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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 5. Treatment of patients with systemic sclerosis characteristics and treatment recommendations for interstitial lung disease, cardiac involvement, pulmonary arterial hypertension, musculoskeletal, gastrointestinal and renal involvement

ABSTRACT

Systemic sclerosis (SSc) is a systemic connective tissue disease characterised by disseminated 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 induration of the skin all over her body. The disease is a rare condition, with an estimated 1 in 10 000 people in Poland suffering from SSC. Women predominate among patients, with a 3–4-fold advantage over men. The disease typically has its onset between the ages of 30 and 50. Early detection and treatment of organ complications are key to improving quality of life and reducing mortality in SSc patients. Given the considerable variability of the clinical course, it seems justified to take an individual approach to patients and cooperate with multiple specialists, both at the stage of diagnosis and at the stage of treatment. Treatment is based on what is known as an organ-specific strategy and consists of tailoring pharmacotherapy to the clinical presentation, disease period and organ complications. In addition to pharmacology, the treatment of patients should also include education of the patient and their family, and — if necessary — surgical treatment or other necessary interventions.

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KEY WORDS: systemic sclerosis; recommendations; treatment; management; rituximab; nintedanib; tocilizumab

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INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease with involvement of internal organs, most commonly the lungs and kidneys, skin fibrosis and microvascular abnormalities. Genetic background, autoimmune disorders, abnormalities in collagen synthesis and environmental factors are considered in the pathogenesis.

According to LeRoy et al., the classification of SSc — in force since 1988 — distinguishes two main clinical forms of the disease, taking into account the extent of induration of skin, i.e. SSc with limited cutaneous sclerosis (lcSSc) and SSc with diffuse cutaneous sclerosis (dcSSc). Induration of skin in the form of lcSSc involves hands, feet, forearms, and lower legs but does not extend beyond the elbows and/or knees. Induration of skin in the form of dcSSc extends proximally to the elbows and/or knees and involves the trunk. The disease in both forms may involve facial skin. Importantly, from a treatment point of view, the two forms of SSc differ in the dynamics of development, the timing of Raynaud's phenomenon, the immunological profile, the type of organ complications and the survival rate of patients. The heterogeneity of the disease is the reason for the constant search for and raising questions about a new classification of forms of the disease. The proposed amendment should take into account, in addition to the extent of skin involvement, the immunological profile of the patient, the molecular profile of skin lesions (inflammatory, fibroproliferative, normal), genetic variability, sex and stage of disease. Taking the above factors into account may help to provide the patient with a personalised — targeted — treatment.

The disease has a high mortality rate due to numerous complications and the lack of effective targeted treatment [2]. It is marked by a highly variable clinical picture due to the different rate of progression and type of organ complications. At present, there are no drugs that may effectively delay the progression of the disease in all patients.

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

TREATMENT OF SSC PATIENTS

Treatment should be decided on an individual basis for each patient after the analysis of the severity of skin lesions, duration of the disease, disease activity, complaints, and changes in internal organs.

RECOMMENDED ORGAN-SPECIFIC TREATMENT

Due to the lack of universal disease-modifying drugs and given the significant clinical heterogeneity, the treatment of SSc is based on so-called organ-specific therapy. This method is based on the use of drugs with proven or probable efficacy for the treatment of specific organ complications in patients with these complications. It is an organ-specific intervention aimed at protecting the organ, possibly initiating early treatment of emerging pathologies and possibly remodelling changes that have already occurred, 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 specific disease entity. Organ-specific therapy in the course of SSc should also include education of the patient and their family, physiotherapy treatments and kinesitherapy (as prevention of joint contractures in joint complaints and myopathy), occupational therapy and psychotherapy.

Early detection of organ lesions and early implementation of appropriate treatment improve patients' quality of life (Tab. 1).

RECOMMENDED ORGAN-SPECIFIC THERAPIES

INTERSTITIAL LUNG DISEASE (ILD)

Respiratory involvement is currently the leading cause of death in SSc. Clinical manifestations are dyspnoea on exertion and dry cough. The progression of the disease leads to respiratory failure and the development of right heart failure (pulmonary heart disease). The decision to choose therapy for ILD in the course of SSc should be based on an individual analysis of the severity and activity of the lung disease, and the balance of potential benefits and risks of treatment.

Before the treatment of ILD is initiated, it is necessary to assess the severity of ILD based on the assessment of dyspnoea. Other useful tests include the 6-minute walk

test (6MWT), saturation evaluation, pulmonary function tests: forced vital capacity (FVC) and total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLCO) and chest high-resolution computed tomography (HRCT) — extent of lesions in % and their characteristics: ground glass/honeycomb/bronchodilatation. Treatment depends

Table 1. Organ-specific treatment of systemic sclerosis (SSc) [own elaboration based on European League Against Rheumatism (EULAR) recommendations and French guidelines]

Clinical manifestation	Treatment
Skin involvement	Mycophenolate mofetil
	Cyclophosphamide
	Methotrexate
	Rituximab
	Tocilizumab
	IVIG
	Glucocorticosteroids
	Colchicine
	Cyclosporine A
	HSCT
Raynaud's phenomenon	Calcium channel antagonists — nifedipine, amlodipine
	Prostacyclin analogues — iloprost, alprostadil
	Fluoxetine
	Phosphodiesterase-5 inhibitors: sildenafil (digital ulcer healing), tadalafil
	Topical nitrates
	Alpha-1 receptor antagonists — prazosin
	Angiotensin receptor blocker — losartan
	Statins
	Angiotensin-converting enzyme inhibitors — captopril
	N-acetylcysteine
	Botulinum toxin
	Autologous fat grafting
	Sulodexide
	Surgical treatment
Fingertip ulcers	Calcium channel antagonists — nifedipine, amlodipine
	Prostacyclin analogues — iloprost, alprostadil
	Endothelin-A and endothelin-B receptor antagonists: bosentan (prevention of new digital ulcer formation)
	Phosphodiesterase-5 inhibitors: sildenafil (digital ulcer healing), tadalafil
	Topical nitrates
	Platelet aggregation inhibitors for macroangiopathy
	Statins
	Rituximab
	Antibiotic therapy
	Analgesic treatment
	Surgical treatment
	Botulinum toxin

