



MODERN METHODS FOR THE TREATMENT OF SYSTEMIC SCLEROSIS: AN EVIDENCE-BASED REVIEW OF CONTEMPORARY THERAPEUTIC STRATEGIES

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Annotatsiya

Systemic sclerosis is a severe multisystem autoimmune connective tissue disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis of the skin and internal organs, and it remains one of the rheumatic diseases with the highest burden of morbidity and mortality. In recent years, the treatment paradigm for systemic sclerosis has shifted from predominantly symptomatic care toward an organ-targeted, risk-stratified, and increasingly evidence-based model supported by updated international recommendations. The objective of this review was to synthesize modern treatment approaches for systemic sclerosis with emphasis on interstitial lung disease, pulmonary arterial hypertension, vascular digital complications, skin fibrosis, renal crisis, and gastrointestinal involvement. A structured narrative review design was used, drawing primarily on updated EULAR recommendations for systemic sclerosis, ACR and CHEST guidance on screening, monitoring, and treatment of interstitial lung disease in systemic autoimmune rheumatic diseases, the ATS clinical practice guideline for systemic sclerosis-associated interstitial lung disease, ESC/ERS pulmonary hypertension guidance, pivotal randomized clinical trials, and current regulatory labeling for tocilizumab and nintedanib. The analysis shows that modern care is no longer based on a single best drug for all patients; rather, it requires early phenotyping, continuous monitoring, and coordinated multidisciplinary treatment. Mycophenolate has emerged as a central therapy for systemic sclerosis-associated interstitial lung disease, whereas cyclophosphamide, rituximab, tocilizumab, and nintedanib occupy important roles depending on inflammatory activity, fibrotic progression, tolerance, and treatment goals. For vascular disease, calcium channel blockers, phosphodiesterase-5 inhibitors, iloprost, and bosentan remain relevant, while pulmonary arterial hypertension is now approached with early combination therapy in appropriately selected patients. Scleroderma renal crisis still

represents a medical emergency in which immediate angiotensin-converting enzyme inhibition is critical, and gastrointestinal disease requires aggressive supportive and pharmacologic management. High-intensity immunosuppression followed by autologous hematopoietic stem-cell transplantation has an established but highly selective role in early severe diffuse cutaneous disease with poor prognosis. Contemporary management therefore depends on rapid recognition of organ involvement, individualized sequencing of immunomodulatory and antifibrotic therapy, careful safety surveillance, and integration of rheumatology, pulmonology, cardiology, nephrology, gastroenterology, rehabilitation, and specialized nursing care.

Kalit so‘zlar:	systemic sclerosis, scleroderma, interstitial lung disease, pulmonary arterial hypertension, mycophenolate, rituximab, tocilizumab, nintedanib, stem-cell transplantation, evidence-based treatment
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Introduction

Systemic sclerosis, also referred to as scleroderma in much of the clinical literature, is a rare but clinically devastating connective tissue disease defined by a pathogenic triad of autoimmunity, vasculopathy, and fibrosis, with highly heterogeneous expression across cutaneous, pulmonary, vascular, gastrointestinal, renal, musculoskeletal, and cardiac domains. Contemporary epidemiologic reviews indicate that the global incidence and prevalence remain low in absolute terms but substantial in clinical impact, while mortality remains high and lung disease together with pulmonary arterial hypertension continues to account for a major share of disease-related deaths. Modern classification still broadly distinguishes limited cutaneous and diffuse cutaneous phenotypes, but current practice has moved beyond skin extent alone because prognosis is increasingly determined by internal organ trajectories, serologic profile, inflammatory activity, and the tempo of fibrotic progression. This is particularly important because diffuse cutaneous disease tends to carry a greater risk of early internal organ involvement, whereas limited cutaneous disease may still evolve toward severe vascular complications and pulmonary hypertension over time. Historically, treatment of systemic sclerosis was frustratingly conservative: clinicians managed Raynaud phenomenon, reflux, pain, and hypertension while lacking therapies convincingly able to alter the natural history of fibrosis. That therapeutic pessimism has weakened considerably over the last decade. A major reason is that randomized trials and guideline efforts have progressively clarified that systemic sclerosis is not a single therapeutic target but a cluster of partially overlapping clinical syndromes requiring organ-specific decision-making. In other words, the modern physician no longer asks only, “Does this patient have systemic sclerosis?” but rather, “Which manifestation is currently driving risk: inflammatory skin progression, fibrosing interstitial lung disease, pulmonary vascular disease, renal vasculopathy, gastrointestinal dysmotility, or an overlap phenotype?” This conceptual shift has practical consequences. For systemic sclerosis-associated interstitial lung disease, updated guidance now supports mycophenolate as a core therapy and recognizes important roles for cyclophosphamide, rituximab, tocilizumab, and nintedanib; for vascular complications, the evidence base now supports more structured escalation

