EUSTAR
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EULAR 2025 Systemic Sclerosis Highlights Brochure

Editorial

The **2025 EULAR Congress** offered a panoramic view into the evolving landscape of systemic sclerosis (SSc), spotlighting major advances across pathogenesis, clinical management, and emerging therapies. This year's findings emphasized a growing paradigm shift: from reactive treatment to proactive, precision-based care.

A central theme was the early molecular footprint of disease. Spatial transcriptomics and proteomic profiling uncovered previously unrecognized fibroblast and immune niches in skin and cardiac tissues. These discoveries, including the identification of specific pro-inflammatory and pro-fibrotic fibroblast subpopulations, are poised to redefine early diagnosis and therapeutic targeting—well before irreversible fibrosis occurs.

In parallel, the clinical science sessions addressed difficult-to-treat manifestations of SSc, offering expert frameworks for conditions such as small bowel dysfunction, critical digital ischemia, and refractory anemia. Of particular note were the updated consensus recommendations for managing gastroesophageal reflux disease (GERD) in SSc, which underscore the importance of multidisciplinary collaboration, high-dose PPI regimens, and individualized care pathways.

Interstitial lung disease (ILD) remained a focal point, with artificial intelligence (AI)-assisted imaging proving superior to traditional visual scoring for disease monitoring. New data demonstrated the utility of routine high-resolution CT (HRCT) in predicting mortality and guiding early intervention. Therapies such as Rituximab, mycophenolate mofetil, nintedanib, and upadacitinib confirmed clinical promise, while combination regimens continue to be evaluated in large cohort studies.

The biggest SSc registry, EUSTAR, provided rich insights into phenotype-genotype associations. Autoantibody profiles, including anti-Ro/SSA and anti-centromere antibodies, as well as anti-Th/To antibodies, were linked to organ-specific risks, helping to refine stratified monitoring and therapeutic decisions. Concurrently, new data on cancer risk, calcinosis, and hematological malignancies underscore the value of longitudinal surveillance and personalized screening algorithms.

Finally, the congress placed a much-needed spotlight on life-threatening emergencies in SSc, including scleroderma cardiac and renal crises. Case-based presentations highlighted the subtlety of clinical onset and the critical importance of rapid diagnosis, cautious steroid use, and intensive supportive management.

Taken together, **the EULAR 2025 highlights brochure** mark a pivotal step forward in systemic sclerosis research and care. From deep molecular mapping to registry-based precision tools, these contributions bring us closer to the vision of personalized, preventive rheumatology.

***Jelena Čolić**, PD, MD, PhD*
Department of Rheumatology, Karolinska Institutet, Stockholm, Sweden
Institute of Rheumatology, Belgrade, School of Medicine,University of Belgrade,

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EULAR 2025

Systemic Sclerosis Highlights Brochure

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CLINICAL SCIENCE OF SYSTEMIC SCLEROSIS – HOW TO MANAGE DIFFICULT CASES OF COMMON MANIFESTATIONS

Chosen and written by:

Noemí Franco Domingo,MD
Hospital Universitario Severo
Universidad de Cantabria
Cantabria, Spain

Carlos Valera Ribera,MD
Department of Rheumatology
Doctor Peset University Hospital
Valencia, Spain

1.1. Small bowel involvement in systemic sclerosis

Prof. Ana-Maria Hoffman-Vold

In this insightful session, Prof. Anna-Maria Hoffmann-Vold addressed a common yet often underexplored manifestation of systemic sclerosis (SSc): small bowel involvement. Affecting up to 88% of SSc patients, small intestinal dysfunction represents the second most impactful organ system in terms of quality-of-life impairment, according to patient-reported outcomes (PROs).

At diagnosis, 66% of patients present with mild symptoms, 20% with moderate, and 3% with severe small bowel disease. Among the various gastrointestinal complications, small intestinal bacterial overgrowth (SIBO) was identified as the most frequent, affecting 39% of patients.

The pathophysiology remains incompletely understood, though Prof. Hoffmann-Vold proposed a multifactorial model involving vasculopathy and immune-mediated neuromuscular damage. These factors may lead to progressive dysmotility, predisposing to SIBO, malabsorption, and chronic pseudo-obstruction. She also highlighted that the underlying pathogenic mechanisms can evolve over the disease course, explaining the heterogeneity in clinical manifestations.

Emerging data on gut microbiota alterations in SSc were briefly discussed, with some microbial signatures being associated with specific symptoms. Using a clinical case of severe SIBO, Prof. Hoffmann-Vold illustrated a practical diagnostic and therapeutic approach.

While standard monitoring includes serial weight measurements and routine labs to screen for nutritional deficiencies, PRO-based tools such as the UCLA GIT 2.0 questionnaire were emphasized for longitudinal follow-up.

Treatment remains largely symptomatic, relying on prokinetic agents, cyclic antibiotics for SIBO, and anti-diarrheal therapies. Notably, recent trials investigating faecal microbiota transplantation (FMT) in SSc have failed to demonstrate efficacy for symptoms like bloating and diarrhoea, underlining the need for more targeted therapies in this setting.

1.2. Critical digital ischaemia in systemic sclerosis

Noemí Franco Domingo

Critical Digital Ischaemia (CDI) represents the most severe form of systemic sclerosis (SSc)-related digital vasculopathy. It is characterized by severely reduced blood flow, ischaemic pain, ulceration, tissue loss, and gangrene. It is a medical emergency associated with high morbidity, amputation rates, and impaired quality of life, requiring prompt hospitalisation.

Best practices are based on expert consensus (Hughes et al., *Rheumatology*, 2015), with emphasis on a multidisciplinary approach combining medical and surgical strategies.

While CDI often results from non-inflammatory SSc vasculopathy, it is essential to rule out other causes—such as large vessel disease, vasculitis, coagulopathy, thromboembolism, and smoking—especially in atypical presentations and evolution. Diagnosis should be grounded in clinical history, patient examination including peripheral pulse assessment, laboratory testing including CRP, ESR, ANCA, dsDNA, complement, antiphospholipid antibodies; and if necessary, assessment of histology changes in amputated digits.

Therapeutical management includes:

- Patient education and early medical consultation within a multidisciplinary framework.
- Use of intravenous prostaglandins, optimization of oral vasodilators, tailored analgesia, and antibiotics when infection is suspected.
- Although evidence for antiplatelets and statins is limited, they are commonly used.
- In refractory cases, botulinum toxin injections or surgical interventions such as sympathectomy, debridement or amputation may be required.

Ongoing research is needed to identify therapies capable of preventing or reversing the vascular injury underlying CDI.

1.3. Refractory anemia in systemic sclerosis

Prof. Yannick Allanore

By Carlos Valera Ribera

In this highly practical session, Prof. Yannick Allanore illustrated the clinical and prognostic significance of anemia in systemic sclerosis (SSc) through two case reports. Anemia at diagnosis affects approximately 20% of patients and has been independently associated with higher mortality at two years in early diffuse cutaneous SSc, as well as better known risk factors like older age, gastrointestinal (GI) involvement, and extent of skin thickness.

The first case featured a female patient with recurrent transfusion-dependent anemia. Upper GI endoscopy revealed the presence of gastric antral vascular ectasia (GAVE), a condition that, while estimated at only 1% prevalence in registries, was present in 22.5% of early diffuse SSc patients in the SCOT trial.

EUSTAR cohort data confirmed that patients with GAVE often display lower DLCO values but less pulmonary fibrosis. A strong association with anti-RNA polymerase III antibodies was noted. Supporting evidence from the Australian cohort further associated GAVE with calcinosis, digital ulcers, telangiectasia, and GI dysmotility, suggesting a broader microvascular phenotype.

In terms of therapy, Prof. Allanore discussed the OCEAN trial, which, though not specific to SSc, compared Octreotide versus standard-of-care in patients with GI bleeding from angiodysplasia. The Octreotide arm required

fewer transfusions, suggesting potential benefit in GAVE-related anemia, and a possible extrapolation with SSc GAVE.

The second case involved a woman with longstanding SSc who developed myelodysplastic syndrome. This example served to highlight the relevance of age-related clonal hematopoiesis and myeloid malignancies in the SSc population. As patients live longer, these hematological complications become increasingly relevant and should be considered in the differential diagnosis of refractory anemia.

This session underscored the importance of structured anemia workup in SSc and vigilance for both vasculopathic and hematologic causes.

1.4. Provisional expert recommendations for the management of refractory gastroesophageal reflux disease in systemic sclerosis: a report from the World Scleroderma Foundation (WSF) gastrointestinal "AdHoc Committee"

M. Hughes

Gastro-oesophageal reflux disease (GERD) affects approximately 75% of patients with systemic sclerosis (SSc). Given the limitations of current guidelines, this project aimed to develop an extended set of practical, consensus-based recommendations for the management of SSc-related GERD.

An international multidisciplinary committee was convened to review the latest definitions of GERD and refractory GERD. Following the drafting of recommendations, a voting process with a good response rate was conducted to determine which items should be accepted.

