
## Bei Plaque-Psoriasis und Psoriasis-Arthritis*

* TREMFYA® ist indiziert: 1) für erwachsene Patienten mit mittelschwerer bis schwerer **Plaque-Psoriasis**, die für eine systemische Therapie in Frage kommen; 2) allein oder in Kombination mit MTX für die Behandlung der aktiven **Psoriasis-Arthritis** bei erwachsenen Patienten, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD-)Therapie unzureichend gewesen ist oder nicht vertragen wurde.[1]

\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0.0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]


1. Aktuelle Fachinformation TREMFYA®.
2. Reich K et al. Lancet. 2019;394(10201):831-839.
3. Griffiths CEM et al. Poster Presentation Coastal Dermatology Symposium 2020, October 15-16th.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)


▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

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# Systemic sclerosis – the dermatological perspective

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## Summary

Systemic scleroderma/systemic sclerosis (SSc) is an inflammatory connective tissue disease clinically characterized by two major subtypes: limited and diffuse SSc. While both conditions present with Raynaud's phenomenon (paroxysmal digital ischemia), diffuse SSc is associated with rapid disease progression and early – prognostically relevant – involvement of internal organs. Treatment is challenging. In addition to general lifestyle modifications, measures include treatments aimed at improving circulation as well as immunosuppressive and immunomodulatory drugs. However, these agents are effective only in terms of slowing disease progression.

## Introduction

The term 'sclerosis' is used both clinically and histologically to describe a "hardening" of tissue. In the case of scleroderma, this process is primarily associated with an increase in dermal connective tissue. Given that numerous disorders may give rise to the clinical phenomenon of sclerosis, there may be considerable differences in etiopathogenesis, clinical course, and treatment options.

The term scleroderma subsumes two fundamentally different clinical entities: circumscribed scleroderma/morphea, which is limited to the skin; and systemic scleroderma/systemic sclerosis, a multiorgan disease.

The term scleroderma subsumes two fundamentally different clinical entities: circumscribed scleroderma/morphea, which is limited to the skin; and systemic scleroderma/systemic sclerosis, a multiorgan disease. While the dermatological terminology is precise with respect to these two entities, internists and rheumatologists use the term scleroderma predominantly in reference to the latter entity [1–3]. As the skin is at least mildly affected in more than 90 % of systemic scleroderma (SSc) cases, albeit not prognostically relevant, use of this term still seems justified in principle. However, in order to account for the entire disease spectrum, including extracutaneous manifestations, it has recently been proposed that the term 'systemic sclerosis' be adopted in the German terminology as well [4]. In many cases, the disease initially manifests itself merely with increased hardening of the skin, which prompts patients to seek dermatological advice. Subsequently, there is progressive involvement of internal organs with associated clinical symptoms. Given this potential (or actual) organ involvement over the course of the disease, SSc poses a challenge for dermatologists and therefore usually requires interdisciplinary patient management.

## Epidemiology

While all three disorders are characterized by female predominance, the ratio is significantly lower for SSc (3 : 1) than for systemic lupus erythematosus (9 : 1).

With a reported annual incidence of 0.3–2.8/100,000 (prevalence: 10–15/100,000), SSc is less common than lupus erythematosus (incidence: 5–10/100,000 per year) yet more frequent than dermatomyositis (incidence: 1/100,000 per year). While all three disorders are characterized by female predominance, the ratio is significantly lower for SSc (3 : 1) than for systemic lupus erythematosus (9 : 1). There are two

 

**Table 1** Subtypes of systemic sclerosis.

| Limited SSc (lSSc) | Diffuse SSc (dSSc) |
|---|---|
| Longstanding Raynaud's phenomenon | Short history of Raynaud's phenomenon |
| Hands, extremities, face | Trunk |
| Late-onset PAH | Early-onset pulmonary fibrosis |
| Calcinosis (CREST) | Early involvement of internal organs |
| Anticentromere antibodies | Anti-Scl70/topoisomerase I antibodies |

*Abbr.:* PAH, pulmonary arterial hypertension; CREST, calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.

major clinical subgroups: limited SSc and diffuse SSc. The two variants show a very different clinical course and are associated with specific autoantibodies (Table 1).

Regular clinical follow-up is recommended for patients with Raynaud's phenomenon and highly specific autoantibodies without evidence of systemic involvement.

Many patients retrospectively report a history of Raynaud's phenomenon starting in early adulthood (2nd or 3rd decade of life). At that time, it is already possible to detect SSc-specific autoantibodies. The eventual onset of progressive sclerosis of the skin and internal organs with associated clinical symptoms occurs in the 4th or 5th decade. Given that epidemiological figures usually refer to the time of initial diagnosis, not to the onset of initial symptoms, they are difficult to interpret. Regular clinical follow-up is therefore recommended for patients with Raynaud's phenomenon and highly specific autoantibodies without evidence of systemic involvement. However, there are currently no disease-modifying treatment options available for early prevention.

## Classification of systemic sclerosis

A few years ago, the diagnostic criteria originally defined by the *American College of Rheumatology* (ACR) were further specified in cooperation with the *European League against Rheumatism* (EULAR). They include clinical, clinical chemistry and immunoserologic criteria that are assigned a certain score based on their significance, resulting in an overall score.