from calcium channel blockers to phosphodiesterase-5 inhibitors, prostacyclin-based therapy, and endothelin receptor antagonism; for pulmonary arterial hypertension, combination therapy has moved to the foreground; and for selected patients with very aggressive diffuse disease, autologous hematopoietic stem-cell transplantation is no longer experimental folklore but a carefully delimited therapeutic option with survival benefit in appropriately chosen cases. At the same time, the field remains full of nuance. Some therapies are approved by regulators for slowing pulmonary function decline but not for reversing established fibrosis; some are recommended by international task forces despite relatively low-certainty evidence because the disease is rare and clinically urgent; some improve skin scores better than lung outcomes, while others stabilize lung function without dramatically changing other domains; and nearly all require attention to toxicity, infection risk, pregnancy considerations, monitoring burden, access, and cost. These complexities matter even more in real-world settings where patients frequently present late, multidisciplinary infrastructure is uneven, and organ screening may be incomplete. The present review therefore addresses a clinically relevant question: what are the truly modern methods for treating systemic sclerosis today, and how should they be understood within an evidence-based, organ-directed framework rather than a fragmented list of drugs?

Materials and Methods

This article was designed as a structured narrative review with IMRaD organization and an explicit evidence-prioritization strategy aimed at reflecting contemporary practice rather than historical therapeutic customs. The literature base was built around high-level sources that can reasonably guide current clinical interpretation as of April 2026: first, updated EULAR recommendations for treatment of systemic sclerosis, which synthesize pharmacologic management across vascular, pulmonary, gastrointestinal, cutaneous, renal, and musculoskeletal domains; second, the 2023 ACR/CHEST guidance for screening and monitoring of interstitial lung disease in people with systemic autoimmune rheumatic diseases; third, the 2023 ACR treatment guideline for autoimmune rheumatic disease-associated interstitial lung disease; fourth, the ATS evidence-based clinical practice guideline for systemic sclerosis-associated interstitial lung disease; fifth, the ESC/ERS pulmonary hypertension guideline; and sixth, pivotal randomized clinical trials and regulatory labeling relevant to key agents, particularly mycophenolate, cyclophosphamide, rituximab, tocilizumab, nintedanib, and autologous hematopoietic stem-cell transplantation. Priority was given to sources that either represent consensus recommendations developed through formal evidence review or provide primary trial data that directly changed treatment recommendations. The review focused on treatment domains with the greatest impact on survival, function, and quality of life: Raynaud phenomenon and digital ischemia, interstitial lung disease, pulmonary arterial hypertension, skin fibrosis, renal crisis, and gastrointestinal disease, alongside the management of severe diffuse cutaneous disease with poor prognosis. Supportive care, monitoring strategies, and safety considerations were also included because modern treatment effectiveness in systemic sclerosis depends not only on drug choice but also on timing, surveillance, and multidisciplinary coordination. Sources primarily addressing pathogenesis without direct therapeutic implications, highly preliminary

single-center interventions, and unreplicated experimental approaches were not emphasized. The goal was not to produce a formal meta-analysis but to integrate current evidence into a clinically coherent narrative that can serve as a publication-ready overview for medical readers, trainees, and specialists involved in the care of patients with systemic sclerosis.