The most relevant aspects of the consensus include:

- Identification of red flags that warrant urgent objective evaluation, and the use of a multidisciplinary approach to rule out other causes.
- Collaborative work with gastroenterology specialists to ensure individualized diagnosis, treatment, and management.
- Optimization of lifestyle measures and promotion of therapeutic adherence.
- First-line use of high-dose proton pump inhibitors (PPIs) in SSc-related refractory GERD, with a careful risk-benefit assessment in patients at high risk for secondary complications. If maximum PPI dosing is not achievable, complementary or alternative therapies should be considered.
- In cases where refractory GERD is accompanied by other gastrointestinal (GI) symptoms related to SSc, the addition of other pharmacological agents may be appropriate.
- There is currently no conclusive evidence to support the use of immunosuppressive therapy for SSc-related GI involvement, including refractory GERD.
- Endoscopic and surgical treatments have limited supporting evidence but may be considered on a case-by-case basis, provided there are no contraindications. Notably, surgical treatment may play a key role when upper GI involvement impacts eligibility for lung transplantation.

Significant knowledge gaps remain, highlighting the need for further study and research.

BASIC ABSTRACT SESSION

Chosen and written by:

Kristina Clark, MD
University of Oxford, UK

Minrui Liang, MD, PhD
Institute of Rheumatology, Immunology and Allergy, Huashan Rare Disease Center, Huashan Hospital, Fudan University, Shanghai

2.1. Spatial transcriptomic-based phenotyping of the fibroblast niches in systemic sclerosis-associated primary heart involvement

Dr Alexandru Micu, Dusseldorf, Germany

This study systematically profiled fibroblast heterogeneity and spatial niche architecture in systemic sclerosis-associated primary heart involvement (SSc-pHI), a major contributor to SSc-related mortality. Using spatial transcriptomic analysis of myocardial biopsies from patients with acute (e.g., AMI) and chronic (e.g., ICM, HCM, PVMF, SSc-pHI) cardiomyopathies, the authors identified a distinct fibroblast landscape in SSc-pHI characterized by the expansion of GSN/DCN+, AP-1+, and TIMP1+ fibroblasts. Spatial mapping revealed disease-specific fibroblast communities (e.g., AP-1+ Fb CN, TIMP1+ Fb CN) that were functionally linked to extracellular matrix remodeling, immune signaling (IL-6, IL-12, IFNα), and apoptosis. These findings delineate a fibro-inflammatory program unique to SSc-pHI myocardium and highlight potential cellular targets for therapeutic intervention in SSc-related cardiac fibrosis.

2.2. Mapping spatially-resolved transcriptomics in systemic sclerosis

Dr Minrui Liang, Shanghai, P.R. China

This study focused on stromal-immune crosstalk, which shapes the pathogenic microenvironment of systemic sclerosis (SSc). They explored tissue organization and cell coordination in SSc skin through multiple spatial omics, providing spatiotemporal insights into disease mechanisms. The key regulatory pathway was validated in experimental fibrosis model.

The integration of transcriptomics and tissue structure revealed a fibrotic niche, enriched with fibroblasts and macrophages, which was significantly expanded in SSc and correlated with mRSS progression and therapeutic non-responsiveness. Furthermore, they identified an imbalance in fibroblast subsets in SSc, characterized by a decrease in SCARA5^{+} fibroblast progenitors and an increase in POSTN^{+}/ACTA2^{+} terminally differentiated myofibroblasts. They also identified three macrophage (Mϕ) populations with distinct transcriptional profile in SSc skin versus controls: increased inflammatory Mϕ (IL-1β^{+}), decreased phagocytic Mϕ (LYVE1^{hi}MHCII^{lo}), but unaltered antigen-presenting

Mϕ (LYVE1^{lo}MHCII^{hi}). Notably, they discovered enhanced interactions between fibroblasts and IL-1β^{+} inflammatory Mϕ, suggesting spatial dependency. We identified specific expression of ACKR3 in fibroblast progenitors that diminishes over SSc progression, which may serve to regulate CXCL12/CXCR4-mediated Mϕ recruitment and tissue fibrotic remodeling. Pharmacological inhibition of CXCR4 attenuated skin and lung fibrosis induced bleomycin in mice.

2.3. In vitro modelling of vasculopathy in systemic sclerosis by human blood vessel organoids

Dr Alexandru-Emil Matei, Dusseldorf, Germany

In this study, we developed a human in vitro model of systemic sclerosis (SSc)-associated microvasculopathy using blood vessel organoids (BVOs) derived from induced pluripotent stem cells of both SSc patients and healthy controls. These organoids reproduced key vascular features of SSc, including early abnormal angiogenesis and later-stage vessel loss and endothelial-to-mesenchymal transition (EndMT), particularly after exposure to serum from patients with active digital ulcers. Multi-omics analyses revealed that these changes were driven by a combination of genetic susceptibility and circulating IgG autoantibodies. We also observed disrupted interactions between endothelial cells and pericytes, along with activation of profibrotic pathways such as TGFβ and Notch signaling. Treatment with bosentan or the γ-secretase inhibitor DAPT mitigated the vascular damage and EndMT induced by SSc serum. These findings highlight the utility of SSc-derived BVOs as a relevant platform for mechanistic studies and preclinical drug evaluation in SSc-related vasculopathy.

2.4. SomaScan proteomic analysis of the skin across the Systemic Sclerosis (SSc) disease continuum reveals a distinct very early specific profile vs a fibrotic profile

Dr Rebecca Ross, Leeds, UK

This study applied SomaScan proteomics to skin biopsies across the spectrum of systemic sclerosis (SSc), including patients with the very early diagnosis of systemic sclerosis (VEDOSS), to identify molecular changes linked to fibrosis. VEDOSS skin showed a distinct proteomic profile, marked by early upregulation of antioxidant and oxidoreductase proteins (e.g., SOD3, GPX3, ALDH3A1, GSTZ1) and activation of glycolysis, ECM–receptor interaction, and focal adhesion pathways. As disease progressed, these shifted toward complement activation, coagulation, and extracellular matrix deposition.

Protective proteins such as MATN4, PCOLEC2, and CFD declined early, while profibrotic markers like THBS1, INHBA, and SERPINE2 increased and correlated with skin thickness. Elevated collagen expression in VEDOSS skin, despite minimal clinical signs, pointed to early fibrotic activity. These findings suggest fibrosis in SSc begins at the molecular level before clinical onset and highlight potential biomarkers and therapeutic targets in redox and metabolic pathways.

2.5. Metabolic phenotyping of systemic sclerosis skin by spatial proteomics

Dr Alexandru-Emil Matei, Dusseldorf, Germany

This study focused on single-cell metabolic phenotyping of fibroblasts, macrophages and endothelial cells from skin biopsies of patients with SSc, using imaging mass cytometry (IMC) and spatial proteomics. They identified a distinct metabolically active profile with high activity of glycolysis, TCA/OXPHOS, hypoxia and ROS signaling in fibroblasts, endothelial cells and macrophages of patients with progressive skin disease. These tended to be associated with profibrotic marker activation in the fibroblasts and endothelial cells. They also demonstrated metabolic niches, where metabolically active fibroblasts potentially induce similar metabolic phenotypes in endothelial cells and macrophages, suggesting a profibrotic cell-cell communication network.

2.6. CD4+ TRAIL+ T Cells with Interferon-Stimulated Gene signature differentially restrict Anti-Nuclear Antigen Responses in Sjogren and Systemic sclerosis

Dr Theodoros Papadimitriou, Radboudumc, Netherlands

This study looked at autoreactive CD4+ T cells in sjogrens and SSc across affected tissues and PET active lymph nodes. They found disease specific autoreactive T-cell immunity between the two diseases. In SSc lymph nodes, there was limited T-B cell interaction, with reduced plasma cell formation and reduced ANAg+ T helper cells, The researchers focused on a novel CD4+ TRAIL+ T cell population with an interferon stimulated gene signature (ISG) which was expanded in PET-avid lymph nodes in SSc. Conversely, in Sjogrens, there was a robust T-B cell interaction, with increased plasma cell formation, increased ANAg+ T helper cells, however reduced naïve and innate-like TRAIL+CD4+ISG T cells. The TRAIL-DR4 axis restricts autoantibody production, thus offers a potential therapeutic target for developing tolerogenic therapies for systemic autoimmune disease.

2.7. Mitochondrial DNA and chemokine (C-X-C motif) ligand 4 (CXCL-4) are in the centre stage of feedback loops that promote mitochondrial DNA release from platelets and neutrophils and amplify interferon driven inflammation in systemic sclerosis

Prof Ulrich Walker, Basel, Switzerland

This group showed that mitochondrial DNA (mtDNA) (unlike nuclear DNA) in SSc is 150 times higher when compared to HCs. Oxidised mitochondrial DNA/CXCL4 complexes are released by SSc platelets are promote platelet activation and also NETotic mtDNA release in neutrophils. Of particular interest was the fact that SSc plasma-derived mtDNA was much more potent than HCs at triggering the type-1 interferon pathway in THP1 reporter monocytes via the cGAS, STING and endosomal TLRs, which in turn promotes NETosis. This highlighted a promising target for therapeutic intervention, which the group demonstrated the effects could be tartgeted in vitro with the use of JAK inhibitors which reduced NET formation and oxidized mtDNA in SSc.

