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Advances in the Understanding, Diagnosis, and Treatment of Systemic Sclerosis: A Comprehensive Review of Recent Developments

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Abstract

Systemic sclerosis (SSc) is a multifaceted autoimmune disorder characterized by widespread organ involvement, impacting the skin, lungs, gastrointestinal tract, and blood vessels. Patients often confront a reduced lifespan, primarily attributed to pulmonary complications. Current therapeutic strategies concentrate on organ-specific interventions to mitigate inflammation and alleviate symptoms. Immunosuppressive drugs, vasodilators, and anti-fibrotic agents are commonly employed, but ongoing research explores novel drugs and therapeutic approaches. Autologous stem cell transplantation is considered in rapidly progressing interstitial lung disease, although potential complications must be carefully weighed. Recent studies delve into the intricate pathogenesis of SSc, revealing abnormalities in metabolic pathways and protein regulation. The disease manifests with diverse symptoms affecting various organs, with vascular involvement significantly contributing to morbidity, especially pulmonary arterial hypertension. Complications, including heightened susceptibility to infections, are exacerbated

by the disease and its treatments. Ongoing research investigates potential treatments such as GPR68 antagonists, soluble guanylate cyclase activators, and melanocortin 1 receptor agonists, displaying promising results in improving pulmonary function. Multiple clinical trials for various drugs are currently underway. In conclusion, addressing the complexities of systemic sclerosis requires a multidisciplinary approach. Understanding its intricate pathogenesis and developing targeted therapies are pivotal for enhancing patient outcomes and extending survival.

Keywords: Scleroderma, systemic; fibrosis; pharmacotherapy

Introduction:

Systemic sclerosis belongs to the group of systemic connective tissue diseases (collagenoses). It is a chronic autoimmune disease, yet its etiology remains incompletely understood. The disease manifests with skin and internal organ fibrosis, affecting various organs, with a predilection for the lungs, gastrointestinal tract, cardiovascular system, and kidneys. Systemic sclerosis presents in several clinical forms, including limited (lSSc), diffuse (dSSc), and a form without skin changes (systemic sclerosis sine scleroderma) [1].

Goal:

The goal of the discussed paper is to provide state-of-the-art information on the etiology, pathogenesis, symptoms, conventional treatment, and drugs undergoing clinical trials for systemic sclerosis (SSc). This autoimmune disease, characterized by its complexity and diverse clinical manifestations, is thoroughly explored in the paper. It aims to offer a comprehensive understanding of SSc, covering its natural course and complications. Additionally, the paper emphasizes the ongoing research efforts to discover novel therapeutic options, presenting promising results from recent studies and clinical trials. The overarching objective is to deliver a holistic overview of SSc, addressing its complexities, challenges, and potential avenues for future research and treatment development.

Epidemiology:

The prevalence of systemic sclerosis is approximately 88-158 cases per 1,000,000 population worldwide. In Poland, it is estimated at around 19 cases per 1,000,000 [2]. While the disease predominantly affects adults, it can also occur in children. In the UK and Ireland, the prevalence of juvenile systemic sclerosis is calculated at 0.27 cases per 1,000,000 residents [3]. Systemic sclerosis is more common in women than men (about 6.7:1 ratio) and typically begins between the third and fifth decades of life. Its occurrence is twice as high in Afro-Americans and Latinos compared to Caucasians [2]. The disease shows a familial predisposition, particularly in families with a history of systemic sclerosis or other autoimmune diseases. Interestingly, no significant difference has been observed between monozygotic and dizygotic twins, suggesting the importance of environmental factors [4].

Etiology and Pathogenesis:

The exact etiology of systemic sclerosis is not fully understood, with both genetic and environmental factors playing crucial roles. Epigenetic changes, such as DNA methylation, mRNA influence, and histone modifications, are implicated. Disturbances involve cells of the immune system, fibroblasts, and endothelial cells. Pathogenesis revolves around disruptions in the transforming growth factor B (TGF-B) pathway, stimulating fibroblasts to produce collagen, platelet-derived growth factor (PDGF) promoting smooth muscle vessel proliferation, and the Wnt/B-catenin pathway regulating genes responsible for tissue fibrosis [2]. The NLRP3 inflammasome also plays a role in disease pathogenesis, influencing macrophages, B lymphocytes, endothelial cells, and fibroblasts. Caspase 1, an effector enzyme in the NLRP3 inflammasome, induces the synthesis of pro-inflammatory cytokines like IL-1β and IL-18. An imbalance between M2 and M1 macrophages may contribute to systemic sclerosis development. Studies suggest a decrease in IRF8, a transcription factor involved in macrophage development towards M1, in patients with systemic sclerosis. IRF8 also participates in regulating NLRP3 inflammasome activation. Further research is needed to explore the broader role of this inflammasome in disease pathogenesis, potentially leading to the development of drugs targeting this protein complex to impede disease progression [5].

