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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 4. Treatment of patients with systemic sclerosis characteristics and recommendations concerning treatment of skin involvement, Raynaud's phenomenon, calcinosis

ABSTRACT

Systemic sclerosis (SSc) is a systemic connective tissue disease marked by diffuse microangiopathy and excessively immune-stimulated fibroblast activity, leading to fibrosis of the skin and internal organs. In the literature, the first report of the disease dates back to 1753 and is attributed to the physician Carlo Curzio of Naples, who described the case of a 17-year-old girl who developed sclerosis of the skin all over her body. The disease is a rare condition. It is estimated that 1 in 10 000 people in Poland suffer from SSc. Women predominate among the patients, with a 3–4-fold prevalence compared to men. Typically, the disease has its onset between 30 and 50 years of age. Early detection and treatment of organ complications are key to improving quality of life and reducing mortality in patients with SSc. Given the significant variability in the clinical course, an individualised approach to patients and multidisciplinary collaboration appear to be justified, both in the diagnostic and treatment phases. The treatment is based on the organ-specific therapeutic strategy, which involves tailoring the pharmacotherapy to the clinical presentation, disease stage, and organ complications. Treatment of patients should include, in addition to pharmacology, education of the patient and family and, if necessary, surgical treatment or other necessary interventions.

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INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease in which internal organs, usually the lungs and kidneys, skin fibrosis and microcirculatory abnormalities occur. The pathogenesis takes into account genetic factors, autoimmune disorders, disturbances in collagen synthesis, and environmental factors.

The current classification of SSc according to LeRoy et al. since 1988 distinguishes two main clinical subtypes of the disease based on the extent of cutaneous sclerosis, i.e., SSc with limited cutaneous sclerosis (lcSSc) and SSc with diffuse cutaneous systemic sclerosis (dcSSc). Cutaneous sclerosis in lcSSc includes the hands, feet, forearms and lower legs but does not extend beyond the level of the elbows and/or knees. Cutaneous sclerosis in the form of dcSSc exceeds proximally beyond the level of the elbows and/or knees and involves the trunk. The disease in both forms can involve the facial skin. Indeed, from a treatment perspective, both forms of SSc differ in terms of disease progression dynamics, time of Raynaud's phenomenon onset, immunological profile, type of organ complications, and patient survival. The heterogeneity of the disease is the reason for the constant search and raising questions about a new classification of the disease form. The proposed amendment should take into account, in addition to the extent of skin involvement, the immunological profile of the individual patient, the molecular profile of the skin lesions (inflammatory, fibro-proliferative, normal), genetic variation, sex and stage of disease. Taking into account the aforementioned factors can help in offering the patient a personalised and targeted treatment approach.

The disease has a high mortality rate due to its numerous complications and the lack of effective targeted treatment [1]. It is marked by a wide variation in the clinical picture due to the different rate of development and type of organ complications. At present, there are no drugs that can effectively delay the progression of the disease in all patients.

Current treatment is mainly aimed at ameliorating the symptoms of SSC, which is why early identification of organ complications and assessment of the risk of disease progression is so important. Altered body image is a cause of low self-esteem and depressive disorders in patients. It should be remembered that SSc is primarily a debilitating disease that leads to irreversible disability.

TREATMENT OF PATIENTS WITH SYSTEMIC SCLEROSIS

The decision on treatment should be made individually for each patient after analysing the severity of the skin lesions, duration of the disease, disease activity, complaints and changes in internal organs. The patient's serological profile, which can indicate which organ lesions can be expected in the course of the disease, is not without significance:

— antibodies against topoisomerase I (anti-Scl-70) are associated with an increased risk of developing interstitial lung disease (ILD);
— antibodies against RNA polymerase I and III (anti-RNAP) are associated with an increased risk of renal crisis;
— anticentromere antibodies are typically associated with a milder course of the disease.

It should be noted that male gender and old age at onset are also poor prognostic factors. To assess the disease severity, the European Scleroderma Study Group has developed a Disease Activity Index (DAI) (Tab. 1). The disease is active when the DAI > 3. This index can be helpful in qualifying patients for immunosuppressive treatment.

RECOMMENDED ORGAN-SPECIFIC TREATMENT

Due to the lack of universal disease-modifying drugs and given the considerable clinical heterogeneity, the treatment of SSc is based on so-called organ-specific therapy. This method involves the use of drugs with proven or probable efficacy in the treatment of particular organ complications in patients with these complications. It is an organ-specific intervention aimed at protecting the organ, possible early treatment of the pathologies that have arisen and possible remodelling of the lesions that have already arisen, taking into account the complexity and individualisation of the management. It presupposes the avoidance of the use of drugs that may cause harm in this particular disease entity. Organ-specific therapy in the course of SSc should also include education of the patient and family, physical therapy and kinesitherapy (as prevention of joint contractures in joint complaints and myopathy), occupational therapy and psychotherapy.

