Natural Resources for Human Health

eISSN: 2583-1194

Original Research

Received 25 July 2026
Revised 24 Aug 2026
Accepted 12 Sep 2026

Natural Resources for Human Health 2026, Vol. 6 (20s): 44–51

KEYWORDS:
Systemic sclerosis, Scleroderma, Interstitial lung disease, Immunosuppression, Antifibrotic therapy, Tocilizumab, Rituximab, Personalized medicine, Multidisciplinary care..

Modern Strategies for the Comprehensive Treatment of Systemic Sclerosis: From Pathogenesis to Personalized Therapy

Larisa V. Kadomseva[1*], Rustam U. Daminov[2], Tamilla A. Valieva[3], Farida R. Mirzakarimova[4], Nazifa V. Agzamova[5], Xadicha Ya. Abduraxmonova[6], Elmurod T. Ibinkhujaev[7], Lola A. Karataeva[8], Galina E. Dergunova[9], Muhametamin M. Shertaev[10], Polykarpova Natalia Vladimirovna[11]

[1] Associate Professor, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, kadomseva.l.v@tashmeduni.uz, ORCID: 0000-0001-6243-7396

[2] Lecturer, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, leo_part@mail.ru, ORCID: 0000-0003-3164-1444

[3] Lecturer, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, valieva0tamila@gmail.com, ORCID: 0000-0002-2987-1702

[4] Lecturer, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, mirzakarimova.f.r@tashmeduni.uz, ORCID: 0000-0002-5498-926X

[5] Associate Professor, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, agzamova.n.v@tashmeduni.uz, ORCID: 0000-0003-4699-4488

[6] Lecturer, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, abduraxmonovaxadicha004@gmail.com, ORCID: 0000-0001-6733-1013

[7] Lecturer, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, ibinxojaevelmurod@gmail.com, ORCID: 0009-0002-4661-959X

[8] Lecturer, Department of Anatomy, Histology, Pathological Anatomy, Tashkent State Medical University, Tashkent, Uzbekistan, lolakarataeva0902@mail.ru, ORCID: 0000-0002-8468-905X

[9] Lecturer, Department of Hospital Pediatrics, Traditional Medicine, Tashkent State Medical University, Tashkent, Uzbekistan, galchik9@mail.ru, ORCID: 0000-0002-3666-7541

[10] Associate Professor, Department of Medical and Biological Chemistry, Medical Biology and Genetics, Tashkent State Medical University, Tashkent, Uzbekistan, shertaev-25@mail.ru, ORCID: 0000-0002-3666-7541

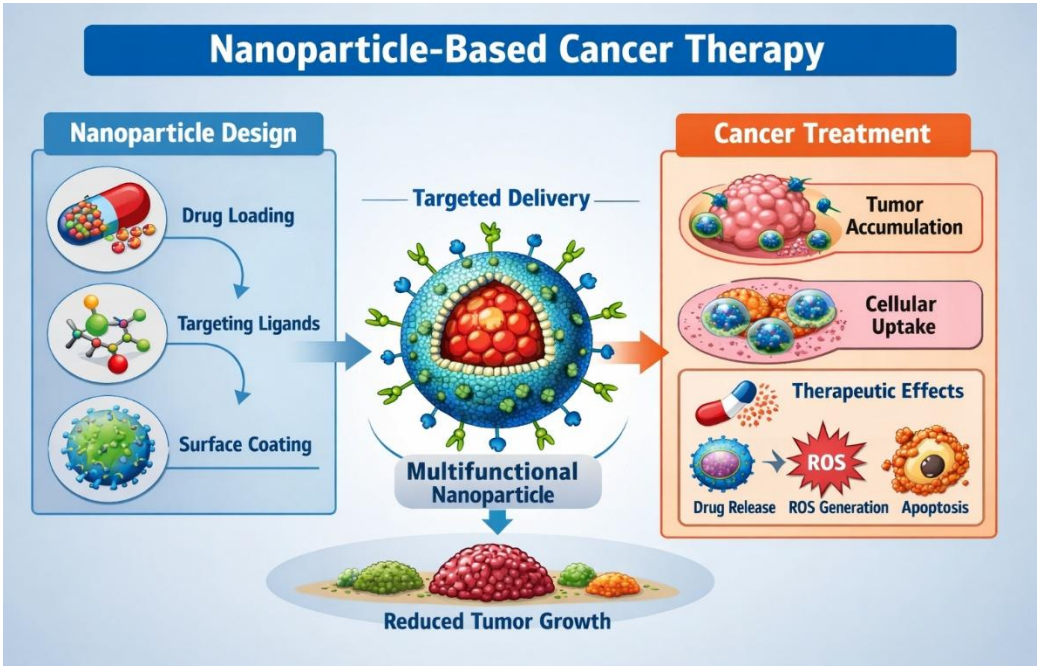
[11] Lecturer, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, nataliapolikarpova11@gmail.com, ORCID: 0000-0002-7892-1307