Given the protracted disease course and uncharacteristic early symptoms, it is difficult to establish a definitive classification. Epidemiological and clinical data have been collected and analyzed both by European and German registries for scleroderma (*European Scleroderma Trial and Research Group* [EUSTAR], *Deutsches Netzwerk Systemische Sklerodermie* [DNSS]). A few years ago, the diagnostic criteria originally defined by the *American College of Rheumatology* (ACR) were further specified in cooperation with the *European League against Rheumatism* (EULAR). They include clinical, clinical chemistry and immunoserologic criteria that are assigned a certain score based on their significance, resulting in an overall score [5] (Table 2). The inclusion of immunoserologic and capillaroscopic criteria allows for earlier and more sensitive diagnosis.

## Pathogenesis

Based on current concepts, the pathogenesis involves collagenous connective tissue as well as the vascular and immune system. To date, the exact temporal sequence or individual significance of the various factors involved are unknown.

## Genetic causes

Although genetic causes are less evident than in other autoimmune diseases, their relevance is reflected by the fact that the disease risk is up to twelve times higher for first-degree relatives than for the general population. Twin studies have shown

**Table 2** Current classification of SSc [6]. An overall score > 9 allows for the definitive diagnosis of SSc. Skin sclerosis proximal to the metacarpophalangeal joints is considered sufficient to diagnose a patient as having systemic sclerosis.

| Main criteria | Additional criteria | Weighting (score) |
|---|---|---|
| Sclerosis of the hands proximal to the metacarpophalangeal joint (sufficient criterion) | | 9 |
| Sclerosis of the fingers (only the higher score) | Puffy fingers<br>Sclerodactyly | 2<br>4 |
| Fingertip lesions (only the higher score) | Fingertip ulcers<br>Pitting scars | 2<br>3 |
| Telangiectasia | | 2 |
| Abnormal nailfold capillaries | | 2 |
| Pulmonary involvement (maximum of 2 points) | PAH<br>ILD | 2<br>2 |
| Raynaud's phenomenon | | 3 |
| SSc-typical autoantibodies (maximum of 3 points) | Anticentromere<br>Anti-topoisomerase I (Scl70)<br>Anti-RNA polymerase III | 3 |

*Abbr.:* PAH, pulmonary arterial hypertension; ILD, interstitial lung disease.

concordance in the occurrence of antinuclear antibodies (ANAs) in 90 % of twins. The extent to which genetic polymorphisms of potentially involved factors – such as HLA antigens, type I interferons, *transforming growth factor beta* (TGF-β), and proteases – may play a role has not been fully elucidated [3]. Given that there is evidence of specific micro-RNAs and global DNA hypomethylation, it seems possible that epigenetic mechanisms may also be pathogenetically relevant by modulating gene expression.

## Environmental factors

Various environmental factors act as important triggers, including infections, environmental toxins, and smoking.

It has been shown that various environmental factors may act as disease triggers, including infections, in particular those caused by cytomegalovirus and parvovirus. This has been highlighted by recent findings regarding the pathogenetic involvement of *toll-like receptors (TLRs)*. These receptors bind to microbial proteins and are thus important mediators of innate immunity. Other environmental factors include toxins such as organic solvents and silicon salts, the latter playing a key role in occupational systemic sclerosis. These toxins are thought to act as nonspecific stimulators of the immune response and fibrosis. Smoking too has a negative impact and should be abandoned, not least because of its aggravating effects on symptoms associated with Raynaud's phenomenon.

## Proinflammatory cytokines

A multitude of mediators and cytokines and their subsequent effects on intracytoplasmic signal transduction have been implicated in the fibrotic processes observed in scleroderma.

A multitude of mediators and cytokines and their subsequent effects on intracytoplasmic signal transduction have been implicated in the fibrotic processes observed in scleroderma [3, 6]. In addition to the key cytokines in the pathogenesis of SSc (type I interferons and TGF-β), there are other mediators that have garnered

 

scientific attention, including adipokines (such as leptin, adiponectin, chimerin, interleukin [IL] 6), which render the adipose tissue a central player in the disease process. Other important cytokines recently shown to be involved include IL-23 and IL-17. Antibodies against IL-23 and IL-17 are approved for the treatment of plaque psoriasis and might therefore become therapeutically relevant for SSc as well. The extent to which antibodies directed against endothelial cells, impaired neovascularization, or nitric oxide may play a significant role has not yet been elucidated in detail. Various endothelial surface molecules, such as ICAM and E-selectin, which also regulate the migration of inflammatory cells, and promote a profibrotic environment. As TGF- β, connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF) act as important mediators in this milieu, they are potential therapeutic targets. Endothelial progenitor cells possibly also play a pathogenetic role and might become relevant as potential biomarkers for disease activity and treatment response [7]. Recent data shows positive effects on digital ulcers following experimental transplantation of these progenitor cells.

The increase in and coarsening of collagen fibers seen on histology is due to a disturbance in collagen metabolism, with increased synthesis and decreased/impaired degradation. Indeed, molecular studies have shown that there is an increase in the production of various collagen subtypes. At the same time, there is abnormal expression and activity of various proteases involved in collagen metabolism, such as matrix metalloproteinases or their inhibitors (tissue inhibitors of metalloproteinases; TIMPs). Experiments have shown that their expression can be modulated by ultraviolet light. This in part explains why phototherapy is clinically effective.

## Cutaneous manifestations

The two major subtypes are limited (43 % of cases) and diffuse SSc (30 % of cases).