If left untreated, the disease, especially dcSSc, quickly leads to serious organ compli-

Table 1. Systemic Scleroderma Activity Index (based on [53])

No.		Scoring	
1.	Rodnan index >14	1	Evaluation of skin hardness from 0 to 3 in 17 areas (0–51)
2.	Sclerodactyly	0.5	
3.	Skin	2	Exacerbation of skin lesions as assessed by the patient in the last month
4.	Digital ulcers	0.5	Presence of minor ulcers to necrosis of the fingers
5.	Vascular lesions	0.5	Raynaud's phenomenon, patient assessment within the last month
6.	Arthritis	0.5	Symmetrical swelling and pain of peripheral joints
7.	DLCO	0.5	< 80%
8.	Heart/lungs	2	Deterioration of cardiopulmonary function as assessed by the patient within the last month
9.	ESR	1.5	> 30 mm after one hour
10.	Hypocomplementemia	1	Decrease in complement C3 or C4 concentration

DLCO — diffusing capacity of the lungs for carbon monoxide; ESR — erythrocyte sedimentation rate

cations and thus disability and death. Early detection of organ lesions and appropriate implementation of treatment offers patients the chance to improve their quality of life (Tab. 2).

RECOMMENDED ORGAN-SPECIFIC THERAPIES

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is an abnormal contractile response of the blood vessels to cold temperatures or emotional stimuli. This disorder affects approximately 5% of the population and is slightly more common in women (11–20%) than in men (1–8%) [2]. It is classically marked by a 3-stage course.

Non-pharmacological management

Above all, patients should be informed about the nature of the disease and how to prevent its attacks. Patients should be advised to avoid provoking factors such as:

— emotional stress;
— consumption of beverages containing caffeine;
— smoking;
— the effect of contraceptive use on the occurrence of Raynaud's phenomenon.

The effects of drugs that cause vasoconstriction (clonidine, ephedrine, pseudoephedrine, bromocriptine, ergotamine, β-blockers and serotonin receptor antagonists) should be discussed with the patient and the use of amphetamine or cocaine should be absolutely prohibited. In addition, patients should be instructed on the principles of protection against exposure to low temperatures, which should consist of appropriate protection (warm clothing, wearing gloves) in winter, during changing weather conditions in other seasons or when using the refrigerator (at home, when shopping). The patient's attention should be drawn to the impact of occupational work in exposure to cold, vibration and finger trauma — these are definitely not recommended situations.

Importantly, the treating physician should also know what dietary supplements the patient is taking, as uncontrolled use of complementary therapies may cause pharmacological interactions.

Pharmacological management

The first-line therapy in SSc patients with Raynaud's phenomenon according to European Alliance of Associations for Rheumatology (EULAR) expert recommendations and French and UK recommendations should be a group of calcium channel antagonists. Given the accepted safety profile and long-term experience with this group of drugs [3–5]. The most effective in such cases are nifedipine and amlodipine that block calcium channels in the cell membranes of vascular wall smooth muscles and in the myocardium. As a result of the drugs, the influx of calcium ions into the cells is inhibited, which in turn leads to vasodilation and improved blood supply to the tissues [6]. The most commonly used preparations include nifedipine — 30 mg *p.o.*, amlodipine — 5 mg/day, diltiazem — 120 mg/day). If there is no improvement within 2 weeks of use, then the dose should be increased over 2–4 weeks to the highest dose, i.e., nifedipine — 90 mg/day, amlodipine — 20 mg/day, diltiazem — 360 mg/day, or to a lower dose if adverse effects occur.

As indicated in the literature, treatment with calcium antagonists may be associated

Table 2. Organ-specific treatment of systemic sclerosis (own elaboration based on [3, 5]

No.	Clinical manifestation	Treatment
1.	Skin involvement	Mycophenolate mofetil
		Cyclophosphamide
		MTX
		RTX
		TOC
		IVIG
		GCs
		Colchicine
		Cyclosporin A
		HSCT
2.	Raynaud's phenomenon	CCBs — nifedipine, amlodipine
		Prostacyclin analogues — iloprost, alprostadil
		Fluoxetine
		Phosphodiesterase-5 inhibitors: sildenafil (digital ulcer healing), tadalafil
		Topical nitrates
		a1-prazosin receptor antagonists
		ARB — losartan
		Statins
		ACEIs — captopril
		N-acetylcysteine
		Botulinum toxin
		Autologous fat grafting
		Sulodexide
		Surgical treatment
3.	Fingertip ulcers	CCBs — nifedipine, amlodipine
		Prostacyclin analogues — iloprost, alprostadil
		Endothelin A and B receptor antagonists: bosentan (prevention of new digital ulcers)
		Phosphodiesterase-5 inhibitors: sildenafil (digital ulcer healing), tadalafil
		Topical nitrates
		Platelet aggregation inhibitors for macroangiopathy
		Statins
		RTX
		Antibiotic therapy
		Pain treatment
		Surgical treatment
		Botulinum toxin
4.	Calcinosis	Minocycline
		Colchicine
		Ceftriaxone
		Probenecid
		Aluminium hydroxide
		IVIG
		Salicylates
		GCs
		ESWL
		CO2 laser
		Infliximab
		RTX

