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REVIEW

New horizons in systemic sclerosis treatment: advances and emerging therapies in 2025

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ABSTRACT

Systemic sclerosis (SSc) is a rare, multisystem autoimmune disease characterised by vasculopathy, immune dysregulation, and progressive fibrosis, leading to significant morbidity and mortality. While recent EULAR recommendations have updated the standard of care for SSc, the field is rapidly evolving with novel therapeutic strategies and precision medicine approaches.

Traditional immunosuppressive therapies—including mycophenolate mofetil, cyclophosphamide and rituximab—remain essential for controlling skin and lung involvement while autologous haematopoietic stem cell transplantation offers a proven disease-modifying option for selected high-risk patients. Tocilizumab and nintedanib have established roles in lung preservation in SSc-associated interstitial lung disease (SSc-ILD). In pulmonary arterial hypertension (PAH), early combination therapy with endothelin receptor antagonists and phosphodiesterase-5 inhibitors, complemented by newer agents such as selexipag and riociguat, has improved survival and quality of life. Advances in gastrointestinal, renal and musculoskeletal management continue to evolve, with promising roles for intravenous immunoglobulin and novel prokinetics.

Crucially, emerging therapies—including CD19-targeted CAR-T cells, bispecific antibodies and agents targeting interferon pathways, BAFF, melanocortin, FcRn and PDE4B—reflect a shift towards personalised and biomarker-driven approaches. These innovations offer the potential to alter disease trajectory and support early, targeted intervention in SSc.

This review provides an up-to-date synthesis of both current organ-based treatment strategies in major organ domains—skin, ILD, PAH, scleroderma renal crisis, raynaud's phenomenon and digital ulcers, gastrointestinal and musculoskeletal involvement—and emerging therapies in SSc, with an emphasis on disease-modifying approaches and future directions in personalised care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent EULAR recommendations outline current treatment approaches for systemic sclerosis (SSc), mainly using immunosuppressants, vasodilators and some biologics based on organ involvement. Despite this, SSc still lacks truly disease-modifying therapies, and interest is growing in more targeted, precision treatments.

WHAT THIS STUDY ADDS

⇒ This review provides a comprehensive overview of the most recent advances in SSc treatment, highlighting the shift towards precision medicine and disease modification. It synthesises evidence on innovative therapies—including CD19-targeted CAR-T cells, bispecific antibodies, type I interferon inhibitors, BAFF and FcRn inhibitors, and agents targeting fibrotic and vascular pathways.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By providing a comprehensive synthesis of current and emerging therapies in SSc, this review supports clinicians and researchers in navigating an increasingly complex treatment landscape. It identifies key therapeutic targets, highlights the potential of precision and early intervention strategies and underscores the need for biomarker-driven clinical trial designs.

INTRODUCTION

Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterised by fibrosis, vasculopathy and inflammation, leading to significant multiorgan involvement and associated high morbidity and mortality.[1] While fibrosis and vascular injury drive organ damage, SSc presents with considerable heterogeneity in clinical manifestations, disease progression and treatment response.

Raynaud's phenomenon (RP) occurs in nearly all patients, and digital ulcers (DUs) affect approximately half.[2] Pulmonary complications, particularly interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), remain leading causes of SSc-related mortality.[3] ILD affects up to 80% of patients, with 25%–30% developing a progressive phenotype that leads to respiratory failure and death.[3–5] Gastrointestinal (GI) involvement is highly prevalent (up to 90%), often

affecting the oesophagus, small bowel and colon and is a major contributor to morbidity through malnutrition and other complications.[5]

The recently published 2023 EULAR recommendations for the treatment of SSc represent an important milestone, integrating targeted synthetic and biological disease-modifying antirheumatic drugs (DMARDs) into the management of key fibrotic manifestations.[6] Haematopoietic stem cell transplantation (HSCT) remains an important option for selected patients with rapidly progressive SSc at risk of organ failure. While early trials reported considerable treatment-related risks, more recent data from experienced centres using optimised conditioning regimens indicate improved safety profiles and lower transplant-related mortality.[7 8] Recent advancements in understanding the disease pathogenesis, along with the discovery of new therapeutic targets, have emerged from recent research on SSc.[7 8]

Advances in understanding disease pathogenesis, combined with improvements in screening, biomarkers and patient stratification, have paved the way for early intervention and precision medicine approaches in SSc. Building on the success of biological DMARDs and small molecules in other autoimmune diseases, numerous novel therapies are now under investigation for SSc, including CD19 CAR-T cell therapy, bispecific antibodies (bsAbs) and agents targeting interferon pathways, BAFF, FcRn and fibrotic pathways.[9–11]

This narrative review provides an overview of established organ-based treatment strategies for SSc, followed by a detailed exploration of emerging therapies that are reshaping the treatment landscape.

METHODOLOGY AND LITERATURE SEARCH

This manuscript was developed as a narrative review with the objective of providing a comprehensive and clinically relevant synthesis of current organ-based management strategies and emerging therapeutic approaches in SSc. To inform the review, a targeted literature search was conducted in PubMed/MEDLINE, ClinicalTrials.gov and the proceedings of major international rheumatology congresses (EULAR, ACR) up to April 2025. Search terms included combinations of: “systemic sclerosis,” “scleroderma,” “interstitial lung disease,” “pulmonary arterial hypertension,” “Raynaud’s phenomenon,” “digital ulcers,” “renal crisis,” “gastrointestinal involvement,” “skin fibrosis,” “emerging therapies,” “clinical trials” and “precision medicine.”

Priority was given to phase II–III clinical trials, recent international guidelines (including the 2023 EULAR recommendations), and ongoing trials investigating novel therapeutic targets in SSc. Foundational or landmark studies published prior to this time frame were also included where they remain essential to guiding current clinical practice. Additional references were identified through citation chaining and based on the authors’ expertise in SSc clinical care and research.

Emerging therapies and novel therapies in SSc

Current treatment approaches largely focus on managing individual organ manifestations—targeting inflammation, fibrosis and vascular dysfunction—rather than addressing the underlying disease mechanisms. Despite advances in immunosuppressive and antifibrotic therapies, the absence of truly disease-modifying treatments capable of altering the disease trajectory highlights a critical gap in care. Table 1 represents emerging and novel therapies in SSc.

Given the pivotal role of B cells in SSc, chimeric antigen receptor T-cell (CAR-T19) therapy—a groundbreaking treatment originally developed for haematological malignancies—has emerged as a potential game-changer for autoimmune diseases, including SSc. CAR-T19 therapy selectively targets and depletes CD19+B cells, offering a more profound and potentially long-lasting immunomodulatory effect compared with conventional B-cell depletion therapies like RTX.

Recent studies evaluating CAR-T19 therapy in dcSSc have yielded promising results. At 6 months post-treatment, patients demonstrated a 100% probability of improvement based on the ACR-CRISS score, suggesting a complete resolution of active disease. Median modified Rodnan skin scores (mRSS) decreased by 31% within the first 100 days, indicating a rapid and substantial reduction in skin fibrosis.[12] Additionally, high-resolution CT scans revealed a 4% decrease in disease extent, with improvements in ground-glass opacities—suggesting a potential protective effect on lung involvement. Importantly, forced vital capacity (FVC) increased by a median of 195 mL, a notable improvement given the typically progressive nature of SSc-ILD.