The two major subtypes are limited (43 % of cases) and diffuse SSc (30 % of cases). While limited SSc presents with slowly progressive involvement of the fingers, feet, and distal extremities, diffuse SSc is characterized by rapidly progressive sclerosis primarily of the trunk, which may be increasingly associated with impaired mobility (Table 1). There are also differences in onset and extent of internal organ involvement. Limited SSc presents with late-onset, slowly progressive extracutaneous manifestations, whereas diffuse SSc shows early and rapidly progressive organ involvement. The various organ manifestations and immunoserologic findings will be discussed in detail below. Another 30 % of affected patients may be diagnosed as having overlap syndrome, which, apart from the aforementioned SSc symptoms, also presents with manifestations of SLE and dermatomyositis and is serologically characterized by anti-U1RNP antibodies.

Common to all subtypes is the early onset of Raynaud's phenomenon. It presents with the "tricolor" sign (white, blue and red) and occurs in more than 90 % of patients.

Common to all subtypes is the early onset of Raynaud's phenomenon. It presents with the "tricolor" sign (white, blue and red) and occurs in more than 90 % of patients. The various colors are caused by paroxysmal ischemia (white), stasis (blue) and reactive hyperperfusion (red). Known triggers include cold, stress and smoking. A similar phenomenon can also occur in internal organs with subsequent pathological changes such as impaired renal perfusion. Initially, the impaired digital perfusion is functional and transient. Eventually, however, the condition may result in tissue damage with subsequent autoamputation of phalanges or entire fingers. Apart from Raynaud-related symptoms, acral edema is another typical finding. Reversible in early stages, it occurs periodically and presents as "*sausage fingers*". In later stages, there is increasing sclerosis that eventually leads to spindle-shaped fingers ("*Madonna fingers*") surrounded by tight skin. Subsequently,

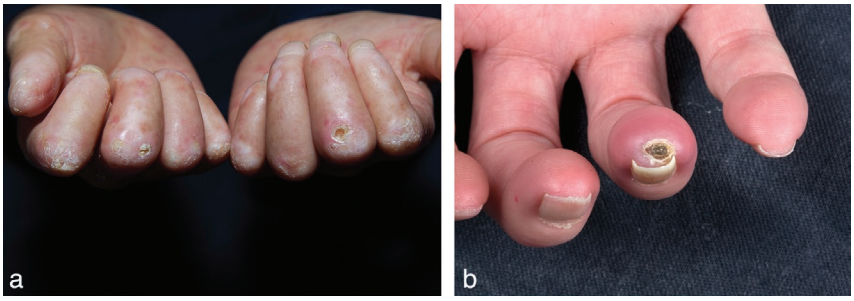


**Figure 1** Sclerosis of the fingers with prominent dermatogenic and tendogenic contracture as well as ulcerations (a). Fingertip necroses ("rat bite" ulcers).

Other typical cutaneous signs include radial perioral furrowing ("tobacco pouch" sign), limited mouth opening, pointed nose and tight facial skin that results in decreased facial expression (amimia).

severe dermatogenic or tendogenic contractures may result in markedly reduced mobility (Figure 1a). Acral necrosis or fingertip ulcers are bluntly referred to as "*rat bite*" ulcers, an alarming term for those affected (Figure 1b). Eventually, the skin can no longer be picked up or squeezed. Other typical cutaneous signs include 1) radial perioral furrowing ("tobacco pouch" sign) (Figure 2), 2) limited mouth opening (Figure 3), 3) pointed nose and 4) tight facial skin (Figure 2) that results in decreased facial expression (amimia). A shortened, sclerotic lingual frenulum is characteristic, albeit rare (Figure 4). Other common findings include facial telangiectasia (Figure 2) as well as dermal and subcutaneous calcifications, in particular

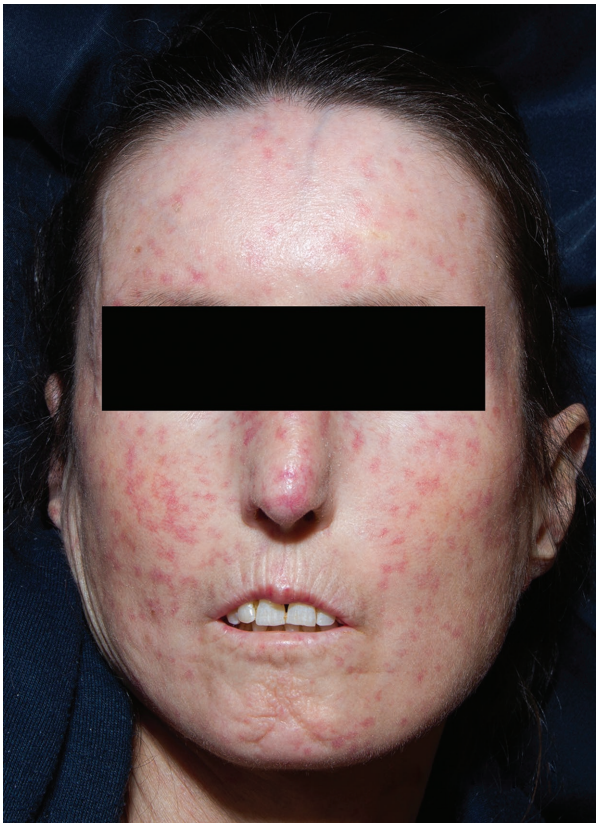

**Figure 2** Sclerosis of the face with radial perioral furrowing ("tobacco pouch" sign), pointed nose and telangiectasias.