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5.	Lung involvement	Cyclophosphamide
		Mycophenolate mofetil
		GCs
		HSCT
		RTX
		TOC
		Nintedanib
		Oxygen therapy
		Lung transplantation
6.	Scleroderma renal crisis	ACEIs
		Intravenous CCBs
		Alpha-blockers
		Dialysis
		Kidney transplantation
7.	Heart involvement	NSAIDs/colchicine
		CCBs
		ACEIs or ARBs or angiotensin II inhibitors, -blockers,
		Diuretics
		Antiarrhythmics
		Defibrillator/artificial cardiac pacemaker
		Sometimes immunosuppressants or GCs in case of myocarditis
		Heart transplant
8.	Pulmonary arterial hypertension	Oxygen therapy
		Diuretics
		Endothelin receptor antagonists: bosentan, ambrisentan, macitentan
		Phosphodiesterase-5 inhibitors: sildenafil, tadalafil, riociguat
		Drugs affecting the prostacyclin pathway: epoprostenol, treprostinil, beraprost, iloprost, selexipag
		CCBs
		Lung or heart-lung transplantation
9.	Gastrointestinal involvement	Oesophagus: proton pump inhibitors, prokinetics (metoclopramide, domperidone)
		Stomach: proton pump inhibitors, erythromycin (125–250 mg × 2/day), clavulanic acid, prokinetics (metoclopramide, metopimazine)
		Small intestine: for motility disorders and/or pseudo-obstruction of the intestines: octreotide (50–100 μg/day)
		Large intestine: in case of constipation, balanced diet with fibre, adequate hydration, regular physical activity, laxatives and enemas, prokinetics for a limited time (metoclopramide, domperidone)
		Enteral and parenteral nutrition: in cases of severe small bowel damage or swallowing disorders
		Bacterial overgrowth of the small intestine: sequential antibiotic therapy (amoxicillin, metronidazole, fluoroquinolones, gentamicin, etc.).
10.	Musculoskeletal involvement	NSAIDS
		GCs
		Abatacept,
		RTX
		TOC
		Oral corticosteroid therapy
		Methotrexate
		Colchicine
		Azathioprine
		IVIG

CCBs — calcium channel blockers; ESWL — extracorporeal shock wave lithotripsy; GCs — glucocorticosteroids; HSCT — haematopoietic stem cell transplantation; IVIG — intravenous immunoglobulin; MTX — methotrexate; NSAIDs — non-steroidal anti-inflammatory drugs; RTX — rituximab; TOC — tocilizumab

with numerous side effects including hot flushes, facial flushing, palpitations, fatigue, headaches and peripheral oedema, and constipation [7]. Particular caution is required if blood pressure is very low.

The second group of applicable drugs are phosphodiesterase-5 (PDE-5) inhibitors, used primarily in patients who have not had a satisfactory response to treatment with calcium channel inhibitors or in patients with severe Raynaud's phenomenon. Some experts consider this group of drugs to be more effective and associated with a lower risk of adverse effects. It is advised to administer sildenafil (25–50 mg 2–3 times per day, starting with a dose of 12.5 mg/day and gradually increasing the dose with good tolerance) or tadalafil (20 mg/day). Side effects that may occur include hypotension, palpitations, tachycardia, temporary hearing loss, peripheral oedema, temporary visual disturbances. A meta-analysis of randomised clinical trials using PDE-5 inhibitors revealed that they were effective in reducing the incidence and severity of Raynaud's phenomenon [3]

According to studies, iloprost administered intravenously (0.3–3 ng/kg b.w./min for 3–5 days) reduces the frequency, severity and duration of Raynaud's phenomenon and promotes healing of ischaemic ulcers [8]. In two randomised clinical trials, iloprost (administered intravenously 0.5–2 ng/kg b.w./min for 3–5 days every 6–8 weeks) was found to be more effective than nifedipine (30–60 mg/day) in reducing the frequency of seizures and the severity of Raynaud's phenomenon [3]. An alternative is the use of another prostanoid, alprostadil (*i.v.* pulses of 20–60 μg every 4–6 weeks).

Despite the relatively low strength of evidence for efficacy, EULAR experts believe that fluoxetine 20 mg/day may be helpful in the treatment of Raynaud's phenomenon, especially in patients who cannot tolerate vasodilators. Attention should be paid to possible side effects including those associated with abrupt cessation of treatment [3].