The rationale for CAR-T19 in SSc builds on the successes observed with rituximab (RTX), but with the potential for more sustained B-cell depletion and disease modification. Unlike rituximab, which temporarily reduces B-cell populations but allows for repopulation over time, CAR-T19 therapy offers the possibility of deeper and more durable immune resetting. This approach may be particularly valuable for patients with aggressive disease phenotypes, where early intervention could prevent irreversible fibrosis and organ dysfunction. Despite its potential, CAR-T19 therapy is not without risks. The most pressing concern is cytokine release syndrome, a potentially life-threatening inflammatory response that could exacerbate the already dysregulated immune activation in SSc. Furthermore, the long-term effects of profound B-cell depletion in autoimmune diseases remain unknown, necessitating further research to assess safety and durability of response.

To address these considerations, Novartis has initiated a Phase 2, multipart, randomised, open-label, assessor-blinded, multicentre study (NCT06655896) to evaluate the efficacy, safety and tolerability of rapcabtagene autoleucel, a CAR-T19 therapy, compared with rituximab in participants with severe refractory dcSSc.[13] This study includes a lead-in cohort, where participants receive

Table 1 Emerging therapies in SSc

Therapy	Mechanism of action	Phase	Notes
CAR-T19	B-cell depletion via CAR-T therapy	Phase I/II	Investigated for refractory autoimmune diseases, including SSc
Anifrolumab	Type I interferon (IFN) receptor blockade	Phase IIb	Previously approved for Systemic Lupus Erythematosus (SLE), now being explored in SSc
Belimumab	B-cell activating factor inhibition	Phase IIb	Targets B-cell survival, reducing autoantibody production
MT-7117	Melanocortin receptor modulation	Phase IIb	Aims to regulate inflammatory and fibrotic pathways in SSc
FcRn inhibitors	Neonatal Fc receptor (FcRn) blockade	Phase II	Reduces IgG autoantibody levels, potential for autoimmune disease treatment
Nerandomilast	Phosphodiesterase 4B inhibition	Phase IIb	Evaluated in progressive pulmonary fibrosis and now in SSc-ILD
Amlitelimab	OX40 ligand inhibition (T-cell modulation)	Phase IIb	Previously studied in atopic dermatitis, now in SSc-ILD trials
Avenciguat	Soluble guanylate cyclase activation	Phase II	Explored for vascular and fibrotic manifestations in SSc
Telitacicept	Dual B lymphocyte stimulator and a proliferation-inducing ligand inhibition	Phase II	Targets B-cell activation and survival; currently under investigation in early dcSSc (NCT06375005)
Bispecific antibodies (bsAbs)	Dual-targeted immunomodulation (eg, CD3/CD19, CD3/CD20) and/or direct antifibrotic targeting (eg, FAP-CD3)	Pre-clinical	Potential to simultaneously modulate autoreactive B cells and pathogenic fibroblasts; promising for SSc but requires further clinical validation

FAP, fibroblast activation protein; ILD, interstitial lung disease; SSc, systemic sclerosis.

rapcabtagene autoleucel, followed by a randomised cohort, in which participants will be assigned to either rapcabtagene autoleucel or rituximab. Following the treatment phase, participants receiving CAR-T19 therapy will enter a long-term follow-up period lasting up to 15 years, aimed at monitoring delayed adverse events and assessing long-term efficacy, including vector persistence.

In parallel with CAR-T approaches, bsAbs emerge as a promising immunotherapeutic strategy in SSc. By simultaneously targeting two disease-driving pathways, bispecific antibodies (bsAbs) offer enhanced specificity and potential synergy. Preclinical models have explored bsAbs designed to engage T cells for selective depletion of autoreactive B cells (eg, CD3/CD19 or CD3/CD20 constructs), which may offer deeper and more durable immune modulation than conventional B-cell depletion alone.[14] Additionally, bispecific constructs targeting fibroblast activation protein (FAP) on pathogenic myofibroblasts have shown potential to directly reduce tissue fibrosis.[15] While clinical application in SSc is still at an early stage, bsAbs represent an exciting frontier for future trials, with the potential to complement or even surpass current monotherapies by simultaneously addressing the complex immune-fibrotic axis of the disease.

Integrating CAR-T19 therapy and other emerging treatments into the management of SSc will require a strategic and personalised approach, prioritising patients with severe, refractory disease or those at risk of rapid progression. Further clinical studies are essential to evaluate the potential of CAR-T19 as an early intervention, particularly in preventing irreversible fibrosis and multi-organ damage. Additionally, ongoing phase 2b and 3 trials of novel biologics Additionally, ongoing phase 2b and 3 trials of novel biologics including Anifrolumab, belimumab (Benlysta), MT-7117, FcRn inhibitors, Nerandomilast, anti-Ox40 ligand and anti-TL1A therapies, among others.

The development of Anifrolumab (NCT05925803), a type I interferon receptor antagonist, reflects a growing focus on interrupting innate immunity pathways upstream, targeting one of the key drivers of autoimmunity and fibrosis.[16] Similarly, belimumab, a BAFF inhibitor, has shown potential in reducing B-cell autoreactivity, which may offer complementary benefits to standard immunosuppression, and it is being investigated in SSc-ILD (NCT05878717).[17]

MT-7117, a melanocortin receptor agonist, represents another novel avenue by modulating immune and fibrotic pathways, potentially addressing both vascular and fibrotic complications of SSc (NCT04440592).[18] The investigation of FcRn inhibitors, which reduce pathogenic IgG autoantibodies, and anti-TL1A therapies, which target pro-fibrotic immune signalling (NCT05270668), further highlights the expanding therapeutic landscape for SSc, moving beyond broad immunosuppression towards precision-driven interventions.[19]

Nerandomilast and amlitelimab are currently being evaluated in the CONQUEST platform trial (NCT06195072), a phase 2b study designed to assess their efficacy and safety in patients with early active SSc-ILD. Nerandomilast, a

phosphodiesterase 4B (PDE4B) inhibitor, has previously shown positive outcomes in idiopathic pulmonary fibrosis and progressive pulmonary fibrosis, making it a promising candidate for SSc-ILD.[20] Similarly, amlitelimab, an anti-OX40 ligand (OX40L) monoclonal antibody, has demonstrated efficacy in atopic dermatitis and is now under investigation within the same trial for SSc-ILD. In addition to these agents, avenciguat, a soluble guanylate cyclase (sGC) activator developed by Boehringer Ingelheim, is undergoing evaluation in the VITALISScE study (NCT05559580), a phase 2 clinical trial assessing its impact on fibrotic and vascular manifestations of SSc.[21] Telitacicept (NCT06375005)—a recombinant fusion protein targeting both B-lymphocyte stimulator and a proliferation-inducing ligand (APRIL)—is under investigation in early diffuse cutaneous SSc.[22]