2.8. Anti-mitochondrial antibodies in systemic sclerosis target enteric neurons and are associated with GI dysmotility

Dr Zsuzsanna McMahan, Houston, USA

Anti M2 mitochondrial antibodies (AM2A) were noted in 12.9% of patients, and tended to be associated with worse upper GI symptoms than AM2A negative patients. specifically significantly slower transit time in the oesophagus and stomach. The AM2A antibodies were shown to target a specific, mitochondria-rich subset of enteric neurons, known as MENS (mesoderm-derived enteric neurons). A2A were able to penetrate live cells and impair mitochondrial respiration. Through histological studies, and co-localisation studies, this group showed that where AM2A antibodies may directly impair enteric neuronal function, thus contributing to SSc GI disease.

CLINICAL ABSTRACT SESSIONS: INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS – CLINICAL CHALLENGES AND EVOLVING TREATMENTS

Chosen and written by:

Maria Iacovantuono, MD
Rheumatology, allergology and clinical immunology
University of Rome Tor Vergata, Italy

3.1. Anti-Ro/SSA+/RF+ double seropositivity in systemic sclerosis is associated with more severe interstitial lung disease: A study from the EUSTAR database

Burja B. presented the results from the EUSTAR database on the characterization of SSc-non-specific antibodies in SSc-ILD patients. The aim was to better define patient's phenotypes by assessing the prevalence of anti-Ro/SSA and rheumatoid factor (RF) antibodies, their association with clinical features and outcomes.

Out of the 3406 eligible patients, 4.1% were double-positive for anti-Ro/SSA and RF. Compared to the single positive or seronegative patients, they presented with higher prevalence of joint synovitis, muscle involvement, pulmonary hypertension, higher prevalence of ILD at baseline. Multivariable logistic regression analysis confirmed a significant positive association between double positivity and the presence of ILD, along with lower FVC% and DLCO% values. However, double autoantibody positivity was not associated with ILD progression or increased mortality.

These findings support the inclusion of anti-Ro/SSA+RF+ in routine clinical assessments to improve ILD risk stratification.

3.2. Evidence-based detection of progression of systemic sclerosis-interstitial lung disease patients: the EUSTAR-PPF study (CP number 148)

The aim of this EUSTAR study by *Campochiaro et al.* was to develop an accurate predictive algorithm to identify patients with SSc-ILD at risk of progression. The goal is to better profile patients - allowing for close monitoring and early treatment of those likely to progress, while avoiding overtreatment in stable cases.

Patients with confirmed ILD and with available pulmonary functional testing (PFTs) were included; disease progression was defined as an absolute decline in %pFVC of ≥5% (Outcome 1) or ≥10% (Outcome 2) within 12 months. A total of 3281 patients were analyzed. Statistical methods included generalized estimating equations (GEE) and gradient boosting, a machine learning (ML) technique.

Baseline FVC, DLCO, ATA, elevated CRP, and dyspnea severity were identified as significant predictors of ILD progression. However, all models - regardless of complexity - demonstrated limited predictive performance (AUC ~0.60–0.64). ML provided no significant enhancement compared to logistic regression, indicating that current routinely collected clinical variables lack sufficient predictive power.

Authors suggest that future research should focus on discovering novel biomarkers and risk factors to improve prediction of ILD progression.

3.3. The 1-year progression of systemic sclerosis-associated interstitial lung disease is predicted applying artificial intelligence tools but not visual quantification of pulmonary CT scans

Motta et al. explored how artificial intelligence (AI)-**assisted HRCT analysis** versus traditional **visual scoring** can help monitoring SSc-ILD progression.

A group of 33 SSc-ILD patients underwent HRCT scans and PFTs at two different time points, about a year apart. AI-assisted analysis was performed using Thoracic VCAR software (GE Healthcare, United States) to quantify volumes and percentages of ground glass opacities (GGO), fibrotic lung involvement, and normal lung.

Increasing percentages of fibrosis and GGO between the time points were observed both with the visual scoring and the AI analysis. Correlation with reduced DLCO% and FVC% resulted more accurate with the AI analysis. Almost 50% of patients progressed according to Erice criteria. The progression strongly correlated with AI-detected fibrosis - something that was not seen with visual scoring.

In conclusion, AI-assisted HRCT analysis appears to be a more accurate and objective method to monitor SSc-ILD over time. It offers better alignment with clinical outcomes and may help detect subtle changes that could be missed by human assessment alone. Larger prospective studies are needed to confirm these results.

3.4. Annual HRCT monitoring is key to early detection of ILD progression and improved survival in SSc

SSc-ILD significantly reduces long-term survival and once progression occurs, prognosis worsens. Even a single episode of progression is associated with reduced survival. This study aimed to evaluate the impact of annual HRCT assessments and its ability to predict mortality.

Patients with SSc-ILD were included and ILD progression was defined according the 2022 ATS/ERS/JRS/ALAT guidelines with three sub-criteria: (1) worsening of respiratory symptoms, (2) absolute decline in FVC ≥5% or in DLCO ≥10%, and (3) disease progression on HRCT, over 12 ±3 months.

306 SSc-ILD were enrolled, 55 (18%) patients showed episodes of progression. During a mean follow-up of 3.5 years, 45 patients (15%) died, 27% of whom had experienced progression.

While progression itself was not independently associated with mortality, specific sub-criteria - particularly FVC decline ≥5% combined with HRCT worsening, and HRCT worsening alone - were significantly associated with reduced survival.

These findings emphasize HRCT worsening as the strongest predictor of poor prognosis in SSc-ILD. Therefore, annual HRCT is essential for timely detection of disease progression and for improved risk stratification. Relying solely on symptoms or pulmonary function tests may miss clinically relevant changes.

3.5. Outcomes of upfront combination vs monotherapy with rituximab or mycophenolate mofetil for systemic sclerosis interstitial lung disease (SSc-ILD): results from an EUSTAR cohort study

In this EUSTAR analysis, *Benfaremo et al.* evaluated the effectiveness of upfront combination therapy with rituximab (RTX) and mycophenolate mofetil (MMF) in patients with SSc-ILD over a 12 ± 3 months period, compared to MMF or RTX alone. Patients receiving nintedanib or tocilizumab at baseline were excluded.

Using adjusted analyses, changes in %pFVC and DLCO% were compared across treatment groups.

The proportion of patients with ILD progression (defined as an FVC decline >5%) was also calculated. Among 425 patients (250 on MMF, 154 on RTX, and 21 on combination therapy), %pFVC and DLCO% remained stable across all groups, with no significant differences between treatments.

At 12 months, ILD progression rates were similar: 29.2% for MMF, 28.1% for RTX, and 27.4% for combination therapy. This analysis found no clear benefit of combination therapy over single agents at 12 months. It confirms the effectiveness of both MMF and RTX and may support the potential use of combination therapy. Further research is needed to clarify the role of combination treatment in SSc-ILD.

3.6. Safety and efficacy of nintedanib in age-based subgroups of patients with interstitial lung disease associated with systemic autoimmune diseases: a post-hoc analysis of combined data from the SENSCIS and INBUILD randomized trials

Toitou et al. designed this study to assess the safety and efficacy of nintedanib in older patients, due to limited data. A post-hoc analysis from the SENSCIS and INBUILD trials was performed. Patients receiving placebo or nintedanib were categorized by age (≤60 years vs. >60 years). Adverse events (AEs), serious AEs, and FVC changes over 52 weeks were reported. A total of 370 patients (49.6%) received nintedanib (42.7% were >60 years old). Older patients (>60 years) had a higher prevalence of rheumatoid arthritis-associated ILD compared to younger ones.

Despite concerns about tolerability, the overall incidence of AEs was similar between the age groups in those treated with nintedanib, though slightly higher than in placebo-treated patients. Nevertheless, these did not result in a higher rate of treatment discontinuation. While dose reductions were more frequent in older patients, discontinuation rates were similar across age groups. Importantly, nintedanib's effect in slowing lung function decline (measured as FVC loss per year) appeared to be slightly greater in patients over 60, although this difference was not statistically significant. The authors suggest this might be due to the higher prevalence of RA-ILD in the older population.

In conclusion, nintedanib was well tolerated in both younger and older patients, with no major safety concerns specific to older age. While side effects were more common in older patients, especially serious ones, they did not lead to higher dropout rates. Therefore, age alone should not be a limiting factor in prescribing nintedanib, although closer monitoring may be warranted.

3.7. Human Pharmacokinetics of Inhaled Liposomal Iloprost Indicates the Potential of Treating Systemic Sclerosis Related Raynaud's Phenomenon and Digital Ulcer

Kan et al. aimed to describe the pharmacokinetics, safety, and tolerability of inhaled liposomal iloprost as a potential home-based alternative to intravenous iloprost.