Other forms of therapy include:

— **Topical nitrates** — nitroglycerin ointment 2% or transdermal patch 0.2 mg/h applied daily for 12 hours for 1 week.
— **Alpha-1 adrenergic receptor** antagonists (prazosin — 1–5 mg/day) — these drugs block the release of norepinephrine, which prevents vasoconstriction. Unfortunately they are usually poorly tolerated.
— **Angiotensin receptor blocker (ARB)** — losartan (25–100 mg/day, usually 50 mg/day) — the efficacy of losartan was significantly higher in patients with primary Raynaud's phenomenon than in patients with symptoms in the course of SSc.
— **Statins** — positive treatment effects were observed [2].
— **N-acetylcystain** — some studies revealed that it reduces the frequency and severity of Raynaud's phenomenon [2].
— **Botulinum toxin (BTX-A)** — some reports show benefit in patients with digital ischaemia, with or without ulceration [6]. The mechanism of action of BTX-A is most likely based on increasing blood flow, reducing pain sensation by blocking the effects of the sympathetic nervous system [9]. The use of BTX-A is a minimally invasive method with a low complication rate and appears to be an effective alternative therapy [10]. This therapy is currently recommended by the British Society of Rheumatology [4]
— **Autologous adipose tissue transplantation** — recent studies show the efficacy of this treatment, while it is required to use adipose tissue-derived stem cells during the procedure (they have a favourable cytokine profile favouring neovascularisation) [11].
— **Angiotensin-converting-enzyme inhibitors (ACEIs)** — captopril (20 mg/day) may be offered to patients intolerant of calcium channel blockers (CCBs) or in cases of concomitant pulmonary arterial hypertension (PAH). Captopril improves the blood supply to the skin but does not reduce the incidence of vasospasm episodes or the severity of symptoms. Enalapril, on the other hand, shows no therapeutic effect in Raynaud's phenomenon [8].
— **Pentoxifylline.**
— **Vitamin PP.**
— Sulodexide — has a prophylactic effect covering all 3 stages of the pathogenetic process in SSc (endothelial cell damage, inflammatory phase and fibrosis period); it improves vascular flow and has a protective effect on the endothelium. Oral preparations of sulodexide are used at 500 LSU per day in 2 divided doses and intravenously at 600–1200 LSU per day [12]. One paper described [13] the therapeutic use of sulodexide as an alternative drug (administered parenterally at 1 ampoule twice a day). Good treatment tolerance was ob-

served, and no adverse effects were noted. An analysis of this work and a review of the literature lead to the conclusion that this drug can be used in patients with Raynaud's phenomenon; the suggested dose is one ampoule every 12 hours for 3 or 4 days a week over 4–6 weeks [13].

— **Surgical treatment and other invasive procedures** — recommended only in the most severe cases of Raynaud's phenomenon after other therapies have failed [8]. One such procedure is sympathectomy, which involves blocking the nerves responsible for the vasculopathy.

— Alternative therapies such as **acupuncture** — insufficient data from clinical trials available at present.

PHALANGEAL ULCERS IN PATIENTS WITH SYSTEMIC SCLEROSIS

Damage to the microcirculation in patients with SSc results in the development of difficult-to-heal and painful ulcers on the fingertips, leaving behind so-called digital pitting scars. Progressive disruption of the blood supply to the distal phalanges leads to bone resorption and shortening of the phalanges, soft tissue necrosis and, in extreme cases, autoamputation [14]. Ulcer development is promoted by changes found in the course of sclerodermic microangiopathy leading to vasoconstriction, remodelling of the vessel wall, fibrosis and narrowing of the vessel lumen, which, together with imbalances in coagulation and fibrinolysis processes, impairs blood flow and promotes prothrombotic states. It is noteworthy that ulcers in SSc are decidedly chronic (healing takes a long time, 3–15 months) and recurring [15]. Also noteworthy is that approximately 4–6% of scleroderma patients also suffer from ulcers of the lower extremities with heterogeneous aetiology. They are usually found in patients with SSc with a long-term course. Leg ulcers in SSc are particularly difficult to treat; they are painful and negatively affect the quality of life and ability to work. According to the literature, ulcer infections were found in more than 2/3 of patients. Infection was most commonly caused by *Staphylococcus aureus* [2], and about 25% of cases were complicated by infection with enteric bacteria (*Escherichia coli* and *Enterococcus faecalis*) [2]. Infection often also involved bone and marrow [16]. Despite proper treatment, digital gangrene was observed in 22.6% of patients [15]. This complication was more common in dcSSc patients.

The treatment of ulcers in patients with SSc is difficult, requires a multidisciplinary therapeutic approach, and includes topical as well as systemic treatment (Tab. 3). Patients should be careful to avoid factors that exacerbate Raynaud's phenomenon, such as cold and stress, and should take proper care of their hands using barrier creams and protect their skin [5].