Biomarker-driven strategies are increasingly central to personalised care in SSc, offering valuable tools for early risk stratification, monitoring and therapeutic targeting. In SSc-associated ILD (SSc-ILD), serum markers such as KL-6, SP-D and CCL18 are correlated with fibrosis severity and progression and are increasingly used in both clinical practice and trials to guide treatment decisions.[23 24] In the vascular domain, CXCL4 and endostatin are associated with vasculopathy and poor outcomes, including DUs and PAH.[25 26] Molecular profiling is also gaining clinical relevance. Gene expression signatures from skin biopsies have identified SSc endotypes—such as inflammatory or fibroproliferative subsets—that may predict response to biological therapies.[27 28] Circulating microRNAs and novel autoantibodies (eg, anti-ETAR, anti-AT1R) further refine risk prediction for severe complications like PAH and scleroderma renal crisis (SRC).[29 30] Non-invasive tools like nailfold capillaroscopy complement serological biomarkers by providing visual evidence of microvascular damage and risk of DUs or PAH. Combining these with cardiac biomarkers (eg, NT-proBNP) enhances early detection of internal organ involvement. Altogether, these biomarker-based tools support a shift towards early, individualised treatment strategies in SSc, facilitating earlier intervention, more precise therapy selection, and improved long-term outcomes.

Ultimately, while SSc remains a highly complex and therapeutically challenging disease, the advent of CAR-T19 therapy and other targeted biologics represents a paradigm shift, moving the field beyond symptom management and organ-specific interventions towards a true disease-modifying approach. Future research should focus on identifying predictive biomarkers to optimise patient selection, refining treatment protocols to enhance both efficacy and safety, and further exploring the long-term implications of immune reprogramming in autoimmune diseases. The era of precision medicine in SSc is emerging, and with these groundbreaking innovations, the field is poised to move towards a future where early intervention, immune correction, and even potential remission become achievable goals for patients facing this debilitating disease.[31]

Organ-based management in SSc

Management of skin manifestations

The mRSS is the standard tool for assessing skin fibrosis, evaluating 17 anatomical sites with a total possible score of 51. A meaningful clinical improvement is typically defined as a 3.5–5.3-point reduction in mRSS.[32] Figure 1

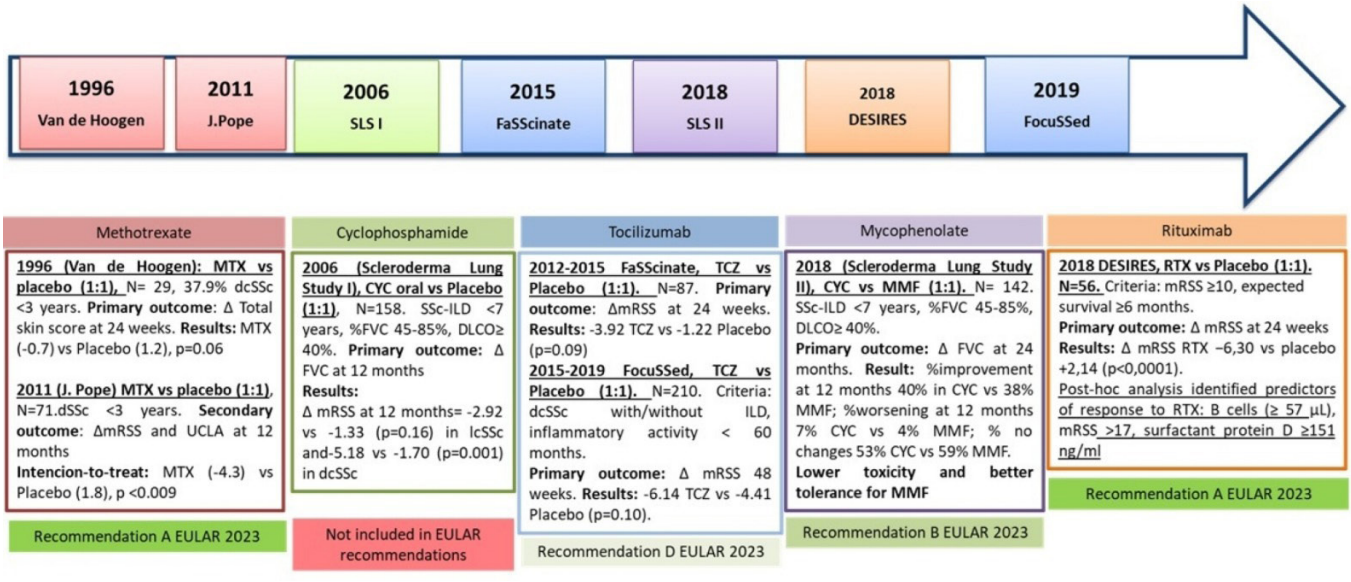

Figure 1 Visual representation of clinical trials in SSc and results for skin involvement. CYC, cyclophosphamide; DLCO, Diffusing capacity of the lungs for carbon monoxide; DESIRES, Safety and efficacy of rituximab in systemic sclerosis; FVC, forced vital capacity; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; ILD, interstitial lung disease; MTX, methotrexate; SLS II, Scleroderma Lung Study II; SSc, systemic sclerosis; TCZ, tocilizumab; ULCA, Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument.

summarises the current clinical trials in SSc and results for skin involvement.

Methotrexate (MTX) has been evaluated for skin disease in dcSSc with mixed results. An early trial over 24 weeks did not demonstrate significant mRSS improvement,[33] but a more recent 2011 study suggested potential benefits, although using relatively low doses (15 mg/week); the efficacy of higher doses commonly used in rheumatology (up to 25 mg/week) remains to be clarified.[34] The Scleroderma Lung Study II (SLS II) compared oral cyclophosphamide (CYC) (administered for 1 year, followed by placebo) with mycophenolate mofetil (MMF) (administered for 2 years) in patients with SSc-ILD and cutaneous involvement.[35] Both treatments led to comparable improvements in lung function (FVC) and skin fibrosis (mRSS) at 12 months, with no statistically significant differences between arms. While MMF was associated with fewer adverse events and lower discontinuation rates, contributing to its adoption as a first-line immunosuppressant for SSc-ILD, it is important to note that SLS II used oral CYC, and comparative data against intravenous CYC remain lacking.

Tocilizumab (TCZ), an IL-6 receptor antagonist, was studied in the FaSScinate and Focused trials, with trends towards improved mRSS that did not reach statistical significance for skin endpoints. Nonetheless, TCZ is considered a reasonable option in patients with active disease due to its anti-inflammatory effects.[36] Rituximab (RTX), a B-cell depleting therapy, demonstrated significant efficacy in skin disease in the DESIRES trial (2018), with an mRSS reduction of −6.3 points vs +2.14 with placebo (p<0.0001), particularly in patients with severe skin involvement (mRSS≥10).[37] Post hoc analyses have proposed candidate biomarkers to predict RTX responsiveness, such as baseline B-cell counts and surfactant protein D.

