and other countries.

The proven and clinically validated effects on vascular remodeling raise the possibility that sGC stimulators could target the two key pathways in the pathogenesis of SSc—vascular remodeling and fibrosis—simultaneously. However, little was known about the effects of sGC stimulators on fibrosis. We have therefore recently addressed the anti-fibrotic effects of different sGC stimulators in vitro and in different animal models of SSc. In vitro, the sGC activator BAY 41–2272 inhibited the release of TGF-β induced extracellular matrix proteins at physiological concentrations both in healthy and SSc primary dermal fibroblasts [14]. This stable and consistent anti-fibrotic effect was mediated via blockade of non-canonical signaling pathways. Specifically, sGC activation inhibited the phosphorylation of ERK which is an important non-canonical TGF-β signaling pathway [15]. Consistently with the in vitro effect, dermal fibrosis was reduced in the bleomycin skin fibrosis model of SSc, which represents inflammatory earlier stages of SSc. Similarly, hypodermal thickening and extracellular matrix accumulation was reduced in the tight-skin (Tsk-1) mice after treatment with BAY 41–2272. The Tsk-1 model is B-cell dependent but does not develop inflammatory skin infiltrates and is therefore a model for later stages of SSc. In both models, anti-fibrotic effects could be achieved not only by preventive treatment strategies but also by therapeutic treatment strategies [14]. Moreover, sGC stimulation also decreased fibrosis in a mouse model, in which skin fibrosis is induced by overexpression of a constitutively active TGF-β receptor [15], and in the sclerodermatous chronic graft-versus-host disease (cGvHD) model [16]. Interestingly, the anti-fibrotic effects with the sGC stimulator riociguat were stronger than with the phosphodiesterase V (PDE5) inhibitor sildenafil even when high doses of sildenafil were used [16]. PDE5 inhibitors also increase the intracellular levels of cGMP. However, this is achieved by inhibition of degradation of cGMP rather than stimulation of production as with the sGC stimulators. These data indicate that in SSc fibroblasts, deficiency in cGMP is primarily caused by impaired formation rather than enhanced degradation of cGMP. Finally, our data are consistent with anti-fibrotic effects of sGC stimulation in other models of organ fibrosis such the heart [17].

These circumstantial preclinical evidences lead to a large randomized, double-blind, placebo-controlled, parallel-group clinical trial with skin fibrosis as the primary endpoint. This trial is currently recruiting and aims to randomize approximately 130 patients. The promises of this approach lay in the simultaneous targeting of vascular and fibrotic pathways, which could lead to a true disease modifying targeted therapy in SSc.

Tyrosine-kinase inhibitors

Considering the multiple and partially independently activated pathways in the pathogenesis of SSc, targeting multiple pathways with the same drug appears to be a promising treatment approach. Tyrosine kinases (TKs) are enzymes that transfer a phosphate group from ATP to a protein leading to its activation. TKs are involved in a wide variety of physiologic and pathological processes including vascular remodeling and fibrogenesis. TK inhibitors are small molecules that can be administered orally. The lead substance imatinib inhibits PDGFR, the TGF-β downstream c-abl and c-kit, which have been shown to be of importance in the pathogenesis of SSc [18]. Imatinib was therefore the first TKI tested in SSc in open-label uncontrolled clinical trials—with however inconsistent and difficult to interpret results [19]. An investigator-initiated randomized controlled clinical trial in idiopathic pulmonary fibrosis (IPF) could not show effects of imatinib on lung function or survival [20].