TOPICAL TREATMENT

Finger ulcers can be treated with nitrates but their use is limited. It is advisable to avoid topical antiseptics due to their cytotoxic effect,

Table 3. Vasodilators recommended for the prevention and treatment of digital ulcers in systemic sclerosis (own modification according to EULAR recommendations [3])

No.		Dosage
1.	Calcium channel blockers	Nifedipine 10–20 mg 3 times a day
		Amlodipine 5–20 mg/day
2.	Phosphodiesterase-5 inhibitors	Sildenafil 25–50 mg 2–3 times a day
		Tadalafil 20 mg every other day or every day for 8 weeks
3.	Angiotensin receptor blockers	Losartan 25–100 mg/day
4.	Selective serotonin reuptake inhibitors	Fluoxetine 20 mg/day
5.	α1-adrenergic receptor antagonists	Prazosin 1–5 mg twice daily
6.	Topical nitrates	2% nitroglycerin ointment 1/4–1/2 fingertip unit daily
7.	Prostanoids	Iloprost 0.5–2 ng/kg b.w./min *i.v.* for 3–5 days every 6–8 weeks
		Alprostadil 0.1–0.4 μg/kg b.w./min *i.v.* for 2–5 days every approx. 4–6 weeks
8.	Endothelin receptor antagonists	Bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily for 12 or 20 weeks

and it is best to use saline solution. Necrotic tissues can be removed mechanically or chemically (enzymatically, e.g. using preparations containing collagenase, papain, trypsin). The choice of dressings depends on the condition of the ulceration — in dry lesions, it is best to use dressings that create a moist environment (hydrocolloid and hydrogel dressings), and in ulcers with exudate — dressings with absorbent properties (hydrofibre dressings — hydrofiber-type dressings, alginate dressings, hydropolymer foam dressings) [17]. There was also a beneficial effect of vitamin E gel on the healing progress of digital ulcers.

VASCULAR TREATMENT

The cornerstone of pharmacological and non-pharmacological management of fingertip ulcers is treatment aimed at improving the vascular disorders associated with Raynaud's phenomenon, in the simplest terms, its effective treatment. In cases of progression of the condition (Raynaud's phenomenon) and ulcer formation, it is always necessary to optimise vascular therapy. This modification should depend on the severity of the symptoms. It should involve increasing the drug dose already in use, adding to it or replacing it with an alternative vasodilator/vasoconstriction inhibitor. A change of therapy is recommended every 3–6 weeks in the absence of clinical improvement. It is worth noting that vascular drugs play an important role in treating skin ulcers in a location other than the fingertips.

A recent meta-analysis of several randomised placebo-controlled clinical trials has shown that PDE-5 inhibitors accelerate ulcer healing [18]. Consequently, they occupy a special place in their treatment [18, 19] which is a direct result of their mechanism of action, as they are stimulators of soluble guanylyl cyclase responsible for cyclic guanosine monophosphate (cGMP) production and lead to an increase in nitric oxide. It inhibits vascular smooth muscle cell proliferation and induces vasodilation. As is well known, reduced nitric oxide production (due to endothelial cell dysfunction) is characteristic of scleroderma microvasculopathy. There are also reports that they may have the effect of reducing the risk of new ulcers — this can be observed with sildenafil as well as tadalafil. Their possible adverse effects include headache, nausea, facial flushing and jaw pain [3].

Intravenous drugs should be considered if oral therapies are ineffective, in refractory Raynaud's phenomenon or with the progression of trophic lesions of the fingertips. Such intensive in-patient treatment is always required in critical ischaemia of the distal phalanges.

Another group of drugs recommended for the treatment of finger ulcers are prostacyclin analogues (iloprost). In 2 randomised placebo-controlled clinical trials, intravenous prostanoids have been shown to be effective in healing finger ulcers [3, 20]. The mechanism of action of iloprost is twofold: it dilates blood vessels and inhibits platelet activity. Studies have shown that iloprost reduces the frequency, severity and duration of Raynaud's phenomenon and promotes the healing of existing ulcers. In particular, it should be emphasised that there is a toxic effect as the dose of iloprost increases. Adverse effects of prostanoids include facial erythema, diarrhoea, headache, drop in blood pressure and skin exanthema. Prostanoids administered orally have proven to be of limited efficacy [21].

In patients with multiple phalangeal ulcers who have not improved after treatment with calcium channel antagonists, PDE-5 inhibitors and prostanoids, endothelin 1 receptor antagonists and bosentan are indicated [18]. In patients with ulcerations over bony prominences and on the lower limbs, significant improvement was observed after using bosentan [19]. Bosentan has not been shown to be effective in the treatment of active finger ulcers; however, it has been shown to be effective in preventing the formation of new finger ulcers, especially in patients with a history of multiple finger ulcers (demonstrated in the RAPIDS-1 and RAPIDS-2). The most common medication regimen is: 62.5 mg twice a day for 4 weeks, then 125 mg twice a day for another 12 or 20 weeks [3]. It is important to be aware of the adverse effects of the preparation, including but not limited to hepatotoxicity, headaches, peripheral oedema, anaemia, teratogenicity of the drug or interactions with other drugs metabolised by cytochrome P450. A particular risk of interaction relates to oral contraception — bosentan may reduce its effectiveness.

Intravenous preparations of pentoxifylline and alprostadil may also be helpful in the treatment of ulcers.

ANTICOAGULANT AND ANTIPLATELET DRUGS

Taking into account the pathogenetic mechanism in SSc, where imbalances in coag-

ulation processes are also observed, it seems reasonable to use acetylsalicylic acid or clopidogrel in all patients with fingertip ulceration, necrosis of the fingers or peripheral arterial insufficiency [20], while short-term heparin therapy should be introduced in the case of acute ischaemia or during exacerbation of finger ischaemia [20]. The use of sulodexide as a method of preventing the risk of vascular thrombosis in SSc is reported extensively in the literature [22]. Its anticoagulant action is based on the inhibition of factor Xa and platelet aggregation and activation of the fibrinolytic system.