AHSCT currently represents the most effective option for severe, rapidly progressive dcSSc. Multiple randomised controlled trials (RCTs) (ASTIS, ASSIST and SCOT) have consistently demonstrated its superiority over CYC in improving long-term skin outcomes[2].[7–13 16–22 32–40] Careful patient selection remains crucial due to potential treatment-related risks. The evolution of AHSCT protocols and risk stratification has further improved safety and efficacy. Table 2 represents a summary of key trials of HSC versus CYC in SSc for skin involvement.

Management of ILD

The management of SSc-ILD has evolved based on extensive clinical trial data evaluating immunosuppressants (CYC, MMF), biologics (TCZ, rituximab (RTX)), antifibrotic agents (nintedanib) and AHSCT. Figure 2 summarises key trials and outcomes.

CYC was historically considered a standard treatment for SSc-ILD, but its long-term use is limited by toxicity concerns. The SLS I (2006) demonstrated that oral CYC significantly improved FVC compared with placebo, with an absolute mean difference of +2.53% (p<0.03), along with improvements in dyspnoea and quality of life. Subsequently, the SLS II (2018) compared MMF and CYC in patients with SSc-ILD. Although the difference in FVC between CYC (−2.88%) and MMF (−2.19%) at 24 months was not statistically significant (p=0.24), MMF had a better safety profile, with a lower mortality rate (7% with MMF vs 15% with CYC). As a result, MMF is now recommended as the first-line therapy for SSc-ILD, particularly for long-term disease stabilisation.[35]

TCZ demonstrated preservation of lung function in FaSScinate and FocuSSed trials, with a +4.2% FVC benefit (p=0.0002), supporting its FDA approval for SSc-ILD.[36] Rituximab (RTX) has shown consistent efficacy. The DESIRES trial reported stabilisation of FVC (+0.09%

Table 2 Comparison of HSCT versus CYC in SSc—summary of key trials and results for skin involvement

	2014, ASTIS (N=156)	2011, ASSIST (N=19)	2018, SCOT (N=75)
Type	Selective non-myeloablative HSCT vs IV CYC 750 mg/m² monthly for 12 months.	Non-selective non-myeloablative HSCT No-myeloablative vs CYC 1 g/m² monthly for 6 months	Selective myeloablative HSCT vs CYC 500 mg/m² 1 dose+750 mg/m² for 11 months
Conditioning	CYC 200 mg/kg for 4 days, anti-thymocyte globulin (ATG) 7.5 mg/kg for 3 days, methylprednisolone 1 mg/kg	CYC 200 mg/kg for 4 days ATG 0.5 mg/kg×1 year 1.5 mg/kg 4 days Methylprednisolone 1 g	CYC 120 mg/kg 2 days ATG 90 mg/kg 6 days Methylprednisolone 1 mg/kg Total body radiation
mRSS	CYC −9 vs HSCT −20 at 20 years (p<0.001). Difference 11 points	CYC+3 vs HSCT −13 at 1 year (p=0.0004). Difference 16 points	CYC vs HSCT. Improvment in 86% en HSCT vs 49% CYC at 4.5 years (p=0.02)
GRADE evidence	MODERATE	LOW	MODERATE

ASSIST, Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial; ASTIS, The Autologous Stem Cell Transplantation International Scleroderma; CYC, cyclophosphamide; DLCO, Diffusing capacity of the lungs for carbon monoxide; DLCO, Diffusing capacity of the lungs for carbon monoxide; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HSC, haematopoietic stem cell; mRSS, modified Rodnan skin score; mRSS, modified Rodnan skin score; SCOT, Scleroderma Cyclophosphamide or Transplantation; SCOT, Scleroderma Cyclophosphamide or Transplantation; SSc, systemic sclerosis.

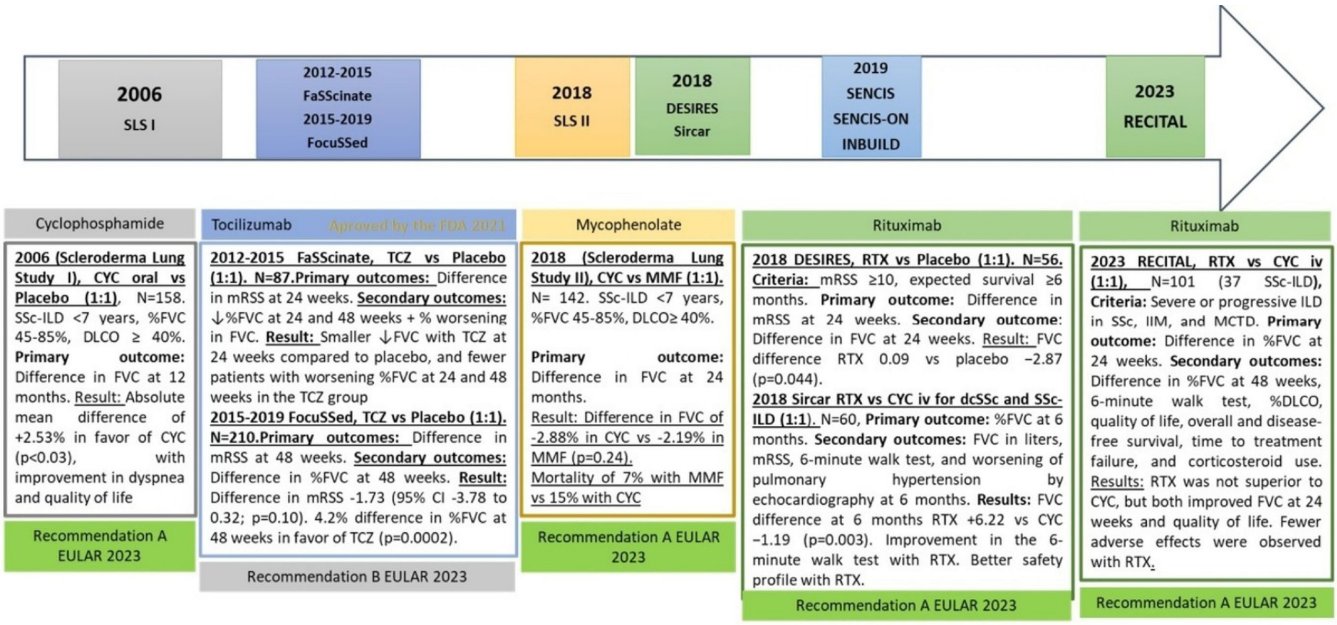

Figure 2 Visual representation of clinical trials in SSc and results for ILD. CYC, cyclophosphamide; FVC, forced vital capacity; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; ILD, interstitial lung disease; MTX, methotrexate; RECITAL, Rituximab Versus Cyclophosphamide in Connective Tissue Diseases-Interstitial Lung Disease SLS II; Scleroderma Lung Study II; SSc, systemic sclerosis; TCZ, tocilizumab.

vs −2.87%; p=0.044), while the Sircar trial demonstrated FVC improvement (+6.22% vs −1.19% with CYC; p=0.003).[37] The RECITAL trial (2023) confirmed similar FVC gains with RTX and CYC, but with fewer adverse events in RTX-treated patients.[41]