Autoantibodies play a significant role in disease pathogenesis, with antinuclear antibodies present in over 90% of patients, most commonly anti-topoisomerase, anti-Th/To, and anticentromere antibodies (in over 60% of patients). It is essential to note that various other antibodies may be present or absent in the disease.

Studies have demonstrated a correlation between major histocompatibility complex class II (HLA) antigens, particularly HLA-DR1, DR2, DR3, DR5, DR52, and others, and systemic sclerosis. Additionally, certain HLA antigens correlate with specific antibody presence, such as HLA-DQB1*0501 (DQ5) and DQB1*)301 (DQ7) with anticentromere antibodies [6].

Recent studies suggest that up to 240 metabolic pathways and abnormalities in protein regulation are involved in the pathogenesis of systemic scleroderma. In addition to those mentioned earlier Certainly, the pathogenesis of systemic scleroderma is much more complex and requires some further studies.

Symptoms:

Systemic scleroderma, like other systemic diseases, can manifest in a wide range of ways. Organ symptoms can be accompanied by general symptoms such as itchy skin or chronic fatigue. Most patients have Raynaud's sign, which may even precede the onset of the disease.

Skin lesions in the course of systemic scleroderma are associated with thickening, hardening, and increased skin tension [7]. These lesions usually progress in 3 phases: edema, induration, and atrophic phase. In the limited form, they mainly affect the distal parts of the limbs, fingers, and face, while in the generalized form, they mainly affect the proximal parts of the limbs and additionally the anterior part of the chest and abdomen. The extent of the lesions correlates with the severity of the disease, so it is important to assess them regularly, such as with the modified Rodnan skin score (mRSS). Skin lesions are often accompanied by joint symptoms such as stiffness, swelling, or pain. Also characteristic of the disease is tendon friction, which is an unfavorable prognostic factor.

In terms of organ symptoms, the respiratory, gastrointestinal, circulatory, and excretory systems are most often affected. Respiratory system involvement is currently the leading cause of death from systemic scleroderma in the form of interstitial lung disease with progressive pulmonary fibrosis. The gastrointestinal symptoms are primarily gastrointestinal motility disorders with complex and incompletely understood mechanisms, accompanied by neuropathic processes in addition to fibrotic processes. It occurs in more than 90% of patients. It is more severe in men and in patients with concomitant inflammatory myopathy. [8] Clinically, it manifests itself in the form of dysphagia, GERD, telangiectasias on gastric endoscopic imaging, malabsorption syndrome, and variable bowel movements.

Inherent in scleroderma is vascular dysfunction, or vasculopathy. Vascular complications occur in both internal organs and skin. Skin lesions involve ischemic tissue changes with consequent fingertip defects and ulcerations. Ulcerations also most often appear on the fingertips but can also occur in areas exposed to trauma. A very dangerous vascular complication is pulmonary hypertension. It can develop against a background of interstitial lung disease and/or as pulmonary arterial hypertension, which occurs in 8-12% of patients with systemic scleroderma. It is also worth mentioning that the cause of pulmonary hypertension can also be left ventricular failure as well as in the course of thromboembolic complications (estimated to affect up to 50% of patients with pulmonary arterial hypertension[9] Clinically, it manifests as exertional dyspnea, syncope, and chest pain. Auscultatory symptoms may also occur.

Systemic scleroderma disorders also affect the heart (which can be associated with primary lesions such as ischemia and myocarditis) but also occur secondary to pulmonary and/or pulmonary vascular disease, known as pulmonary heart. Most often it is diastolic dysfunction, less often arrhythmias, pericardial effusions may occur.

The main complication from the excretory system is renal involvement in the form of scleroderma renal tubularis, which is a life-threatening condition. It affects about 10% of patients (more often in the generalized form) and is caused by the narrowing of the renal arterioles [10]. Clinically, it manifests as rapidly progressive hypertension and worsening renal filtration capacity with proteinuria. Hypertension may not occur, especially if the patient has previously used angiotensin-converting enzyme inhibitors. The introduction of this group of drugs into treatment has significantly reduced the mortality associated with this complication.

For the diagnosis of systemic scleroderma, we use the ACR/EULAR 2013 classification criteria. The update of the diagnosis criteria is related to access to new tests such as capillaroscopy, as well as a better understanding of the disease and consideration of its presenting symptoms. It is also associated with an increase in the rate of diagnosis of the disease.