 

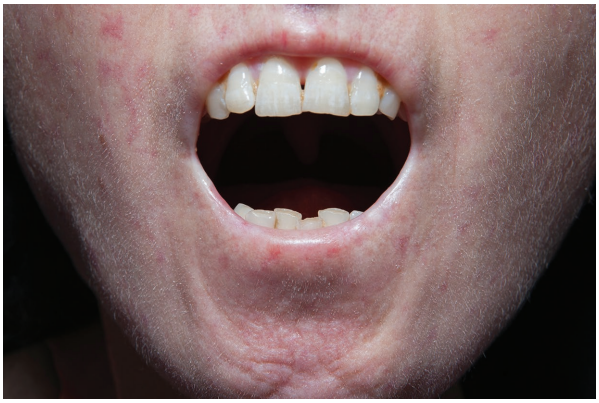

**Figure 3** Limited mouth opening.

over the finger joints, elbows, and knee. The latter are not only cause for cosmetic impairment but may also be very painful and ulcerate.

There are also morphological changes in nailfold capillaries [8, 9], showing a disturbance in the physiological arrangement of hairpin capillaries (usually in two orderly rows) in advanced disease. Dependent on disease stage and activity, findings include megacapillaries, loss of capillaries, and hemorrhages (Table 3). Visible to the naked eye, these changes can be visualized particularly well on capillaroscopy. However, they are not a separate diagnostic criterion (Table 2). Dermoscopy (magnification x 10–20) followed by higher resolutions or video-assisted capillaroscopy (magnification up to x 400) may be diagnostically useful in this context.

Dependent on disease stage and activity, megacapillaries, loss of capillaries, and hemorrhages can be seen on capillaroscopy. Visible to the naked eye, these changes can be visualized in detail on dermoscopy (magnification x 10–20), followed by higher resolutions or video-assisted capillaroscopy (magnification up to x 400).

The extent of skin sclerosis over time can be quantified using the modified *Rodnan Skin Score* (mRSS), which assesses skin thickness at various body sites (Table 4). Included in the overall score are 17 sites (face, décolleté/frontal thorax, abdomen, right and left lower and upper arms, fingers, hands, lower and upper legs, feet). The individual sites are assigned a score between 0 and 3 depending on the extent of local sclerosis (0 = normal skin, 1 = mild sclerosis, 2 = moderate sclerosis, 3 = severe sclerosis). Adding up individual scores results in an overall score between 0 (no sclerosis) and 51 (severe sclerosis at all sites).

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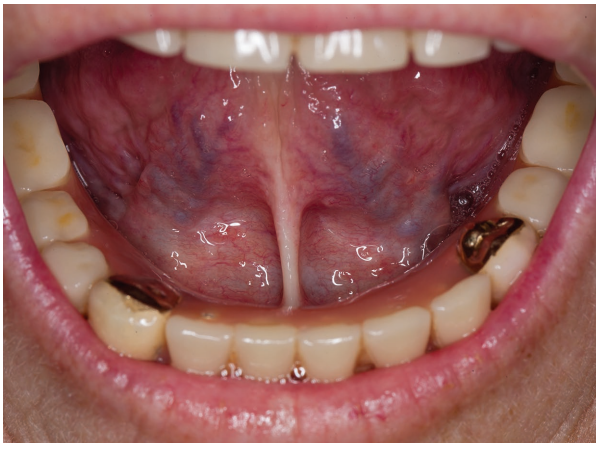

**Figure 4** Sclerosis of the frenulum.

**Table 3** Nailfold capillaroscopy is more reliable, yet technically more complex. As dermatologist are experienced in the use of dermoscopy, this method is a suitable tool in routine clinical practice for making (at least) a rough assessment of possible nailfold abnormalities.

| | Capillary pattern | Loss of capillaries | Giant capillaries | Hemorrhages | |
|---|---|---|---|---|---|
| Early | Well-preserved | None | Few | Few | |
| Active | Mildly abnormal | Moderate | Numerous | Numerous | |
| Late | Severely abnormal | Significant | Few | Few | "Bushy" capillaries |

**Table 4** Modified Rodnan Skin Score (mRSS).

| Severity of skin sclerosis | mRSS |
|---|---|
| 0 normal | 0 |
| 1 mild | 1–14 |
| 2 moderate | 15–29 |
| 3 severe | 30–39 |
| 4 final stage | > 40 |

## Immunoserologic detection of specific autoantibodies

Ninety percent of SSc patients are ANA positive. Limited disease is characterized by anticentromere antibodies; diffuse disease by anti-Scl70/topoisomerase I antibodies.

Autoantibodies are an important criterion in terms of diagnosis and classification of SSc (Table 2). Ninety percent of SSc patients are ANA positive. Limited disease is characterized by anticentromere antibodies; diffuse disease by anti-Scl70/topoisomerase I antibodies (Table 1). However, even though patients usually present with high antibody levels, there is no correlation with disease activity. Unlike SLE patients, individuals with SSc show a rather limited number of specific antibodies (Table 1). Other autoantibodies define certain subgroups with organ involvement and associated complications, such as pulmonary involvement or renal crisis (Table 5) [10–12].

## Organ involvement

Internal organs most commonly involved include the heart, lungs, and kidneys. Based on the individual rapidity and severity of organ involvement, there is a significant impact on patients' quality of life and survival prognosis.

