International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	PATHOGENESIS, DIAGNOSIS, AND TREATMENT OF SYSTEMIC SCLEROSIS – AN INTEGRATIVE REVIEW OF THE CURRENT APPROACHES
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6270
RECEIVED	15 April 2026
ACCEPTED	29 June 2026
PUBLISHED	14 July 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

PATHOGENESIS, DIAGNOSIS, AND TREATMENT OF SYSTEMIC SCLEROSIS – AN INTEGRATIVE REVIEW OF THE CURRENT APPROACHES

Olaf Krawczyk *(Corresponding Author, Email: olaf.krawczyk.12@interia.pl)*
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0009-1493-5652

Wojciech Kopyciński
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0005-2538-0534

Norbert Krawczyk
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0000-7304-2226

Piotr Wilczkowski
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0004-8118-1188

Natalia Krzysztofek
Collegium Medicum, Jan Kochanowski University, Kielce, Poland
ORCID ID: 0009-0001-6545-3962

Monika Kamela
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0000-2503-2058

Katarzyna Boszczyk
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0005-9974-3668

Małgorzata Grzybowska
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0002-6611-3983

Adrianna Baran
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0002-3986-2559

Aleksandra Palka
Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0005-5346-3871

ABSTRACT

Systemic sclerosis is a rare autoimmune connective tissue disorder marked by immunological dysregulation, vasculopathy, and progressive fibrosis of the skin and internal organs, resulting in considerable morbidity and mortality. The disease results from a complex interaction between genetic susceptibility, epigenetic modifications, environmental triggers, endothelial dysfunction, and aberrant immune responses. These mechanisms promote persistent inflammation, stimulation of fibroblasts and abundant extracellular matrix deposition, eventually causing irreversible tissue fibrosis and organ dysfunction. The diagnosis is based on clinical manifestations, supported by specific antibodies detection, capillaroscopy, and appropriate functional and imaging tests. To facilitate diagnosis, the American College of Rheumatology/European League Against Rheumatism issued guidelines in 2013, enabling earlier diagnosis and more accurate prognostic assessment. Although no curative therapy is currently available, treatment has advanced considerably and focuses on suppressing disease activity, slowing fibrosis, and preventing organ complications. Current therapeutic strategies include immunosuppressive agents, biologic therapies, antifibrotic drugs, and targeted vasodilator treatments tailored to individual organ involvement. Emerging approaches, such as JAK-STAT pathway inhibitors, CAR-T cell therapy, and stem cell transplantation, may further improve long-term outcomes in selected patients. Despite substantial progress in understanding disease mechanisms and expanding therapeutic options, systemic sclerosis remains a clinically heterogeneous disorder requiring early diagnosis, multidisciplinary management, and individualized treatment to optimize survival and quality of life.

KEYWORDS

Systemic Sclerosis, Fibrosis, Vasculopathy, Autoantibodies, Immunosuppressants

CITATION

Olaf Krawczyk, Wojciech Kopyciński, Norbert Krawczyk, Piotr Wilczkowski, Natalia Krzysztofek, Monika Kamela, Katarzyna Boszczyk, Małgorzata Grzybowska, Adrianna Baran, Aleksandra Palka. (2026) Pathogenesis, Diagnosis, and Treatment of Systemic Sclerosis – an Integrative Review of the Current Approaches. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6270

Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a rare autoimmune disease of the connective tissue, occurring at a rate of approximately 17.6–18.9 per 100,000 individuals, respectively. [1] The prevalence of SSc is markedly higher among women and typically manifests between 30 and 50 years of age. [2, 3] According to studies, SSc is associated with the highest mortality rate among rheumatic diseases. [4] Although mortality rates, particularly among younger patients, have declined over the past five decades, overall survival remains limited. A meta-analysis reported 5- and 10-year survival rates of approximately 75% and 63%, respectively, following diagnosis. [5] The skin and internal organs, particularly the gastrointestinal tract, lungs, heart, and kidneys, are the principal targets of SSc, with progressive involvement often resulting in severe and potentially life-threatening complications. [6] Owing to its heterogeneous clinical manifestations and the risk of irreversible organ damage, optimal patient care relies on a multidisciplinary approach that enables early recognition of the disease, comprehensive diagnostic assessment, and prompt initiation of appropriate therapeutic interventions. This review provides an overview of the current understanding of the pathophysiological mechanisms, diagnostic strategies, and contemporary management of SSc.

Methodology

A narrative literature review was conducted using the PubMed and Google Scholar databases. Publications were screened, with preference given to studies specifically investigating SSc. The review focused on recent aspects of the disease, including its pathophysiology, diagnostic approaches, and current therapeutic strategies.

Discussion

1. Pathogenesis

1.1. Susceptibility

The pathogenesis of SSc is still not fully understood, although numerous factors have been suggested, including those that increase susceptibility, trigger the disease, and cause its progression and severity. [7] Theories seek to explain how immunological and non-immunological processes are interrelated. To simplify the process of elucidating the etiology, SSc should be regarded as a syndrome comprising three fundamental pathophysiological components: abnormal immune system activation, fibrosis, and vasculopathy. [8]

The risk of developing SSc is considerably higher among first-degree relatives of affected individuals than in the general population, indicating substantial familial clustering. The estimated risk is 1.6% for first-degree relatives, compared with 0.026% in the general population. [9]

The HLA complex, situated on the short arm of chromosome 6, consists of genes encoding histocompatibility antigens known as HLA molecules. These molecules are essential for immune surveillance and the establishment of immunological tolerance. Their primary function is to facilitate the discrimination between self and non-self-antigens. Recognition of foreign antigens activates adaptive immune mechanisms, while self-antigens are tolerated, preventing the destruction of the body's own tissues by lymphocytes. [10] Recent studies suggest that particular polymorphisms within the HLA regions are associated with a higher frequency of distinct autoantibody profiles characteristic of SSc. These genetic variants have also been implicated in modulating disease susceptibility, contributing to either an elevated or a reduced risk of disease onset. [11] For example, HLA-DRB111, HLA-A30, HLA-DRB101, and HLA-A32 are associated with an elevated risk of developing the disease, while HLA-Cw*14, HLA-DRB1*1501, HLA-DQA1*0201, HLA-DRB1*0701, and HLA-DQB1*0202 appear to be linked to a lower susceptibility to SSc. [12-13]