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Calcinosis	Minocycline
	Colchicine
	Ceftriaxone
	Probenecid
	Aluminium hydroxide
	IVIG
	Salicylates
	Glucocorticosteroids
	ESWL
	CO2 laser
	Infliximab
	Rituximab
Lung involvement	Cyclophosphamide
	Mycophenolate mofetil (MMF)
	Glucocorticosteroids
	HSCT
	Rituximab
	Tociclizumab
	Nintedanib
	Oxygen therapy
	Lung transplantation
Scleroderma renal crisis	Angiotensin-converting enzyme inhibitors
	Intravenous calcium channel blockers
	Alpha-blockers
	Dialysis
	Kidney transplantation
Cardiac involvement	NSAIDs/colchicine
	Calcium channel blockers
	Angiotensin II-converting enzyme inhibitors or angiotensin II receptor blockers or angiotensin II inhibitors, beta-blockers
	Diuretics
	Antiarrhythmic drugs
	Defibrillator/cardiac pacemaker
	Sometimes immunosuppressants or glucocorticosteroids in case of myocarditis
	Heart transplantation
PAH	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
	Calcium channel blockers
	Lung or heart-lung transplantation

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Table 1. Organ-specific treatment of SSc (own elaboration based on European League Against Rheumatism [EULAR] recommendations and French guidelines)

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: octreotide (50–100 μg/day) in case of intestinal motility disorders and/or intestinal pseudo-obstruction
	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 case of severe small bowel damage or difficulty in swallowing
	Small intestinal bacterial overgrowth (SIBO): sequential antibiotic therapy (amoxicillin, metronidazole, fluoroquinolones, gentamicin, etc.).
Musculoskeletal involvement	NSAIDS
	Glucocorticosteroids
	Abatacept,
	Rituximab
	Tocilizumab
	Corticosteroid therapy *p.o.*
	Methotrexate
	Colchicine
	Azathioprine
	IVIG

IVIG — intravenous immunoglobulin; HSCT — haematopoietic stem cell transplantation; ESWL — extracorporeal shock-wave lithotripsy; NSAIDs — non-steroidal anti-inflammatory drugs; PAH — pulmonary arterial hypertension; *p.o.* — *per os*

on the progressive nature (or not) of the ILD. The duration of ILD, the extent of the lesions and the type of lesions on CT scan, as well as subjective symptoms such as dyspnoea, should also be considered in the choice of treatment. The classification proposed by Goh et al. may be used to assess the severity of ILD: limited ILD if the extent of CT abnormalities is < 20% of the lung surface area (or FVC ≥ 70% when CT coverage is indeterminate); diffuse ILD when FVC < 70% or if the extent of CT abnormalities exceeds 20% of the lung surface area.

Regardless of the criteria used, before considering specific ILD treatment, it is also important to do a discernment of the patient's comorbidities that may impair function and will not respond to ILD treatment, such as pulmonary embolism, severe anaemia, etc.

Observations of ILD patients indicate that approximately 30% of patients experience ILD progression in the first 12 months [3]. A patient diagnosed with ILD should undergo continuous monitoring, which includes assessment of symptoms (exercise tolerance, cough severity), pulmonary function tests and, if warranted, chest HRCT. It seems reasonable to schedule clinical and functional assessment (spirometry, diffusion) every 3–6 months and radiological assessment (HRCT) every 1–2 years. It is common to establish a monitoring cycle on an individual basis.

Symptomatic treatment includes:

— complete and definitive smoking cessation and avoidance of passive exposure to tobacco smoke;
— vaccination: annual influenza and pneumococcal vaccination is recommended for all patients with confirmed ILD, and COVID-19 vaccination remains to be considered [4];
— optimisation of the treatment of gastroesophageal reflux disease (GERD), a potential exacerbating factor of ILD;
— oxygen therapy: similar to other causes of chronic respiratory failure. Long-term oxygen therapy (LTOT) is recommended for severe respiratory failure defined by the partial pressure of oxygen in arterial blood (PaO2) ≤ 55 mm Hg (7.3 kPa) or PaO2 between 55 and 60 mm Hg (7.3–8.0 kPa) with at least one of the following criteria: polycythaemia (haematocrit > 55%). Signs of pulmonary hypertension and signs of right heart failure (RHF) [4];

— respiratory rehabilitation;
— treatment of cough: there are no precise recommendations for the treatment of cough associated with ILD. The first step is to rule out GERD. There are no studies on inhaled corticosteroids; their use in treatment is an individual decision [4].

TARGETED TREATMENT

The essential treatment for SSc-associated ILD is immunosuppressive therapy.

CYCLOPHOSPHAMIDE

The indication for the implementation of oral (*p.o.*) or intravenous (IV) cyclophosphamide (CYC) for 6–12 months are cases of ILD with a severe, progressive course, which are unresponsive to treatment with mycophenolate mofetil (MMF). CYC was found to improve FVC in ILD patients. The improvement was accompanied by a significant reduction in dyspnoea and disability index assessed by the Health Assessment Questionnaire (HAQ), while there was no significant improvement in DLCO. Several randomised trials on ILD revealed that patients treated with CYC had a slower decline in FVC after one year of treatment compared with the placebo group. A study evaluating the efficacy of 2 years of MMF therapy compared to 1 year of CYC therapy revealed a comparable effect of both drugs with less toxicity of the former [5].

The dose of CYC is 0.7 g/m^2 or 0.5 g/m^2 in patients aged over 65 . or those with a glomerular filtration rate (GFR) below 30 ml/min/m^2, every 28 days for 12 months. The dose of CYC is limited to 1200 mg/injection. Whenever CYC is used, the balance of benefits and risks should be considered. According to European League Against Rheumatism (EULAR) recommendations, the dose and duration of treatment should be determined individually. Due to similar efficacy and a much lower cumulative dose of the drug, intravenous infusions appear to be preferable to oral treatment [4, 6].

