Systemic sclerosis (SSc) is a chronic, autoimmune, life-threatening disease characterized by excessive accumulation of extracellular matrix within connective tissue. It leads to the failure of some organs, especially the skin, heart, lung, kidney, and digestive tract. The clinical features of systemic sclerosis differ among patients. Nearly all patients have skin lesions, i.e. skin hardening and thickening. The first symptom of SSc is usually Raynaud’s phenomenon. After exposure to cold, the skin of the fingers changes color to white, blue, and red. This sometimes precedes the diagnosis by even several years. The next symptoms are musculoskeletal pain, fatigue, and swelling, usually of the hands, but sometimes also other parts of the body. Many patients develop digital ulcers. Scleroderma patients have a high risk of internal organ involvement; they may suffer from interstitial lung disease, heart complications (such as conduction abnormalities, pericardial effusion), pulmonary hypertension, kidney complications with scleroderma renal crisis (SCR), and gastrointestinal disorders (such as esophageal disease, bloating, diarrhea, or constipation).

There are two major clinical subtypes of systemic sclerosis, limited and diffuse, and the main
criterion is the extent of skin affection. Limited systemic sclerosis is characterized by the skin thickening distally from the elbows and knees. The lesions involve mostly the face and hands. It starts with Raynaud’s phenomenon and progression of the disease is usually slow. It may even last for many years. Previously, this type of systemic sclerosis was called CREST syndrome after its cardinal features: calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia. In this type of systemic sclerosis, anticientromere autoantibodies are usually detected in the serum. Diffuse systemic sclerosis is characterized by skin thickening in areas distal as well as proximal to the elbows and knees, with or without changes in the face and trunk. The prognosis in this type is worse than in limited systemic sclerosis (lSSc). Patients with anti-SCL70 or topoisomerase antibodies have a high risk of pulmonary fibrosis [1, 2].

**Etiology**

The etiology of systemic sclerosis is still not clear. Genetic factors play a role in all autoimmune diseases. The strong female predilection for systemic sclerosis indicates an influence of hormones. Many epidemiological studies suggest an association with some inciting agents such as cytomegalovirus (CMV) infection or toxic exposure (silica, tryptophan) [3].

**Pathogenesis**

The pathophysiology of this disorder is also unclear, but there are three general hypotheses based on the roles of immunological cells, endothelium cells, and fibroblasts. All reactions are united in one process leading to fibrosis and organ damage and can be seen as a pathophysiological triangle. Immunological cell activation and inflammation, vascular damage, and excessive collagen production and deposition are the milestones in the pathogenesis of SSc. Different pathways cause disorders in various organs, so the treatment strategy is targeted to the affected organs. Unfortunately, there is no therapy dealing with all the symptoms and complications of systemic sclerosis [1–3].

**Immune activation**

Evidence of immune system activation is the presentation of autoantibodies in systemic sclerosis. It is also clear that the profile of the antibodies is connected with the clinical pattern and prognosis in systemic sclerosis. Another sign is the presence of immune-cell infiltration in the skin and pulmonary tissue. These are usually macrophages and T cells. Good clinical examples for immune activation are early scleroderma with typical hand skin changes (puffy fingers) and alveolitis, the first stage of intestinal lung disease. The presence of alveolitis is confirmed by examination of the bronchoalveolar lavage (BAL) fluid, where an increase in cellularity, especially macrophages, is observed. A “ground glass” pattern of opacification on high-resolution computer tomography (HRCT) scanning was associated with inflammatory alveolitis. Many studies have demonstrated increased amounts of IL-2, IL-4, and IL-6 in patients with systemic sclerosis, and recent studies concentrate on the level of profibrotic chemokines in the blood and tissue, for example TGFβ (transforming growth factor beta) and CTGF (connective tissue growth factor) [3]. Activation of the immune cells leads to the release of proinflammatory and profibrotic cytokines and growth factors. This may cause impairment of endothelial cell function, proliferation of fibroblast, and collagen production [4].