A phase I, randomized, double-blinded, placebo-controlled study (NCT05938946) was conducted. Eight healthy volunteers received increasing doses (5–40 mcg per inhalation) of liposomal iloprost using a nebulizer. The treatment was well tolerated at all doses, with no serious adverse events or treatment discontinuations. Plasma levels remained detectable for up to 12 hours, and the half-life exceeded 3 hours, which is considerably longer than the 20 - 30 minutes observed with conventional inhaled iloprost. Systemic exposure was dose-proportional and

higher than that of standard intravenous administration. In conclusion, inhaled liposomal iloprost shows potential for home use as a systemic alternative to intravenous iloprost.

3.8. Upadacitinib as a Potential Therapeutic Option in Treatment of Scleroderma related ILD: Randomized double blind clinical trial

This randomized, double-blind trial evaluated the efficacy and safety of upadacitinib compared to MMF in patients with SSc-ILD. 57 patients were enrolled and received either upadacitinib 15 mg daily or MMF 2000 mg daily in a 1:1 ratio. The primary endpoint was the rate of decline in FVC over 12, 24, and 52 weeks. At week 52, the decline in FVC was smaller in the upadacitinib group compared to MMF (−52.4 ml vs. −73.3 ml), with a difference of 20.9 ml per year (p=0.05). Fewer patients in the upadacitinib group experienced a clinically meaningful FVC decline (>5% or >10%) compared to MMF.

Secondary end points at week 52 were the rate of decline in DLCO, changes of HRCT patterns, in mRSS and in the bronchoalveolar lavage (BAL) fibroblast pattern. DLCO declined less in the upadacitinib group (−62.7 ml vs. −93.3 ml). A modest trend toward improvement in mRSS was observed in the dcSSc group. A significant reduction in fibroblast migration from BAL was observed in the upadacitinib group.

In conclusion, upadacitinib showed potential as an effective and safe treatment for SSc-ILD, slowing lung function decline and possibly benefiting skin involvement in diffuse SSc.

CLINICAL ABSTRACT SESSIONS: SYSTEMIC SCLEROSIS – INSIGHTS FROM REGISTRIES INTO CLINICAL MANIFESTATION AND DISEASE PATTERNS

Chosen and written by:

Cristiana Sieiro Santos MD, MSc, PhD student
Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

4.1. Clinically significant events are better early indicators of disease progression in systemic sclerosis beyond ACR/EULAR criteria: insights from the VEDOSS EUSTAR cohort

Stefano Di Donato et al., United Kingdom

In this longitudinal study (OP0215), 442 VEDOSS patients who did not meet ACR/EULAR 2013 classification criteria at baseline were followed for up to 60 months. Over half (51.1%) developed at least one clinically significant event (e.g., mRSS ≥1, DLCO decline, digital ulcers, ILD), with a median time to progression of 22 months. Notably, 62.4% of these events occurred prior to patients fulfilling classification criteria, challenging the reliance on ACR/EULAR scores for early identification. Multivariable Cox regression identified age, anti-topoisomerase I, anti-centromere antibodies, oesophageal symptoms, and giant capillaries as independent predictors. Clinically meaningful events precede classification, supporting VEDOSS as a window for early therapeutic intervention.

4.2. Spatial transcriptomics of skin biopsies from Very Early Systemic Sclerosis unveils early drivers of skin fibrosis within the epidermis

Ifeoluwa Emmanuel Bamigbola et al., United Kingdom

Utilizing digital spatial transcriptomics (OP0216), this study profiled epidermal and dermal regions of skin biopsies from patients with VEDOSS and established SSc. Transcriptional activity in the epidermis demonstrated upregulation of DAMPs (e.g., CXCL14, S100A4) and fibrotic pathways (e.g., Hedgehog, NOTCH4), even in the absence of overt fibrosis. Simultaneous downregulation of keratinocyte signalling pathways (EIF2, PTEN) was observed. The epidermis is an active participant in early fibrotic remodelling, presenting novel targets for pre-fibrotic intervention.

4.3. Disease characteristics of anti-centromere positive systemic sclerosis patients and risk factors for organ involvement: data from the EUSTAR cohort

Jelena Colic et al., Serbia

In this comprehensive EUSTAR analysis of 7,723 ACA+ patients, progressive organ involvement—particularly gastrointestinal, musculoskeletal, ILD, pulmonary hypertension, primary heart involvement, renal crisis and digital vasculopathy —was observed across all disease durations. The most important risk factors for end-organ damage included male sex, late capillary patterns, elevated CRP, and reduced lung function at baseline. These results challenge the perception of ACA+ SSc as indolent and support proactive monitoring and early risk stratification, especially in newly diagnosed patients.

4.4. The clinical phenotype of anti-Th/To+ patients in Systemic Sclerosis: a case-control study within the European Scleroderma Trials and Research (EUSTAR) cohort

Liala Moschetti et al., Italy

This international case-control study of 306 patients demonstrated that anti-Th/To+ SSc is characterized by limited cutaneous disease and a relatively mild disease course, with lower overall damage accrual and mortality. However, ILD was still present in 42%, with a higher prevalence of UIP pattern. Synchronous malignancies were reported in ~17%, with a non-significant trend toward more cancer-related deaths. Anti-Th/To antibodies delineate a distinct clinical phenotype, reinforcing their importance in classification and surveillance.

4.5. Clinical and epidemiological characteristics of juvenile-onset systemic sclerosis from a national survey in Japan

Utako Kaneko et al., Japan

The largest Japanese cohort to date (n=130) revealed high anti-topoisomerase I antibody prevalence (62%) and frequent ILD (41%) among children and young adults with jSSc. Overlap with lupus, myositis, and Sjögren's syndrome was reported in over one-fourth of patients. Notably, myositis was more common in younger patients (<20 years), while Raynaud's and renal involvement increased with age. These findings highlight potential racial or genetic differences in jSSc and call for dedicated paediatric monitoring protocols.

4.6. Clinical characteristics and risk factors for calcinosis cutis in systemic sclerosis: insights from the European Scleroderma Trial and Research Group (EUSTAR) database

Aslihan Avanoglu Guler et al., Türkiye

Among 7,114 EUSTAR patients, 11.9% had calcinosis cutis at baseline, with rates rising to 40–46% at 5 and 10 years, respectively. Strong associations were found with digital ulcers, telangiectasias, late capillaroscopy pattern, PAH, and cardiac involvement. Female sex and diffuse cutaneous disease also conferred higher risk. These data provide robust evidence that vascular and ischemic injury are central to calcinosis cutis pathogenesis, offering a target for prevention strategies.

4.7. Risk factors for cancer in systemic sclerosis, impact on disease phenotype and prognosis, and proposal of machine learning-based personalized screening strategies: insights from an EUSTAR study

Antonio Tonutti et al., Italy

This EUSTAR case-control study (n=588) dissected cancer risk across temporal categories. Synchronous and subsequent cancers had the greatest impact on survival, with breast and lung cancer being most frequent. Key risk factors included diffuse SSc, smoking, elevated CRP, and anti-POLR3, PM/Scl, or RNP antibodies. Machine learning algorithms (Random Forest, XGBoost) achieved >85% AUC in predicting patients at high risk of cancers detectable at

an early stage, identifying ILD, ulcers, telangiectasias, and MMF use as top features. This study introduces personalized cancer screening tools for SSc, combining clinical and immunological profiles with artificial intelligence.

4.8. Haematological malignancies in systemic sclerosis, a population-based nationwide register study

Karin Gunnarsson et al., Sweden

In a national register study including 1,720 SSc patients and over 16,000 controls, the incidence of haematological malignancies was significantly increased (HR 2.2), especially lymphoid neoplasms and B-cell cancers. The risk was particularly elevated in men and younger patients, with temporal patterns suggesting lymphoid malignancies develop later, while myeloid neoplasms cluster around diagnosis. These data emphasize the need for long-term cancer vigilance, particularly in young-onset SSc patients.

Take-Home Messages

This session highlighted several crucial advances in systemic sclerosis:

- *Clinically significant events and molecular alterations precede classification, offering a window for early intervention.*
- *Serology matters—distinct autoantibody profiles are now firmly linked with organ-specific risks and long-term outcomes.*
- *Comorbidities like calcinosis and malignancy are common, impactful, and now increasingly predictable through registry data and AI models.*
- *Together, these studies reinforce the central role of large-scale registries (e.g., EUSTAR, VEDOSS) in transforming SSc research into personalized, predictive, and preventive care.*

MANAGING LIFE-THREATENING MANIFESTATIONS IN SYSTEMIC SCLEROSIS

Chosen and written by:

Margarida Lucas Rocha, MD
Rheumatology Department,
Unidade Local de Saúde do Algarve, Faro, Portugal