Nintedanib (also known as BIBF 1120) is a next generation, potent, indolinone-derived small molecule tyrosine-kinase inhibitor which targets multiple TKs. Nintedanib inhibits several central molecules involved in fibroblast activation such as PDFGR-α and PDFGR-β, FGFR-1, FGFR-2, FGFR-3, VEGFR-1, VEGFR-2, VEGFR-3, and Src [21–23]. In addition, nintedanib may exert anti-inflammatory effects via inhibition of Lyn and Lck, though it binds to these targets with somewhat lower affinity. This broad inhibition of pro-fibrotic targets may be more beneficial than the more selective inhibition with imatinib and its related TKIs. Notably, nintedanib has been shown to slow disease progression in IPF in two replicate phase 3 trials (INPULSIS-1 and INPULSIS-2) including more than 1000 patients [24]. These promising clinical effects in IPF hold great promise for similar anti-fibrotic effects in SSc. Indeed, we could recently provide further scientific rationale that nintedanib could be efficient in SSc: Nintedanib reduced in biologically relevant doses the differentiation of myofibroblast and the release of collagen of dermal fibroblasts from patients with SSc and healthy individuals. Nintedanib also showed anti-fibrotic effects in a dose-dependent manner in different animal models of SSc including the bleomycin skin fibrosis model both in preventive and therapeutic applications, the chronic graft-versus-host disease model and the Tsk-1 model [25]. Interestingly, in the Fra-2 tg mouse model, nintedanib did not only inhibit skin and lung fibrosis but also improved the pulmonary vascular lesions resembling PAH in this model [26]. Based on these results, a large, randomized, placebo-controlled trial with nintedanib is currently initiated in patients with SSc. Pulmonary fibrosis (forced vital capacity) has been selected as the primary outcome, and more than 500 patients are planned to be recruited for this trial.

Serotonin receptor blockers

Outside the central nervous system, serotonin (5-HT) is stored in platelets and is released upon platelet activation. Platelet activation is a common feature of SSc patients [27], resulting from the microvascular damage that occurs in early disease stages leading to capillary malformations and loss of capillaries. Accordingly, increased levels of 5-HT have been found in the blood of patients with SSc [28–30].

5-HT exerts its effects via seven families of receptors, 5-HT1 to 5-HT7, and dermal fibroblasts can mostly express 5-HT1 and 5-HT2 receptors. We and others could show that serotonin is—in the dose range found in the blood of patients with SSc—a potent pro-fibrotic factor that mediates its pro-fibrotic effects via 5-HT2B receptors on dermal fibroblasts [31]. 5-HT2B was overexpressed by myofibroblasts in patients with SSc as compared to healthy control tissue. The pro-fibrotic effects of 5-HT were mediated via an induction of TGF-β, as neutralizing antibodies to TGF-β were able to completely block the pro-fibrotic effects of 5-HT.

Both in vitro as well as in vivo, blockade of 5-HT2B had strong anti-fibrotic effects. For example, in the mouse model of bleomycin-induced dermal fibrosis, the 5-HT2 inhibitors terguride and cyproheptadine, the selective 5-HT2B inhibitor SB 204741 as well as genetic knockdown using 5-HT2B deficient mice efficiently prevented bleomycin-induced dermal fibrosis. A modified therapeutic model of bleomycin-induced skin fibrosis showed also anti-fibrotic efficacy of 5-HT2B inhibitors. Similarly, strong anti-fibrotic effects were seen in the non-inflammatory Tsk-1 model using both genetic and pharmacological inhibition of 5-HT2B. To confirm the link between platelet activation, increased 5-HT/5-HT2B signaling and dermal fibrosis, mice deficient for tryptophan hydroxylase (TPH) 1 were challenged with bleomycin or crossed with Tsk-1 mice to generate Tsk-1/TPH1−/− mice. TPH1 is the rate limiting enzyme for the synthesis of 5-HT in platelets. Blood levels of 5-HT in TPH1−/− mice are therefore strongly reduced compared to wild-type animals. Both approaches resulted in an efficient amelioration of fibrosis with reduced hypodermal thickening, decreased hydroxyproline content, and lower myofibroblast counts in TPH1−/− mice. Similar anti-fibrotic effects of 5-HT2 inhibition have been described in other experimental organ fibrosis such as liver fibrosis, heart fibrosis, and pulmonary fibrosis [32–34]. Based on these results, an investigator-initiated controlled clinical proof of concept study was performed in SSc patients with the 5-HT2 inhibitor terguride, which is already clinically available in Japan for the treatment of hyperprolactinemia. This proof of concept study showed a favorable safety profile, strong and consistent effects on skin biomarkers of fibrosis, and positive effects on the modified Rodnan skin score as a measure of skin fibrosis. A larger long-term confirmatory randomized placebo-controlled clinical trial is in planning.