**Treatment Targeting Immune Activation**

Experience with the immunosuppressive treatment of other inflammatory connective tissue diseases led to analogous therapy trials in systemic sclerosis. Several studies suggested the efficacy of immunosuppressive drugs in SSc. In two randomized placebo-controlled trials, methotrexate (MTX) was given orally or parenterally. A dose of 15–25 mg has been reported in the treatment of diffuse systemic sclerosis. A single-center study in the Netherlands (17 patients treated with MTX and 12 placebo patients) and a multicenter Canadian study (35 MTX-treated patients and 36 placebo patients) showed improvement in skin score; in the Canadian study there was an additional tendency to improve lung capacity, but not significantly [5, 6].

A drug currently in widespread use for the treatment of scleroderma is cyclophosphamide (CYC). CYC is considered for treatment of systemic sclerosis-related intestinal lung disease, especially in the early stage with alveolitis [7]. Many open studies have been published about treatment with CYC administered orally (1–2.5 mg/kg/day) or in monthly infusions (500–1000 mg/m²) with or without prednisolone [8]. Two recent double-blinded, randomized, placebo-controlled trials were performed in the United States (158 patients) and the United Kingdom (45 pat-
Mycophenolate mofetil (MMF) is widely used in nephrology as a long-term therapy to prevent solid-organ transplant rejection. It seems to have good tolerance and low toxicity. It has recently been used in lupus nephritis. In a few recent studies, treatment with MMF has shown improvement in skin thickening and beneficial effect in alveolitis [16].

The use of corticosteroids in systemic sclerosis is controversial. They have anti-inflammatory effects and are usually used in intestinal lung disease as a co-medication with CYC with good results [17]. They can also be indicated in myositis related to systemic sclerosis. The use of corticosteroids is a risk factor in scleroderma renal crisis; it is recommended not to use corticosteroids in doses > 10 mg/day [18].

Eicosanoids play a key role in the regulation of inflammation. A few recent studies showed that there is an overproduction of proinflammatory and profibrotic leukotrienes in the lungs and skin of patients with systemic sclerosis and upregulation of anti-inflammatory and antifibrotic lipoxins. Using leukotriene inhibitors or lipoxin analogues can be a new approach to the treatment of systemic sclerosis [19, 20].

Vascular Damage

Many investigators consider that endothelial damage could be the earliest lesion in systemic sclerosis. The first clinical manifestations of vascular dysfunction are Raynaud’s phenomenon and abnormal nail-fold capillaries; the next symptoms are digital ulcers, renal crisis, and pulmonary hypertension. Recent studies suggest that when endothelium cells are damaged, circulating leukocytes become activated and migrate into the intimal layer. The activated leukocytes secrete inflammatory mediators and cytokines (TGFβ, CTGF, PDGF, endothelin, etc.), which promote fibroblast proliferation, overproduction of extracellular matrix, and fibrosis. This leads to alteration in endothelial function, thickening of intima, narrowing of the vessel lumen, and reduced blood flow. Endothelial damage causes the overproduction of vasoconstrictors such as endothelin and impaired release of vasodilatators such as prostacyclin and nitric oxide. The impaired production of vasoactive substance leads to ischemia, then to endothelial damage, increased inflammation, and fibrosis [1–3].

Treatment Targeting Vascular Pathology

Treatment with angiotensin-converting enzyme inhibitors (ACE-I) in systemic sclerosis is recommended by experts in renal crisis and at the first sign of hypertension. There are no randomized trials with ACE-I, but knowledge based on database analysis has shown one-year survival in about 70% of patients treated with ACE-I compared with
20% without ACE-I [21]. Is it still not clear if ACE-I should be used in all scleroderma patients for prevention of renal crisis or perhaps only in patients treated with corticosteroids. AT1-inhibitors probably also have a positive effect.