Results

The evidence reviewed demonstrates that the modern treatment of systemic sclerosis is best understood as a layered therapeutic architecture built around early detection of organ involvement, prompt risk stratification, and selective use of immunomodulatory, antifibrotic, vasodilatory, and supportive interventions rather than a uniform disease-wide regimen. In the vascular domain, management of Raynaud phenomenon remains foundational because uncontrolled vasospasm and structural vasculopathy can lead to ischemic pain, tissue loss, infection, and disability. Updated EULAR recommendations continue to place dihydropyridine calcium channel blockers, usually oral nifedipine, as first-line therapy for systemic sclerosis-associated Raynaud phenomenon, while phosphodiesterase-5 inhibitors are recommended for additional benefit and intravenous iloprost is advised for severe disease after failure of oral therapy; in patients with active digital ulcers, phosphodiesterase-5 inhibitors and or intravenous iloprost should be considered for treatment, and bosentan should be considered to reduce the occurrence of new ulcers rather than to accelerate healing of existing ones. This distinction is clinically important because ulcer treatment and ulcer prevention are often conflated, but modern evidence supports bosentan chiefly for prevention of new lesions, not as a universal rescue therapy for all ischemic digital problems. In pulmonary arterial hypertension associated with systemic sclerosis, the field has moved away from delayed monotherapy toward earlier combination approaches in appropriate candidates. EULAR supports first-line combination of a phosphodiesterase-5 inhibitor with an endothelin receptor antagonist for systemic sclerosis-associated pulmonary arterial hypertension, with intravenous epoprostenol reserved for advanced functional class III to IV disease, other prostacyclin analogues or agonists considered according to severity and tolerance, and riociguat as another option in selected cases; importantly, warfarin is not recommended as routine treatment for systemic sclerosis-associated pulmonary arterial hypertension. This is a noteworthy evolution because older habits of empiric escalation and broad anticoagulant use have not held up well against contemporary evidence and risk-benefit analysis. Renal crisis remains one of the few manifestations in rheumatology where timing can be brutally decisive: updated recommendations clearly support immediate initiation of angiotensin-converting enzyme inhibitors at diagnosis of scleroderma renal crisis, and they also emphasize regular blood pressure monitoring in patients exposed to glucocorticoids because corticosteroids remain a recognized risk factor for renal crisis. The ATS interstitial lung disease guideline similarly warns that systemic corticosteroids should be used cautiously in systemic sclerosis and, whenever possible, daily exposure should not exceed the equivalent of 15 mg of prednisone, a reminder that what seems like anti-inflammatory common sense in other autoimmune diseases may become nephrovascular mischief in this one. Gastrointestinal disease, although sometimes overshadowed by lung and heart complications, is nearly universal across

the systemic sclerosis spectrum and materially affects nutrition, aspiration risk, oral intake, quality of life, and treatment adherence. Current guidance supports proton pump inhibitors for systemic sclerosis-related gastroesophageal reflux disease and prevention of esophageal ulcers and strictures, prokinetic therapy for symptomatic motility disturbance, and rotating antibiotics for small intestinal bacterial overgrowth, thereby confirming that supportive care in systemic sclerosis is not secondary medicine but organ-preserving medicine. Cutaneous fibrosis, the historically visible hallmark of systemic sclerosis, is now approached more strategically. EULAR recommends considering methotrexate, mycophenolate mofetil, and or rituximab for skin fibrosis, while tocilizumab may be considered in early inflammatory diffuse cutaneous disease. The emphasis on inflammatory phenotype matters because not all skin thickening behaves the same way; rapidly progressive, inflammatory diffuse disease may justify a more assertive immunomodulatory approach than stable longstanding fibrosis. Rituximab has gained particular attention because clinical trial and cohort data increasingly support benefit for skin and, in selected patients, lung outcomes, although access and regional regulatory acceptance still vary. The most consequential therapeutic progress, however, has occurred in systemic sclerosis-associated interstitial lung disease, now recognized as a leading cause of death. The ATS guideline gives the strongest recommendation among currently available agents to mycophenolate for treatment of systemic sclerosis-associated interstitial lung disease, while conditionally supporting cyclophosphamide, rituximab, tocilizumab, nintedanib, and the combination of nintedanib plus mycophenolate. EULAR similarly recommends considering mycophenolate, cyclophosphamide, or rituximab, with nintedanib used alone or together with mycophenolate, and tocilizumab considered in systemic sclerosis-associated interstitial lung disease. This is not a cosmetic consensus but a genuine reconfiguration of care. Mycophenolate has become the practical anchor because it balances efficacy, tolerability, and long-term usability better than cyclophosphamide in many patients. Cyclophosphamide still retains value, particularly when the disease is severe or rapidly progressive, but its toxicity profile makes it harder to sustain as a chronic backbone. The Scleroderma Lung Study II established that mycophenolate was at least a serious competitor to oral cyclophosphamide and generally better tolerated, helping it become central in contemporary algorithms. Nintedanib, by contrast, represents the antifibrotic turn in systemic sclerosis treatment: rather than functioning as a broad immunosuppressive agent, it slows the rate of decline in pulmonary function and is specifically indicated for systemic sclerosis-associated interstitial lung disease in several regulatory environments. Its role is especially relevant in progressive fibrotic phenotypes and in patients whose inflammatory suppression alone is insufficient to control structural lung deterioration. Tocilizumab occupies a more phenotype-sensitive niche. It is indicated in some jurisdictions for slowing the rate of decline in pulmonary function in adults with systemic sclerosis-associated interstitial lung disease and is supported by trial data showing preservation of lung function, especially in patients with inflammatory disease features. In practice, its appeal is greatest when inflammatory markers, early diffuse disease, or combined skin-lung activity suggest that interleukin-6 pathway blockade may address the dominant biology. Rituximab has similarly become harder to ignore: although not