French recommendations emphasise the need to prevent *Pneumocystis jiroveci* infection — this involves the use of trimethoprim 80 mg/day + sulfamethoxazole 400 mg/day (or trimethoprim 160 mg + sulfamethoxazole 800 mg 3 times a week). If the patient is allergic to sulphonamides, aerosol pentamidine (300 mg/dose) may be administered every 3 or 4 weeks or oral atovaquone (1500 mg/day) [4].

MYCOPHENOLATE MOFETIL (MMF)

In the randomised, double-blind SLS-II trial, MMF was found to be as effective as CYC in the treatment of ILD patients in the course of SSc. Mycophenolate mofetil (MMF) was administered *per os* (*p.o.*) at a target dose of 3 g/day for 2 years while CYC was administered at a target dose of 1 to 2 mg/ kg bw per day for one year. The follow-up period was 2 years. It was also revealed that both drugs improved skin lesions to a similar extent. MMF was better tolerated than orally administered CYC [6]. MMF has significantly less toxicity and is better tolerated by patients. It follows from the above that MMF may be an alternative as first-line treatment.

GLUCOCORTICOSTEROIDS (GCS)

Some experts recommend the use of low-dose corticosteroids in combination with CYC or MMF. Given the risk of renal breakthrough in SSc patients, corticosteroids are recommended at a dose of ≤ 15 mg/day of oral prednisone [4].

HAEMATOPOIETIC STEM-CELL TRANSPLANTATION (HSCT) OF THE BONE MARROW

Results from two randomised trials indicate that high-dose CYC treatment with subsequent HSCT improves lung vital capacity compared with standard CYC therapy. Moreover, this treatment is associated with improved long-term survival of SSc patients.

TOCICLIZUMAB (TOC)

An interesting new therapeutic option in ILD is the use of TOC, the administration of which was associated with a statistically significant reduction in lung function impairment (inhibition of FVC decline). The resulting data allowed the U.S. Food and Drug Administration (FDA) to register TOC administered subcutaneously (SC, sub cutem) in 2021 in SSc-ILD patients [4].

The results of two randomised double-blind trials on TOC in the treatment of patients with early active dcSSc revealed an improvement in skin lesions and a significant improvement in FVC in patients treated with TOC compared with placebo (the focuSSed trial and the faSScinate trial discussed when treating skin involvement). When other therapies fail, TOC may prove to be the treatment of last resort for a SSc patient.

RITUXIMAB (RTX)

Rituximab (RTX) is another promising biologic used so far in patients with rheumatoid arthritis (RA) that appears to be effective in the treatment of SSc-associated ILD. In a small Japanese trial, rituximab improved both skin condition (reduction in the modified Rodnan skin score [mRSS]), FVC and lung radiographs [7]. A retrospective study by Naidu and Sharma, which enrolled 11 patients who had primary or secondary CYC failure and each patient received two doses of RTX (each 1000 mg) two weeks apart, revealed improvement/stabilisation in FVC after one year of follow-up [8]. Another study confirming the beneficial effect of RTX on the respiratory system is an observational study conducted under the aegis of the European Scleroderma Trials and Research Group) (EUSTAR), which included 63 patients [9]. Another retrospective study, which was also conducted under the aegis of the EUSTAR, revealed improvement in FVC.

ACETYLCYSTEINE, AZATHIOPRINE (AZA), PIRFENIDONE

Acetylcysteine (*p.o.* at a dose of 3 x 600 mg per 24 hours) in combination with azathioprine (AZA) was found to be effective in the treatment of patients with idiopathic pulmonary fibrosis (IPF). It has been postulated that pirfenidone — an antifibrotic drug that was first registered for the treatment of IPF patients — may have similar potential to nintedanib in terms of slowing down fibrosis in fibrosing ILDs other than IPF, including SSc-ILD. However, pirfenidone is now only registered for the treatment of IPF.

NINTEDANIB

Patients with progression of IPF should be immediately eligible for antifibrotic treatment with nintedanib — this therapy has been reimbursed for Polish patients since 1 July 2022 under the National Health Fund (NHF) drug programme (B.135 drug programme).

The SENSCIS trial, which is a randomised and placebo-controlled study lasting 52 weeks, demonstrated the clinically relevant efficacy of nintedanib in inhibiting FVC decline in SSc-ILD patients (compared with the placebo group) [10]. In the SENSCIS-ON trial, nintedanib was continued in willing patients who participated in the SENSCIS trial to assess safety and long-term tolerability — a similar safety profile was observed to the 52-week therapy, and an inhibitory effect on progression of interstitial lesions was demonstrated over three years of ongoing therapy. It is noteworthy that the smallest FVC declines were observed in patients who additionally took MMF [11, 12].

Eligibility criteria for treatment in the drug programme include meeting one of the following a–c criteria:

a) fibrotic lesions on HRCT occupy at least 10% of the lung volume and the following were documented:
— a decline in FVC of at least 10%
or
— a decline in FVC of at least 5% and a decline in TLCO of at least 15%, despite MMF or CYC therapy, if their use is not contraindicated and there are no restrictions on their use, each of which has been used in accordance with current recommendations for at least 6 months or less in case of intolerance or adverse effects,
or
b) fibrotic lesions on HRCT occupy at least 10% of the lung volume and FVC is < 70% of the normal value
or
c) fibrotic lesions on HRCT occupy at least 20% of the lung volume, and meeting both of the following d-e criteria:
d) FVC ≥ 40% of the normal value,
e) TLCO greater than 30% of the reference value.

The recommended dose of nintedanib is 150 mg twice daily, administered at approximately 12-hour intervals. A dose of 100 mg twice daily is recommended for use only in patients who cannot tolerate a dose of 150 mg twice daily. In the INPULSIS trial, diarrhoea was the most common gastrointestinal (GI) adverse reaction reported by 62.4% of patients. In the majority of patients, this adverse effect was mild to moderate in severity and occurred during the first three months of treatment.