Claudia Iannone, MD
ASST Gaetano Pini – CTO
Milao, Italy

5.1. Scleroderma cardiac crisis

5.1.1. Learn how to diagnose and treat Scleroderma cardiac crisis

Prof. Luc Mouthon

Professor Luc Mouthon first presented the case of a 35 years-old-female patient with diffuse cutaneous systemic sclerosis (dcSSc, mRSS 18/51), with positive anti-Scl-70 antibodies and GERD involvement, Raynaud's phenomenon that had both severe complications of the SSc disease: scleroderma renal crisis (SRC) and scleroderma cardiac crisis (SCC). Initially, the patient presented with renal crisis associated with thrombotic microangiopathy. The patient was initially treated with captopril 50 mg tid, later switched to ramipril 10 mg/day and amlodipine 10 mg/day, achieving adequate blood pressure control. Between September 2018 and September 2019, she received mycophenolate mofetil 1 g three times daily with poor adherence due to gastrointestinal side effects, along with monthly intravenous pulses of cyclophosphamide. During this period, she maintained active digital ulcers, progressed to chronic dialysis, and required parenteral nutrition due to worsening gastrointestinal involvement (including gastroparesis and oesophageal dilatation). She developed digital osteitis requiring arthroplasty, persistent pericardial effusion, and worsening skin involvement. Despite these complications, adherence remained poor, and she experienced recurrent episodes of intestinal pseudo-obstruction. It was at this point that the cardiac crisis occurred. On 14–16 September, she developed chest pain pain (relieved by leaning forward), dyspnoea, and signs of low cardiac output (abdominal pain, diarrhoea), leading to hospital admission on 17 September. At presentation: normothermic, BP 126/105 mmHg, HR 105 bpm, pulmonary crepitations, ECG with diffuse anterior T wave inversion, troponin 700 ng/L, CT angiography excluded pulmonary embolism but revealed early pulmonary oedema. On 18 September, ICU admission was required for cardiogenic shock. Echocardiography showed a dilated LV with LVEF 15%, global hypokinesia, severe functional mitral regurgitation, RV dysfunction (TAPSE 12 mm), and low cardiac output (ITV ssAo = 5 cm), without pericardial effusion. She was managed with high-dose dobutamine, levosimendan for weaning failure, norepinephrine (transiently), and amiodarone for supraventricular tachycardia. Mechanical ventilation was initiated along with renal replacement therapy and drainage of 3 L of ascites. By 1 October, there was gradual haemodynamic improvement with LVEF increasing to 40%. Inotropes were discontinued on 30 September, and extubation was achieved on 1 October.

This patient presented with dcSSc, a history of scleroderma renal crisis, and acute biventricular dysfunction without pericardial effusion or structural valvular disease. Cardiac function gradually recovered with inotropic support alone, without benefit from diuretics, reflecting a true SCC. Despite cardiac improvement, the patient's overall condition progressively worsened. During her final hospitalisation in 2020, she presented with refractory gastrointestinal failure, cachexia, severe malnutrition, persistent pseudo-obstruction, recurrent infections, thrombocytopenia, and uncontrolled hypertension. Although no recurrence of the cardiac crisis was observed, she ultimately died from multiorgan failure nearly two months later.

Professor Mouthon emphasised that SCC is a **diagnosis of exclusion**. Clinicians must systematically rule out:

- **Infection** (based on fever and inflammatory markers),
- **Takotsubo cardiomyopathy** (characteristic ECG/imaging pattern and emotional trigger),
- **Myocarditis** (evidence of oedema and late gadolinium enhancement on cardiac MRI), and
- **Ischaemic heart disease** (excluded by coronary CT angiography and ECG findings of infarction).

Professor Mouthon also addressed emergency scenarios in SSc, including: Scleroderma renal crisis, cardiac shock, severe sepsis, acute respiratory failure, anemia (severe thrombotic microangiopathy or gastrointestinal bleeding), digital ischaemia or gastrointestinal emergencies (obstruction, peritonitis, pneumatosis).

He cited an analysis of incident cardiac manifestations from the EUSTAR database (n=695), where diastolic dysfunction was most common, followed by conduction blocks, pericardial effusion, and LVEF <50% (Jaeger VK et al., 2016).

Finally, he discussed outcomes of SSc patients admitted to intensive care (Pène F et al., 2015), showing poor prognosis: ICU survival: 68%, hospital survival: 61%, 6-month survival: 53%, 1-year survival: 39%

He also cited the study *Scleroderma Cardiac Crisis: a life-threatening but reversible complication of systemic sclerosis* (Vigneron et al., 2022) retrospectively analyzed 9 female patients (median age 49) with SSc admitted to a 24-bed ICU between January 2012 and June 2021 for acute left ventricular dysfunction. Patients met the 2013 SSc classification and showed altered left ventricular ejection fraction (LVEF). Key features included 67% anti-topoisomerase I positivity, 78% diffuse cutaneous SSc, frequent interstitial lung disease, and common Raynaud's phenomenon. Prior cardiac involvement was rare. ICU admission symptoms included dyspnea (44%) and chest pain (33%), with median LVEF dropping to 20%. Treatments varied, but vasodilators were often lacking. ICU mortality was 22%, and 6-month mortality 44%. The authors hypothesize that myocardial microvascular alterations and vasospasm cause a reversible "myocardial stunning" similar to SRC.

The study *SRC-related clinical symptoms in 50 SSc patients at the time of SRC* (Teixeira et al., 2008) found left ventricular failure in 48%, pericarditis in 8%, and arrhythmias in 18%.

Additional studies showed recurrent Takotsubo cardiomyopathy in SSc patients (Vreburg et al., 2024) and a higher prevalence of Takotsubo syndrome in hospitalized SSc patients compared to the general population, with worse outcomes (Gandhi et al., 2020).

Clinicians should monitor cardiac function via echocardiography in SSc patients with suspected cardiac crisis. Although ICU deaths from cardiac dysfunction were not recorded, 6-month prognosis remains poor, underscoring the severity of this SSc complication.

5.1.2. Management and Prognosis of Scleroderma Cardiac Crisis

Invasive supportive measures such as mechanical ventilation, inotropic and vasopressor agents, and renal replacement therapy should be considered—or at the very least discussed—in order to prevent patient death.

Nevertheless, the prognosis of SSc patients admitted to the ICU remains poor, particularly when intubation is required.

Take-Home Messages

- *SCC represents an acute, yet potentially reversible, cardiac (left ventricular) dysfunction. It is is a rare but potentially fatal complication of dcSSc;*
- *It predominantly affects patients with severe SSc; nearly all affected individuals had either active digital ulcers or a past medical history of SRC. It may occur despite ongoing immunosuppressive therapy;*
- *Patients typically presented with acute cardiac symptoms. (non-specific symptoms of low cardiac output), electrocardiographic abnormalities, and consistently elevated troponin levels*
- *The diagnosis is based on exclusion of other causes (myocarditis, ischaemia, Takotsubo syndrome, infection);*
- *Cardiac function may be reversibly restored with supportive care alone (no corticosteroids or cyclophosphamide);*
- *Greater awareness is needed to recognise and manage this underdiagnosed and life-threatening emergency.*

5.2. Scleroderma Renal Crisis

Prof. Ingrid De Jong and Prof. Madelon Vonk

5.2.1. Case Summary

Dr. Ingrid De Jong presented a compelling case of a female patient born in 1972 in Turkey who developed scleroderma renal crisis following disease progression from limited to diffuse cutaneous systemic sclerosis. The patient had a complex medical history including parasitic liver cyst treatment in 2008 and breast cancer with chemoradiation therapy in 2011. Initially diagnosed with limited cutaneous systemic sclerosis in 2015 based on Raynaud's phenomenon, positive ANA with anticentromere antibodies, telangiectasia, abnormal nailfold capillaroscopy, and gastrointestinal complaints, the patient remained stable for several years on conservative management with proton pump inhibitors and calcium channel blockers. The clinical course changed dramatically in August 2023 when she developed metacarpophalangeal joint arthritis and significant skin progression, with her modified Rodnan skin score increasing from 5 to 11, prompting methotrexate initiation. By February 2024, her condition had deteriorated markedly with further skin involvement (mRSS 22), substantial weight loss of 13kg, and constitutional symptoms.

The critical turning point occurred in March 2024 when she was hospitalized with severe skin involvement (mRSS 29), tendon friction rubs, gastrointestinal complications, respiratory symptoms, and cardiac involvement including pericardial effusion and myocardial inflammation. Treatment with high-dose intravenous methylprednisolone followed by oral prednisolone and cyclophosphamide was initiated. **The renal crisis developed during this treatment escalation.** Her creatinine rose progressively from 69 to 110 and ultimately to 183 µmol/L, accompanied by new-onset hypertension (170/90 mmHg). Laboratory findings confirmed thrombotic microangiopathy with thrombocytopenia, elevated reticulocytes, suppressed haptoglobin, elevated LDH, markedly elevated NT-proBNP, and presence of schistocytes. Despite intensive management including hemodialysis and immunosuppressive therapy, the patient's condition continued to deteriorate, and she ultimately died in December 2024 at age 52.

5.2.2. Definition and Clinical Recognition

Scleroderma renal crisis is defined as an acute elevation of serum creatinine in patients with systemic sclerosis, with or without new-onset moderate to severe hypertension. Importantly, hypertension is absent in approximately 10%

of patients, and microangiopathic hemolytic anemia is evident in 50% of cases. Currently, no validated diagnostic criteria exist, though the SCTC is developing classification criteria incorporating blood pressure, kidney injury, MAHA and thrombocytopenia, target organ dysfunction, and renal histology. The incidence remains relatively low at 3.75 per thousand patient-years in large cohorts, with the classic profile being a male patient with short disease duration and diffuse cutaneous subtype. Key risk factors include anti-RNA polymerase III antibodies, male gender, short disease duration, diffuse cutaneous involvement, and critically, high-dose corticosteroid exposure.