The next important group of “vascular drugs” are analogues of prostacycline. Epoprostenol improves exercise capacity and hemodynamic measures in arterial hypertension, but a limitation of its use is drug administration by continuous intravenous route [22]. Iloprost and treprostinil represent more stable analogues of prostacyclin; they are used in intravenous infusion or inhalation with a good clinical efficacy.

Bosentan, an inhibitor of endothelin receptor, is recommended in the therapy of pulmonary hypertension. In randomized control trials it has shown functional and survival rate improvements. Bosentan treatment prevents the formation of new ulcers [23]. Sitaxentan is a selective oral endothelin A receptor antagonist with proven efficacy in the treatment of pulmonary hypertension [24]. Sildenafil is an inhibitor of NO degradation with a potential good influence on endothelial and vascular damage. Its effect in the treatment of pulmonary hypertension and digital ulcers was reported by Badesch et al. [25]. Other treatments used in the therapy of systemic sclerosis with potential effect on vascular injury include calcium channel blockers, nitroglycerin, statins, serotonin inhibitors, and anticoagulant drugs.

**Fibroblast Activation**

Fibrosis is the last process in the pathogenesis of systemic sclerosis, and it leads to organ damage. Activated fibroblasts excessively produce collagen and extracellular matrix, which results in fibrosis. The skin and lungs are the major organs that are severely affected by fibrosis. There are many cytokines and other factors with profibrotic effect. TGFβ is a cytokine directly responsible for fibroblast proliferation, induction of extracellular matrix production, and inhibition of its degradation. CTGF is induced in activated fibroblasts by TGFβ. CTGF enhances and supports the fibrotic process [1–3].

In the last few years, great progress has been made in explaining the pathophysiological pathways of fibrosis, indicating an important role of platelet-derived growth factor and its receptor on fibroblasts. Investigators have described the presence of autoantibodies against PDGF receptor in all scleroderma patients. These antibodies stimulate PDGF receptor, inducing signaling cascades which lead to increased type 1 collagen gene expression and its deposition [26].

**Treatments Targeting Fibrosis**

In *in vitro* experiments, D-penicillamine shows an effect in disturbing the synthesis and connection of collagen fractions. D-penicillamine was earlier often used in the therapy of systemic sclerosis. A multicenter randomized control trial compared high-dose (750–1000 mg/day) versus low-dose (250 mg/day) D-penicillamine. The two groups were not different in mortality, onset of new renal crises, and skin score. This study did not answer the question whether D-penicillamine is an effective therapy of systemic sclerosis [27]. The benefit of D-penicillamine treatment did not show improvement in any randomized trial and remains doubtful.

Relaxin is a pregnancy-related hormone that has connective tissue remodeling and antifibrotic effects. It could play a potential role in the therapy of systemic sclerosis. In randomized control trials the effectiveness of relaxin was not confirmed [28].

New experiments are focused on understanding the molecular pathology pathways in systemic sclerosis. The therapy of the future includes some substances that can selectively block mediators in signaling pathways. TGFβ antagonist, CTGF antagonist, and PDGF-receptor signaling inhibitor are being tested; the first reports have been published and further studies are underway. The therapy of systemic sclerosis is still a great challenge for researchers and clinicians [29].

The authors concluded that 1) currently, there is no clear standard or even recommendation for the therapy of systemic sclerosis, 2) randomized, placebo-controlled trials on systemic sclerosis are difficult to conduct because of the heterogeneity in clinical symptoms, multifactorial pathogenesis, and relative rarity of the disease, 3) improved understanding of the pathophysiology pathways and molecular biology of systemic sclerosis are the keys to develop effective therapy.

**References**


Address for correspondence:

Ewa Morgiel
Department of Rheumatology and Internal Diseases
Silesian Piasts University of Medicine
Wroclaw
Poland
Tel. (+48) 694122543
E-mail: ewa.morgiel@gmail.com

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