Nintedanib, a tyrosine kinase inhibitor, has emerged as an important antifibrotic agent in SSc-ILD. The SENSCIS Trial (2014) demonstrated that nintedanib reduced the annual rate of FVC decline by 41.0 mL/year compared with placebo (p=0.04).[42] The INBUILD Trial (2022) further confirmed its benefits across various fibrosing ILDs, showing a 102.7 mL/year reduction in FVC decline (p=0.012). While nintedanib does not significantly impact skin fibrosis, its ability to slow ILD progression makes it a valuable therapeutic option, particularly for patients with progressive lung involvement.[43]

AHSCT offers disease modification for severe, rapidly progressive SSc-ILD. The ASTIS (+6% FVC at 2 years; p=0.004), ASSIST (+12% FVC at 1 year; p=0.004) and SCOT (+4% FVC at 4.5 years; p=0.005) trials demonstrated its superior efficacy.[38–40] Long-term data indicate sustained stabilisation of lung function, though careful patient selection and multidisciplinary management are essential to optimise outcomes. Table 3 compares HSCT versus CYC in SSc, highlighting changes in %FVC and %DLCO over time in the HSCT trials.

Table 3 Comparison of HSCT versus CYC in SSc: change in %FVC and %DLCO over time in HSCT trials

	2014, ASTIS (N=156)	2011, ASSIST (N=19)	2018, SCOT (N=75)
Type	Selective non-myeloablative HSCT vs IV CYC 750 mg/m² monthly for 12 months.	Non-selective non-myeloablative HSCT No-mieloablativo vs CYC 1 g/m² monthly for 6 months	Selective myeloablative HSCT vs CYC 500 mg/m² 1 dose+750 mg/m² for 11 months
%FVC	CYC: −3% vs HSCT: +6% a at 2 years (p=0.004) Difference: 9 points	CYC: −6% vs HSCT: +12% at 1 year (p=0.004) Difference: 18 points	CYC: −14% vs HSCT: +4% a los 4.5 years (p=0.005) OR: 1.63 (95% CI 0.75 to 3.51)
%DLCO	CYC: −4% vs HSCT: −5% a at 2 years (p=0.84) Difference 1%	CYC −1% vs HSCT: + 11% at 1 year (p=0.34) Difference: 12%	Probability ↓ < 50% DLCO: CYC: ~92% vs HSCT: ~20% at 4.5 years (p=0.001)
GRADE evidence	MODERATE	LOW	MODERATE

ASSIST, Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial; ASTIS, The Autologous Stem Cell Transplantation International Scleroderma ; CYC, cyclophosphamide; FVC, forced vital capacity; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HSCT, haematopoietic stem cell transplantation; SSc, systemic sclerosis.

Management of PAH

PAH is a severe and life-threatening complication of SSc, with multiple targeted therapies demonstrating efficacy in clinical trials. Endothelin receptor antagonists (ERAs), including ambrisentan, bosentan and macitentan, are key components of PAH treatment. *ARIES-1/2* trials confirmed sustained benefits of ambrisentan on symptoms and 6 min walk distance (6MWD).[44] Bosentan (*BREATHE-1* and *EARLY-1*) showed mixed results in SSc-PAH, with potential benefits in early-stage disease.[45 46] Macitentan (*SERAPHIN*) improved functional status and survival, further reinforcing the role of ERAs.[47]

Phosphodiesterase-5 inhibitors (PDE-5i)—sildenafil (*SUPER-1*) and tadalafil (*PHRIST*)—have also demonstrated efficacy in improving exercise capacity, quality of life and pulmonary haemodynamics in SSc-PAH.[48 49] Combination therapy with ambrisentan and tadalafil (AMBITION) has emerged as the preferred first-line regimen for low-risk to intermediate-risk patients, providing superior outcomes over monotherapy.[50] Additional therapies include riociguat, which modestly improves haemodynamics (PATENT-1)[51] and prostacyclin pathway agents. Intravenous epoprostenol and inhaled iloprost improve haemodynamics and functional class, though parenteral delivery remains complex.

Selexipag, an oral selective prostacyclin receptor agonist, has expanded the therapeutic landscape for SSc-PAH by offering an effective alternative to traditional intravenous or subcutaneous prostacyclin therapies. The GRIPHON trial, a large phase III, double-blind, placebo-controlled study, assessed selexipag's impact on PAH, including SSc-PAH, in 1156 patients over a median follow-up of 74.6 weeks. The trial's primary endpoint—time to first morbidity or mortality event—demonstrated a 40% reduction in disease progression and mortality with selexipag compared with placebo (HR: 0.60; 99% CI: 0.46 to 0.78; p<0.001). These benefits were consistent across PAH subgroups, reinforcing selexipag's role in improving long-term outcomes. Selexipag was effective both as monotherapy and in combination with ERAs or PDE-5i, further broadening its utility.[52]

Emerging therapies include sotatercept, a first-in-class activin signalling modulator, which showed significant improvement in pulmonary vascular resistance and 6MWD in the *STELLAR* trial.[53] While data in SSc-PAH specifically are still limited, sotatercept represents a promising new avenue for future treatment.

The 2022 ESC/EULAR guidelines recommend combination therapy with PDE-5i and ERAs as first-line treatment, reserving prostacyclin analogues and riociguat for high-risk or refractory cases. Routine anticoagulation is discouraged in SSc-PAH due to bleeding risks.[54] Selexipag is a valuable option for patients requiring prostacyclin pathway-targeting therapy while avoiding the complications of intravenous or subcutaneous administration.[52] Epoprostenol remains reserved for severe cases due to its efficacy, despite its complex administration.

Importantly, current evidence is based on the historical PAH definition (mPAP≥25 mm Hg). The recent lowering of this threshold to mPAP ≥20 mm Hg introduces new uncertainties, as the optimal management of earlier-stage patients (mPAP 20–24 mm Hg) remains to be established. Future studies will be critical to guide treatment in this evolving population.

Management of RP and DUs

The management of RP and DUs in SSc remains a complex challenge, requiring a combination of pharmacological and non-pharmacological strategies. Calcium channel blockers, particularly nifedipine, remain the first-line therapy for RP, with a meta-analysis of 38 RCTs confirming their efficacy in significantly reducing attack frequency and severity.[55] PDE5 inhibitors have also shown promise, with a meta-analysis reporting significant improvements in Raynaud's Condition Score, attack frequency and episode duration. Intravenous iloprost is an effective alternative for severe or refractory cases, though cost and accessibility may limit widespread use. Other options, such as nitrates, losartan, botulinum toxin and sympathectomy, are primarily supported by observational data and remain second-line choices for resistant cases.