Internal organ most commonly involved include the heart, lungs, and kidneys. Based on the individual rapidity and severity of organ involvement, there is a significant impact on patients' quality of life and survival prognosis [1–3, 10, 11].

Renal abnormalities include nephrosclerosis associated with arterial hypertension, increased urea and creatinine levels as well as reduced creatinine clearance and proteinuria. These parameters should therefore be measured at the time of diagnosis and at least at annual intervals thereafter, depending on disease activity and progression as well as the individual treatment approach chosen (see section on follow-up below). Renal crisis is a feared, albeit rare complication that typically occurs after a several-week history of systemic corticosteroid therapy (> 15 mg of prednisolone equivalent) [10, 11, 13].

Cardiac involvement occurs in 10–25 % of patients. In addition to pericardial/myocardial fibrosis and pericardial effusion, manifestations primarily include sclerosis of the heart valves and conduction system with subsequent arrhythmia.

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Pulmonary involvement occurs in 40–80 % of cases. Progressive sclerotic remodeling eventually leads to fibrosis associated with impaired pulmonary function and reduced diffusion capacity. These parameters should therefore be checked on a regular basis. Given that x-ray studies show pulmonary changes only

 

**Table 5** Association of organ involvement and specific autoantibodies in systemic sclerosis.

| Organ involvement | SSc-associated antibodies |
|---|---|
| Arthritis | Anti-CCP |
| Arthritis | Rheumatoid factor |
| Liver (primary biliary cirrhosis) | Anti-mitochondrial antibodies (anti-M2) |
| Parotitis (secondary Sjogren's syndrome) | Anti-Ro/La |
| Muscle involvement (SSc/polymyositis overlap) | Anti-PM-Scl |
| Myositis overlap | Anti-RuvBL1/RuvBL2 |
| SSc/SLE overlap (rare) | Anti-dsDNA |
| **Organ involvement** | **SSc-specific antibodies** |
| PAH | Anticentromere (ACA) |
| DUs, ILD | Anti-topoisomerase I/Scl70 (ATA) |
| Myositis, ILD | Anti-PM-Scl |
| Renal crisis, skin fibrosis, associated with cancer | Anti-RNA polymerase III |
| Joints (MCTD) | Anti-U1-RNP |

*Abbr.:* PAH, pulmonary arterial hypertension; ILD, interstitial lung disease, MCTD, mixed connective tissue disease, DUs, digital ulcers.

Pulmonary involvement occurs in 40–80 % of cases. Progressive sclerotic remodeling eventually leads to fibrosis associated with impaired pulmonary function.

in advanced, clinically manifest disease, computed tomography should be the imaging method of choice once relevant reduction in pulmonary diffusion has occurred. Pulmonary arterial hypertension (PAH) (pulmonary arterial pressure > 25 mmHg) is a characteristic finding in limited SSc and can be detected by echocardiography. If the pulmonary arterial pressure rises to > 35 mmHg, right heart catheterization is warranted for direct pressure measurement. In diffuse SSc, PAH usually presents at a later stage and is frequently a sequela of pulmonary fibrosis

Involvement of the gastrointestinal tract is characteristic for SSc, clinically presenting with impaired motility of the esophagus, gastro-esophageal reflux, and Barrett's esophagus. If there is intestinal sclerosis, complications may also include malabsorption and changes in the gut microbiome with alternating constipation and diarrhea as well as flatulence.

Involvement of the gastrointestinal tract is characteristic for SSc, clinically presenting with impaired motility of the esophagus, gastro-esophageal reflux, and Barrett's esophagus. If there is intestinal sclerosis, complications may also include malabsorption and changes in the gut microbiome with alternating constipation and diarrhea as well as flatulence.

However, it has been shown in autopsy specimens that 80–90 % of patients have some form of intestinal sclerosis, even though they never explicitly reported any symptoms; on the other hand, physicians may not have paid too much attention to such symptoms.

Sicca symptoms frequently affect the oral cavity, eyes and genitalia.

The same is true for sicca symptoms, which affect the oral cavity and eyes but also the genitalia. They are caused by progressive rarefaction and sclerosis of eccrine glands. Sicca symptoms may be alleviated by using artificial tears and saliva.

The topic of sexual activity is very sensitive and often not actively addressed by patients themselves. Once a stable and trusting physician-patient relationship has been established, it is important and useful to inquire about impaired sexual activity.

The topic of sexual activity is very sensitive and often not actively addressed by patients themselves. Once a stable and trusting physician-patient relationship has been established, it is important and useful to inquire about impaired sexual activity. For women, genital sicca symptoms may cause extreme discomfort and should be alleviated with mucosal lubricants/emollients. In men, erectile dysfunction caused by cutaneous, vascular or neurological disturbances may pose a significant therapeutic challenge.


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Given that the inability to fully open the mouth frequently stands in the way of proper tooth brushing, patients should be encouraged to ensure adequate oral hygiene.

Given that the inability to fully open the mouth frequently stands in the way of proper tooth brushing, patients should be encouraged to ensure adequate oral hygiene. This is aggravated by xerostomia due to hyposalivation, which may cause early and progressive dental damage, especially increased cavities. Moreover, teeth may become loose or fall out due to resorptive processes involving the jaw bone and periodontium. It is therefore essential that the dental status be assessed on a regular basis. Larger oral surgery procedures should be planned well, as they may be associated with disease aggravation/activation as well as impaired or delayed wound healing.