Interleukin-6

There is circumstantial evidence from different research groups that interleukin-6 (IL-6) is playing an important role in the fibrogenesis of SSc, in particular in patients with early inflammatory disease stages. Serum levels of IL-6 were found to be elevated in SSc patients in several studies, and high levels of IL-6 were associated with diffuse cutaneous SSc, early disease stages, increased inflammatory markers, more severe skin fibrosis, and worse long-term survival [35–37]. IL-6 can directly stimulate cultured fibroblasts to release collagens via JAK2 and ERK dependent pathways. Moreover, inactivation of IL-6 either by blocking antibodies, by knockdown, or by immunization against a murine IL-6 peptide prevented bleomycin-induced skin fibrosis [36, 38]. Similarly, IL-6 blockade prevented the development of murine sclerodermatous chronic graft-versus-host disease, while treatment of established disease did not show anti-fibrotic effects [39]. The preferential role of IL-6 in early inflammatory rather than in later non-inflammatory stages of SSc is underlined by experiments with the non-inflammatory Tsk-1 mice, in which IL-6 blockade did not exert anti-fibrotic effects [36]. In addition to SSc, IL-6 has been implicated in different organ fibrosis including pulmonary fibrosis [40, 41].

In parallel to the conduction of the preclinical studies, a phase 2 clinical trial with tocilizumab, a monoclonal antibody against the IL-6-receptor, was performed in patients with early inflammatory diffuse cutaneous SSc. The results of this randomized, placebo-controlled study have been presented in abstract form showing beneficial effects on skin fibrosis and lung function, particularly after 12 months of treatment [42]. A phase 3 confirmatory study is currently launched.

Localized scleroderma—clinical presentation and workup

The term localized scleroderma (LS) contains a spectrum of sclerosing diseases of the skin, which may also involve neighboring tissues (fascia, muscle, bone, and underlying tissues). Other than in SSc, however, there is no involvement of internal organs in LS. All subtypes of LS are rare diseases with a cumulative incidence rate ranging from 0.4 to 2.7/100,000/year [43, 44]. According to Peterson, LS is classified into plaque, generalized, deep, bullous, and linear types, whereas Kreuter and colleagues propose an AWMF-classification into the 5 groups of limited, generalized, linear, deep, and mixed type of LS [45] (Table 1), which will be used in this overview.

Clinical aspects

LS shows a gynaecotropism (f:m=4:1) in adults and children and affects primarily the trunk, less frequently the lower and

Table 1 Localized scleroderma (according [45])

Limited type	Generalized type	Linear type	Deep type	Mixed type
• Morphea (plaque type of localized scleroderma)	• Generalized localized scleroderma	• Linear localized scleroderma of the extremities	• Deep morphea	
• Guttate morphea	• Disabling pansclerotic morphea	• Linear localized scleroderma "en coup de sabre"		
• Atrophoderma idiopathica of Pierini and Pasini (superficial morphea)	• Eosinophilic fasciitis (Shulman syndrome)	• Progressive facial hemiatrophy (Parry Romberg syndrome)		