The role of ERAs in vascular complications of SSc has been a focus of investigation, particularly for DUs. While macitentan failed to show benefit in reducing new DU development in the DUAL-1 and DUAL-2 trials, bosentan demonstrated a significant preventive effect in the RAPID-2 trial, reducing new ulcer formation by approximately 30% compared with placebo. However, neither bosentan nor macitentan was effective in promoting the healing of existing ulcers or improving pain and disability, underscoring the need for combination approaches in DU management.[56 57]

Current recommendations favour bosentan for DU prevention, while PDE5 inhibitors and intravenous iloprost remain preferred for promoting ulcer healing.[6] Beyond their role in vascular complications, ERAs may have a broader impact in SSc management, particularly in PAH prevention. Given the progressive nature of vascular remodelling in SSc, early endothelial dysfunction may precede clinically apparent PAH. By targeting endothelin-mediated vasoconstriction and fibrosis, ERAs could play a role in modifying disease progression beyond their established use in PAH treatment.[58] However, long-term data on this preventive strategy remain limited. Interestingly, the interplay between therapies targeting specific organ manifestations in SSc must also be considered. While agents like PDE5 inhibitors, ERAs and prostacyclin analogues improve vascular function, they may also influence other aspects of SSc pathogenesis, potentially impacting fibrosis and immune dysregulation.[59]

Specialised wound care, patient education on cold avoidance and emerging therapies such as botulinum toxin, fat grafting and sympathectomy warrant further investigation to refine treatment algorithms. As research

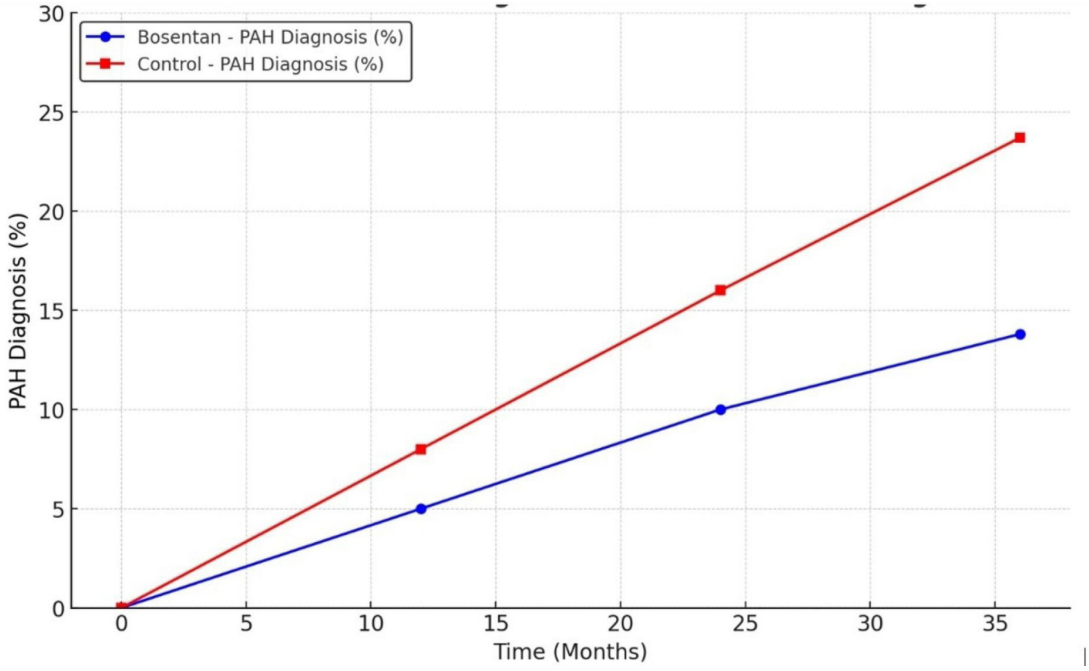

Figure 3 Graphic representation of the impact of early treatment on PAH Risk in SSc patients with digital ulcers. PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

progresses, a more comprehensive understanding of how vascular-targeted therapies intersect with other SSc manifestations will be essential in improving long-term patient outcomes.

Management of SRC

The management of SRC relies primarily on ACE inhibitors (ACEi), which remain the cornerstone of treatment despite the absence of RCTs. Observational studies strongly support their efficacy in controlling hypertension, slowing disease progression and improving survival. Captopril is the most frequently used ACEi, typically initiated at low doses (6.25–12.5 mg) and titrated up to 300–450 mg/day as needed. However, ACEi is not recommended for prophylactic use, as studies suggest an increased incidence of SRC and poorer outcomes in patients who were on ACEi before crisis onset. In cases of uncontrolled blood pressure, some experts suggest combining ACEi with angiotensin receptor blockers (ARBs), though evidence for ARBs is limited.

For patients with refractory hypertension, some experts advocate for the cautious addition of ARBs, though evidence for their efficacy remains limited. CCBs, particularly dihydropyridines like nifedipine, may serve as adjunctive therapy for vasodilation in resistant cases, though they are not considered first-line agents. Emerging therapies, such as eculizumab, have shown promise in observational studies, particularly in patients with renal biopsy findings of C5b9 deposition, suggesting a role for complement-mediated microangiopathy in SRC pathogenesis. Additionally, iloprost, a prostacyclin analogue, has demonstrated potential in reducing renal artery resistance, though its use remains investigational. In cases of advanced renal failure, haemodialysis is generally preferred over peritoneal dialysis due to better survival outcomes. Recovery from SRC-induced renal failure is highly variable, with approximately 30% of patients requiring long-term dialysis, while others may regain renal function over a period of 8 months to 2 years.[60]

Given the heightened risk of SRC in SSc patients receiving glucocorticoids, routine blood pressure monitoring is essential for early detection and intervention. Further research is needed to refine treatment strategies, explore the role of novel therapeutics and improve long-term outcomes in SRC.

Management of GI involvement

Proton pump inhibitors (PPIs) remain the cornerstone of gastro-oesophageal reflux disease (GERD) management in SSc, despite limited robust evidence. In a trial of 243 patients receiving omeprazole (20 mg two times per day), only 53.9% achieved a partial response, with less than 50% improvement in GERD symptoms.[61] Adjunctive therapies, such as domperidone and alginic acid, have shown added benefits when combined with PPIs, as demonstrated in an RCT of 148 patients51. Emerging agents like vonoprazan, a potassium-competitive acid blocker, have also demonstrated potential in small studies by enhancing lower oesophageal sphincter pressure and reducing gastric acidity, offering an alternative for PPI-refractory cases.[62]

Prokinetics play a crucial role in addressing dysfunction of motility. Buspirone has been shown to improve lower oesophageal sphincter tone and reduce acid exposure when used alongside PPIs. For gastric motility, prucalopride has demonstrated efficacy in alleviating nausea, bloating, and early satiety. The PROGRASS study further