Apart from the established role of HLA genes, evidence from candidate gene analyses and large-scale genome-wide association studies (GWAS) has further elucidated the genetic basis of SSc. [14] Through the evaluation of single-nucleotide polymorphisms (SNPs), these approaches have identified multiple genomic regions significantly related to disease risk, such as STAT4, IRF5, BANK1, CSK, and many other genes. [15-18]

What is more, epigenetic regulation is also thought to play a role in the pathogenesis of SSc. [19] A study conducted by Dees et al. demonstrates a correlation between DNA methylation and abnormal Wnt signaling in SSc. Promoter hypermethylation was found to silence the Wnt antagonists DKK1 and SFRP1, whereas DNMT inhibition re-established their expression and attenuated experimental fibrosis by blocking canonical Wnt signaling. The downregulation of DKK1 may lead to increased activation of pro-fibrotic pathways, potentially facilitating the development and progression of fibrosis. [20]

1.2 Triggers

Infectious agents are considered potential environmental triggers of SSc. They may promote the loss of T- and B-cell tolerance through molecular mimicry, whereby pathogen antigens resemble self-proteins and induce autoimmune responses. [21] Additionally, activation of innate immunity through interactions between pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs) can amplify immune activation and contribute to tissue damage. Several pathogens, including cytomegalovirus (CMV), Epstein–Barr virus (EBV), and parvovirus B19 have been suggested as possible initiators of SSc in susceptible individuals. [22-23]

Regarding environmental determinants, evidence indicates that exposure to silica and organic solvents represents one of the most important risk factors, although other agents, including vinyl chloride, tryptophan, and contaminated oil, have also been studied in the pathogenesis of scleroderma. [24]

It has also been proposed that, in certain oncological patients, tumor-associated antigens may activate the immune system and induce the production of autoantibodies similar to those observed in SSc, including antibodies targeting RNA polymerase III. [25]

1.3 Progression

The underlying theory of vasculopathy progression is based on primary epithelial damage, the development of perivascular inflammation, and platelet aggregation leading to an imbalance between vasoconstricting and vasodilating factors. [26] The overexpression of endothelin-1 (ET-1), a potent vasoconstrictor, together with reduced nitric oxide (NO) production, a key vasodilatory mediator, contributes to an increased susceptibility to ischemic events. This imbalance may promote the formation of reactive oxygen species (ROS) and anaerobic metabolic products, resulting in tissue damage and the development of fibrosis in the internal organs. [27-28] Sustained disturbances in microvascular tone damage the endothelial barrier, leading to disruption of intercellular junctions and increased vascular permeability. [29] In SSc, platelet activation further contributes by releasing thromboxane A2 (TXA2), which has a strong platelet-aggregating effect. Concurrently, activated endothelial cells upregulate adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1) and intercellular adhesion molecule (ICAM), promoting recruitment of circulating inflammatory cells and amplifying vascular inflammation. [30]

Microvascular endothelial cell damage and programmed cell death are central processes in the pathogenesis of SSc-associated vasculopathy and play a crucial role in triggering immune system activation. [31] This process, in turn, leads to the production of profibrotic cytokines such as interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 13 (IL-13), and transforming growth factor β (TGF β), which stimulate fibroblasts and myofibroblasts to produce the extracellular matrix (ECM) and type 1 collagen, thereby contributing to the process of tissue fibrosis. [32-33] A summary of the pathophysiological processes underlying SSc is presented in Figure 1.

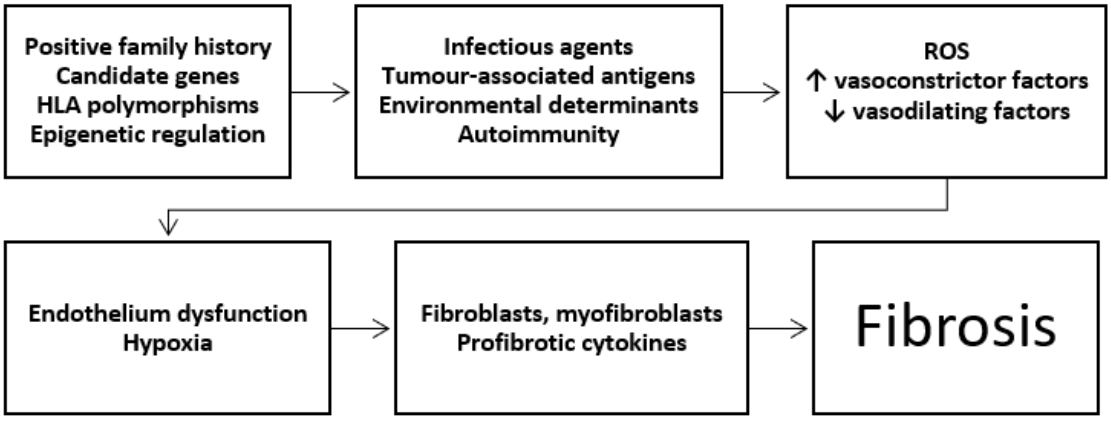

Fig. 1. *A summary of the pathophysiological processes underlying systemic sclerosis*

2. Diagnosis

Autoantibodies are detected in the sera of approximately 90–95% of patients with scleroderma, the majority of which are disease-specific antibodies. [34] The most important and specific of these are anti-centromere antibodies (ACA), anti-topoisomerase I antibodies (anti-TopoI), also known as anti-Scl-70, and anti-RNA polymerase III antibodies (antiRNAP3). [35] Although disease-specific autoantibodies are not thought to play a major role in the pathogenesis of SSc, they remain the most valuable biomarkers for clinical practice. [36] Their presence supports disease diagnosis and provides important prognostic information, helping to predict distinct clinical manifestations and disease phenotypes. [37] Interestingly, the detection of more than one scleroderma-specific autoantibody in an individual patient's serum is a relatively rare phenomenon. [38]