As is the case for many chronic inflammatory diseases, affected patients are at an increased risk of cancer. Possible reasons include the underlying systemic inflammation and long-term immunosuppressive therapy. In addition, there may be cancer-associated disease subgroups that cannot be definitively defined at present. Cancer-associated SSc should be included in the diagnostic considerations in patients with sudden onset and rapid disease progression as well as insufficient response to treatment and unusual clinical course.

## Follow-up

Depending on clinical symptoms and disease progression, it is generally recommended that patients be followed up at annual or biennial intervals. This includes clinical examination, blood tests and imaging studies.

Depending on clinical symptoms and disease progression, it is generally recommended that patients be followed up at annual or biennial intervals. This includes clinical examination, blood tests and imaging studies. Procedures include pulmonary function and lung diffusion tests, echocardiography and TEE, imaging studies including CT of the lungs, cardiac MRI, and esophagogastroscopy and manometry, and, if required, colonoscopy. Laboratory tests such as CBC with differential, liver and kidney function tests, NT-proBNP (N-terminal prohormone of brain natriuretic peptide), complement factors and troponin T should also be performed at least once a year. While serum levels of specific autoantibodies do not correlate with clinical disease activity, their sequential annual measurement helps assess the risk of organ involvement.

## Treatment of systemic sclerosis

Avoidance of cold exposure and mechanical injuries, proper skin care and physical therapy (physical exercises, lymphatic drainage, paraffin baths) are useful measures.

All patients should be educated about general lifestyle modifications, including proper skin care, protection against injury and cold, adequate oral hygiene, and dietary measures [3, 6, 14, 15].

Local protection from cold (gloves) or application of heat (hot gel packs or "thermo pads") are useful measures in addition to the pharmacological measures aimed at improving circulation listed below. While patients like to apply "antirheumatic ointments" containing glyceryl trinitrate (nitroglycerin) or benzyl nicotinate for subjective, temporary relief, there is only little evidence for this approach. Paraffin baths (for hands and/or feet) may improve acral perfusion and reduce the number and severity of Raynaud's attacks when used on a regular basis. Devices for home use are available. However, there are no adequate clinical studies regarding their efficacy.

Affected patients should eat several small meals a day along with plenty of fluids and chew their food sufficiently. Antacids and proton pump inhibitors should be taken for gastro-esophageal reflux; prokinetics may be used for indigestion.

Affected patients should eat several small meals a day along with plenty of fluids and chew their food sufficiently. Antacids and proton pump inhibitors should be taken for gastro-esophageal reflux. Prokinetics may be used to facilitate the orderly transport of chyme, as they promote forward peristalsis and inhibit reverse peristalsis. Available drugs include *1)* dopamine receptor antagonists (metoclopramide, domperidone), *2)* direct (carbachol) and indirect parasympathomimetic

 

agents (neostigmine), and *3)* serotonin (5-TH4) receptor antagonists, in particular prucalopride. However, the latter is only approved for the treatment of chronic idiopathic constipation. It promotes intestinal motility and thus defecation. The most common adverse effects are abdominal pain, nausea, diarrhea and headache. Prucalopride is contraindicated in patients with chronic kidney disease requiring dialysis, constipation due to structural and functional abnormalities of the intestinal wall, and severe inflammatory bowel disease.

Given its highly varied clinical presentation, SSc is not only associated with organ-specific morbidity and mortality but also with significant impairment in quality of life, a fact that should be observed when making treatment decisions. To date, there is no pathogenesis-based treatment that targets the root cause of SSc in terms of preventing or delaying disease progression and organ involvement. Apart from proper skin care and avoidance of mechanical stimuli and injuries to the skin (see above), initial treatment measures should primarily be aimed at improving the impaired peripheral circulation.

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Effective agents in this regard include calcium antagonists, which may also help maintain renal function. Alternatively, ACE inhibitors can be given as second-line drugs; however, their use may be restricted in patients with preexisting arterial hypotension. If this approach fails, effective alternatives include intravenous prostaglandin derivatives such as prostaglandin E1 (alprostadil) and the stable prostacyclin derivative iloprost. The latter is approved for the treatment of advanced thromobangiitis obliterans and has been routinely used in patients with primary and secondary Raynaud's phenomenon. Clinical studies have shown the drug to be effective in reducing the frequency and severity of Raynaud's attacks, in promoting healing of digital ulcers, and in improving digital perfusion at a dose of 20 µg/day given at 1–2 ng/kg/min for five days. Given that the effects usually last for only 4–8 weeks, it is recommended to repeat this treatment especially in the wintertime.

Treatment of SSc continues to pose a challenge. It is based on measures aimed at improving peripheral circulation using vasoactive agents such as calcium antagonists and prostacyclin derivatives (e.g., iloprost), endothelin receptor antagonist (e.g., bosentan), or phosphodiesterase inhibitors (e.g., sildenafil).

The only substance currently approved for the treatment of digital ulcers (DUs) is the selective endothelin 1 receptor antagonist bosentan, which may be combined with other rheologic measures. While clinical studies showed no significant effects on ulcer healing itself, they did show a significant decrease in the number of recurrences. Adults are usually started on a dose of 62.5 mg BID for four weeks, which is subsequently increased to the standard maintenance dose of 125 mg BID. Important adverse effects include flush, edema, and hypotension (as the drug interferes with blood pressure regulation), headache and fatigue, disorders of the gastrointestinal tract (dyspepsia and gastro-esophageal reflux) as well as elevated liver function tests.