The long-term use of platelet aggregation inhibitors or oral anticoagulants in SSc depends on the individual indications. A thorough analysis of the benefits and potential losses should precede it.

Statins

Although there is insufficient evidence to support the efficacy of treatment with statins, it is worth considering these drugs as complementary therapy given their antioxidant, anti-inflammatory and antifibrotic effects.

Rituximab

Two scientific reports are worth noting here. The first concerns the healing of therapy-resistant phalangeal ulcerations after rituximab (RTX) treatment [23]. The second concerns its efficacy in 2/3 of patients with lower limb ulcers in the course of lSSc coexisting with cryoglobulinemia and vasculitis [24].

Antibiotic therapy

It should be reserved strictly for cases of ulcers with clinical signs of infection. It is worth noting that in chronic fingertip ulcers, however, this complication is common. Antibiotic therapy should then be started quickly, and the antibiotic should be selected based on the antibiogram. In cases of suspected central osteitis, antibiotic treatment should be administered intravenously.

Pain management

Fingertip ulcers are usually very painful for the patient. The perception of pain affects adrenergic receptors and can exacerbate vasospasm and ischaemia. Administration of acetaminophen is preferred, but sometimes opioid drugs are necessary; however, great caution should be exercised because there is evidence that they slow wound healing processes [25].

Surgical treatment

The indications for surgical intervention are relatively limited. They mainly involve surgical debridement in cases of gangrene to remove necrotic tissues or amputation of the necrotic finger. In therapy-resistant ulcers, it is advisable to consider allogeneic skin grafts.

Other methods

Beneficial outcomes have been described for treating phalangeal ulcers using hyperbaric oxygen therapy, negative pressure therapy, acoustic waves and intermittent pneumatic compression [26]. Trials of botulinum toxin in the prevention and treatment of fingertip ulcers are also reported in the literature, with promising results. Botulinum toxin has also been used in treating Raynaud's phenomenon, as discussed at the beginning of this article.

SOFT TISSUE CALCINOSIS

In some SSc patients, calcium deposits develop in the skin, causing local inflammation, secondarily leading to the development of ulcerations and fistulas of the skin [14, 27]. The most common locations for deposits are the fingers and the extensor surfaces of the elbow and knee joints. Severe calcinosis in the course of SSc is called the Thibierge–Weissenbach syndrome. Calcinosis is observed to be particularly common in people with anti-centromere antibodies present.

Various drugs have been tried to reduce skin calcification, but therapeutic effects have been mediocre and occurred only in isolated cases. Calcium channel antagonists are proposed as first-line drugs, with most studies investigating the use of diltiazem. Its action reduces the amount of calcium that fills cells and macrophages in damaged tissues; it is used at doses of 240–480 mg/day for 1–12 years [28, 29].

There are reports in the literature on the use of bisphosphonates, however, mainly in cases of concomitant osteoporosis. It is worth noting that data on their efficacy in reducing calcification are scarce [30]. Alendronate is used orally at 70 mg/week and pamidronate intravenously at 90 mg/week.

Warfarin has also been suggested to have a beneficial effect in the treatment of skin calcinosis [28, 29] — this applies to low-dose warfarin treatment (at 1 mg/day) in patients who have small and relatively recent calcifications.

Other drugs that have the potential to inhibit the accumulation of calcium deposits include the following:

— **Minocycline** — reduced skin calcinosis and associated inflammatory reactions and ulcerations were observed in a clinical trial conducted between 1994 and 2000 [31]. Its mechanism of action involves inhibiting metalloproteinases present in the intercellular substance, resulting in reduced inflammation; in addition, it chelates calcium. The drug is used at a dose of 50–100 mg/day.
— **Colchicine** — the most exploited property of colchicine is its ability to reduce inflammation around calcifications, rather than its ability to reduce the calcifications themselves; the risk of adverse effects with long-term use should be emphasised; these include diarrhoea, abdominal pain and numerous drug interactions.
— **Ceftriaxone** — affects metalloproteinases, chelates calcium and has anti-inflammatory effects. It is recommended to use at a dose of 2 g/day for 20 days.
— **Probenecid** — inhibits uric acid reuptake in the kidneys and increases phosphate secretion. It is used at a dose of 1.5 g/day.
— **Aluminium hydroxide** — can be used to reduce soft tissue calcinosis in patients with scleroderma and dermatomyositis [32].
— **Intravenous immunoglobulin (IVIG)** — a positive effect is reported in some scientific reports, including a case report of an lcSSc patient by Schanz et al. [33], who used IVIG treatment for 5 months, achieving complete regression of the lesions. It is customarily administered at a dose of 2 mg/kg body weight [29].
— **Salicylates.**
— **Glucocorticosteroids (GCs)** injected into different sites — used in lcSSc.
— **Extracorporeal shock wave lithotripsy** — a minimally invasive, safe and well-tolerated method; isolated cases of good patient response to this therapy have been described
— **CO2 laser** is used for the treatment of small and superficial deposits; it is a bloodless technique, and there have been cases reported in the literature of complete removal of deposits using this method.
— In severe cases, **surgical removal of deposits** may be useful.
— **Infliximab** — there are isolated reports, including one of a patient with SSc and polymyositis overlap syndrome and concomitant calcinosis who was treated with infliximab at 3 mg/kg administered intravenously at 0.2 and 6 weeks and every 8 weeks after that. After 41 months, a significant reduction in the size of calcifications and no development of new ones was described [34].
— **Rituximab** — appears to be the most promising of the therapies to date. During therapy with RTX, improvements have been observed in the resolution of calcinosis foci and pain in CREST syndrome [35]. Daoussis et al. described a case of an lcSSc patient with multiple deposits who had a significant reduction in the size of the calcifications and a significant improvement in pain one year after treatment. Two cycles of RTX were administered (4 weekly infusions at 375 mg/m^2 each) with an 18-month interval between each cycle [35]. Another case report concerns a female patient with lcSSc, who was treated for ILD and arthritis, incidentally achieving complete regression of deposits in her hands 7 months after treatment [36]. Giuggioli et al. described 10 cases of patients treated with one or more cycles of RTX (4 infusions of 375 mg/m^2 at weekly intervals). Due to ILD, skin or joint involvement, 3 of the 6 patients with calcium deposits had a significant reduction in deposits 6 months after the first treatment cycle. It continued to improve gradually over the following months [21]. There is also a report by Hurabielle et al., in which the researchers describe a case of a woman with deposits in the wrist area. In a patient who received two (2 weeks apart) infusions of RTX 1 g each for ILD and arthritis, progression of existing calcifications and formation of new deposits in other locations was observed [37].

SKIN INVOLVEMENT

The skin in SSc patients undergoes 3 phases: swelling, hardening and atrophy. The skin loses its elasticity, there is a loss of sweat and sebaceous glands as well as hair follicles and hair, and there may also be pigmentation and/or depigmentation of the skin. There may also be telangiectasias, especially of facial skin (also mucous membranes) and pruritus (mainly in dcSSc). The modified Rodnan skin score (mRSS) is used to assess the severity of skin lesions. This method involves assessing the thickness of the skin on a four-point scale by

palpation of 17 areas of the body. The total of all measurements is the final score, and it can range from 0 to 51.

The treatment of cutaneous scleroderma should be guided by the phase of the fibrotic process (early *vs.* late), disease activity and progression of fibrosis. General measures include protecting the skin from cold and trauma, skin care with moisturising creams, lymphatic drainage and active physiotherapy to prevent contractures. These general measures may suffice in mild, non-progressive forms of scleroderma.

The skin should be treated topically to ensure it is well hydrated. Moisturising and softening creams and lotions are recommended to be applied several times a day. Paraffin baths for hands or castor oil have not been thoroughly researched scientifically. Personalised physiotherapy with massages to soften the skin or subcutaneous tissues can be offered, although no studies have been conducted on this topic to date [5]. Antihistamines may be offered for pruritus. Additional treatment may include UV therapy.

METHOTREXATE

According to EULAR expert recommendations, methotrexate (MTX) (initially 15 mg/week *administered subcutaneously* for 24 weeks or 10 mg/week administered orally, then increasing the dose) is recommended as first-line therapy for cutaneous scleroderma. In case of adverse effects or ineffectiveness, intravenous mycophenolate mofetil (MMF) or cyclophosphamide (CYC), low-dose GCs or RTX may be used [3].

Two randomised controlled trials have shown that MTX reduces skin fibrosis in early dcSSc. A positive effect on other organs, such as the lungs, has not been demonstrated [38, 39]. The recommended dose should not exceed 0.3 mg/kg/week, administered orally or subcutaneously. There is no set duration of treatment, but in case of clinical improvement, treatment for at least 2 years is recommended [5]

MYCOPHENOLATE MOFETIL

The use of MMF is recommended by the EULAR Scleroderma Trials and Research (EUSTAR) group as second-line therapy after MTX. The recommended standard dose is approximately 1–2 g/day (target 2–3 g/day if treatment is well tolerated) for at least 2 years [40].

In the Scleroderma Lung Study-II (SLS-II), MMF use was associated with a reduction in the mRSS after 24 months. An analysis of the SLS-II *vs.* placebo Scleroderma Lung Study-I (SLS-I) group would suggest that MMF use was associated with an improvement in the mRSS compared with the placebo group at 24 months.

Reports from US researchers at Thomas Jefferson University (Philadelphia, USA) indicate that more than a quarter of patients with rapidly progressive dcSSc who discontinue MMF therapy or have their drug dose reduced experience progression of skin lesions over the following 5 years.