Anti-centromere antibodies (ACA) occur in 20-40% of all SSc patients, and their specificity exceeds 95%, making them a highly specific serological marker of SSc. [39, 40] They are most commonly associated with the limited cutaneous subtype of the disease (lcSSc), while diffuse cutaneous involvement is observed only infrequently in ACA-positive patients. [41] The presence of ACA is also linked to a higher prevalence of cutaneous calcinosis. [42] Clinically, ACA-positive individuals generally exhibit a more favorable prognosis, characterized by longer survival, a lower frequency of diffuse skin involvement, and reduced rates of pulmonary and renal complications. [43] However, ACA positivity is associated with an increased risk of pulmonary arterial hypertension (PAH), which typically develops during the later stages of the disease course. [44]

Anti-RNA polymerase III antibodies occur in 4-11% of all SSc patients. [45] With a specificity exceeding 99%, they are strongly associated with the diffuse cutaneous subtype of SSc (dcSSc). [39, 46] Patients positive for anti-RNAP3 typically exhibit the highest risk of diffuse skin involvement, increased frequency of joint contractures, and poorer overall survival. [43, 46] Although skin fibrosis often progresses rapidly during the early stages of the disease, skin thickening may subsequently stabilize or even regress over time. [47] Anti-RNAP3 positivity is also strongly associated with internal organ complications, particularly scleroderma renal crisis (SRC), for which these patients have the highest risk among all SSc autoantibody subsets. [48] Moreover, increasing evidence suggests a substantial correlation between anti-RNAP3 antibodies and malignancy that arises in close temporal proximity to the onset of SSc. Compared with anti-RNAP3-negative individuals, patients carrying these antibodies have a substantially increased likelihood of receiving a cancer diagnosis around the time of disease onset. [49]

Anti-topoisomerase I antibodies occur in 9-42% of all SSc patients and are highly specific serological markers of SSc, with a specificity exceeding 99%. [39, 40] They are considered important predictive biomarkers of disease progression in patients who initially present with isolated Raynaud's phenomenon. [50] Patients with anti-Topo I antibodies frequently exhibit flexion contractures of the metacarpophalangeal and proximal interphalangeal joints and ischemic digital ulcers. [51] Anti-Topo I positivity is strongly associated with the dcSSc and considered a significant risk factor for the early development of diffuse skin involvement, particularly during the first years of the disease course. [52] Among SSc-specific autoantibodies, anti-Topo I is most strongly linked to interstitial lung disease (ILD), which represents one of the most severe organ complications and a leading cause of mortality in SSc. [44, 53]

Autoantibodies that occur infrequently in SSc have not been incorporated into the classification criteria, largely due to limited evidence regarding their diagnostic and prognostic value. Consequently, their relationship with distinct clinical phenotypes remains incompletely characterized. [54] The diagnosis of SSc is a comprehensive process and is not limited solely to laboratory testing for antibodies in patients' serum. Depending on the individual clinical case, it may also be necessary to carry out appropriate imaging and functional tests. In 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed classification criteria for SSc, which can be found in Table 1. [55]

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Category	Subitems	Score
Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints[a]		9
Skin thickening of the fingers[b]	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions[b]	Digital tip ulcers	2
	Pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease[c]	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies[d]	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

These criteria are applicable to any patient considered for inclusion in a SSc study. The criteria do not apply to patients exhibiting skin thickening that spares the fingers or to those with a scleroderma-like illness that more adequately accounts for their symptoms. Patients with a total score of ≥9 are classified as having definite SSc

[a] it is a sufficient criterion for SSc classification

[b] only count the highest score

[c] maximum score is 2

[d] maximum score is 3

Source: [55]

As shown in the table, the diagnostic criteria include a physical examination finding known as Raynaud's phenomenon, which presents as a biphasic colour change of the digits involving pallor and cyanosis in response to multifactorial vasospasm. [56]

During capillaroscopy, on the other hand, we are able to observe “abnormal nailfold capillaries”, which is also mentioned in the guidelines. Their characteristic features in the initial phase of the disease are enlarged capillaries (also known as megacapillaries) and mild micro-hemorrhages, whereas in the final phase, there is a significant loss of capillaries. [57]

3. Treatment

Systemic sclerosis still remains an incurable disease, and current treatment strategies are primarily intended to inhibit progression, maintain control over disease activity, and minimize organ injury. Immunosuppressive drugs constitute the cornerstone of therapy, although their long-term use is associated with a risk of adverse effects. [58] For this reason, treatment is focused on organ-based complications.

3.1 Treatment of Raynaud's Phenomenon and Digital Ulcers

Calcium channel blockers (CCBs), particularly dihydropyridine derivatives such as amlodipine or nifedipine, are recommended as first-line therapy for Raynaud’s phenomenon associated with systemic sclerosis (SSc-RP), as they effectively reduce the frequency and severity of vasospastic attacks. [59-60] Phosphodiesterase type 5 inhibitors (PDE-5Is), including sildenafil and tadalafil, are considered second-line treatment, improving the severity and frequency of Raynaud’s attacks while promoting the healing and prevention of digital ulcers. [59, 61] Intravenous iloprost is reserved for patients with severe ischemia or threatened digital loss, whereas bosentan, an endothelin receptor antagonist, has been shown to reduce the occurrence of new digital ulcers but does not accelerate healing of existing lesions. [59, 61-63]