upper extremities, and rarely the face (linear LS). The limited type LS, known as *morphea* or the *classical plaque type of LS* is the most prevalent form. It presents as a painless localized round to oval-shaped, centrifugally growing, indurated patch-plaque lesion with destruction of adnexal structures in the center. The lilac ring, frequently seen around morphea lesions, is a clinical sign of inflammatory activity at the border of a growing lesion. Later on, lesions become hypo- or hyperpigmented. *Atrophodermia idiopathica et progressiva of Pierini and Pasini* is a superficial atrophying form of the classical plaque-type LS. *Guttate-type LS* presents with disseminated confetti-like lesions with usually less than 1 cm diameter, predominantly on the trunk. The diagnosis of generalized LS can be made if three or more anatomic sites are affected (predominantly trunk, thighs, lumbosacral region), with plaques at the same or different stages of disease [45]. *Disabling pansclerotic morphea* describes a severe, very rare variant of generalized LS that occurs mainly in childhood. Trophic therapy-refractory ulcerations and disabling contractures are frequent and severe consequences of this disease; systemic involvement is not seen. According to the AWMF guidelines [45], *Shulman syndrome* or *eosinophilic fasciitis* is classified as a form of generalized LS presenting with rapidly progressive symmetric inflammatory edema of the extremities with a tendency of fibrotic induration. In childhood, linear types of LS are the most frequent form of LS. It occurs most often on the extremities with various degrees of inflammation. In mild, *superficial forms of linear LS*, patients may present with superficial hyperpigmentation without impairment. Depending on the depth of inflammation, linear LS may, in more severe cases, lead to joint contractures, arthritis, and asymmetric growth of extremities. Weibel and colleagues described a Blaschko-linear distribution of linear LS [46]. *Scleroderma "en coup de sabre"* is most frequently found in the face/capillitium, in mild forms with hyperpigmented skin lesions à niveau, and, in more severe forms, with sclerotic involvement of skin, muscles and bone shaped as a sword thrust. Central nervous involvement with consecutive seizures or headache is frequently observed in these patients. In clinical series of linear LS, *progressive facial hemiatrophy* or *Parry Romberg syndrome* has been discussed together with LS en coup de sabre as disease variants [47–49]. However, if Parry Romberg syndrome presents with inflammation of extracutaneous structures (muscle, bone) without involvement of the skin layers, it may also be considered as a deep form of LS, as proposed by Kreuter [45]. Deep forms of LS involve the subcutaneous tissue, fascia, and muscle. It is the rarest form of LS and may present already in childhood, frequently on the extremities in symmetric distribution [45].

The differential diagnosis of LS is large and has been discussed elsewhere [45]. Recurrence rate has been investigated in a recent retrospective study of 344 patients by Mertens et al. [50]. Pediatric LS showed higher relapse rates of 27 % than adult-onset LS (17 %), and linear LS recurs more frequently (37 %) than the two most prevalent forms of adult LS, morphea, and generalized LS (16 and 25 %, respectively). Recurrences may occur after years of quiescent diseases, a fact treating doctors should be aware in order to prevent doctor's and patient's delay in retreatment [50].

Patients with LS have a higher risk of developing other autoimmune disorders; Leitenberger and colleagues found the highest correlation of autoimmune diseases such as thyroiditis, rheumatologic diseases, lupus erythematodes, myasthenia gravis, vitiligo, autoimmune hepatitis, or type-I-diabetes in patients with generalized type of LS. Antinuclear antibody positivity was most frequent in mixed and generalized subtypes of LS [51]. Based on greater-than-expected prevalence of autoimmune diseases in LS, it has been proposed that LS is a systemic autoimmune syndrome and not a skin-only phenomenon, with generalized LS having concomitant autoimmune diseases in 45.9 % (approximately 12 times the risk of the non-LS population) [49, 51] .

Workup

Pathogenetic aspects of LS show similarities to SSc and will be discussed there. The trigger factors for the cutaneous inflammatory and, consecutively, sclerosing stages of LS are not yet fully understood. Borrelia infection has been associated with LS in a European population [52], others failed to find a correlation [53, 54], and its pathogenetic role remains to be clarified. Currently, AWMF guidelines do not recommend Borrelia-specific antibiotic treatment in patients with LS [45]. Similarly, Borrelia screening should only be performed in cases with clear clinical suspicion.