uniformly licensed for this indication across jurisdictions, both EULAR and ATS place it among meaningful options, reflecting increasing evidence that B-cell depletion may benefit selected patients with fibrotic and inflammatory overlap. As for pirfenidone, the ATS panel did not recommend routine use and instead called for further research, which is a sober reminder that not every antifibrotic concept automatically earns a place in systemic sclerosis care. Monitoring strategies also emerged as therapeutically relevant results rather than mere administrative details. The ACR and CHEST guidance recommends pulmonary function tests and high-resolution chest CT for people with systemic autoimmune rheumatic diseases at increased risk of interstitial lung disease, and for established systemic sclerosis-associated interstitial lung disease it conditionally supports serial monitoring with pulmonary function tests and high-resolution CT, suggesting pulmonary function testing every three to six months during the first year and then less frequently once stable. This is crucial because treatment success in systemic sclerosis is often defined not by dramatic reversal but by preventing silent decline. Finally, in the subgroup with early severe diffuse cutaneous systemic sclerosis and poor prognosis, high-intensity immunosuppression followed by autologous hematopoietic stem-cell transplantation may be considered in the absence of advanced cardiorespiratory involvement. Here the evidence is powerful enough to command respect but hazardous enough to forbid casual enthusiasm. Trials such as SCOT and ASTIS showed superior long-term outcomes compared with cyclophosphamide-based approaches in carefully selected patients, yet treatment-related mortality and cardiopulmonary screening remain decisive concerns, meaning that stem-cell transplantation belongs in expert centers, not in therapeutic improvisation. Overall, the modern evidence base supports a treatment logic in which vasodilators, targeted immunomodulators, antifibrotic drugs, organ-specific emergency therapies, and highly selective transplantation strategies are combined according to phenotype, disease tempo, and organ threat, while structured screening and monitoring determine when apparent stability is real and when it is merely a quiet prelude to irreversible damage.

Discussion

The reviewed evidence suggests that the central intellectual advance in systemic sclerosis therapy is not simply the arrival of new drugs, but the replacement of a disease-label approach with a phenotype-and-organ trajectory approach. This distinction matters because systemic sclerosis patients do not fail treatment for one uniform reason: some fail because vasculopathy dominates and ischemic injury advances despite control of skin disease; others fail because interstitial lung disease progresses under inadequate surveillance; others decline because pulmonary arterial hypertension is recognized too late; and still others are harmed by well-intentioned but poorly matched therapies, such as liberal glucocorticoid use in a renal-crisis-prone patient. Accordingly, contemporary management should be viewed as a sequence of linked decisions. The first is early characterization: cutaneous subset, antibody profile, inflammatory markers, pulmonary function, high-resolution CT pattern and extent, echocardiographic and hemodynamic pulmonary vascular assessment when indicated, blood pressure trend, renal function, gastrointestinal burden, nutritional status, and functional impairment. The second is biological interpretation: is the dominant