3.2 Treatment of Skin Manifestations

Mycophenolate mofetil (MMF) is considered the first-line treatment due to its favorable safety profile and efficacy comparable to cyclophosphamide (CYC) in reducing skin fibrosis. [59, 64] Although CYC remains an effective option, its use has declined because of treatment-related toxicity and the availability of safer alternatives. [65] Rituximab (RTX) has also demonstrated beneficial effects, including significant improvements in skin thickening and inflammatory markers, supporting its use in selected patients and therefore can be considered a second-line therapy. [59, 66] Methotrexate (MTX) may be considered in patients with dsSSc, particularly when musculoskeletal manifestations predominate, although its effect on skin fibrosis is modest. [59, 67] In patients presenting early with inflammatory dsSSc, tocilizumab may be considered as a treatment of skin fibrosis. [59] For carefully selected patients with early, rapidly progressive disease, autologous hematopoietic stem cell transplantation (HSCT) offers the greatest improvement in skin involvement but is reserved for severe cases because of the associated treatment-related risks. [68]

3.3 Treatment of Scleroderma Renal Crisis (SRC)

Prompt initiation of angiotensin-converting enzyme (ACE) inhibitor therapy is the standard of care following the diagnosis of scleroderma renal crisis. In addition, patients with SSc receiving glucocorticoids should undergo regular blood pressure monitoring to facilitate early detection of this potentially life-threatening complication. [59, 69] ACE inhibitors are not recommended for preventive use in SRC, as current evidence is insufficient to support such an indication. [70]

3.4 Treatment of Interstitial Lung Disease (ILD)

Mycophenolate mofetil is considered the first-line treatment and has demonstrated efficacy comparable to CYC in improving or stabilizing forced vital capacity (FVC), with a more favorable tolerability profile. [59, 71] Rituximab has also shown beneficial effects, with evidence of FVC stabilization and improved outcomes compared with placebo in randomized and meta-analytic data. [59, 72] Cyclophosphamide provides short-term improvement in lung function but is limited by toxicity and loss of sustained benefit after treatment cessation. [59, 73] Nintedanib is suggested as a second-line or supplementary antifibrotic treatment and has demonstrated a significant reduction in the rate of FVC decline, with possible additional advantages when used in conjunction with MMF. [59, 74] Tocilizumab may be particularly effective in patients with "early inflammatory" disease phenotypes, where it has been associated with stabilization of lung function. [59, 75] In contrast, HSCT has demonstrated superior long-term efficacy compared with CYC in selected patients, leading to significant improvements in FVC. [68] Emerging approaches, including JAK-STAT pathway inhibitors and CAR-T cell–based strategies, have shown promising early results, with evidence of reduced inflammation, B-cell depletion, and radiological and functional improvement in lung involvement. [76-77] In selected patients with systemic sclerosis–associated interstitial lung disease (SSc-ILD), lung transplantation may be considered as a therapeutic option when disease progression persists despite available pharmacological treatments. [78]

3.5 Treatment of Pulmonary Arterial Hypertension (PAH)

First-line treatment in newly diagnosed patients typically includes PDE-5i in combination with an endothelin receptor antagonist (ERA), which has been shown to significantly reduce clinical failure events compared with monotherapy. [59, 79] In class III and IV of SSc-PAH, intravenous epoprostenol remains an effective therapy and should be considered for treatment. [59, 80] Additional therapeutic options include prostacyclin receptor agonists such as selexipag, which has demonstrated a reduction in morbidity–mortality outcomes, and riociguat, a guanylate cyclase stimulator, which presented sustained long-term benefits observed in clinical trials. [59, 81-82] It is also worth noting that anticoagulant therapy is not recommended for the management of SSc-PAH. [83]

3.6 Treatment of Gastrointestinal Manifestations

In patients with symptomatic peristalsis disturbances, the use of prokinetic drugs may be beneficial. [59] Constipation resulting from colonic dysmotility is most commonly managed with osmotic laxatives, as well as stimulant laxatives. [84] For the management of systemic sclerosis–related gastroesophageal reflux disease (SSc-GERD) and the prevention of esophageal ulcers and esophagitis, proton pump inhibitors (PPIs) should be considered. [85]

Conclusions

Systemic sclerosis remains a significant challenge for the understanding of the complex pathophysiological mechanisms underlying disease onset and progression. Marked clinical heterogeneity complicates its diagnosis, classification, and therapeutic decisions. Despite these limitations, substantial advances have been achieved in the treatment of SSc. The expansion of immunosuppressive regimens, alongside the development of targeted and biologic therapies, has considerably broadened therapeutic options. Although no currently available treatment is capable of fully reversing disease progression, improved insight into the interplay between immune dysregulation, vasculopathy, and fibrosis has facilitated more individualized and increasingly effective treatment strategies.

Author's contribution:

Conceptualization: Olaf Krawczyk, Katarzyna Boszczyk

Methodology: Monika Kamela, Katarzyna Boszczyk, Małgorzata Grzybowska

Software: Olaf Krawczyk, Piotr Wilczkowski, Natalia Krzysztofek

Check: Wojciech Kopyciński, Norbert Krawczyk, Adrianna Baran, Piotr Wilczkowski

Formal analysis: Adrianna Baran, Aleksandra Palka, Monika Kamela

Investigation: Olaf Krawczyk, Adrianna Baran, Małgorzata Grzybowska

Resources: Monika Kamela, Aleksandra Palka, Natalia Krzysztofek

Data curation: Wojciech Kopyciński, Norbert Krawczyk, Piotr Wilczkowski

Writing – rough preparation: Olaf Krawczyk, Katarzyna Boszczyk, Aleksandra Palka, Małgorzata Grzybowska

Writing – review and editing: Katarzyna Boszczyk, Wojciech Kopyciński, Piotr Wilczkowski

Visualization: Natalia Krzysztofek, Monika Kamela, Norbert Krawczyk, Natalia Krzysztofek

Supervision: Olaf Krawczyk, Wojciech Kopyciński, Norbert Krawczyk

Project administration: Olaf Krawczyk

All authors have read and agreed with the published version of the manuscript.