*Corresponding Author: Larisa V. Kadomseva, Department of Family Medicine 2 and Clinical Pharmacology, Tashkent State Medical University, Tashkent, Uzbekistan, l.kadomtseva@tashpmi.uz

Natural Resources for Human Health
eISSN: 2583-1194

ABSTRACT: Systemic sclerosis (SSc) is a severe autoimmune connective tissue disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis of the skin and internal organs. The clinical heterogeneity of SSc presents significant challenges in early diagnosis and treatment. Over the past decade, the therapeutic paradigm has shifted from symptomatic management to pathogenetically oriented strategies, including immunosuppression, targeted immunomodulation, and antifibrotic therapy, underpinned by a "treat-to-target" approach and risk stratification. This review synthesizes contemporary evidence on comprehensive, domain-based management of SSc. We detail the central roles of immunosuppressants like mycophenolate mofetil and cyclophosphamide in interstitial lung disease (ILD), the antifibrotic agent nintedanib for SSc-ILD, and targeted therapies such as the IL-6 receptor inhibitor tocilizumab and the B-cell depleting agent rituximab. The importance of early diagnosis within a "window of opportunity," rigorous screening for organ involvement, and a mandatory multidisciplinary approach is emphasized. The article concludes that modern SSc management requires a personalized strategy integrating early phenotypic characterization, continuous monitoring, and rational combination therapy to modify disease progression and improve patient outcomes.

GRAPHICAL ABSTRACT



INTRODUCTION

Systemic sclerosis (SSc), or systemic scleroderma, represents one of the most complex and severe systemic autoimmune rheumatic diseases, with a pathogenesis triad encompassing immune-inflammatory activation, generalized microangiopathy, and progressive fibrosis of the skin and visceral organs (Allanore et al., 2021). Its clinical spectrum is remarkably heterogeneous, encompassing limited and diffuse cutaneous subsets, variable organ involvement (lungs, heart, kidneys, gastrointestinal tract), and differing progression rates, which collectively complicate early diagnosis, prognosis, and therapeutic decision-making (Denton & Khanna, 2017).

For many years, SSc management was predominantly reactive and focused on alleviating symptoms and managing vascular complications, such as Raynaud's phenomenon and digital ulcers, and severe organ crises like scleroderma renal crisis (SRC).

However, the last 10–15 years have witnessed a profound transformation in the therapeutic landscape, driven by a deeper understanding of its multifaceted pathogenesis. The current paradigm is proactive and pathogenetically oriented, moving from universal schemes to a domain-based, personalized approach (Distler et al., 2019; Khanna et al., 2020). This shift recognizes the existence of a critical "window of opportunity" in early disease, where inflammatory and vascular drivers are more dominant and potentially reversible, before irreversible fibrotic remodeling becomes established (Del Galdo et al., 2024).