5.2.3. Pathogenesis and Clinical Manifestations

The central mechanism involves intrarenal vasoconstriction through three pathways: anti-endothelial cell antibody-mediated injury promoting prothrombotic cascades, juxtaglomerular apparatus hyperplasia increasing renin release, and endothelial B-cell receptor overexpression causing additional vasoconstriction.Clinical manifestations typically include hypertension in 90% of patients (>150/90 mmHg) with acute kidney injury signs. Severe complications encompass neurological symptoms such as headaches and seizures, pulmonary edema from renin-angiotensin-mediated fluid overload, cardiac dysfunction related to hypertension, and hematological abnormalities including MAHA diagnosed by schistocytes, decreased haptoglobin, and elevated LDH.

5.2.4. Management and Treatment Outcomes

Scleroderma renal crisis represents a medical emergency requiring immediate intensive care management. The cornerstone of treatment remains ACE inhibitor therapy initiated immediately upon diagnosis, with additional antihypertensive agents including calcium channel blockers and alpha-blockers as needed. Target blood pressure should be maintained below 120/80 mmHg with careful monitoring for target organ dysfunction. Despite optimal management, outcomes remain challenging. Approximately 60% of patients require renal replacement therapy, and while mortality has improved from over 80% historically to approximately 35% with modern care, the prognosis remains serious. The case presented illustrates these challenges, with the patient requiring long-term hemodialysis despite initial stabilization.

5.2.5. Research Advances and Future Directions

Several experimental therapies are being investigated, though evidence remains limited. Endothelin receptor antagonists showed no significant benefit in open-label studies, while plasma exchange and eculizumab targeting complement factor V show potential in case series but lack randomized controlled trial evidence. A particularly important clinical debate centers on ACE inhibitor prophylaxis. Meta-analysis data suggests patients with previous ACE inhibitor exposure have significantly better outcomes, though the interpretation is complicated by potential confounding factors. Large international collaborations involving over 7,500 patients provide increasingly robust evidence for clinical decision-making.

Take-Home Messages

Early recognition is crucial *as SRC can occur in patients with longer disease duration and even limited skin involvement, challenging traditional risk stratification. The absence of hypertension in 10% of cases and the critical association with corticosteroid exposure require heightened clinical vigilance. While ACE inhibition remains the treatment cornerstone, the role of preventive therapy in high-risk patients continues to evolve. The case presented exemplifies the rapid progression possible in systemic sclerosis and underscores the importance of multidisciplinary collaboration between rheumatology, nephrology, and intensive care teams.* ***Immediate blood pressure control and ACE inhibitor initiation are essential****, though the overall prognosis remains guarded even with optimal management.*

Dr. Vonk emphasized that greater awareness among clinicians is needed to recognize this underdiagnosed emergency, while ongoing research continues to refine diagnostic criteria and explore new therapeutic approaches for this challenging complication of systemic sclerosis.

BASIC POSTER TOURS: SYSTEMIC SCLEROSIS

Chosen and written by:

Muriel Elhai, PD, MD, PhD
University Hospital Zürich

Devis Benfaremo, MD
Department of Clinical and Molecula Science, Marche Polytechnic University, Ancona, Italy

6.1. POS0246. Single-Cell RNA Sequencing Identifies a Prominent Pro-Inflammatory Gene Signature in Fibroblasts of Very Early Systemic Sclerosis

Lumeng Li et al., Switzerland

This study by Li L et al. investigates the early molecular events in systemic sclerosis (SSc) by analyzing skin biopsies from patients with very early SSc (veSSc), early SSc (eSSc), and healthy controls. Single-cell RNA sequencing revealed increased fibroblast abundance and a distinct pro-inflammatory fibroblast signature in veSSc, marked by upregulation of HLA class II genes and cytokines. Notably, this inflammatory profile precedes fibrosis and is sustained in eSSc. One fibroblast subcluster (cluster 1) was primarily responsible for this inflammatory signature. Cell-cell communication analysis showed enhanced signaling between fibroblasts and T cells, supporting early immune activation. These findings suggest that targeting early fibroblast-driven inflammation may help prevent progression to fibrotic SSc disease.

6.2. POS0247. Peripheral CXCR4+ immune cells correlate with CXCR4 uptake in lung regions on positron emission tomography scan in systemic sclerosis-related interstitial lung disease

Chirag Rajkumar Kopp et al., India

This study examined the link between CXCR4 expression on peripheral immune cells and lung tissue involvement in different subsets of systemic sclerosis-associated interstitial lung disease (SSc-ILD). Using PET imaging and flow cytometry in 22 patients, the authors found that progressive and early SSc-ILD subsets showed moderate to strong correlations between CXCR4+ immune cells and specific lung subregions, particularly in dorsobasal and middle lung areas. No significant correlations were observed in stable patients. While the progressive group had higher levels of CXCR4 expression on immune cells, the differences were not statistically significant. These findings suggest that CXCR4 expression on peripheral immune cells could reflect localized lung involvement and may serve as a potential biomarker for early and progressive SSc-ILD activity.

6.3. POS0248. Systemic Sclerosis Synovitis Is Less Invasive and Inflammatory Than Rheumatoid Arthritis

Celina Geiss et al., Switzerland

This study compared synovial tissue from ultrasound-guided synovial biopsies from systemic sclerosis (SSc), rheumatoid arthritis (RA), and non-inflammatory controls to better understand the unique features of SSc synovitis. Histologically, RA showed much more acute inflammation than SSc. Single-cell RNA sequencing revealed that, while both RA and SSc had infiltrating $MERTK^{-}$ macrophages, RA macrophages expressed high levels of inflammatory and invasive markers like SPP1 and TNF-related genes. In contrast, SSc macrophages and synovial fibroblasts (SF) showed a strong interferon (IFN) signature with minimal pro-inflammatory or invasive gene expression. RA synovial fibroblasts also had higher levels of matrix metalloproteinases (MMP1, MMP3) and the invasion-associated transcription factor ETS1. These findings indicate that SSc synovitis is less inflammatory and invasive than RA, with IFN pathways emerging as potential therapeutic targets.

6.4. POS0249. Spatial proteomic-based phenotyping of fibroblast subpopulations and their microenvironment in systemic sclerosis primary heart involvement

Ayla Stütz et al., Germany

This study used imaging mass cytometry to investigate the cellular landscape of primary heart involvement in systemic sclerosis (SSc-pHI), comparing it with autoimmune and idiopathic virus-negative myocarditis. Seven distinct fibroblast subpopulations were identified, with $SOX9^{+}$ and PI16high/POSTNhigh fibroblasts significantly enriched in SSc-pHI. The immune landscape was also unique, with increased CD163high/$HLA\text{-}DR^{+}$ macrophages and HLA-DRhigh monocytes. Distinct fibroblast niches were identified, showing altered cellular interactions and immune microenvironments in SSc-pHI compared to other myocarditis forms. These findings highlight the complex fibroblast remodeling and immune crosstalk in SSc-pHI, offering potential avenues for targeted anti-fibrotic therapies.

6.5. POS0250. Induced pluripotent stem cell-derived tissue resident macrophage induce profibrotic fibroblast responses in organotypic skin models of systemic sclerosis

Xuezhi Hong et al., Germany

This study investigated the role of tissue-resident macrophages (TR-Macs) in systemic sclerosis (SSc) using iPSC-derived macrophages and a 3D human skin equivalent model. TR-Macs from SSc patients exhibited M2-like polarization, with elevated CD206 and CD163 expression and enhanced phagocytic activity. RNA-seq revealed upregulation of pro-inflammatory and pro-fibrotic pathways in SSc TR-Macs. When integrated into skin equivalents, SSc TR-Macs alone were sufficient to drive fibroblast-to-myofibroblast transition and collagen I deposition. Single-cell RNA-seq confirmed that these models replicated key macrophage-fibroblast interactions seen in SSc skin. Antifibrotic treatments targeting either fibroblasts (nintedanib) or macrophages (CD206-targeting RP-832c) effectively reduced fibrosis, highlighting TR-Macs as therapeutic targets and the skin equivalent model as a platform for drug testing.

6.6. POS0251. Profibrotic monocyte-derived alveolar macrophages are associated with disease severity in patients with systemic sclerosis-associated interstitial lung disease

Nikolay Markov et al., USA

This study investigated profibrotic monocyte-derived alveolar macrophages (MoAM) in systemic sclerosis-associated interstitial lung disease (SSc-ILD). Spatial transcriptomics of explants from patients with SSc-ILD revealed that MoAM localize specifically to lung airspaces in SSc-ILD patients. Single-cell RNA sequencing of bronchoalveolar lavage fluid showed that MoAM were more abundant in SSc-ILD than in healthy controls. Their presence was negatively

correlated with lung function and positively with fibrosis extent on HRCT. Transcriptomic signatures in MoAM, alveolar macrophages, and T cells were also linked to mycophenolate treatment status. Findings suggest MoAM are functionally distinct, correlate with disease severity, and may serve as biomarkers and therapeutic targets in SSc-ILD.