An oral phosphodiesterase 5 inhibitor, sildenafil has been successfully used in small clinical trials for the treatment of scleroderma-associated Raynaud's phenomenon and DUs. The drug is given for 3–6 months (at the highest tolerated dose [up to 150 mg]). Major adverse events include dizziness, headache, and dyspnea.

In addition to pharmacological agents, digital ulcers should be treated with adequate wound management using modern wound dressings. When planning surgical procedures including amputations, it is important to consider the overall situation in terms of poor acral perfusion and the increased risk of impaired wound healing.

In addition to pharmacological agents, digital ulcers should be treated with adequate wound management using modern wound dressings. When planning surgical procedures including amputations, it is important to consider the overall situation in terms of poor acral perfusion and the increased risk of impaired wound healing.

As regards dermatology-specific options, whole-body UV therapy, in particular medium-dose or high-dose UVA1 therapy, is a useful modality to slow down the process of cutaneous sclerosis. While treatment approaches using photopheresis have also been described, they have not been sufficiently evaluated.


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UV therapy is an effective and well-tolerated modality for treating cutaneous sclerosis. Immunosuppressive drugs such as methotrexate and mycophenolate mofetil, on the other hand, are characterized by differences in their effectiveness for the various types of organ involvement. Systemic corticosteroids should only be given short term and only in patients with high inflammatory activity, arthritis, and in the edematous stage.

Treatment with tyrosine kinase inhibitors to block intracytoplasmic signal transduction and thus the expression of proinflammatory cytokines is currently being investigated in clinical trials.

As is the case for other autoimmune diseases, SSc in particular is associated with significant physical and psychological sequelae for patients (and their social environment). Adequately dealing with the disease in its various stages is pivotal, especially in the family and social environment setting. Crucial components in this context include extensive discussions about the nature and course of the disease, facilitating contact to support groups, as well as psychotherapy and physical therapy.

Further studies are required to determine the extent to which anti-cytokine and/or anti-cytokine receptor antibodies (IL-6 receptor Ab: tocilizumab, IL-17A Ab: e.g., secukinumab), which have been evaluated in clinical studies and are approved for psoriasis/psoriatic arthritis, are also effective for the treatment of SSc.

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Topical and systemic corticosteroids merely play a minor role in the treatment of SSc. While systemic corticosteroids may be useful in the initial edematous stage, they should be avoided on account of the aforementioned risk of inducing renal crisis [3, 14, 15]. Cyclophosphamide has been evaluated in a number of controlled trials that investigated its effect on pulmonary – rather than cutaneous – involvement. More recently, it has been shown that mycophenolate mofetil (MMF) is effective in the treatment of cutaneous sclerosis; there are, however, no placebo-controlled clinical studies available [15]. At a dose of 15 mg/week, methotrexate is effective in terms of mitigating skin sclerosis, yet less effective for pulmonary fibrosis. Azathioprine and cyclosporine are second- and third-line alternatives.

A recent publication presented cumulative data on autologous stem cell transplantation, which has been performed at specialized centers for a number of years [16]. Myeloablation (conditioning) destroys the host's immune system and thus eliminates the immunological disturbance that gives rise to autoimmunity. Compared to cyclophosphamide and corticosteroids, transplantation is well tolerated and demonstrates positive effects on organ-specific morbidity and mortality, in particular with respect to pulmonary and cutaneous manifestations. Even though this approach has to date only been employed in patients with severe and advanced disease, cases marked by rapid disease progression may possibly also warrant its use early on.

Treatment with tyrosine kinase inhibitors to block intracytoplasmic signal transduction and thus the expression of proinflammatory cytokines is currently being investigated in clinical trials [6]. Imatinib is a specific tyrosine kinase inhibitor that has been approved for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML). In vitro, this agent has antifibrotic effects, which prompted investigators to initiate clinical studies with low-dose and high-dose imatinib in patients with systemic scleroderma. As the results obtained in these studies have not been conclusively analyzed, it is impossible to definitively comment on the potential clinical application of this – otherwise approved – drug. Other tyrosine kinase inhibitors may possibly have a better efficacy-tolerability profile.

Further studies are required to determine the extent to which anti-cytokine and/or anti-cytokine receptor antibodies (IL-6 receptor Ab: tocilizumab, IL-17A Ab: e.g., secukinumab), which have been evaluated in clinical studies and are approved for psoriasis/psoriatic arthritis, are also effective for the treatment of SSc.

## References

1 Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009; 360(19): 1989–2003.
2 Riemekasten G. Fortschritte bei der Systemischen Sklerose. Dtsch Med Wochenschr 2019; 144: 189–93.
3 Knobler R, Moinzadeh P, Hunzelmann N et al. 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. J Eur Acad Dermatol Venereol 2017; 31: 1401–24.
4 Aringer M, Müller-Ladner U, Burkhardt H et al. [Common German language nomenclature for systemic sclerosis]. Z Rheumatol 2015; 74: 100–3.
5 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: 1747–55.
6 Distler O, Cozzio A. Systemic sclerosis and localized scleroderma – current concepts and novel targets for therapy. Semin Immunopathol 2016; 38: 87–95.