The evolving treatment arsenal now includes refined use of classical immunosuppressants, introduction of targeted biologic agents against specific immune pathways (e.g., IL-6, B-cells), and the groundbreaking advent of antifibrotic drugs. Landmark clinical trials such as Scleroderma Lung Study (SLS) II, SENSCIS, focuSSced, and DESIRES have provided high-level evidence shaping modern guidelines (Tashkin et al., 2016; Distler et al., 2019; Khanna et al., 2020; Ebata et al., 2021). Furthermore, the management of SSc is inherently multidisciplinary, requiring close collaboration among rheumatologists, pulmonologists, cardiologists, nephrologists, gastroenterologists, and rehabilitation specialists to address the diverse organ manifestations that dictate morbidity and mortality.

PURPOSE OF THE RESEARCH

The purpose of this comprehensive review is to analyze and synthesize the contemporary strategies for the holistic management of systemic sclerosis, with a focus on the transition from pathogenesis-driven insights to personalized clinical application. We aim to detail the evidence base for modern therapeutic interventions across different organ domains, underscore the critical importance of early diagnosis and risk stratification, and discuss the implementation of a multidisciplinary, "treat-to-target" model within a clinical setting, specifically contextualizing these principles for the advancement of patient care at the Tashkent State Medical University and affiliated institutions.

MATERIALS AND METHODS

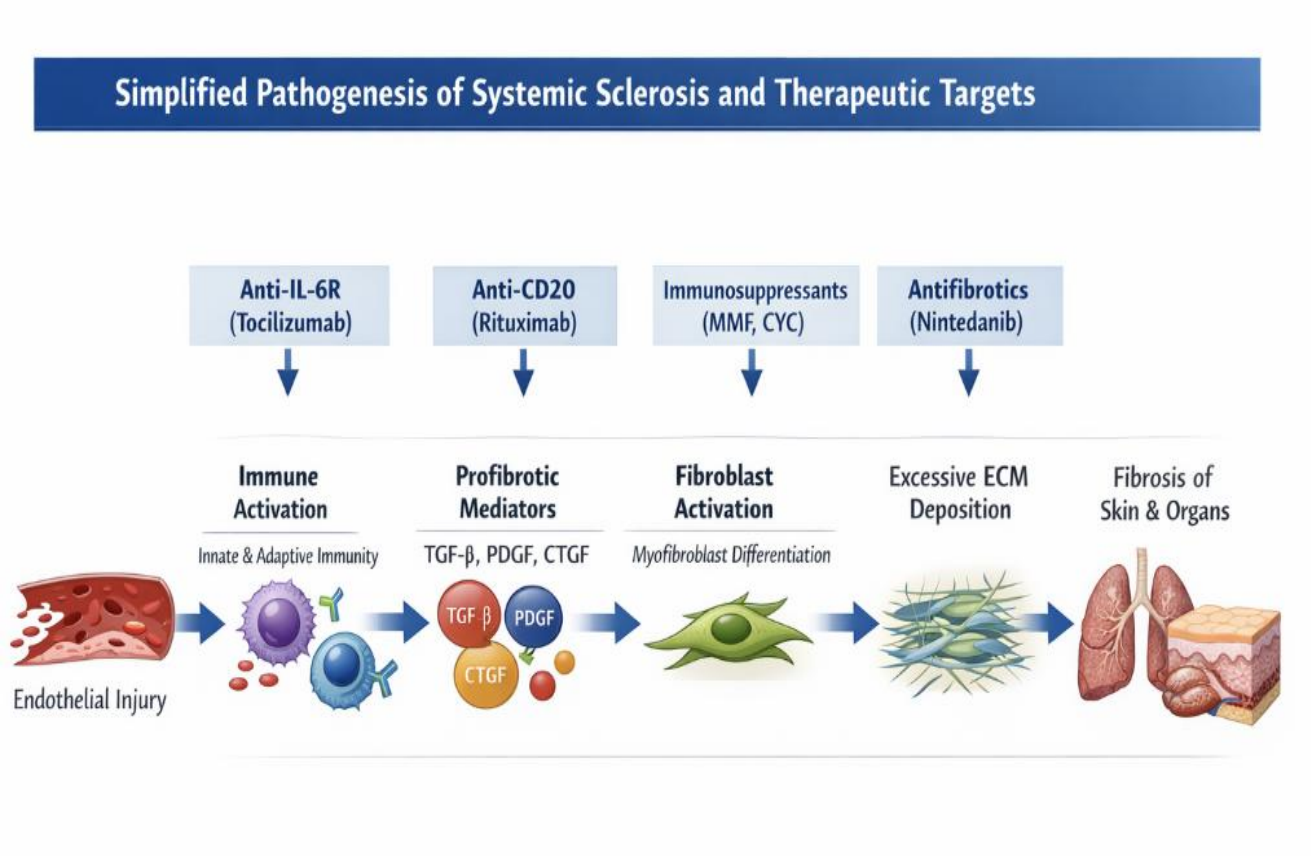
This narrative review was conducted through an extensive analysis of current international scientific literature. The primary sources for data retrieval were peer-reviewed databases including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. The search period focused on publications from 2015 to 2025, with inclusion of seminal older trials. Key search terms included: "systemic sclerosis," "scleroderma," "interstitial lung disease," "mycophenolate mofetil," "nintedanib," "tocilizumab," "rituximab," "treatment guidelines," "pathogenesis," and "personalized therapy." We prioritized meta-analyses, large randomized controlled trials (RCTs), and updated international guidelines (EULAR, BSR). The authors' contributions, indexed via ORCID profiles, encompass literature analysis, data synthesis, clinical expertise interpretation, and manuscript preparation, ensuring a comprehensive overview grounded in both evidence and practical clinical experience from the Tashkent State Medical University.