6.7. POS0252. Identification of fibroblast populations and their pathogenic niches in systemic sclerosis by imaging-based spatial transcriptomics

Yi-Nan Li et al., Germany

This study used cyclic in situ hybridization (cISH), a spatial transcriptomic technique, to characterize fibroblast populations and their microenvironments in systemic sclerosis (SSc) skin tissue. Nine fibroblast subtypes were identified, including COL8A1+, SFRP2+, and CCL19+ fibroblasts, each occupying distinct dermal regions and exhibiting specific functions. SFRP2+ fibroblasts in the reticular dermis showed high extracellular matrix production, while COL8A1+ fibroblasts engaged in immune interactions, particularly with macrophages. Importantly, COL8A1+ fibroblast abundance in certain niches correlated with progressive skin fibrosis and outperformed total COL8A1+ fibroblast levels in predicting disease progression, highlighting their potential as prognostic biomarkers.

6.8. Differences in the effect of C4A and C4B copy numbers on SSc serological and clinical subtypes

Javier Martinez-Lopez et al., Spain

In this study (POS023), C4, C4A, and C4B CNs were imputed from genotypes of thousands of SSc patients stratified by serological and clinical subtypes, alongside controls. The results showed that higher C4 CNs, particularly C4A, were protective against SSc, especially in anti-topoisomerase I positive (ATA+) and diffuse cutaneous SSc (dcSSc) patients. C4B CN was associated with protection in anti-centromere antibody positive (ACA+) and limited cutaneous SSc (lcSSc) patients. Novel HLA alleles associated with specific subtypes were identified, some independent of C4 CN. The study confirmed distinct genetic contributions of C4A and C4B in SSc subtypes.

CLINICAL ABSTRACT SESSIONS: SYSTEMIC SCLEROSIS – VASCULOPATHY AND THERAPEUTIC ADVANCED

Chosen and written by:

Rahma Elziaty, MD
Unit of Rheumatology and Clinical Immunology
Ain Shams University, Cairo, Egypt

Radoslaw Dziedzic, MD
Jagiellonian University Medical C
Doctoral School of Medical and Health Sciences,
Kraków, Poland

7.1. Association between vasoactive-vasodilating therapy and reduced detection of pre capillary pulmonary hypertension in systemic sclerosis: evidence from EUSTAR study (OP0331)

Nicola Farina, Italy

This was a retrospective analysis of prospectively collected data of 944 SSc patients with complete information on first right heart catheterization (RHC) and vasoactive-vasodilating drugs (VVD) exposure was identified from the EUSTAR database including categories such as endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5i) and prostanoids. Regarding VVD exposure ≥ 3 months; patients are further categorized into the following subgroups: **ever** (patients exposed to VVD at any time during the 3 years prior to the RHC date) and **ongoing** (still on at RHC date).

There was increased prevalence of exposure to *ERA,ever* and *PDE5i,ever* in patients with pre-capillary pulmonary hypertension (pPH) (pvalue <0.001 for both). Marginal estimates showed a non-significant protective association between exposure to ERAs and the detection of pPH in patient with current digital ulcers (DU). On the other hand, Exposure to ERAs was associated with an increased risk of pPH detection in patient without current DU.

Exposure to specific VVD molecules "**Bosentan ever**" was protective towards the detection of pPH regardless of the presence of digital ulcers. When considering the ongoing exposure to bosentan; marginal effects estimates showed a protective association between **ongoing bosentan** (vs non exposure) in patients with Current DU and detection of pPH. However, no association was shown between **ongoing bosentan** and pPH detection in patients without current DU.

This study concluded that PDE5i and prostanoids did not reduce the risk of pPH in SSc patients while bosentan had a clear protective effect toward such detection. The protective effect ERA was more pronounced in patients with current DU.

7.2. What we know about glucocorticoids in systemic sclerosis randomized trials (OP0332)

Lulia-Simona Chirica, Romania

A systematic review was conducted following **P**referred **R**eporting **I**tems for **S**ystematic reviews and **M**eta-**A**nalyses (**PRISMA**) 2000 guidelines though electronic research of MEDLINE via PubMed to identify randomized control trails (RCTs) on SSc published since 2000 using the Cochrane highly sensitive search strategy applied for identified randomized trials. Seventy-six primary reports of RCTs recruiting systemic sclerosis patients published since 2000 and testing pharmacologic treatment **were included** in the study. However, the studies including scleroderma like patients, secondary publications of RCTs, non-randomized studies, observational studies, meeting abstracts and studies not in English language **were excluded**.

Regarding studies providing information about glucocorticoid (GCS) use, in most of them GCS are considered as concomitant medication and administered orally at ≤ 10 mg per day. The use of GCS in all trials with median proportion around 45% and most frequent in trials targeting skin, lung manifestations with median proportion near 50% in contrast to trials focusing on Raynaud's and digital ulcers reported glucocorticoid use in around 29%. This study concluded that reporting of GCS use could be improved in SSc-RCTs. The proportion of GC users is heterogenous, with high rate of GCS users in skin and lung.

7.3. Initial therapy in SSc- PAH improves outcomes Across Haemodynamic thresholds and risk stratification: Insights from EUSTAR database (OP0333)

Dr. Hilda Jenssen BjØrkekjær, Norway

This study conducted on international cohort of 301 Treatment-nieve SSc-patients fulfilling 2022 Haemodynamic criteria of precapillary pulmonary arterial hypertension (PAH) in absence of severe (interstitial lung disease) ILD from the EUSTAR database. Among the studied group, the mortality rate was 42% over 3.9 years in treatment-naïve SSc-PAH. 1, 3, 5 survival was 93%, 79% and 66% respectively. The PAH progression within 36 months reported in 37% of the patients".

Upon comparing treated and untreated patients; the treated patients had worse haemodynamics and risk profiles "higher mPAP/PVR, worse DLCO, WHO-FC III-IV, diastolic dysfunction or other organ manifestations" while comorbidities and disease specific organ manifestation that likely influence PAH treatment decisions there were no differences in the prevalence of limited ILD, diastolic dysfunction or other available organ manifestations.

The adjusted analyses revealed significant reduction in mortality and PAH progression with initial monotherapy and combination therapy. In a subgroup analysis of 83 patients with milder haemodynamic impairment; 24% of patients died with a median period of 5.1 years and 15% of then have PAH progression. 31% received initial therapy, and the treated group showed high mPAP while other risks were non-significant, also there was no significant mortality benefits with initial therapy. The study concluded that early intervention with initial therapy improves survival and reduces PAH progression in SSc-PAH, independent of baseline and risk stratification.

7.4. Vasodilation reduces the risk of new onset of interstitial lung disease in systemic sclerosis: an association study from the EUSTAR database (OP0334)

Cosimo Bruni, Switzerland

Observational, longitudinal, retrospective analysis of prospectively collected data of 444 new onset interstitial lung disease (ILD) from 13,113 visits of 4,091 SSc patients from the EUSTAR database without ILD on high-resolution computed tomography (HRCT) at the baseline.

The SSc patients with ILD present on HRCT at follow up were having more inflammatory phenotype from musculoskeletal point of view as well as inflammatory biomarkers, more diffuse cutaneous involvement with anti-topoisomerase 1 antibody and more frequent peripheral vascular complications namely digital ulcers and digital pitting scars. Accordingly, those patients were receiving more immunosuppression particularly mycophenolate mofetil, regarding vascular medications there was almost equal distribution of administration of PDEi5 inhibitors and prostanoids while slightly higher exposure to ERAs.

This study demonstrated that prostanoids “iloprost” are associated with reduce risk of developing ILD in SSc patients “OR 0.54, 95% Cl 0.37-0.78”. The marginal estimate revealed that PDEi5 “sildenafil” decrease the risk of ILD onset in patients with history of DU, “OR 0.27, 95% Cl 0.13-0.57”. These findings suggest that vasodilators may play a protective role in the pulmonary complications of SSc beyond their established cardiovascular benefits.

7.5. Long=Term Effect of Selexipag in Systemic Sclerosis-Associated Digital Ulcers: A Case Control, Mulitcentre, Observational Study (OP0335)

Claudia Iannone, Italy

This study from 4 different Italian centers to evaluate the long-term efficacy of Selexipag, an oral selective prostacyclin receptor agonist on SSc patients with digital ulcers and also compare its efficacy in refractory digital ulcers (DU) to with intravenous iloprost.

Each patient in the Selexipag group (n = 32) was matched with two controls who received ilioprost (n = 64) and the results were collected at baseline, and 6, 12 and 24 months after treatment. The median dose of Selexipag was 1600 mg/day and only 2 patients discontinued drugs due to intolerance at 12 months.

Selexipag showed better outcomes regarding healing, with lower relapse rates and a recuded frequency of developing new DU than iloprost during follow up at 6, 12, 24 months with significant p-value 0.001 for all, indicating its potential as a more effective long-term therapy for DU management in SSc.