Ethical approval: Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding statement: No external funding was received to perform this review.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Good, S. D., Lee, J. Y., Johnson, R. E., & Volkmann, E. R. (2025). A scoping review of the epidemiology of systemic sclerosis and its organ manifestations: 2018–2024. *Current Opinion in Rheumatology, 37*(2), 103–112. https://doi.org/10.1097/BOR.0000000000001063
2. Bairkdar, M., Rossides, M., Westerlind, H., Hesselstrand, R., Arkema, E. V., & Holmqvist, M. (2021). Incidence and prevalence of systemic sclerosis globally: A comprehensive systematic review and meta-analysis. *Rheumatology, 60*(7), 3121–3133. https://doi.org/10.1093/rheumatology/keab190
3. Alba, M. A., Velasco, C., Simeón, C. P., Fonollosa, V., Trapiella, L., Egurbide, M. V., Sáez, L., Castillo, M. J., Callejas, J. L., Camps, M. T., Tolosa, C., Ríos, J. J., Freire, M., Vargas, J. A., Espinosa, G., & RESCLE Registry. (2014). Early- versus late-onset systemic sclerosis: Differences in clinical presentation and outcome in 1,037 patients. *Medicine, 93*(2), 73–81. https://doi.org/10.1097/MD.0000000000000018
4. Elhai, M., Meune, C., Boubaya, M., et al. (2017). Mapping and predicting mortality from systemic sclerosis. *Annals of the Rheumatic Diseases, 76*(11), 1897–1905. https://doi.org/10.1136/annrheumdis-2017-211448
5. Rubio-Rivas, M., Royo, C., Simeón, C. P., Corbella, X., & Fonollosa, V. (2014). Mortality and survival in systemic sclerosis: Systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism, 44*(2), 208–219. https://doi.org/10.1016/j.semarthrit.2014.05.010
6. Volkmann, E. R., Andréasson, K., & Smith, V. (2023). Systemic sclerosis. *The Lancet, 401*(10373), 304–318. https://doi.org/10.1016/S0140-6736(22)01692-0
7. Stern, E. P., & Denton, C. P. (2015). The pathogenesis of systemic sclerosis. *Rheumatic Disease Clinics of North America, 41*(3), 367–382. https://doi.org/10.1016/j.rdc.2015.04.002
8. Desbois, A. C., & Cacoub, P. (2016). Systemic sclerosis: An update in 2016. *Autoimmunity Reviews, 15*(5), 417–426. https://doi.org/10.1016/j.autrev.2016.01.007
9. Agarwal, S. K., Tan, F. K., & Arnett, F. C. (2008). Genetics and genomic studies in scleroderma (systemic sclerosis). *Rheumatic Disease Clinics of North America, 34*(1), 17–40. https://doi.org/10.1016/j.rdc.2007.10.001
10. Medhasi, S., & Chantratita, N. (2022). Human leukocyte antigen (HLA) system: Genetics and association with bacterial and viral infections. *Journal of Immunology Research, 2022*, Article 9710376. https://doi.org/10.1155/2022/9710376
11. Tan, F. K. (2003). Systemic sclerosis: The susceptible host (genetics and environment). *Rheumatic Disease Clinics of North America, 29*(2), 11–37. https://doi.org/10.1016/S0889-857X(03)00015-2
12. Gladman, D. D., Kung, T. N., Siannis, F., Pellett, F., Farewell, V. T., & Lee, P. (2005). HLA markers for susceptibility and expression in scleroderma. *The Journal of Rheumatology, 32*(8), 1481–1487.
13. Arnett, F. C., Gourh, P., Shete, S., et al. (2010). Major histocompatibility complex (MHC) class II alleles, haplotypes, and epitopes which confer susceptibility or protection in the fibrosing autoimmune disease systemic sclerosis: Analyses in 1,300 Caucasian, African American, and Hispanic cases and 1,000 controls. *Annals of the Rheumatic Diseases, 69*(5), 822–827. https://doi.org/10.1136/ard.2009.111906