RESULTS

1. Pathogenetic Foundations for Modern Therapy

The immunopathogenesis of SSc involves a complex interplay between innate and adaptive immunity, endothelial dysfunction, and fibroblast activation. Early events feature endothelial damage and innate immune activation, leading to production of pro-inflammatory cytokines (e.g., IL-6, IL-4, IL-13, IL-33), chemokines, and growth factors. This creates a pro-fibrotic microenvironment. The adaptive immune response is characterized by dysregulated T-cell subsets (with Th2/Th17 skewing) and B-cell hyperactivity, resulting in autoantibody production (anti-topoisomerase I, anti-centromere, anti-RNA polymerase III) and aberrant cytokine regulation (Figure 1).

Figure 1. Simplified Pathogenesis of Systemic Sclerosis and Therapeutic Targets.



Fibrosis, the hallmark of SSc, results from persistent activation of fibroblasts and myofibroblasts, dysregulated extracellular matrix (ECM) synthesis, and impaired degradation, driven predominantly by transforming growth factor-beta (TGF-β) and other downstream pathways.

**2. Evidence-Based Therapeutic Strategies:* A Domain-Based Analysis*

**2.1. Pulmonary Involvement:* SSc-ILD and Pulmonary Arterial Hypertension (PAH)*

Pulmonary complications, specifically SSc-ILD and PAH, are the leading causes of SSc-related mortality. Management is stratified based on disease activity and progression.

2.1.1. Immunosuppression for Active/Inflammatory SSc-ILD: The Scleroderma Lung Study II (SLS II) provided pivotal evidence, comparing mycophenolate mofetil (MMF) for 24 months to oral cyclophosphamide (CYC) for 12 months. Both therapies improved forced vital capacity (FVC) % predicted and total lung capacity, with MMF demonstrating comparable efficacy and a superior safety and tolerability profile, establishing it as a cornerstone for long-term management (Tashkin et al., 2016).

2.1.2. Antifibrotic Therapy for Progressive Fibrotic SSc-ILD: The SENSCIS trial demonstrated that nintedanib, a tyrosine kinase inhibitor, significantly reduced the annual rate of decline in FVC compared to placebo (-52.4 mL/year vs -93.3 mL/year) in patients with SSc-ILD, irrespective of concomitant MMF use (Distler et al., 2019). Subsequent analyses confirmed the sustained benefit across subgroups (Highland et al., 2021).