LUNG TRANSPLANTATION

In selected cases where ILD progresses and the patient has no contraindications, lung transplantation should be considered. In daily practice, lung transplantation is rarely performed in SSc patients. Factors that affect a worse prognosis for survival after lung transplantation are female sex and the presence of pulmonary hypertension (when both factors were present, the risk of death was high-

er). The group of SSC patients is still a group at high risk of failure.

PULMONARY ARTERIAL HYPERTENSION (PAH)

Pulmonary arterial hypertension (PAH) is one of the most severe complications of SSc, developing in approximately 12% of patients. PAH not only leads to a significant deterioration in exercise tolerance but also accounts for 50% of patient mortality within three years of diagnosis. Symptoms heralding the onset of PAH may include severe vascular involvement in the form of the frequently occurring Raynaud's phenomenon, the presence of digital ulcers, multiple telangiectasias, myocardial involvement and renal complications.

According to current European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, all asymptomatic patients with SSc and connective tissue diseases at risk of developing scleroderma should be monitored for the development of PAH. Any SSc patient with suspected pulmonary hypertension needs to have their indication determined for right heart catheterisation (RHC), which is the only examination to confirm the diagnosis of pulmonary hypertension [13].

Recommended monitoring tests include transthoracic echocardiography, DLCO and N-terminal pro-brain natriuretic peptide (NT-proBNP) determination early in the course of the disease. Echocardiography should be repeated annually. Based on the statistical analysis of the results obtained in the DETECT study, an algorithm was developed for the diagnosis of PAH in SSc, which is available online (https://detect-pah.com/pah-risk-calculator/calculator-step-1). This algorithm is not recommended for monitoring patients with DLCO > 60%. Treatment of PAH is always done at a reference centre — a list of centres is available online (https://www.skp.ptkardio.pl/osrodki_dorosli/, https://www.skp.ptkardio.pl/osrodki-dzieci/) [13].

For secondary forms of pulmonary hypertension, treatment of the primary cause (e.g. ILD) and symptomatic management are recommended.

GENERAL RECOMMENDATIONS AND FOLLOW-UP TREATMENT

General recommendations and complementary therapy include:

— encouraging patients to be physically active if there are no medical contraindications;
— mandatory influenza and pneumococcal vaccination; COVID-19 vaccination.
— considering regular monitoring of iron levels in PAH patients, and when iron deficiency is detected — searching for the cause and considering iron supplementation in patients with iron deficiency [4];
— initiating passive oxygen therapy when the oxygen partial pressure of arterial blood is reduced < 60 mm Hg or when the arterial blood oxygen saturation is < 91%;
— educating the patient on knowledge of PAH [4];
— avoiding (by the patient) staying at altitudes above 1500–2000 m a.s.l. without oxygen supplementation;
— in PAH patients with symptoms of right ventricular failure (RVF) and fluid retention — administration of diuretics, the choice and dosage of which should be considered individually;
— during elective surgical procedures, epidural anaesthesia should be preferred to general anaesthesia whenever possible [4];
— the administration of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta-blockers and ivabradine is generally contraindicated in PAH patients, unless comorbidities are present (e.g. hypertension, coronary artery disease or left ventricular failure) [4];
— anticoagulant treatment was not revealed in trials to have a survival benefit in SSc-associated PAH. They are not advised to be used routinely for PAH alone, but only when indicated [4].

It should be noted that bosentan and sitaxentan affect the metabolism of warfarin. When the patient is already taking warfarin and therapy with any of the above-mentioned drugs is initiated, the measurement of coagulation parameters should be intensified [4, 13].

SPECIFIC TREATMENT OF PAH

Under the NHF drug programme for the treatment of PAH in Poland, it is possible to use bosentan, macitentan, sildenafil, riociguat, epoprostenol (IV), iloprost (inhalation), treprostinil (SC) and selexipag. All these drugs have a vasodilatory effect and lower pulmonary artery pressure but also have an antiproliferative effect. Prostacyclins used parenterally have the strongest effect; in addition, they are the most potent endogenous inhibitors of platelet aggregation.

Three groups of drugs are used in the treatment of PAH:

— drugs that affect the **endothelin pathway**: endothelin receptor antagonists (ERAs). In trials, therapy with endothelin receptor antagonists was revealed to significantly improve exercise capacity, survival time and some haemodynamic parameters in PAH patients. Adverse effects should be noted. In addition to their hepatotoxic and teratogenic effects, these drugs may cause peripheral oedema, palpitations, headache, chest pain, swelling of nasal mucous membranes, and anaemia. Drugs in this group include ambrisentan, bosentan and macitentan [4, 13]:

a) **bosentan** — an endothelin-A and endothelin-B receptor antagonist. The drug is administered orally, starting at a dose of 62.5 mg twice a day and increasing after 4 weeks to 125 mg twice a day. Bosentan should not be used in combination treatment with sildenafil due to possible interactions. Monthly liver function tests and routine haemoglobin monitoring are mandatory during treatment,

b) **ambrisentan** — acts selectively on the endothelin-A receptor. It is less likely than bosentan to cause liver enzyme elevations. It is well tolerated at a dose of 5 mg once daily *p.o.* and may be increased to 10 mg daily. Monthly liver function tests are recommended but not mandatory. A complete blood count (CBC) every 1–3 months is also recommended. Ambrisentan is contraindicated in cases of IPF; however, there are no data on SSc-associated ILD.