Table 4 Priority pathways for clinical trials

Pathogenic target/pathway	Mechanistic rationale	Representative approaches	Clinical focus
B cell survival and activation	Central in autoantibody production and immune dysregulation	BAFF/APRIL blockade (eg, belimumab, telitacicept)	Early diffuse SSc, autoantibody-positive patients
CD19+B cell depletion	Promotes immune reset and autoimmunity control	CD19-directed CAR-T cell therapy	Refractory SSc
Type I interferon signalling	Associated with innate immune activation and fibrosis	IFNAR blockade (eg, anifrolumab)	Immune activation, early dcSSc
T cell costimulation	OX40-OX40L promotes pathogenic T effector cell expansion	OX40L inhibitors (eg, amlitelimab)	SSc-ILD, skin fibrosis
Regulatory T cell enhancement	Restores immune tolerance, counters inflammation	Low-dose IL-2 therapy	Early inflammatory SSc
IL-6 pathway	Drives fibroblast activation, inflammation, and lung involvement	IL-6 inhibition (eg, ziltivekimab, olokizumab)	Skin+ILD
Connective tissue growth factor (CTGF)	Mediator of fibrosis downstream of TGF-β	Anti-CTGF antibody (eg, pamrevlumab)	SSc-ILD
Lysophosphatidic acid (LPA) signalling	Promotes fibroblast recruitment, activation and fibrosis	LPA1 receptor antagonists (eg, SAR100842)	Skin fibrosis
Melanocortin receptor activation (MC1R)	Regulates inflammation and dermal fibrosis	MC1R modulators (eg, MT-7117)	Inflammatory skin disease
Phosphodiesterase 4B (PDE4B)	Amplifies inflammatory cytokine production	PDE4B inhibition (eg, nerandomilast)	Progressive SSc-ILD
FcRn–IgG recycling	Sustains pathogenic autoantibodies in circulation	FcRn inhibition to lower IgG burden	ILD, vasculopathy
Endothelial dysfunction/NO–sGC axis	Impaired vasodilation and vascular repair	sGC stimulators (eg, avenciguat)	PAH, digital ulcers
Dual immune-fibrotic engagement	Simultaneous targeting of immune and stromal drivers	Bispecific antibodies (eg, CD19/CD3, FAP/CD3)	Multidomain disease
Immune-fibrotic synergy (combination)	Reflects multifactorial pathogenesis of SSc	MMF+RTX+nintedanib	Progressive SSc-ILD
Precision medicine approaches	Improves trial efficiency and treatment targeting	Biomarkers: KL-6, SP-D, CCL18, skin transcriptomics, NFC	Patient stratification

FAP, fibroblast activation protein; ILD, interstitial lung disease; MMF, mycophenolate mofetil; PAH, pulmonary arterial hypertension; sGC, soluble guanylate cyclase; SSc, systemic sclerosis.

confirmed its benefits, showing significant improvements in bowel movements, GERD severity and abdominal bloating in SSc patients.[63] Small intestinal bacterial overgrowth, a frequent complication in SSc, is often managed with cyclic antibiotic therapy. A meta-analysis of nine studies involving 158 patients found a 60.4% overall symptom improvement, with rifaximin (800–1200 mg/day) proving twice as effective as other antibiotics (77.8% vs 44.8% symptom resolution).[64] Intravenous immunoglobulin (IVIG) has emerged as a potential therapeutic option for severe, refractory GI involvement in SSc, particularly in patients with dysmotility, autoimmune-mediated enteropathy or severe malabsorption.[65] Its immunomodulatory effects may help mitigate autonomic dysfunction and inflammatory-driven gut dysmotility. Case series and small observational studies have reported improvements in intestinal pseudo-obstruction, severe diarrhoea and weight stabilisation in SSc patients receiving IVIG.

Faecal microbiota transplantation has yielded mixed results—while trials such as ReSScue 2020 and 2023 suggested benefits in reducing bloating and diarrhoea,

no significant improvements were observed in overall GI symptom scores.[66]

Despite these advancements, major gaps remain in the management of SSc-related GI complications. Larger, well-designed studies are urgently needed to refine treatment strategies, optimise symptom control and improve long-term outcomes for patients with severe GI involvement.

Management of musculoskeletal involvement

Musculoskeletal involvement is a prevalent and debilitating feature of SSc, yet evidence supporting effective treatments for joint symptoms remains limited. Despite the significant disease burden, there is a lack of robust data confirming the efficacy of corticosteroids, TCZ or rituximab in improving joint outcomes in SSc.

MTX remains the most widely used first-line therapy for SSc-associated arthritis, primarily based on expert consensus rather than high-quality trial data. While anti-TNF agents such as etanercept and infliximab have shown some benefits in case series, concerns have been raised regarding potential disease exacerbation, particularly worsening skin involvement. IVIG has demonstrated modest improvements in joint symptoms in a small, atypical trial, but further studies are needed to validate its efficacy.[67] The role of JAK inhibitors in SSc musculoskeletal involvement remains unclear. While some case reports suggest potential benefits, a randomised trial of tofacitinib failed to demonstrate significant improvements in joint-related outcomes.[68] Abatacept and TCZ have shown promise in select patient populations, with abatacept improving joint symptoms in some cases and TCZ demonstrating positive effects in phase II trials for polyarthritis. However, their broader impact on musculoskeletal involvement in SSc is uncertain.[69] Overall, while musculoskeletal symptoms, particularly joint involvement, remain a significant challenge in SSc, current treatment options offer only partial relief. Further high-quality trials are essential to establish evidence-based therapies and refine treatment strategies for improving musculoskeletal outcomes in SSc.

Early intervention in SSc: addressing cross-organ effects of therapy

Effective management of SSc requires careful navigation of its complex pathophysiology, which encompasses widespread vascular dysfunction, immune dysregulation and progressive fibrosis across multiple organ systems.[1 69] The intricate interplay among these processes presents significant therapeutic challenges, as targeting one disease domain may inadvertently impact others. This inherent complexity highlights the need for a comprehensive, individualised treatment approach that addresses the systemic nature of SSc and carefully considers potential cross-effects between therapies.[70] Preventive medicine plays a pivotal role in managing SSc, emphasising early intervention to halt disease progression before irreversible organ damage occurs. Identifying patients at risk and implementing targeted therapies can slow or prevent the transition from one disease manifestation to another.[15]

Emerging evidence supports the concept that early intervention in SSc leads to better long-term outcomes across multiple organ systems. In SLS II, patients receiving MMF within 18 months of first non-Raynaud symptom had a significantly slower decline in FVC compared with those treated later.[35] Similarly, in the faSScinate and Focused trials, TCZ initiated at a median disease duration of 1.7 years preserved FVC and reduced skin fibrosis progression.[36] Three randomised trials of AHSCT (ASTIS, ASSIST, SCOT) showed survival and functional benefits when performed in patients with early, rapidly progressive diffuse cutaneous SSc (mean duration <5 years).[38–40]

Vascular dysfunction is a key driver of both DUs and PAH, and patients with recurrent, severe DUs often exhibit signs of systemic vasculopathy, which may precede the development of PAH.[71] While previous studies have investigated the clinical association between DUs and PAH, the findings remain inconclusive.[70 72] The Canadian Scleroderma Research Group and a large Spanish cohort study found no significant association between DUs and PAH, whereas the German Network in SSc identified PAH as a risk factor for DUs.[62 73] Patients with recurrent, severe DUs often exhibit signs of systemic vasculopathy, which can precede the development of PAH. Given the shared vascular damage mechanisms in SSc, there is growing interest in whether therapies targeting one vascular complication might prevent others. ERAs, such as bosentan, initially approved for DU prevention, have demonstrated additional benefits in reducing vascular resistance and slowing PAH progression.[58 59] Bosentan has been shown to improve NYHA functional class, exercise capacity and survival in PAH, and its early use may delay clinical worsening.[45 46] In a recent Spanish cohort, bosentan treatment was associated with a lower incidence of PAH development in SSc patients with DUs, suggesting a potential protective vascular effect beyond digital circulation.[74] This suggests that early, aggressive treatment of vascular dysfunction in SSc may prevent later complications like PAH, supporting a preventive vascular-targeted strategy in at-risk patients (figure 3).