14. Truchetet, M. E., Brembilla, N. C., & Chizzolini, C. (2023). Current concepts on the pathogenesis of systemic sclerosis. *Clinical Reviews in Allergy & Immunology, 64*(3), 262–283. https://doi.org/10.1007/s12016-021-08889-8
15. Radstake, T. R., Gorlova, O., Rueda, B., et al. (2010). Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus. *Nature Genetics, 42*(5), 426–429. https://doi.org/10.1038/ng.565
16. Allanore, Y., Saad, M., Dieudé, P., et al. (2011). Genome-wide scan identifies TNIP1, PSORS1C1, and RHOB as novel risk loci for systemic sclerosis. *PLOS Genetics, 7*(7), e1002091. https://doi.org/10.1371/journal.pgen.1002091
17. Dieude, P., Wipff, J., Guedj, M., et al. (2009). BANK1 is a genetic risk factor for diffuse cutaneous systemic sclerosis and has additive effects with IRF5 and STAT4. *Arthritis & Rheumatism, 60*(11), 3447–3454. https://doi.org/10.1002/art.24885
18. Martin, J.-E., Broen, J. C., Carmona, F. D., et al. (2012). Identification of CSK as a systemic sclerosis genetic risk factor through genome-wide association study follow-up. *Human Molecular Genetics, 21*(12), 2825–2835. https://doi.org/10.1093/hmg/dds099
19. Wang, Y., Fan, P. S., & Kahaleh, B. (2006). Association between enhanced type I collagen expression and epigenetic repression of the FLI1 gene in scleroderma fibroblasts. *Arthritis & Rheumatism, 54*(7), 2271–2279. https://doi.org/10.1002/art.21948
20. Dees, C., Schlottmann, I., Funke, R., Distler, A., Palumbo-Zerr, K., Zerr, P., Lin, N. Y., Beyer, C., Distler, O., Schett, G., & Distler, J. H. (2014). The Wnt antagonists DKK1 and SFRP1 are downregulated by promoter hypermethylation in systemic sclerosis. *Annals of the Rheumatic Diseases, 73*(6), 1232–1239. https://doi.org/10.1136/annrheumdis-2012-203194
21. Suliman, B. A. (2024). Potential clinical implications of molecular mimicry-induced autoimmunity. *Immunity, Inflammation and Disease, 12*(2), e1178. https://doi.org/10.1002/iid3.1178
22. Randone, S. B., Guiducci, S., & Cerinic, M. M. (2008). Systemic sclerosis and infections. *Autoimmunity Reviews, 8*(1), 36–40. https://doi.org/10.1016/j.autrev.2008.07.022
23. Moroncini, G., Mori, S., Tonnini, C., & Gabrielli, A. (2013). Role of viral infections in the etiopathogenesis of systemic sclerosis. *Clinical and Experimental Rheumatology, 31*(2, Suppl. 76), 3–7.
24. Rubio-Rivas, M., Moreno, R., & Corbella, X. (2017). Occupational and environmental scleroderma: Systematic review and meta-analysis. *Clinical Rheumatology, 36*(3), 569–582. https://doi.org/10.1007/s10067-016-3533-1
25. Shah, A. A., Rosen, A., Hummers, L., Wigley, F., & Casciola-Rosen, L. (2010). Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. *Arthritis & Rheumatism, 62*(9), 2787–2795. https://doi.org/10.1002/art.27549
26. Ko, J., Noviani, M., Chellamuthu, V. R., Albani, S., & Low, A. H. L. (2023). The pathogenesis of systemic sclerosis: The origin of fibrosis and interlink with vasculopathy and autoimmunity. *International Journal of Molecular Sciences, 24*(18), 14287. https://doi.org/10.3390/ijms241814287
27. Vona, R., Giovannetti, A., Gambardella, L., Malorni, W., Pietraforte, D., & Straface, E. (2018). Oxidative stress in the pathogenesis of systemic scleroderma: An overview. *Journal of Cellular and Molecular Medicine, 22*(7), 3308–3314. https://doi.org/10.1111/jcmm.13630
28. Ntelis, K., Solomou, E. E., Sakkas, L., Liossis, S. N., & Daoussis, D. (2017). The role of platelets in autoimmunity, vasculopathy, and fibrosis: Implications for systemic sclerosis. *Seminars in Arthritis and Rheumatism, 47*(3), 409–417. https://doi.org/10.1016/j.semarthrit.2017.05.004
29. Cutolo, M., Soldano, S., & Smith, V. (2019). Pathophysiology of systemic sclerosis: Current understanding and new insights. *Expert Review of Clinical Immunology, 15*(7), 753–764. https://doi.org/10.1080/1744666X.2019.1614915
30. Bruni, C., Frech, T., Manetti, M., Rossi, F. W., Furst, D. E., De Paulis, A., et al. (2018). Vascular leaking, a pivotal and early pathogenetic event in systemic sclerosis: Should the door be closed? *Frontiers in Immunology, 9*, 2045. https://doi.org/10.3389/fimmu.2018.02045
31. Matucci-Cerinic, M., Kahaleh, B., & Wigley, F. M. (2013). Review: Evidence that systemic sclerosis is a vascular disease. *Arthritis & Rheumatism, 65*(8), 1953–1962. https://doi.org/10.1002/art.37988
32. Denton, C. P. (2016). Advances in pathogenesis and treatment of systemic sclerosis. *Clinical Medicine, 16*(1), 55–60. https://doi.org/10.7861/clinmedicine.16-1-55
33. O'Reilly, S. (2013). Role of interleukin-13 in fibrosis, particularly systemic sclerosis. *BioFactors, 39*(6), 593–596. https://doi.org/10.1002/biof.1117
34. Guillevin, L., Bérezné, A., Seror, R., Teixeira, L., Pourrat, J., Mahr, A., et al. (2012). Scleroderma renal crisis: A retrospective multicentre study on 91 patients and 427 controls. *Rheumatology, 51*(3), 460–467. https://doi.org/10.1093/rheumatology/ker271
35. Günther, J., Rademacher, J., van Laar, J. M., Siegert, E., & Riemekasten, G. (2015). Functional autoantibodies in systemic sclerosis. *Seminars in Immunopathology, 37*(5), 529–542. https://doi.org/10.1007/s00281-015-0513-5
36. Berger, M., & Steen, V. D. (2017). Role of anti-receptor autoantibodies in pathophysiology of scleroderma. *Autoimmunity Reviews, 16*(10), 1029–1035. https://doi.org/10.1016/j.autrev.2017.07.019
37. Hasegawa, M. (2016). Biomarkers in systemic sclerosis: Their potential to predict clinical courses. *The Journal of Dermatology, 43*(1), 29–38. https://doi.org/10.1111/1346-8138.13156