— drugs affecting the **nitric oxide pathway**: phosphodiesterase type 5 (PDE-5) inhibitors. The action of the drugs in this group is through selective inhibition of cGMP-phosphodiesterase (PDE) type 5. This results in increased intracellular levels of cyclic guanosine monophosphate (c-GMP). Under the influence of elevated levels of this nucleotide, vascular smooth muscle cells (VSMCs) relax. High levels of PDE type 5 are found in the pulmonary vasculature, so the use of inhibitors is beneficial in pulmonary hypertension. Results of trials revealed that PDE-5 inhibitors (sildenafil and tadalafil) also improve physical fitness and prevent disease progression. The following adverse effects were observed: facial flushing, dyspepsia, diarrhoea, headaches, and muscle pain. Drugs in this group include sildenafil, tadalafil, vardenafil and stimulators of soluble guanylyl cyclase (sGC) — riociguat [4, 13]:

a) **sildenafil** — several trials described the beneficial effects of this drug in PAH patients. The drug was registered at a dose of 20 mg administered three times a day *p.o.*; however, in terms of practicality, the dosage often needs to be increased to 80 mg three times a day to achieve a long-term treatment effect,

b) **tadalafil** — administered once daily. There is no specific biological monitoring for these therapies,

c) **riociguat** — a soluble guanylyl cyclase (sGC) stimulator; trials found that this drug used in PAH therapy, like the previously discussed drugs, improved physical fitness, haemodynamic parameters and prevented disease progression in SSc patients. Adverse effects may include syncopes, elevated levels of liver enzymes, dizziness, acute renal failure, and decreased blood pressure;

— drugs affecting the **prostacyclin pathway:** prostacyclins. In trials of patients with severe PAH, IV epoprostenol was found to significantly reduce pulmonary vascular resistance, effectively improving exercise capacity and haemodynamic parameters. Other prostacyclin analogues (iloprost, treprostinil) had a similar effect. Possible adverse effects include headaches, mandibular pain, abdominal pain, arthralgia, and diarrhoea [4]. Drugs in this group include beraprost, epoprostenol, iloprost, treprostinil and the prostacyclin IP receptor agonists — selexipag [4, 13]:

a) **epoprostenol** — the drug should be administered continuously using a pump due to instability of the molecule. In emergency situations, it may be administered via a peripheral vein for a short period of time. It is started at a dose of 2–4 ng/kg/min and the dosage is increased if no adverse effects occur; in most patients, the optimal dose is 20–40 ng/kg/min. Adverse effects include emesis, anorexia, hypersensitivity to sunlight and erythema. It is the reference treatment in severe forms of PAH;

b) **iloprost** — may be administered in oral, intravenous and inhaled forms. It was revealed to improve physical fitness, with beneficial effects on symptoms. The drug is well tolerated. Possible adverse effects

are usually erythema, mandibular pain, and pain in the maxillofacial area;

c) **treprostinil** — an analogue of epoprostenol, but more stable, and may be administered both intravenously and subcutaneously. Trials revealed improvements in physical fitness, haemodynamics and symptoms. The most common adverse effect was pain at the infusion site. Treprostinil is administered by continuous *s.c.* infusion into the subcutaneous tissue area of the abdomen and the dosage of the drug is based on body weight. Initially, 1.25 ng/kg/min is administered and a good effect is obtained at a dose of approximately 15–20 ng/kg/min;

d) **selexipag** — a selective prostacyclin receptor agonist, administered orally. It is prescribed in ascending doses over several weeks up to the maximum tolerated dose, up to a maximum of 1600 μg 2 per day. Monitoring for adverse effects is necessary: headaches, hot flushes, digestive disorders, etc.

CALCIUM CHANNEL BLOCKERS

There are no recommendations for the use of calcium channel blockers in the treatment of SSc-associated PAH. As many patients are treated with calcium channel blockers for Raynaud's phenomenon or digital ischaemia, these may be continued for PAH. However, it should be noted that these blockers should be used in low doses and provided that a calcium channel blocker that does not cause bradycardia is chosen (hence amlodipine or nifedipine rather than diltiazem or verapamil) [4].

LUNG OR HEART-LUNG TRANSPLANTATION

This is the treatment of last resort for severe PAH that was not sufficiently controlled by maximal conservative treatment.

CARDIAC INVOLVEMENT

Cardiac involvement in the course of SSc may be primary or a consequence of other organ complications; pericardial effusions are rare; however, they worsen the prognosis. Heart damage in the course of SSc manifests itself as arrhythmias and conduction disorders (most often in the form of tachyarrhythmias), as well as myocardial dysfunction. Progressive heart failure occurs, with signs of left ventricular dysfunction — diastolic dysfunction is the most common (30% of patients). However, myocarditis is rarely observed.

Many studies analysed electrocardiographic changes in SSc patients. Various types of abnormalities were found to occur in 25–75% of patients and may affect patients without clinical signs of cardiovascular involvement. Therefore, it seems important to extend the diagnosis to include Holter ECG monitoring even in asymptomatic patients.

PERICARDITIS

For symptomatic pericarditis, non-steroidal anti-inflammatory drugs (NSAIDs) (to be used with caution in case of upper GI problems)/colchicine may be used as first-line treatment. When this treatment is not sufficient, GCs may be necessary — in combination with pericardial drainage in justified situations [4].

ARRHYTHMIAS AND CONDUCTION DISORDERS

Arrhythmias should be treated with usual antiarrhythmics with standard precautions (class 1 antiarrhythmics should not be used in cases of ischaemic heart disease (coronary artery disease) and/or left ventricular dysfunction). Beta-blockers are not contraindicated; however, their use is limited due to the risk of exacerbating Raynaud's phenomenon and and the risk of digital ulcers, with cardioselective beta-blockers being preferred. It should be noted that amiodarone may exacerbate pulmonary fibrosis.

Antithrombotic therapy is necessary for supraventricular arrhythmias (SVAs) unless CHA2DS2-VASc is 0. If the score is 1, consideration should be given to oral anticoagulant therapy with a vitamin K antagonist (VKA) or a direct thrombin inhibitor (dabigatran), or a factor Xa inhibitor (rivaroxaban, apixaban) administered *p.o.* based on an assessment of bleeding risk and individual patient preference.

The implantation of a pacemaker or defibrillator should be considered, if necessary [4].

MYOCARDIAL DISEASE

A calcium channel blocker may be proposed to improve perfusion and coronary flow reserve and, in case of intolerance, angiotensin-converting enzyme II inhibitors, and combinations of drugs from these groups are also allowed. In advanced dysfunction, conventional treatment of systolic heart failure should be used in the absence of contraindications (ACEI or ARB and beta-blockers at maximum

tolerated doses, mineralocorticoid receptor antagonists, diuretics at minimum doses, ivabradine in case of sinus tachycardia > 70/min, possibly digoxin).