problem inflammatory, fibrosing, vascular, or mixed? The third is therapeutic matching. Mycophenolate often becomes first-line for systemic sclerosis-associated interstitial lung disease because it offers a favorable balance between efficacy and tolerability, but this should not harden into dogma; nintedanib deserves earlier consideration in progressive fibrotic phenotypes, tocilizumab in inflammatory skin-lung disease, rituximab in selected refractory or overlapping immune-fibrotic patterns, cyclophosphamide when rapid control is needed and toxicity can be managed, and autologous stem-cell transplantation when the disease is severe enough to justify risk yet not too advanced to make the procedure unsafe. In pulmonary arterial hypertension, the shift toward initial combination therapy reflects a broader principle: waiting for a systemic sclerosis patient to declare severe disease before escalating treatment is often a luxury the biology does not grant. The same logic applies to monitoring. In systemic sclerosis, structured follow-up is treatment, because delayed recognition of pulmonary decline, occult desaturation, renal instability, or progressive gastrointestinal failure directly changes prognosis. Another major implication of the literature is that evidence certainty, while improved, is still uneven. Many recommendations remain conditional, not because the therapies are trivial, but because rare diseases rarely enjoy the trial abundance of common cardiometabolic conditions. This creates a clinical environment in which high-quality judgment still matters immensely. The physician must decide not only which drug is supported by trial data, but which patient resembles the trial population, which comorbidities magnify toxicity, whether local monitoring capacity can sustain the regimen, and whether the treatment goal is symptom relief, stabilization of function, slowing of fibrosis, rescue from rapidly progressive disease, or all of the above. In lower-resource or unevenly specialized settings, this may require rational sequencing: securing reliable screening with pulmonary function tests and high-resolution CT before escalating lung therapy; using mycophenolate where biologics are unavailable; prioritizing ACE inhibitor readiness and blood pressure vigilance; and ensuring aggressive reflux and nutritional care so that sophisticated immunotherapy is not undermined by preventable aspiration, weight loss, or poor oral adherence. The literature also reinforces that multidisciplinary care is not a fashionable add-on but a structural requirement. Rheumatologists alone do not interpret all pulmonary function trends, pulmonologists alone do not always capture systemic immune context, cardiologists are indispensable in pulmonary hypertension pathways, nephrologists are critical when renal crisis emerges, gastroenterologists and nutrition specialists prevent chronic attritional decline, and rehabilitation professionals preserve hand function, endurance, and daily participation. In a disease where skin thickness, lung capacity, ulcer burden, esophageal dysfunction, renal risk, and right ventricular stress can evolve on different clocks, fragmented care practically invites therapeutic error. Yet one should resist the temptation to call every new mechanism a revolution. Some therapies clearly slow decline rather than reverse damage; some improve surrogate markers better than hard survival outcomes; some appear promising mainly in subsets; and some are best thought of as domain-specific tools rather than global disease modifiers. That is why the most useful contemporary model is not triumphalist but strategic: identify the threatened organ early, decide whether inflammation or fibrosis is currently leading the process, initiate the most evidence-aligned therapy quickly, monitor tightly,

escalate without procrastination when objective progression appears, and avoid interventions whose risk profile is especially unfavorable in systemic sclerosis.

Conclusion

Modern treatment of systemic sclerosis has entered an evidence-based era in which organ-specific therapeutic strategy is both possible and necessary. The best-supported contemporary approach combines early screening, phenotype-based risk stratification, multidisciplinary monitoring, and timely use of targeted therapies: calcium channel blockers, phosphodiesterase-5 inhibitors, iloprost, and bosentan for vascular disease; combination pulmonary arterial hypertension therapy for appropriate patients; immediate ACE inhibitor treatment for renal crisis; proton pump inhibitors and adjunctive gastrointestinal measures for digestive involvement; and, most importantly, a structured lung strategy centered on mycophenolate with selective use of cyclophosphamide, rituximab, tocilizumab, nintedanib, and in carefully chosen severe cases, autologous hematopoietic stem-cell transplantation. The central clinical message is that systemic sclerosis should no longer be managed as a static diagnosis but as a dynamic pattern of organ threats that must be repeatedly measured and actively intercepted. The future of care will likely be defined not by a single universal drug, but by better biomarker-guided personalization, earlier recognition of progression, smarter combination therapy, and tighter integration of immunologic and antifibrotic treatment principles.

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