Recommendations for blood and serologic tests include a blood differential, clinical chemistry, urine test, ANA, and their differentiation, hypergammaglobulinemia, rheumatoid factor (RF), and eosinophilia in linear LS. Especially in patients with generalized LS, concomitant autoimmune disorders should be examined [45]. Imaging by MRI is warranted in patients with linear "coup de sabre" type of LS to detect neurologic or ophthalmologic involvement [45, 47, 54] and in the diagnosis and follow-up of Shulman syndrome/eosinophilic fasciitis [55].

Current established treatment options

Currently, there is no causal treatment for LS. Furthermore, LS lacks standardized assessment in clinical trials. It is widely accepted that treatment should occur early on in the disease, i.e., in the inflammatory phase of the disease, as the late stage scleroderma is less responsive to treatment. Further factors influencing the choice of therapy are depth of involvement, speed of clinical progression, involvement of functionally or cosmetically sensitive body sites, and extent of involved body surface area. Generally, whereas the limited LS forms may be treated with skin-directed therapies (topical anti-inflammatory drugs, UV phototherapy), generalized, linear, deep, or mixed LS usually require early systemic therapies [56] (Table 2).

Topical moderate to potent corticosteroids are for most of the treating dermatologists the first-line treatment in limited LS despite lack of well-controlled clinical studies. They are usually applied 1× daily, for ≥4 weeks, and then tapered off over another 4 to 8 weeks. Application of occlusive bandage may increase the potency of topical corticosteroid therapy. The topical calcineurin inhibitor tacrolimus has been used in 3 clinical studies [57–59] with resolution of early inflammatory lesion and softening of late sclerotic lesions upon 2× daily treatment over at least 1 month. Atrophy and scarring was not improved. In one small study, the authors did not observe a relapse of the target lesion in patients with good response after 1 year [59]. Small uncontrolled studies have been performed for calcipotriol and imiquimod, but evidence for their benefit is not clear [60, 61]. Given the limited penetration depth of all topical application, these off-label applications should only be considered in limited LS.

Phototherapy: UV phototherapy has been used in LS over more than 20 years, and there is a large body of evidence for its clinical efficacy. Furthermore, none of the published studies reported adverse effects. Given the penetration depths of UVB narrow band (nb) (epidermis), UVA/PUVA, UVA1 (mid/lower dermis), UV treatment should be considered primarily in limited LS and should be, if used at all, combined with systemic treatment in deep variants of LS. In the largest randomized UV trial for morphea/limited LS, low-dose UVA1 (10–20 J/cm^2), medium-dose UVA1 (30–50 J/cm^2), and narrow band UVB 311 nm have been compared. While all three regimen led to improved modified skin scores, medium-dose UVA1 sowed, based on skin thickness and percentage of body surface area involved, significantly better results than UVB or low-dose UVA1 [62]. Based on 11 studies on UV treatment in LS, reviewed in [63], UVA1, PUVA, and nbUVB are considered effective therapies for limited LS, and UVA1 and PUVA are considered effective therapies for deep LS. As LS recurs frequently after UV treatment [64], and given its lower carcinogenic potential, nbUVB and low-dose UVA1 have been proposed as safest treatment for LS [65].

Probably the most frequently used primary systemic therapy of LS, especially of the generalized, linear, and deep form

Table 2 Treatment algorithm for localized scleroderma depending on the clinical subtype and extent of disease (adapted from [45])

Subtype with limited skin Involvement	Subtype with severe skin and/or deep inflammatory involvement
Reaching to the dermis	Inflammation of fat tissue, fascia, muscle, joints and bones or widespread skin involvement (judged by histology and/or MRI)
↓	↓
Topical corticosteroids (cs)	Methotrexate
potent cs, 1xdaily, 5 days/week, 6–12 weeks.	Adults: 12.5–25 mg/week
Reduce to 2–3×/weekly, if longer treatment necessary	Children: 0.3–0.6 mg/kg/week,
Combine or alternate with calcineurin-inhibitors (off-label use), 1-2×/daily	(max 25 mg/week)
Reduced intensity in facial location	Therapy duration ≥6 months
↓	↓
and/or	and/or
UVA1-phototherapy	systemic corticosteroids
(20–80 J/cm^2, 3–5/week, 40 sessions) or	500–1000 mg/day methylprednisolone i.v. for 3 consecutive days monthly for ≥6 months
PUVA-therapy	Children: 30 mg methylprednisolone/kg/day i.v. (maximum 1000 mg/day) on 3 consecutive days monthly for ≥6 months
2–4 times per week, 30 sessions	