In the case of rare myocarditis, the drug of choice is GCs preferred over cyclophosphamide because of the risk of cardiotoxic adverse effects after treatment with cyclophosphamide. Dosing of GCs is recommended as in severe forms of myositis. If there is no improvement, cyclophosphamide is included [as in ILD, i.e. in high doses — 750–1000 mg/m^2 BSA (body surface area) in the form of repeated IV drip infusions] with caution [4].

SCLERODERMA RENAL CRISIS

Renal arterial lesions affect the majority of SSc patients; however, it is only the onset of clinical signs of renal involvement that significantly worsens the prognosis. The course of scleroderma renal crisis (SRC), which is associated with rapid impairment of renal function and the development of severe hypertension, may be particularly severe and dramatic. In the past, SRC had a mortality rate of up to 76% for patients. The situation has changed significantly since the introduction of ACEIs into treatment (late 1970s). Such treatment reduced the mortality rate to less than 10%. Risk factors for SRC are the first four years of the disease, its rapid course, urinary tract infection (UTI), sudden dehydration, uncontrolled hypertension, use of medications such as GCs, NSAIDs, cyclosporine A.

According to EUSTAR recommendations, ACEIs (especially captopril) are first-choice drugs due to their short half-life. They allow rapid dose adjustment to blood pressure values. Captopril should be administered at an initial dose of 6.25–12.5 mg. The dose should be gradually increased to achieve a reduction of 20 mm Hg in systolic blood pressure and 10 mm Hg in diastolic blood pressure per day, and thereafter until blood pressure values are normalised, even if there are still elevated creatinine levels [6].

For second-line treatment, calcium antagonists are recommended. In the third-line treatment, a drug from the alpha-blocker group is used. If this monotherapy is ineffective, a drug from the group of calcium channel blockers or angiotensin receptor inhibitors may be included as an alternative [14, 15]. In contrast, angiotensin II receptor blockers used in monotherapy were not found to be effective.

If patients require initiation of dialysis, it is still advisable to provide them with ACEIs.

If renal failure is accompanied by overhydration or malignant hypertension persists, dialysis therapy is necessary. The patient may only require dialysis for a certain period of time (6–24 months) and during this time renal function may still return to normal; however, in some cases, the patient may require chronic dialysis therapy. For this reason, the decision on kidney transplantation should be delayed and performed after two years. It should be emphasised that kidney transplantation is an effective procedure for patients in these cases.

Prophylactic administration of ACEIs in all cases of scleroderma to prevent SRC is not accepted as a rule (in the absence of clear medical indications). More recently, it has even been highlighted that the use of these drugs may even increase the risk of a worse clinical course of SRC and the need for chronic dialysis therapy.

MUSCULOSKELETAL COMPLAINTS

In the course of SSc, there are adverse changes in musculoskeletal function. Arthralgia is reported by approximately 25% of patients, sometimes as the first manifestation of the disease. In approximately 60% of cases, joint inflammation (arthritis) is the underlying cause [16]. In some patients, inflammation also involves the system of tendons, which is the cause of the audible friction of the tendon structures of the wrist. This symptom is considered a poor prognostic factor — it is associated with the development of increased skin induration and a higher incidence of organ complications [17]. Synovitis is a predictor of new digital ulcers and decreased left ventricular ejection fraction (LVEF), and tendon friction further increases the risk of SRC. Symptoms of musculoskeletal damage are found in 5–96% SSc patients. Most often, myopathy does not produce overt clinical symptoms and is only detectable by elevated levels of muscle enzymes in the bloodstream, electromyography (EMG) or muscle biopsy. In addition to inflammatory changes in the muscles, muscle weakness is also underpinned by increased fatigue due to cardiorespiratory failure, atrophy-inducing drugs used in SSc.

NSAIDs, excluding their topical use, are not recommended for arthralgia due to the risk of SRC [4]. Recommendations do not exclude

short-term use of NSAIDs — accompanied by monitoring of renal function and after excluding the risk of upper GI bleeding (UGIB). It is generally considered that paracetamol and tramadol are the drugs of choice for analgesic therapy, and colchicine may also be effective in this regard.

In the first-line immunosuppressive therapy, methotrexate [*p.o.*, intramuscular (*i.m.*) or *s.c.*, 10–15 mg 1 × week, the dose is gradually increased to a maximum of 25–30 mg/week] is most commonly used. At the same time, folic acid (≥ 5 mg/week) or folinic acid is administered to nullify the adverse effects of the drug (e.g. cytopenia, oral ulcers and nausea), followed by low-dose GCs and hydroxychloroquine (at doses of 200 mg 1–2 × daily *p.o.*) [6]. According to French guidelines [4] and EULAR guidelines [6], oral GCs (prednisone) may be used for a short period of time, at a dose not exceeding 10-15 mg/day. Their use is in the treatment of symptoms of carpal tunnel syndrome (CTS), arthralgia or myositis, and they are commonly used to treat skin lesions in early SSc and ILD. In view of the risk of developing SRC, close monitoring of patients treated with GCs for this complication is recommended.

Cyclophosphamide was not found to be effective in the treatment of joint complaints, however, the drug is used with good effect for symptoms of myositis in SSc patients.

In cases of mild to moderate myositis, treatment is initiated with azathioprine (50–100 mg/day) or methotrexate (7.5–25 mg/week). If there is no improvement, GCs (prednisone) may be included at a dose of < 20 mg/day. In more severe forms, methylprednisolone is administered at a dose of 500–1000 mg in 3–4 drip infusions, at one- to two-day intervals, followed by prednisone at a dose of < 20 mg/day. These drugs are administered with extreme caution, monitoring the patient for SRC.

There are publications that describe the positive therapeutic effect of *i.v.* immunoglobulins (IVIGs) (using *i.v.* infusions at a dose of 2 g/kg bw for 4 consecutive days/month). There were reductions in C-reactive protein (CRP) and creatine kinase (CK) [18].