<table>
<tr><td colspan="3">Systemic Sclerosis – ACR-EULAR classification criteria (2013)</td></tr>
<tr><td colspan="3">1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are not applicable to:
a) Patients having a SSc-like sidorder better explaining their manifestations, such as: neprohenic sclerosing fibrosis, generalized morphea, eosinophilic fasciiitis, scleredema diabetoricum, scleromyxedema, erythomyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic cheiropathy
b) Patients with „Skin thickening sparing the fingers”</td></tr>
<tr><td>Items</td><td>Sub-items</td><td>Weight/Score</td></tr>
<tr><td>Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)</td><td></td><td>9</td></tr>
<tr><td rowspan="2">Skin thickening of the fingers (only count the highest score)</td><td>Puffy fingers</td><td>2</td></tr>
<tr><td>Sclerodactyly of the fingers (distal to metacarpophalangeal joint but proximal to the proximal interphalangeal joints)</td><td>4</td></tr>
</table>

Finger tip lesions (ony count the highest score)	Digital tip ulcers Finger tip pitting scars	2 3
Teleangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Intestitial lung disease * (* Maximum score is 2)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon		3
Sclerodermra related antibodies** (any of antri-centromere, anti-topoisomerase I [anti-Sd 70], anti-RNA polymerase III) (** Maximum score is 3)	Anti-centromere Anti-topoisomerase I Anti-RNA polymerase III	3
	Total score:	
Patients having a total score of 9 or more are being classified as having definite systemic sclerosis		

Differential diagnosis:

The differential diagnosis should include the Reynaud's sign of another etiology, mixed connective tissue disease, overlap syndromes, dermatomyositis, rheumatoid arthritis. In terms of skin lesions, the disease should be differentiated from eosinophilic fasciitis, morphea, lichen sclerosus and atrophic fasciitis, AIH skin sclerosis, scleroderma, and scleroderma-like edema, late cutaneous porphyria or drug lesions after, for example, bleomycin, vibratory disease, reflex sympathetic dystrophy

Natural course:

People with systemic scleroderma have a shorter life expectancy than the general population. A meta-analysis [11] found 5- and 10-year survival rates for establishing a diagnosis of systemic scleroderma of 74.9% and 62.5%, respectively. Pulmonary manifestation of the disease remains the main cause of death.

It is noteworthy that people with systemic scleroderma have a 1.5- to 5-fold higher risk of developing cancer [12]. This applies not only to hematologic proliferations as in RA, but also to solid tumors primarily derived from inflamed tissues. Tumor risk also depends on specific antinuclear antibodies found in systemic scleroderma. These cancers include lung cancer, breast cancer, gastrointestinal cancers, gynecologic cancers, and leukemias [11].

Treatment:

There is no causal treatment for the disease. So-called organ-specific therapy is used, aimed at slowing down the inflammatory process and reducing discomfort in the involved tissues. Treatment includes immunosuppressive drugs, drugs that improve blood flow in the vessels and prevent ulceration of the fingers and drugs that inhibit pulmonary fibrosis. In addition to pharmacological methods, non-pharmacological management to improve patients' quality of life is no less important. Patients are advised to quit smoking, avoid exposure to cold to avoid the onset of Reynaud's sign and maintain constant physical activity. It is also important to pay attention to the impact of the disease and the resulting dysfunctions affecting, among other things, the hands, mouth (including microstomia), and physical performance related to lung disease [13].

New recommendations for the pharmacological treatment of systemic scleroderma are expected to be issued in 2023. Currently, the EULAR 2017 recommendations are still in use [14].

Calcium channel antagonists such as nifendipine and prostanoids such as iloprost are used to treat vascular lesions of the fingers, i.e. Raynaud's sign and ulcers. Calcium antagonists have been shown to reduce the recurrence of Reynaud's sign; however, the results of the 2023 cohort study did not show a protective role in preventing finger ulcers, either primary or recurrent lesions. [Ross] Iloprost is used to treat both severe forms of Raynaud's sign and active ulcers.

The treatment of pulmonary arterial hypertension uses endothelin receptor antagonists (e.g., bosentan), phosphodiesterase 5 inhibitors such as (sildenafil), and prostacyclin analogs such as iloprost or epoprostenol. The soluble guanylyl cyclase stimulator Riociguat can also be used [15].

For the treatment of skin lesions, methotrexate can be considered.

In the gastrointestinal manifestation of the disease, symptomatic drugs such as proton pump inhibitors (e.g. pantoprazole), prokinetic drugs, and, according to the recommendations of some experts, antimicrobial drugs are used to prevent SIBO syndrome, which can occur up to 10 times more often than in the general population[16].

Scleroderma renal crisis is treated with angiotensin-converting enzyme inhibitors. It is worth mentioning here that the use of glucocorticosteroids increases the risk of renal breakthrough and also adversely affects skin lesions, so they should only be used if there are organ complications of the disease, such as severe myositis.