Beyond pharmacological interventions, non-pharmacological strategies are critical in early disease management. Structured exercise programmes, patient education on cold exposure and smoking cessation, and close vascular monitoring are essential components of a multidisciplinary approach.[6 59] Nailfold capillaroscopy has proven valuable in identifying patients at higher risk for progressive vasculopathy, allowing for early therapeutic decisions before irreversible vascular damage occurs.[58 59]

Ultimately, a personalised, preventive approach is essential for optimising long-term outcomes in SSc. Future research should focus on identifying early biomarkers of disease transition, allowing for timely therapeutic interventions that not only treat established complications

but actively prevent them from developing.[11 69] By integrating early skin-directed therapies to mitigate ILD risk and targeting vascular dysfunction before PAH emerges, the management of SSc could shift towards a more proactive model, improving both quality of life and long-term survival for patients.

Priority targets for future clinical trials

A mechanistic understanding of SSc pathogenesis is increasingly shaping the design of future clinical trials, shifting focus from empirical immunosuppression towards rationally selected biological pathways. These pathogenic axes—rooted in immune dysregulation, fibrosis and vasculopathy—offer distinct windows for therapeutic intervention. Table 4 represents priority pathways to consider for future clinical trials.

One of the most central and well-validated targets is B cell activation and survival, given the early emergence of autoantibodies and their close association with disease phenotype and progression. The persistence of autoreactive B cells, supported by cytokines such as BAFF and APRIL, not only drives autoantibody production but also contributes to antigen presentation and cytokine release.[22 75] In more refractory cases, deeper immune reset strategies—such as CD19-targeted cellular therapies—are being explored to eliminate long-lived memory B cells and reshape the autoreactive repertoire.[12]

Another recognised axis involves type I interferon signalling, which is highly active in early diffuse disease and associated with poor prognosis.[76] This pathway bridges innate and adaptive immunity, amplifying inflammation through dendritic cell activation and downstream cytokine networks. Targeting the interferon receptor or its transcriptional output holds promise for dampening the early inflammatory cascade and potentially modifying disease trajectory if intervened on promptly.[77]

Beyond the B and interferon axes, T cell costimulatory pathways such as the OX40–OX40L system are implicated in the propagation of effector T cells and maintenance of chronic inflammation.[78] These pathways support the persistence of Th2 and Th17 responses, both of which are implicated in fibroblast activation and vascular damage. Conversely, strategies to enhance regulatory T cell (Treg) populations, such as low-dose IL-2, aim to restore immune tolerance and suppress aberrant effector activity—particularly relevant in early or active disease stages.[79]

IL-6 signalling stands at the intersection of immune and fibrotic pathways, promoting B cell differentiation, T cell polarisation and fibroblast activation. Elevated IL-6 levels are consistently associated with progressive skin and lung involvement, making this a logical target for intervention in patients with both inflammatory and fibrotic disease manifestations.[80]

Fibrogenesis in SSc is driven by a complex interplay between immune signals and stromal activation, particularly via TGF-β downstream mediators such as connective tissue growth factor (CTGF). Targeting CTGF is mechanistically justified due to its role in stimulating extracellular matrix production and myofibroblast persistence, both of which are hallmarks of irreversible organ fibrosis.[81] Similarly, lysophosphatidic acid signalling contributes to fibroblast migration, differentiation and contractility, and its blockade may reduce skin thickening and tissue stiffness.[82]

Emerging inflammatory-fibrotic axes include the melanocortin system, where activation of melanocortin receptors has been shown to suppress NF-κB signalling and reduce dermal fibrosis, and phosphodiesterase 4B (PDE4B), which regulates the production of pro-inflammatory cytokines implicated in fibrosing ILD.[83] Both pathways offer dual modulation of inflammation and fibrosis with the potential to stabilise or reverse early lung and skin pathology.

Vascular damage—both as a primary and secondary phenomenon—is a defining feature of SSc. The NO–sGC–cGMP axis, central to vascular tone and endothelial repair, is impaired in SSc. Activating sGC may restore endothelial homeostasis and reduce complications such as PAH and DUs.[84] In parallel, FcRn-mediated IgG recycling maintains elevated levels of pathogenic autoantibodies; inhibiting this pathway offers a strategy to reduce autoantibody burden and its downstream vascular and inflammatory sequelae.[85]

Collectively, these pathways not only reflect distinct mechanistic drivers of disease but also offer a basis for precision targeting across heterogeneous patient subsets. The integration of biomarker-based enrichment strategies—including serum markers like KL-6, CCL18, surfactant protein D, as well as transcriptomic profiles and capillaroscopic patterns—will be essential to match therapeutic mechanisms to individual disease biology. This pathway-centred approach is poised to redefine therapeutic development in SSc, emphasising upstream immunological intervention, modulation of fibrotic commitment and preservation of vascular integrity.

CONCLUSIONS

SSc remains a complex and heterogeneous disease with substantial unmet needs in long-term disease modification and prevention of organ damage. While the 2023 EULAR recommendations have advanced standard care by integrating immunosuppressive, antifibrotic and vasodilator strategies, current treatments largely address organ-specific manifestations and offer only partial disease control.

Emerging therapies—including CD19 CAR-T cell therapy, bsAbs and novel agents targeting interferon pathways, BAFF, FcRn and pro-fibrotic signalling—represent a shift towards precision medicine and immune reprogramming in SSc. These approaches are particularly promising for patients with early diffuse disease, inflammatory signatures or refractory complications.

Ongoing advances in early intervention, biomarker-driven risk stratification and cross-organ treatment

strategies offer the potential to move beyond symptom management towards true disease modification. For example, early targeting of skin or vascular involvement may prevent progression to ILD or PAH, respectively. Similarly, optimised AHSCT and novel biologics are now enabling deeper and more durable control of aggressive disease phenotypes.

Despite these advances, significant challenges remain. Reliable predictors of therapeutic response are still lacking for most agents. The long-term safety of emerging immunotherapies, especially cellular and checkpoint-targeted treatments—must be rigorously evaluated. Additionally, optimal sequencing and combination strategies for therapies across clinical subsets are not yet established.

A critical goal for upcoming research is to validate early biomarkers of disease trajectory and incorporate them into treatment algorithms to enable personalised and preventative strategies. The development of adaptive, mechanism-based trial designs will be essential to capture the heterogeneity of SSc and accelerate the implementation of novel therapies in clinical practice.

The era of precision medicine in SSc is rapidly unfolding. With continued innovation in targeted immunotherapies, organ-protective agents and risk-adapted strategies, the field is poised to move beyond symptomatic control towards a future where early intervention, immune restoration and even remission may become realistic outcomes for patients living with this devastating disease.

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