Elhai et al. presented the results of a multicentre observational EUSTAR study involving 20 patients with SSc and polyarthritis and seven with scleroderma and refractory myopathy. Within this group, 15 patients received *i.v.* tocilizumab at a dose of 8 mg/kg bw once a month and 12 patients received abatacept (all patients with myopathy received abatacept). The mean Disease Activity Score in Rheumatoid Arthritis (DAS-28) significantly increased over the course of the study; in addition, the following parameters improved significantly: mean number of painful joints, mean number of swollen joints, duration of morning stiffness, and CRP levels. Observations showed that treatment with abatacept did not improve muscle parameters, nor were there any clinically beneficial pulmonary or skin lesions with it. A good response to tocilizumab treatment was also observed in other papers describing cases of SSc patients with symptoms of myositis [19].

There are numerous reports showing a positive effect of rituximab on arthralgia in SSc patients, in addition to its positive effects on ILD and skin [20–23]. Therefore, it seems that rituximab should be considered as an alternative therapy in SSc patients. Single case reports also suggest a therapeutic effect of rituximab on SSc-associated myositis [24].

The prevention and treatment of osteoporosis in SSc patients should also be kept in mind. Physiotherapy support is also necessary.

GASTROINTESTINAL INVOLVEMENT

In 74–90% of patients, there is gastrointestina involvement (GI), resulting in fibrosis of the GI walls and atrophy of the smooth muscle tissue. Clinically, symptoms of upper gastrointestinal (GI) involvement predominate (70% of patients), resulting from motor atrophy of the lower 2/3 of the oesophagus and gastroparesis. However, motility disorders may affect any other section of the GI tract, resulting i.a. in prolonged intestinal transit and a tendency to persistent constipation, often alternating with diarrhoea. This is caused by a pathological small intestinal bacterial overgrowth (SIBO) [25–27]. Furthermore, maldigestion and malabsorption syndrome is the second GI complication of SSc following oesophageal involvement. At the outset, the association of upper GI involvement with ILD should also be highlighted. If there is evidence of a swallowing disorder in a SSc patient , at any stage, the patient should be referred urgently to an appropriate physiotherapist who specialises in, among other things, masticatory dysfunction. The therapist will help the patient optimise the mechanism of swallowing to minimise the risk of aspiration of food content.

ORAL CAVITY

It seems necessary to educate patients on importance of oral hygiene by teaching them the correct brushing methods to prevent cavities and periodontal lesions. After the first oral check-up at the time of diagnosis (combining clinical and radiographic examination), systematic checks every two years are recommended to detect any abnormalities early. Hyposialia should be treated by prescribing saliva substitutes and/or saliva production stimulators (pilocarpine hydrochloride) to reduce the risk of periodontal diseases and cavities. For oral ulcers, topical antiseptics and anaesthetics (such as chlorhexidine and lidocaine 2%) may be considered. Microstomia involves assistance from a physiotherapist and a masticatory dysfunction dentist to reduce the progressive limitation of mouth opening. There are no contraindications to the use of dental implants in SSc patients [4].

OESOPHAGUS

Non-pharmacological management includes lifestyle changes — avoiding a supine position for approximately three hours after a meal. In addition, it is advised to refrain from wearing tight clothing, drinking coffee, alcohol, smoking and eating fatty foods. Frequent, low-volume meals and prevention of constipation are recommended. In advanced stages of the disease, patients may require nutritional treatment [4].

Pharmacological management includes the use of:

— prokinetics for the treatment of GI motility disorders (cisapride, metoclopramide, domperidone — but with the need to monitor adverse effects including QT interval prolongation in the ECG, erythromycin, octreotide), calcium channel blockers (diltiazem);
— proton pump inhibitors (PPIs) (in doses up to 2–3 times higher than standard doses) — for the treatment of SSc-related gastro-oesophageal reflux and prevention of oesophageal ulcers and strictures — and immunosuppressants (D-penicillamine) [4].

Endoscopic treatment involving balloon dilatation of the oesophagus or destruction of vascular lesions is considered for certain medical indications. Surgical treatment is recommended for strictures or severe reflux (fundoplication procedures).

STOMACH

In non-pharmacological treatment, dietary recommendations play an important role in the management of gastric emptying disorders by limiting the amount of fats in foods and replacing them with medium-chain triglycerides (MCTs) [4].

Pharmacotherapy of gastroparesis involves the use of prokinetics; it should be borne in mind that prokinetics used in excessively high doses have a negative effect on small bowel motility. The following medications are used: metoclopramide (in a dose of 10 mg, 30 min before a meal; the maximum dose is 4 × 10 mg/day; the drug should not be administered for more than 12 weeks), cisapride (in a dose of 3–4 × 10 mg/day, 15 min before a meal; the drug may cause prolongation of the QT interval in the ECG and severe ventricular arrhythmias, thus it is advised to start treatment in hospital), erythromycin (in a dose of 200 mg *p.o.*, 30 min before meals, used in cases of resistance to existing treatment; it has strong prokinetic properties but is not registered for the treatment of patients with gastroparesis). A percutaneous endoscopic gastrostomy (PEG) should be performed in patients with very severe delayed gastric emptying.

In the case of "watermelon stomach" (GAVE, gastric antral vascular ectasia), PPIs should be included in the therapy, and endoscopic treatment (including ND:YAG laser) may be necessary [4].

INTESTINES

At the outset, it should be noted that one of the most common causes of malabsorption syndrome in SSc — bacterial contamination syndrome (also known as bacterial proliferation syndrome) — may, at least in part, be related to the chronic use of high-dose PPIs for the treatment of gastro-oesophageal reflux symptoms.

Maldigestion and malabsorption syndrome may lead to malnutrition [4]. Dietary treatment should consider gluten-free diet, fibre-rich diet, MCT-enriched diet, or nutritional treatment with polymeric, oligomeric or elemental diets, appropriate vitamin supplementation and, in extreme cases, total parenteral nutrition [4].