38. Heijnen, I. A. F. M., Foocharoen, C., Bannert, B., et al. (2013). Clinical significance of coexisting antitopoisomerase I and anticentromere antibodies in patients with systemic sclerosis: A EUSTAR group-based study. *Clinical and Experimental Rheumatology, 31*(2, Suppl. 76), 96–102.
39. Stochmal, A., Czuwara, J., Trojanowska, M., & Rudnicka, L. (2020). Antinuclear antibodies in systemic sclerosis: An update. *Clinical Reviews in Allergy & Immunology, 58*(1), 40–51. https://doi.org/10.1007/s12016-018-8718-8
40. Villalta, D., Imbastaro, T., Di Giovanni, S., et al. (2012). Diagnostic accuracy and predictive value of extended autoantibody profile in systemic sclerosis. *Autoimmunity Reviews, 12*(2), 114–120. https://doi.org/10.1016/j.autrev.2012.07.005
41. Caetano, J., Nihtyanova, S. I., Harvey, J., Denton, C. P., & Ong, V. H. (2018). Distinctive clinical phenotype of anti-centromere antibody-positive diffuse systemic sclerosis. *Rheumatology Advances in Practice, 2*(1), rky002. https://doi.org/10.1093/rap/rky002
42. Valenzuela, A., & Chung, L. (2015). Calcinosis: Pathophysiology and management. *Current Opinion in Rheumatology, 27*(6), 542–548. https://doi.org/10.1097/BOR.0000000000000220
43. Harvey, G. R., & McHugh, N. J. (1999). Serologic abnormalities in systemic sclerosis. *Current Opinion in Rheumatology, 11*(6), 495–502.
44. Affandi, A. J., Radstake, T. R., & Marut, W. (2015). Update on biomarkers in systemic sclerosis: Tools for diagnosis and treatment. *Seminars in Immunopathology, 37*(5), 475–487. https://doi.org/10.1007/s00281-015-0506-4
45. Nihtyanova, S. I., Sari, A., Harvey, J. C., Leslie, A., Derrett-Smith, E. C., Fonseca, C., et al. (2020). Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. *Arthritis & Rheumatology, 72*(3), 465–476. https://doi.org/10.1002/art.41153
46. Kuwana, M. (2017). To-do list at diagnosis of systemic sclerosis with positive anti-RNA polymerase III antibodies. *The Journal of Rheumatology, 44*(5), 550–552. https://doi.org/10.3899/jrheum.170037
47. Wirz, E. G., Jaeger, V. K., Allanore, Y., et al. (2016). Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: A 10-year longitudinal study from the EUSTAR database. *Annals of the Rheumatic Diseases, 75*(7), 1285–1292. https://doi.org/10.1136/annrheumdis-2015-207271
48. Cavazzana, I., Vojinovic, T., Airo', P., Fredi, M., Ceribelli, A., Pedretti, E., Lazzaroni, M. G., Garrafa, E., & Franceschini, F. (2022). Systemic sclerosis-specific antibodies: Novel and classical biomarkers. *Clinical Reviews in Allergy & Immunology, 64*(3), 412–430. https://doi.org/10.1007/s12016-022-08946-w
49. Shah, A. A., Rosen, A., Hummers, L., Wigley, F., & Casciola-Rosen, L. (2010). Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. *Arthritis & Rheumatism, 62*(9), 2787–2795. https://doi.org/10.1002/art.27549
50. Koenig, M., Joyal, F., Fritzler, M. J., Roussin, A., Abrahamowicz, M., Boire, G., et al. (2008). Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: A twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. *Arthritis & Rheumatism, 58*(12), 3902–3912. https://doi.org/10.1002/art.24038
51. Radić, M., Martinović Kaliterna, D., & Ljutić, D. (2006). The level of anti-topoisomerase I antibodies highly correlates with metacarpophalangeal and proximal interphalangeal joint flexion contractures in patients with systemic sclerosis. *Clinical and Experimental Rheumatology, 24*(4), 407–412.
52. Herrick, A. L., Assassi, S., & Denton, C. P. (2022). Skin involvement in early diffuse cutaneous systemic sclerosis: An unmet clinical need. *Nature Reviews Rheumatology, 18*(5), 276–285. https://doi.org/10.1038/s41584-022-00765-9
53. Gelber, A. C., Manno, R. L., Shah, A. A., Woods, A., Le, E. N., Boin, F., et al. (2013). Race and association with disease manifestations and mortality in scleroderma: A 20-year experience at the Johns Hopkins Scleroderma Center and review of the literature. *Medicine, 92*(4), 191–205. https://doi.org/10.1097/MD.0b013e31829be125
54. Graf, S. W., Hakendorf, P., Lester, S., et al. (2012). South Australian Scleroderma Register: Autoantibodies as predictive biomarkers of phenotype and outcome. *International Journal of Rheumatic Diseases, 15*(1), 102–109. https://doi.org/10.1111/j.1756-185X.2011.01688.x
55. van den Hoogen, F., Khanna, D., Fransen, J., et al. (2013). 2013 classification criteria for systemic sclerosis: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Annals of the Rheumatic Diseases, 72*(11), 1747–1755. https://doi.org/10.1136/annrheumdis-2013-204424
56. Nawaz, I., Nawaz, Y., Nawaz, E., Manan, M. R., & Mahmood, A. (2022). Raynaud's phenomenon: Reviewing the pathophysiology and management strategies. *Cureus, 14*(1), e21681. https://doi.org/10.7759/cureus.21681
57. Wiąk-Walerowicz, K., Wielosz, E., & Majdan, M. (2024). The usefulness of nailfold capillaroscopy in scleroderma-spectrum disorders: A single-centre observational study. *Postępy Dermatologii i Alergologii, 41*(3), 296–300. https://doi.org/10.5114/ada.2024.141158
58. Chasov, V., Mukhametshin, S., Gilyazova, E., Davletshin, D., Tikhomirova, M., Topchu, I., Valiullina, A., Prete, M., & Bulatov, E. (2026). Emerging cell-based therapies for systemic sclerosis: From stem cells to CAR-T cells. *Current Issues in Molecular Biology, 48*(1), 76. https://doi.org/10.3390/cimb48010076
59. Del Galdo, F., Lescoat, A., Conaghan, P. G., et al. (2024). EULAR recommendations for the treatment of systemic sclerosis: 2023 update. *Annals of the Rheumatic Diseases, 84*(1), 29–40. https://doi.org/10.1136/ard-2024-226430