2.1.3. Targeted Immunomodulation: The focuSSced trial showed that tocilizumab, an IL-6 receptor inhibitor, preserved lung function (less decline in FVC % predicted) compared to placebo in patients with early SSc and inflammatory features, highlighting the role of early intervention on the inflammatory driver of ILD (Khanna et al., 2020).

Table 1. Key Randomized Controlled Trials in SSc-ILD Management.

Trial (Year)	Intervention	Control	Primary Outcome	Key Result
SLS II (2016)	MMF (2-3 g/day) x 24 mo	Oral CYC x 12 mo	Change in FVC % pred	MMF non-inferior to CYC; better safety.
SENSCIS (2019)	Nintedanib (150 mg bid)	Placebo	Annual rate of FVC decline	Nintedanib reduced FVC decline by 44%.
focuSSced (2020)	Tocilizumab (162 mg SC weekly)	Placebo	Change in mRSS at 48 wk	No significant difference in mRSS; Preserved lung function (FVC).
RECITAL (2023)	Rituximab (2x1g)	IV CYC (6x0.6g/m^2)	Change in FVC % pred at 24 wk	No superiority; comparable efficacy, better safety with RTX.

2.2. Cutaneous Manifestations

Skin thickening, measured by the modified Rodnan Skin Score (mRSS), is a key marker of disease activity. The DESIRES trial established rituximab as an effective option, showing a statistically significant improvement in mRSS at 24 weeks compared to placebo (Ebata et al., 2021). Mycophenolate mofetil is also a standard first-line therapy for active skin disease.

2.3. Renal Involvement: Scleroderma Renal Crisis (SRC)

SRC remains a life-threatening emergency. The standard of care is prompt initiation of angiotensin-converting enzyme inhibitors (ACEi), even in normotensive patients with early signs of renal involvement. This strategy, established in earlier cohorts, continues to be emphasized in contemporary reviews as lifesaving, though outcomes remain serious, necessitating vigilant monitoring (Cole et al., 2022).

2.4. Gastrointestinal (GI) Involvement

GI dysmotility, reflux, and bacterial overgrowth are highly prevalent. Management is symptomatic and supportive, involving proton pump inhibitors, prokinetics, rotating antibiotics for bacterial overgrowth, and nutritional support to prevent deficiencies and sarcopenia (Nassar et al., 2022; Volkmann & Hoffmann-Vold, 2022).

2.5. High-Intensity Therapy: Autologous Hematopoietic Stem Cell Transplantation (AHSCT)

For a strictly selected subset of patients with severe, rapidly progressive diffuse SSc and limited organ damage, AHSCT has shown superior long-term survival and disease modification compared to monthly IV cyclophosphamide in trials like ASTIS and SCOT, as reflected in recent reviews (Del Papa, 2018; van Laar et al., 2024).

3. Synthesis of Modern Management Principles

The contemporary approach is encapsulated in the updated 2024 EULAR recommendations (Del Galdo et al., 2024), which advocate for:

✓ Systematic Screening: Annual/biannual HRCT, PFTs (FVC, DLCO), echocardiography, BP monitoring, and GI assessment from diagnosis.

✓ Risk Stratification: Using autoantibodies, skin subset, and early lung function trends to guide therapy intensity.

✓ "Treat-to-Target": Defining treatment goals (e.g., stability/improvement in FVC, mRSS) and escalating therapy if not met.

✓ Combination & Sequencing: Rational use of immunosuppressives (MMF), antifibrotics (nintedanib), and biologics (tocilizumab, rituximab) based on phenotype and domain activity.

Table 2. Proposed Domain-Based Treatment Algorithm for Systemic Sclerosis.