Pharmacological treatment includes:

— cholestyramine or colestipol for diarrhoea;
— pancreatic enzyme substitution;

— antibiotic therapy in case of bacterial contamination syndrome. Antibiotics are most commonly recommended for 2–3 weeks each month, using tetracyclines, ciprofloxacin, clarithromycin, ampicillin, metronidazole, cotrimoxazole, neomycin [4], rifaximin used at a dose of 3 × 200 mg for 7 days;
— prokinetic drugs for motility disorders and persistent constipation — metoclopramide (3 × 10 mg), cisapride (3–4 × 10 mg), erythromycin (3 × 250 mg *p.o.*), octreotide (1 × 50 μg *s.c.* for 3 weeks) and laxatives;
— administration of octreotide to patients with intestinal pseudo-obstruction may restore normal intestinal motility; this drug is used at a dose of 50 μg/day, *s.c.* for 3 weeks [4].

AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

EULAR experts included treatment with autologous HSCT in patients with progressive SSc. The recommendation is based on the results of two randomised trials showing that HSCT is more effective than the use of monthly IV infusions of cyclophosphamide. Autologous HSCT improves skin lesions, pulmonary lesions, and longer prognosis in patients with early progressive SSc [6]. The risk of serious adverse effects was highlighted, including death from complications of this treatment. Appropriate qualification of patients and experience of the treatment team is necessary. According to another randomised trial conducted in 2018, the risk of death due to adverse effects of treatment was 3% at 54 months and 6% at 70 months, so a beneficial effect of HSCT was proved [28].

The efficacy of HSCT in SSc patients is evidenced by the results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) and Scleroderma: Cyclophosphamide or Transplantation (SCOT). HSCT is mainly targeted at patients with severe and rapidly progressive SSc.

Indications for HSCT include patients:
— with a confirmed diagnosis of SSc, according to the 2013 ACR/EULAR criteria;
— with systemic disease who scored at least 16 points on the mRSS assessment and experienced a progression of at least 25% in the last 6 months during immunosuppressive therapy;
— with interstitial lung involvement, with a decline in FVC or DLCO of more than 10% in the last 6 months, during immunosuppressive therapy.

Contraindications to HSCT include [4]:
— age > 65 years;
— active smoking;
— pregnancy: ongoing pregnancy or refusal to use effective contraception;
— mental illness, including alcohol or drug abuse;
— inability to give informed consent
— in terms of liver function, elevated aminotransferases or bilirubin elevated above twice normal, failure of this organ or confirmed cirrhosis;
— neoplasm: myelodysplastic syndrome or severe haematological disease;
— infections: acute or chronic infections related to human immunodeficiency virus (HIV), human T-cell leukemia virus type 1/2 (HTLV-1/HTLV-2), hepatitis B or C;
— in terms of cardiac function: left ventricular ejection fraction < 45%, mean pulmonary arterial pressure (PAPm) > 25 mm Hg or systolic PAP (PAPs) > 40 mm Hg unfilled or PAPm > 30 mm Hg or PAPs > 45 mm Hg filled — test with injection of 1000 cm^3 of isotonic saline over 10 minutes; constrictive pericarditis, cardiac tamponade, cardiac arrhythmias that cannot be controlled pharmacologically or via cardioversion/ablation;
— in terms of pulmonary function: FVC < 65% of reference value, DLCO < 40% of reference value.

REHABILITATION IN SSC PATIENTS

Rehabilitation should be tailored to individual patient's needs according to the severity of the disease and the extent of the lesions. A rehabilitation programme is needed to improve posture, breathing, muscle tone and general health. The most important goal of rehabilitation in SSc patients is to prevent or delay the formation of contractures in the joints, maintain or increase the range of motion in the joints, maintain or improve the ability to open the mouth, maintain or improve respiratory function, and reduce pain. Patients are advised to engage in moderate daily physical activity, walking, cycling on flat ground, gentle exercise.

Massage is also important, with the aim of improving blood circulation, reducing oedema, and decreasing pain (dry massage or — in patients without ulcers — vortex massage, con-

nective tissue massage). In SSc patients, manual lymphatic drainage (MDL) may be used, especially in the early stage of the disease when swelling occurs. This method stimulates the lymphatic system, causing an increase in suction forces in lymphatic vessels, which improves the removal of excess fluid accumulated in the interstitial tissue [29].

Thermotherapy (e.g. paraffin baths, poultices, and peat baths) is indicated but should be carried out with caution. Ultrasound therapy, short-wave diathermy and iontophoresis with potassium iodide are also applicable. Transcutaneous electrical nerve stimulation (TENS) improves the blood supply to the skin and also has an analgesic effect in patients with inflammatory lesions in the joints. Hydrokinesitherapy , i.e. exercise in water at 30°C, is recommended for patients without ulcers. It was found that special exercises performed in a swimming pool, using the physical properties of water, have a beneficial effect on the overall mobility of SSc patients.

The following methods are currently applicable in SSc patients:

— in the region of the face: neurorehabilitation using the Kabat method, connective tissue massage, kinesitherapy — exercises to improve the ability to open the mouth; facial muscle stretching exercises are recommended, e.g. wide yawning; the physician/physiotherapist's aim is to improve oral functions such as chewing and swallowing, restore facial expressions and restore correct positioning of the head. Facial stretching exercises involve exaggerating normal facial movements and exercises that strengthen the muscles of the oral cavity.
— in the area of hands: connective tissue massage, vortex massage, joint manipulation using the Mennell technique, iontophoresis with potassium iodide. In patients with swollen fingers, manual lymphatic drainage may be effective — this method stimulates the lymphatic system and thus improves the removal of excess fluid that accumulates in the interstitial tissue. If necessary, a deep connective tissue massage is performed.

CONCLUSIONS

These recommendations are based on contemporary literature data and incorporate elements of current recommendations from other scientific societies, including dermatology scientific societies, EULAR Scleroderma Trial and Research Group recommendations [6], French recommendations [4] and ESC recommendations.

In each case, treatment should be tailored to the individual patient's needs, clinical presentation, disease duration and organ complications. Patient management should include patient and family education in addition to pharmacology.

CONFLICT OF INTEREST

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