CYCLOPHOSPHAMIDE

An analysis of the results of 85 SLS-I patients with dcSSc who received CYC for 12 months showed a significant improvement and difference in the mRSS compared with a placebo group [41]. In the SLS-I, oral CYC resulted in a reduction in the mRSS, which was significant after 12 months of assessment. This effect disappeared one year after the discontinuation of CYC. Cyclophosphamide is recommended after the failure of MTX and MMF due to the high incidence of adverse effects [40]. According to EULAR recommendations, CYC should be considered, particularly in patients with progressive ILD. It also appears to be a drug worthy of consideration for rapidly progressive skin lesions in dcSSc. The dose and duration of CYC treatment should be considered individually depending on the clinical condition and response to treatment. The potential risk of bone marrow inhibition, teratogenic effects, gonadal failure and haemorrhagic cystitis should always be considered.

GLUCOCORTICOSTEROIDS

The systemic use of GCs, which is considered standard therapy for most autoimmune diseases, does not play a role in the treatment of fibrosis in patients with SSc [3]. In addition, glucocorticosteroid treatment is associated with an increased risk of scleroderma renal crisis (SRC).

INTRAVENOUS IMMUNOGLOBULIN

Numerous papers reported a significant reduction in skin involvement, although most reports had no control groups or a small number of patients [40]. It is worth mentioning that IVIG may be an effective adjunctive therapy, along with other immunosuppressive therapies, for the treatment of active dcSSc in

patients in whom other therapies have failed. The detailed results of the therapy used in improving the patient's skin thickening are described in a 2015 article [42].

COLCHICINE

There appears to be no basis for using colchicine to treat cutaneous lesions in SSc. Evidence for its efficacy is lacking, and the risk of adverse effects with long-term use of high doses is high.

CYCLOSPORIN A

The use of cyclosporine in scleroderma patients is controversial, mainly due to the potential nephrotoxicity of this drug. However, cyclosporine used long-term at doses of 1.5–5 mg/kg b.w./day was found to reduce cutaneous sclerosis to some extent. It was not found to have a significant effect on organ changes.

RITUXIMAB

There are very numerous reports of beneficial effects of RTX on the skin in SSc. The beneficial effects of RTX on the respiratory system and skin are confirmed by an observational study conducted under the aegis of the EUSTAR group of 63 patients and the control group of 25 patients. In most cases, RTX was administered in 2 intravenous infusions of 1000 mg, 2 weeks apart. After a follow-up period of approximately 7 months in the RTX-treated group, the mean forced vital capacity (FVC) did not change significantly compared to the decrease in FVC in the control group. The mRSS decreased by an average of approximately 15%. In the group of patients with the most severe lesions according to the mRRS — the score above or equal to 16 – the decrease in the mRSS was even more significant [43].

In another retrospective EUSTAR study, 248 patients were randomised; the indication for RTX treatment was lung involvement, joint symptoms and skin involvement. Over the course of the study, the mean mRSS decreased from 15 to 10, and FVC improved. The number of painful and swollen joints decreased in patients with joint symptoms [44].

Daoussis et al. studied 8 patients who received 4 cycles of RTX. Each cycle consisted of 4 weekly infusions of RTX (375 mg/m^2), with a follow-up of 2 years. Improvements in skin tone were observed, as well as improvements in skin histopathology — in the form of a reduction in skin collagen deposits and myofibroblast score [45, 46]. Similar observations were made by Smith et al. [47] and Lafyatis et al. [48], who showed a close relationship between the number of myofibroblasts and the mRSS, which confirms the role of these cells in skin fibrosis. The number of myofibroblasts decreased in both studies after RTX treatment. In addition to the apparent improvement in the mRSS during RTX therapy, there is also a reduction in the severity of other skin symptoms, including hypermelanosis, pruritus and calcinosis.

TOCILIZUMAB

High levels of interleukin 6 are found in both skin and serum of patients with SSc. A correlation has been shown between interleukin 6 levels and the severity of skin lesions. The efficacy of the therapy in SSc has been demonstrated in 2 double-blind clinical trials: the focuSSed study and the faSScinate study. The first study covered 212 patients — 105 received TOC and 107 received placebo, with no significant change in mean FVC in the TOC group. While it was reduced in the placebo group, no significant differences were found between the 2 groups in the skin assessment. The second study found subjective but not statistically significant improvement in FVC and mRSS values in the group treated with TOC [49, 50]. There are more reports that skin lesions may resolve after TOC treatment [51, 52].

SUMMARY

The recommendations are based on contemporary literature and take into account elements of current recommendations from other scientific societies, including dermatological societies, EULAR Scleroderma Trial and Research Group recommendations [3], British recommendations [4], French recommendations [5], and European Society of Cardiology recommendations.

In each case, treatment should be tailored to the individual needs of the patient, the clinical form of the disease, the stage of the disease, and organ complications. Treatment of patients should include not only pharmacology but also patient and family education.

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AUTHOR CONTRIBUTIONS

The authors declared that the percentage contribution to the manuscript is as follows: MB 70%, MKM 10%, OGS 10%, KP 5%, PK 5%.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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