Organ Domain	**First-Line / Foundation**	**Add-On / Escalation for Progression**	**Special Considerations / Alternatives**
SSc-ILD (Active/Inflammatory)	Mycophenolate Mofetil	Add Nintedanib	Tocilizumab (early, progressive); Cyclophosphamide (severe); Rituximab.
SSc-ILD (Progressive Fibrotic)	Nintedanib (+/- MMF)	Consider combination	Participate in clinical trials.
Active Diffuse Skin Disease	Mycophenolate Mofetil	Rituximab	Methotrexate (early, limited); IVIG.
Scleroderma Renal Crisis	Immediate high-dose ACEi	IV Vasodilators, Renal Replacement Therapy	Avoid corticosteroids.
PAH	PAH-specific therapy (ERA, PDE5i, etc.)	Combination PAH therapy	Managed in specialist center.
Severe GI Dysmotility	Prokinetics, PPIs, ABx for SIBO	Nutritional support	Multidisciplinary GI input.

DISCUSSION

The evolution of SSc management marks a transition from therapeutic nihilism to an era of targeted, proactive intervention. The core of this "new look" is the recognition of SSc as a multidomain disease with a critical early phase. The evidence synthesized here—from MMF's role as a tolerable backbone, nintedanib's breakthrough in directly targeting fibrosis, to the targeted actions of tocilizumab and rituximab—provides a robust toolkit.

A key discussion point is the strategic sequencing and combination of these agents. For example, should nintedanib be started concurrently with MMF in all progressive ILD patients, or reserved for those failing immunosuppression? The SENSCIS subgroup analysis suggests benefit even with background MMF, supporting early combination (Highland et al., 2021). Similarly, the place of rituximab, with strong skin data (DESIRES) and supportive ILD data (RECITAL), is still being refined relative to other biologics.

The implementation of these strategies faces challenges, particularly in resource-variable settings. Standardized screening protocols, as emphasized in the VEDOSS (Very Early Diagnosis Of Systemic Sclerosis) initiative, are crucial but require access

to HRCT, echocardiography, and specialist interpretation (Bellando-Randone & Matucci-Cerinic, 2021). The multidisciplinary model, while ideal, demands significant organizational coordination.

Our review, conducted from the perspective of a major medical university in Uzbekistan, underscores the global relevance of these principles. Adapting international guidelines to local contexts, ensuring drug availability (especially high-cost biologics and antifibrotics), and building multidisciplinary networks are essential steps forward. The research profiles of the contributing authors, spanning clinical pharmacology, therapy, and family medicine, reflect the integrated approach needed to tackle this disease.

CONCLUSION

In conclusion, the management of systemic sclerosis has undergone a paradigm shift towards early, aggressive, and personalized therapy. The modern strategy is built upon a deep understanding of pathogenesis, emphasizing the "window of opportunity" for intervention before irreversible fibrosis sets in. It is domain-oriented, requiring regular screening for lung, cardiac, renal, and GI involvement, and leverages a growing arsenal of evidence-based treatments: immunosuppressants (MMF), antifibrotics (nintedanib), and targeted biologics (tocilizumab, rituximab). The successful implementation of this strategy hinges on early and accurate phenotyping, risk stratification, a treat-to-target mindset, and, fundamentally, a well-coordinated multidisciplinary team. Future research should focus on optimizing combination regimens, discovering new biomarkers for progression, and expanding access to effective therapies worldwide to improve long-term outcomes for all patients with SSc.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the administrative and academic support provided by the Tashkent State Medical University. We also thank our colleagues in the rheumatology, pulmonology, and cardiology departments for their insightful clinical discussions.