To date, the standard treatment for pulmonary lesions has been cyclophosphamide or mycophenolate mofetil, with a preference for the latter due to its less severe side effects [17]. It also uses drugs such as nintedanib, rituximab, and tocilizumab for treatment. Meta-analyses conducted for the American Thoracic Society showed significantly improved respiratory volume and lesion severity with Rituximab [18]. In a similar meta-analysis for tocilizumab, a slowing of disease progression was observed by an average of 6.5% less decrease in expected % volumetric respiratory capacity after 48 weeks relative to the control group. The safety and tolerability profile of the treatment was also better[19] When nintedanib was used alone and in combination with mycophenolate mofetil, significantly slower lesion progression was demonstrated compared to placebo; however, an increased risk of gastrointestinal complications and thus lower treatment tolerability was demonstrated[20]

The limitation of the above studies is the small number of source studies, which limits the quality of recommendations. At the same time, no superiority of rituximab over cyclophosphamide has been demonstrated. They are primarily used to inhibit the fibrosis process in the lungs – one of the main causes of death in these patients. New therapies are still being sought to inhibit disease progression and prolong the survival of patients.

One method of treatment is the use of autologous bone marrow transplantation, especially in cases of rapid progression of interstitial lung disease. However, potential complications associated with this method should be taken into account, such as an increased risk of infections, heart failure, kidney problems, thyroid cancer, or myelodysplastic syndrome[21].

Research on New Drugs:

Currently, intensive research on targeted drugs is ongoing. One such attempt was a drug called Zirataxestat, an ATX inhibitor; unfortunately, further studies were discontinued [22]. Promising results are reported in studies on Romilkimab, a drug designed to inhibit skin changes, with antibodies against interleukin-4 and interleukin-13. However, phase III studies are still needed [23]. Another substance, brodalumab, an interleukin-17 inhibitor, showed improvement in skin changes in phase I studies [24].

Obinutuzumab is in phase II studies for systemic sclerosis. Another group of drugs under investigation includes Janus kinase inhibitors such as itacitinib, baricitinib, and tofacitinib. Improvement in skin changes was observed in 88% of 59 patients, and no progression of interstitial lung disease was observed in 28 out of 29 patients [25].

Lenabasum is an agonist of cannabinoid type 2 receptors. In phase III studies, unfortunately, no statistically significant difference was found in the primary and secondary endpoints. Interestingly, the study showed an unexpectedly high degree of improvement in the control group, which may be associated with the fact that patients using mycophenolate mofetil were also included in the study [26].

Research is also underway on the use of calcineurin inhibitors. In the case of tacrolimus, a study comparing it with mycophenolate mofetil showed comparable improvement in the primary and secondary endpoints. The primary endpoint was the difference in change in forced vital capacity (FVC%) at 24 weeks; secondary outcomes included absolute change in FVC, skin scores, 6-minute walk distance, Mahler's transitional dyspnea index, ACR-CRISS, revised CRISS responses, and adverse outcomes [27]

FT011 is a G protein-coupled receptor 68 (GPR68) antagonist. Promising results were obtained in Phase II studies of this molecule. The study demonstrated improvement in the percentage of forced vital capacity (% FVC) in pulmonary changes and on the SSHAQ-DI scale (Scleroderma Health Assessment Questionnaire-Disability Index). [28]

Ongoing Phase II studies are investigating the use of molecules such as soluble guanylate cyclase activators [29].

Dersimelagon (MT-7117) is an oral agonist for melanocortin 1 receptor. In studies on bleomycin-induced pulmonary fibrosis, it has shown anti-inflammatory, anti-fibrotic effects, and improved vascular dysfunction [30].

Studies in preparation:

- ANti-TGF I and II phases
- Anifrolumab – Phase III
- CCL24 (eotaxin-2): CM101 – Phase II
- CD 19 CAR T

Complications:

Patients with systemic sclerosis are more susceptible to infections than the general population. This susceptibility arises not only from the nature of the disease itself, which involves immune system dysregulation, but also from the use of medications that inhibit immune system activity. In a study conducted in Italy during the COVID-19 pandemic, it was found that patients with systemic sclerosis statistically experienced more cases of COVID-19 and had significantly more severe infections. However, it should be noted that they also had other risk factors for severe COVID-19 outcomes, including older age. The study did not show an impact of the infection on the symptoms of systemic sclerosis or on the activity and levels of serologic biomarkers[31]. The same study demonstrated reduced efficacy of SARS-CoV-2 vaccines, both in terms of humoral and cellular responses. No significant difference in deaths related to COVID-19 was observed between the period before and after access to vaccinations.

Conclusions

In conclusion, systemic sclerosis poses a complex clinical challenge, necessitating a multidisciplinary approach. Understanding its intricate pathogenesis and developing targeted therapies remain crucial for improving patient outcomes and extending survival.

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