 

7 Del Papa N, Pignataro F. The role of endothelial progenitors in the repair of vascular damage in systemic sclerosis. Front Immunol 2018; 9: 1383.
8 Trombetta AC, Smith V, Pizzorni C et al. Quantitative alterations of capillary diameter have a predictive value for development of the capillaroscopic systemic sclerosis pattern. J Rheumatol 2016; 43(3): 599–606.
9 Cutolo M, Sulli A, Smith V. How to perform and interpret capillaroscopy. Best Pract Res Clin Rheumatol 2013; 27: 237–48.
10 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 (Oxford) 2008; 47(8): 1185–92.
11 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 group database. Ann Rheum Dis 2007; 66(6): 754–63.
12 Igusa T, Hummers LK, Visvanathan K et al. Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer. Ann Rheum Dis 2018; 77: 1179–86.
13 Moinzadeh P, Kuhr K, Siegert E et al. Scleroderma renal crisis (SRC): risk factors for an increasingly rare organ complication. J Rheumatol 2019; Apr 1: pii: jrheum.180582. [Epub ahead of print].
14 Kowal-Bielecka O, Fransen J, Avouac J et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017; 76: 1327–39.
15 de Vries-Bouwstra J, Allanore Y, Matucci-Cerinic M, Balbir-Gurman A. Worldwide expert agreement on updated recommendations for the treatment of systemic sclerosis. J Rheumatol 2019; May 1: pii: jrheum.181173. [Epub ahead of print].
16 Sullivan KM, Goldmuntz EA, Keyes-Elstein L et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. N Engl J Med 2018; 378: 35–47.



 

# Fragen zur Zertifizierung durch die DDA

**1. Welches der folgenden klinischen Symptome ist typisch für die systemische Sklerodermie?**

a) Auspitz-Phänomen
b) Tabaksbeutelmund
c) roter Dermographismus
d) Darier Zeichen
e) Nikolski-Zeichen

**2. Welche der folgenden Verlaufsformen gehört nicht zur systemischen Sklerodermie?**

a) limitierte Sklerodermie
b) diffuse Sklerodermie
c) zirkumskripte Sklerodermie
d) paraneoplastische Formen
e) Overlap-Formen

**3. Welche der folgenden Aussagen zur diffusen und limitierten Sklerodermie trifft nicht zu?**

a) Nachweis von Anti-Scl70-Antikörpern bei der limitierten Sklerodermie
b) schneller Progress bei der diffusen Sklerodermie
c) langfristig bestehendes Raynaud-Syndrom bei der limitierten Sklerodermie
d) Die limitierte Sklerodermie zeigt eher eine akrale Betonung.
e) Bei beiden Formen sind in einem hohen Prozentsatz antinukleäre Antikörper nachweisbar.

**4. Welche Aussage zur Pathogenese trifft nicht zu?**

a) Bei der systemischen Sklerodermie findet sich eine gestörte Neovaskularisation.
b) *transforming growth factor* β (TGFβ) wird als eines der bedeutsamsten Zytokine angesehen.
c) Die Fibroblastenzahl ist in der sklerotischen Haut deutlich erhöht.
d) Es zeigt sich eine gestörte Balance zwischen Synthese und Degradation der extrazellulären Matrix.
e) Endotheliale Progenitorzellen sind für die Gefäßreparation bedeutsam.

**5. Welche Organbeteiligung ist für die systemische Sklerodermie nicht typisch?**

a) Gastrointestinaltrakt
b) Herz
c) Lungen
d) Nebennieren
e) Nieren

**6. Welche Aussage zu durchblutungsfördernden Therapeutika trifft nicht zu?**

a) Bosentan ist zur Vorbeugung rezidivierender akraler Hautulzerationen zugelassen.
b) Phosphodiesterasehemmer sind eine mögliche Alternative. Sie sind für die Indikation akraler Hautulzerationen jedoch nicht zugelassen.
c) Prostacyclinderivate können nur intravenös verabreicht werden.
d) ACE-Hemmer sind aufgrund renaler Komplikationen kontraindiziert.
e) Calciumantagonisten sind als unterstützende nephroprotektive Therapie sinnvoll.

**7. Welche der folgenden Untersuchungsmethoden wird eher nicht zur Diagnostik der systemischen Sklerodermie eingesetzt?**

a) Herzsonographie
b) Lungenbiopsie
c) Ösophagusmanometrie
d) Lungendiffusionskapazität
e) Kreatininclearance

**8. Welches Therapeutikum findet bei der systemischen Sklerodermie eher keine Anwendung?**

a) Mycophenolatmofetil
b) Methotrexat
c) Cyclophosphamid
d) D-Penicillamin
e) 5-Fluorouracil

**9. Welche der folgenden Untersuchungsmethoden eignet sich nicht zur Bestimmung der Hautdicke?**

a) Modifizierter *Rodnan skin score*
b) 20 Mhz-Ultraschall-Untersuchungen
c) Mundöffnung
d) Kapillarmikroskopie
e) Faustschluss

**10. Welcher der folgenden antinukleären Antikörper ist nicht charakteristisch für die systemische Sklerodermie?**

a) Anti-Zentromer-Antikörper
b) Anti-Scl-70-Antikörper
c) Anti-dsDNA-Antikörper
d) Anti-RNA-Polymerase
e) Anti-Fibrillarin-Antikörper

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 13. September 2019. Die richtige Lösung zum Thema „Pathophysiologie der atopischen Dermatitis“ in Heft 4 (April 2019) ist: (1b, 2c, 3e, 4c, 5a, 6d, 7c, 8b, 9b, 10b).

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