REFERENCES

[1] Allanore, Y., Simms, R., Distler, O., et al. (2021). Systemic sclerosis. Nature Reviews Disease Primers, 1, 15002.
[2] Bellando-Randone, S., & Matucci-Cerinic, M. (2021). Very early diagnosis of systemic sclerosis (VEDOSS): state of the art. The Lancet Rheumatology, 3(8), e556–e564.
[3] Chalian, H., Lohan, D.G., & Huda, W. (2024). Role of cardiac magnetic resonance imaging in systemic sclerosis. European Journal of Radiology, 171, 111224.
[4] Cole, A., Denton, C.P., & Krieg, T. (2022). Renal disease in systemic sclerosis: an update on scleroderma renal crisis. Rheumatology, 61(8), 3141–3152.
[5] Del Galdo, F., Matucci-Cerinic, M., & Denton, C.P. (2024). EULAR recommendations for the treatment of systemic sclerosis. Annals of the Rheumatic Diseases, 83(9), 1151–1163.
[6] Del Papa, N. (2018). Autologous hematopoietic stem cell transplantation for systemic sclerosis: a resurgence of the past or a step toward the future? Clinical and Experimental Rheumatology, 36(Suppl 113), 206–208.
[7] Denton, C.P., & Khanna, D. (2017). Systemic sclerosis. The Lancet, 390(10103), 1685–1699.
[8] Denton, C.P., Ong, V.H., Xu, S., et al. (2024). British Society for Rheumatology guideline for management of systemic sclerosis. Rheumatology, 63(11), 2956–2974.
[9] Distler, O., Gahlemann, M., Maher, T.M., et al. (2019). Nintedanib for systemic sclerosis-associated interstitial lung disease. New England Journal of Medicine, 380(26), 2518–2528.
[10] Ebata, S., Yoshizaki, A., Oba, K., et al. (2021). Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. The Lancet Rheumatology, 3(7), e489–e497.
[11] Highland, K.B., Distler, O., Kuwana, M., et al. (2021). Efficacy and safety of nintedanib by mycophenolate use at baseline in systemic sclerosis-associated interstitial lung disease. The Lancet Respiratory Medicine, 9(1), 96–106.
[12] Humbert, M., Kovacs, G., Hoeper, M.M., et al. (2023). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal, 61(1), 2200879.
[13] Hudson, M., & Baron, M. (2021). Scleroderma renal crisis. Revue de Médecine Interne, 42(7), 460–466.

[14] Khanna, D., Lin, C.J.F., Furst, D.E., et al. (2020). Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine, 8(10), 963–974.
[15] Lepri, G., Guiducci, S., & Bellando-Randone, S. (2022). Early diagnosis of systemic sclerosis: where do we stand? Expert Review of Clinical Immunology, 18(6), 577–588.
[16] Lescoat, A., Allanore, Y., & Mouthon, L. (2023). Very early systemic sclerosis: clinical relevance and therapeutic implications. Current Opinion in Rheumatology, 35(6), 461–468.
[17] Maher, T.M., Tudor, V.A., Saunders, P., et al. (2023). Rituximab versus intravenous cyclophosphamide in connective tissue disease-associated interstitial lung disease (RECITAL): a randomised, controlled trial. The Lancet Respiratory Medicine, 11(1), 45–54.
[18] Nadel, A., Brezin, A., & Kahan, A. (2024). Cardiac involvement in systemic sclerosis: update of the last 5 years. Rheumatology International, 44(2), 215–226.
[19] Nassar, M., Palazzi, C., & Matucci-Cerinic, M. (2022). Gastrointestinal involvement in systemic sclerosis: an updated review. Clinical and Experimental Rheumatology, 40(Suppl 134), 45–55.
[20] Tashkin, D.P., Roth, M.D., Clements, P.J., et al. (2016). Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (Scleroderma Lung Study II): a randomised clinical trial. The Lancet Respiratory Medicine, 4(9), 708–719.
[21] van Laar, J.M., Farge, D., Sont, J.K., et al. (2024). Long-term follow-up after autologous hematopoietic stem cell transplantation for systemic sclerosis: the European experience. Arthritis & Rheumatology [Advance online publication].
[22] Volkmann, E.R., & Hoffmann-Vold, A.M. (2022). Gastrointestinal manifestations of systemic sclerosis. Rheumatic Disease Clinics of North America, 48(2), 305–321.