of LS, is corticosteroid. However, there is only one published study on single therapy with corticosteroids with 17 patients with generalized and deep LS. It showed clear improvement in the majority of the patients [66]. Interestingly, 6 out of 17 patients relapsed upon cessation of corticosteroid intake. Evidence for efficacy of methotrexate in LS is better: Zulian and colleagues compared in a prospective, double-blind, placebo-controlled study in 70 patients the outcome of MTX 15 mg/m^2 vs placebo after an induction phase of oral prednisone for 3 months [67]. Whereas the side effect rate was comparable in the two groups with no severe adverse events, patients in the MTX group showed a significantly lower relapse rate of 32.6 % than the placebo group (70.8 %). Two prospective studies in children and adults observed the combination therapy of corticosteroids and MTX; 9 out of 10 children improved with a median of 3 months (2–13 months) and were inactive at follow-up (8–33 months) [68], and similarly, LS in 14 out of 15 adults became inactive [69]. Both author groups concluded that the combination therapy of initial pulsed i.v. corticosteroids (30 mg/kg/day for 3 days per month in children, and 1000 mg/day for 3 days per month in adults) and consecutive MTX (0.6 mg/kg/week in children, and 15 mg/week in adults) are efficacious treatments in widespread, severe, and persistent cases of LS. A retrospective study of Weibel and colleagues with corticosteroid pulse and MTX therapy showed significant clinical improvement in 94 % of the patients within 5.7±2.9 months. However, when treatment was stopped after clinical inactivity of LS, 44 % of the patients relapsed and necessitated repeat treatment [70]. Taken together, there is a large body of evidence of efficacy for MTX in LS.

Treatment with other systemic medication such as penicillin, penicillamine, calcitriol, mycophenolat mofetil, cyclosporin A, chloroquine, retinoids, IVIG, rituximab, or imatinib have been published in small case series, case reports, or, in the case of calcitriol, in a prospective clinical study without significant efficacy for calcitriol. Extracorporeal photopheresis has only been described in case reports of generalized LS with or without bullous course of disease, with good individual responses [71–73].

Taken together, there is a wealth of topical treatment available with best evidence for UV therapy, and there is also clear evidence for systemic treatment with corticosteroids and/or methotrexate. Kreuter and colleagues proposed in the current AWMF guidelines a pragmatic and easy flow chart for treatment of LS [45].

Can the novel targeted therapies for SSc be applied to localized scleroderma?

While knowledge about the pathophysiology of SSc has rapidly increased over the last years, still little is known about key pathways in LS. Serum levels of sIL-6R have been found to be increased in patients with LS compared to healthy controls and increased serum levels correlated with the number of linear lesions and the number of involved body areas [74–76]. This provides some rationale for use of IL-6 blockade in LS, but analysis of expression in tissues and functional data are lacking. Little is also known about targets of the multityrosine-kinase inhibitor nintedanib. Expression of PDGF beta-receptor was elevated in the dermis and in cultured fibroblasts from patients with LS compared to healthy controls [77]. Other nintedanib targets have not been described in LS. Increased serotonin levels have been found in the blood of patients with severe generalized morphea [30], but no other data exist regarding the serotonin pathway. sGC has not been described in LS. Overall, the potential benefit of these novel targeted therapies for LS has to be weighed against potential harmful side-effects in a non-systemic disease such as localized scleroderma. For more severe forms such as inflammatory generalized localized scleroderma resistant to the conventional treatment approaches, IL-6 blockade might have some rationale as an experimental therapy.

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