60. Hughes, M., Ong, V. H., Anderson, M. E., et al. (2015). Consensus best practice pathway of the UK Scleroderma Study Group: Digital vasculopathy in systemic sclerosis. *Rheumatology, 54*(11), 2015–2024. https://doi.org/10.1093/rheumatology/kev201
61. Roustit, M., Blaise, S., Allanore, Y., et al. (2013). Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: Systematic review and meta-analysis of randomised trials. *Annals of the Rheumatic Diseases, 72*(10), 1696–1699. https://doi.org/10.1136/annrheumdis-2012-202836
62. Hughes, M., Allanore, Y., El Aoufy, K., et al. (2021). A practical approach to the management of digital ulcers in patients with systemic sclerosis: A narrative review. *JAMA Dermatology, 157*(7), 851–858. https://doi.org/10.1001/jamadermatol.2021.1463
63. Korn, J. H., Mayes, M., Matucci Cerinic, M., et al. (2004). Digital ulcers in systemic sclerosis: Prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis & Rheumatism, 50*(12), 3985–3993. https://doi.org/10.1002/art.20676
64. Omair, M. A., Alahmadi, A., Johnson, S. R., et al. (2015). Safety and effectiveness of mycophenolate in systemic sclerosis: A systematic review. *PLOS ONE, 10*(5), e0124205. https://doi.org/10.1371/journal.pone.0124205
65. Namas, R., Tashkin, D. P., Furst, D. E., et al. (2018). Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: Post hoc analyses from two randomized placebo-controlled trials. *Arthritis Care & Research, 70*(3), 439–444. https://doi.org/10.1002/acr.23282
66. Campochiaro, C., De Luca, G., Lazzaroni, M. G., et al. (2020). Safety and efficacy of rituximab biosimilar (CT-P10) in systemic sclerosis: An Italian multicentre study. *Rheumatology, 59*(12), 3731–3736. https://doi.org/10.1093/rheumatology/keaa136
67. Pope, J. E., Bellamy, N., Seibold, J. R., et al. (2001). A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis & Rheumatism, 44*(6), 1351–1358. https://doi.org/10.1002/1529-0131(200106)44:6%3C1351::AID-ART227%3E3.0.CO;2-I
68. Van Laar, J. M., Farge, D., Sont, J. K., et al. (2014). Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: A randomized clinical trial. *JAMA, 311*(24), 2490–2498. https://doi.org/10.1001/jama.2014.6368
69. Trang, G., Steele, R., Baron, M., et al. (2012). Corticosteroids and the risk of scleroderma renal crisis: A systematic review. *Rheumatology International, 32*(3), 645–653. https://doi.org/10.1007/s00296-010-1697-6
70. Xiong, A., Cao, Y., Xiang, Q., et al. (2022). Angiotensin-converting enzyme inhibitors prior to scleroderma renal crisis in systemic sclerosis: A systematic review and meta-analysis. *Journal of Clinical Pharmacy and Therapeutics, 47*(6), 722–731. https://doi.org/10.1111/jcpt.13621
71. Volkmann, E. R., Tashkin, D. P., Li, N., et al. (2017). Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: An analysis of Scleroderma Lung Studies I and II. *Arthritis & Rheumatology, 69*(7), 1451–1460. https://doi.org/10.1002/art.40114
72. Maher, T. M., Tudor, V. A., Saunders, P., et al. (2023). Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): A double-blind, double-dummy, randomised, controlled, phase 2b trial. *The Lancet Respiratory Medicine, 11*(1), 45–54. https://doi.org/10.1016/S2213-2600(22)00359-9
73. Tashkin, D. P., Elashoff, R., Clements, P. J., et al. (2006). Cyclophosphamide versus placebo in scleroderma lung disease. *The New England Journal of Medicine, 354*(25), 2655–2666. https://doi.org/10.1056/NEJMoa055120
74. Highland, K. B., Distler, O., Kuwana, M., et al. (2021). Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: A subgroup analysis of the SENSCIS trial. *The Lancet Respiratory Medicine, 9*(1), 96–106. https://doi.org/10.1016/S2213-2600(20)30330-1
75. Roofeh, D., Lin, C. J. F., Goldin, J., et al. (2021). Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. *Arthritis & Rheumatology, 73*(7), 1301–1310. https://doi.org/10.1002/art.41668
76. Junfei, Z., Meihua, G., Shuai, Z., et al. (2023). Retrospective comparative study of the efficacy of JAK inhibitor (tofacitinib) in the treatment of systemic sclerosis-associated interstitial lung disease. *Clinical Rheumatology, 42*(10), 2823–2832. https://doi.org/10.1007/s10067-023-06660-2
77. Wang, X., Wu, X., Tan, B., et al. (2024). Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis. *Cell, 187*(18), 4890–4904.e9. https://doi.org/10.1016/j.cell.2024.06.027
78. Bes, C., & Çetinkaya, E. (2022). Current treatment of systemic sclerosis-associated interstitial lung disease. *Tuberkuloz ve Toraks, 70*(1), 85–92. https://doi.org/10.5578/tt.20229910
79. Galiè, N., Barberà, J. A., Frost, A. E., et al. (2015). Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *The New England Journal of Medicine, 373*(9), 834–844. https://doi.org/10.1056/NEJMoa1413687
80. Badesch, D. B., Tapson, V. F., McGoon, M. D., et al. (2000). Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: A randomized, controlled trial. *Annals of Internal Medicine, 132*(6), 425–434. https://doi.org/10.7326/0003-4819-132-6-200003210-00002
81. Gaine, S., Chin, K., Coghlan, G., et al. (2017). Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. *European Respiratory Journal, 50*(2), 1602493. https://doi.org/10.1183/13993003.02493-2016

82. Rubin, L. J., Galiè, N., Grimminger, F., et al. (2015). Riociguat for the treatment of pulmonary arterial hypertension: A long-term extension study (PATENT-2). *European Respiratory Journal, 45*(5), 1303–1313. https://doi.org/10.1183/09031936.00090614
83. Morrisroe, K., Stevens, W., Huq, M., et al. (2017). Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. *Arthritis Research & Therapy, 19*(1), 122. https://doi.org/10.1186/s13075-017-1341-x
84. Vigone, B., Caronni, M., Severino, A., et al. (2017). Preliminary safety and efficacy profile of prucalopride in the treatment of systemic sclerosis (SSc)-related intestinal involvement: Results from the open-label cross-over PROGASS study. *Arthritis Research & Therapy, 19*(1), 145. https://doi.org/10.1186/s13075-017-1340-y
85. Hughes, M., Allanore, Y., Baron, M., et al. (2022). Proton pump inhibitors in systemic sclerosis: A reappraisal to optimise treatment of gastro-oesophageal reflux disease. *The Lancet Rheumatology, 4*(11), e795–e803. https://doi.org/10.1016/S2665-9913(22)00183-7