7.6. Modulation of Genetic Markers of Fibrosis and Skin Score in Patients with Systemic Sclerosis Following Administration of Tadalafil (OP0336)

Lekshmi Minikumari Rahulan, India

This study investigated the potential antifibrotic effects of tadalafil, a PDEi5, in patients with systemic sclerosis (SSc). The researchers aimed to evaluate changes in the modified Rodnan skin score (mRSS) and the microRNA (miRNA) profile of profibrotic genes over a 6-month period.

A total of 40 patients with SSc were included in the final analysis: 25 received standard-of-care therapy combined with tadalafil, while 15 received standard-of-care therapy alone for comparison. The study found that patients treated with tadalafil showed a significant reduction in mRSS over time compared to those receiving standard care alone with significant p-value 0.001 and many patients in the tadalafil group experienced a decrease in mRSS of more than 5 points after 6 months. Furthermore, there was a significant downregulation in the expression of four genetic biomarkers associated with fibrosis (*THS1*, *COMP*, *IFI44*, and *SIGLEC1*) in the tadalafil group. In conclusion, the study suggests that tadalafil may have antifibrotic effects and could contribute to reduced fibrosis in patients with systemic sclerosis.

7.7. Trajectories of the EUSTAR AI, ACR CRISS and Revised CRISS upon CD19.CART treatment in patients with diffuse cutaneous Systemic Sclerosis (OP0337)

Christina Bergmann, Germany

This study investigated the trajectories of three different composite scores, namely the EUSTAR Activity Index (EUSTAR-AI), ACR-CRISS, and Revised ACR-CRISS, in 12 patients with diffuse cutaneous systemic sclerosis (dcSSc) treated with CD19-directed CAR T-cell therapy, reflecting the center's initial experience with this therapy in SSc.

All included patients had lung involvement. CD19-CAR T-cell therapy led to marked clinical improvement, as shown by a significant decrease in EUSTAR-AI and a rapid increase in ACR-CRISS scores. Most patients reached clinically meaningful responses within the first 2-3 months of treatment. In conclusion, most patients with dcSSc showed clinical improvement after CD19-CAR T-cell therapy, achieving key response thresholds in EUSTAR-AI and ACR-CRISS within a median of 279 days. The measures used (EUSTAR-AI, ACR-CRISS, and Revised CRISS) revealed complementary patterns, but controlled studies are needed to confirm these findings

7.8. RESET-SScTM: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), A Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Systemic Sclerosis (OP0338)

Prof. Dinesh Khanna, USA

The RESET-SSc™ clinical trial evaluates resecabtagene autoleucel (Rese-cel), a fully human, autologous, 4-1BB anti-CD19 CAR T-cell therapy in systemic sclerosis (SSc). Early insights into this novel therapy suggest potential disease-modifying effects, offering a promising avenue for future personalized immunotherapy in SSc.

In this study, no unexpected safety findings were observed in the two SSc patients treated with Rese-cel at the time of presentation. Rese-cel demonstrated evidence of efficacy off all immunomodulatory medications and steroids, with sustained benefit observed out to 6 months in one patient. Peak expansion of Rese-cel occurred approximately 11 days after infusion. B cells were rapidly and transiently depleted in both peripheral blood and tissue following Rese-cel infusion.

Take-Home Messages

This session highlighted several important advances in systemic sclerosis (SSc) research:

- *Tissue-resident and monocyte-derived macrophages have distinct pro-fibrotic roles in skin and lung fibrosis, underscoring macrophage heterogeneity as potential biomarkers and therapeutic targets.*
- *Spatial transcriptomics and single-cell profiling revealed diverse fibroblast populations with unique ches and immune interactions that predict skin fibrosis progression.*
- *Genetic studies emphasize the protective role of higher Complement component 4 (C4), especially C4A copy number, across SSc subtypes, alongside novel HLA allele associations influencing disease susceptibility.*
- *Early clinical events and molecular changes in very early SSc (VEDOSS) precede classification criteria, offering a critical window for intervention.*
- *Integrated human skin models recapitulate SSc pathology and enable testing of antifibrotic drugs targeting both fibroblasts and macrophages.*

Together, these studies leverage advanced multiomic and spatial technologies, combined with large cohorts and functional models, to deepen understanding of SSc pathogenesis and pave the way for personalized, targeted therapies.

CLINICAL POSTER TOURS: DIFFERENT SYMPTOMS AND ORGAN MANIFESTATIONS OF SYSTEMIC SCLEROSIS

Chosen and written by:

Anna Rita Prata, MD
Unidade Local de Saúde Região de Aveiro, Aveiro,
Aveiro Rheumatology Research Centre,
Egas Moniz Health Alliance, Aveiro, Portugal

Elena Bianchi, MD
University Hospital of Siena
Italy

8.1. POS0263. Monitoring Raynaud's Phenomenon response to therapy using Dynamic Ultrasound Microvascular Imaging

Y. El Miedany et al.

This study evaluated the effect of 2% glyceryl trinitrate (GTN) ointment on digital microvascular circulation using ultrasound microvascular imaging in patients with primary and secondary Raynaud's Phenomenon (RP). Vascularity in three digits (treated with GTN ointment, placebo, or left untreated) was graded from 1 to 4, before and after application. A significant increase in the blood flow was observed in the GTN group compared to placebo, in both primary RP and SSc patients. There was also an improvement in the blood flow over time (at 10 and 20 minutes) in the GTN group compared to placebo and control groups.

8.2. POS0264. High serum levels of Vascular Cell Adhesion Molecule 1 associate with a vasculopathic phenotype in systemic sclerosis with higher mortality

T.Kenna et al.

This study investigated disease-specific associations of serum vascular cell adhesion molecule-1 (VCAM-1) levels and associated mortality in 388 patients with SSc from the Australian Scleroderma Cohort Study (ASCS). Patients in the highest VCAM-1 quartile (Q4) had significantly higher mortality from pulmonary arterial hypertension (PAH), SSc-myocardial disease and all-cause cardiovascular disease. Importantly, Q4 patients did not have a disproportionate frequency of other risk factors for higher mortality, suggesting that VCAM-1 levels may play an independent role in disease pathophysiology.

8.3. POS0265. Age and Timing of onset of Raynaud's Phenomenon and First Non-Raynaud Sign/Symptom as prognostic factors in Systemic Sclerosis: a retrospective analysis from the SPRING (Systemic Sclerosis Progression InvestiGation) Registry of the Italian Society for Rheumatology

S.Peretti et al.

This cross-sectional study based on the SPRING registry aimed at exploring whether the age and timing of onset of RP and first non-RP(NRP) symptom were associated with phenotype and prognosis in SSc. Patients with simultaneous onset of RP and NRP symptoms (simultaneous group) showed a higher prevalence of anti-topoisomerase I antibodies and diffuse cutaneous subtype compared to patients with RP onset> 1 year after or before the first NRP symptom (NRP and RP groups, respectively). In the simultaneous group, multivariate analysis revealed an increased odd of the diffuse cutaneous subtype and higher mortality.

8.4. POS0266. Development of an articular score in systemic sclerosis (ASSESS): identification of core instruments to assess disease activity

B.Burja et al.

The purpose of this scoping review was to develop a consensus-based composite score to assess articular activity in SSc. An international, multi-disciplinary SSc experts and patient partners committee identified in the literature six feasible core instruments to assess articular activity in SSc patients: number of tender and swollen joints, presence of tendon friction rubs, C-reactive protein and visual analogic scale for disease activity (patient and physician). This represents the basis for further development of a composite score for articular involvement in SSc for use in clinical practice and clinical trials.

8.5. POS0267. Radiographic hand assessment of acro-osteolysis in systemic sclerosis provides novel insights into pathogenesis and evolution of disease burden over time

M.Hughes et al.

In this study, the objective was to investigate the distribution and severity of hand acro-osteolysis in patients with SSc and its change over time and to explore methods of dealing with missing digit data. Hand radiographs from 90 patients of a single SSc referral centre were presented to a one blinded observer for assessment of the terminal tufts resorption (using the system described by Johnstone et al.), and also for comparison over time. The index and middle fingers scored the highest, suggesting preferential involvement. Additionally, there was a worsening of the acro-osteolysis over time in 31% of the patients, while 65% showed no change. Longitudinal studies are needed to determine predictors of digital bone loss in SSc.

8.6. POS0268. Esophageal dysmotility patterns are associated with more severe features and worse outcomes in patients with systemic sclerosis

L.G. Alcala-gonzalez et al.

This retrospective cohort study evaluated esophageal motility patterns via high-resolution manometry (HREM) in 201 SSc patients using updated Chicago 4.0 criteria. Absent contractility (AC) and ineffective esophageal motility (IEM) were significantly associated with more severe clinical features, including digital ulcers, pulmonary hypertension, and gastric vascular ectasia. Late nailfold capillary patterns were more common in patients with AC. Over a median follow-up of 442 person-years, 18% of patients experienced death or lung transplantation, with esophageal dysmotility significantly linked to these adverse outcomes. HREM patterns remained largely stable over time, supporting its role in SSc risk stratification and prognosis.

8.7. POS0269. Prognostic value of systemic sclerosis-associated primary heart involvement

C.J.Gharibian et al.

This study assessed the prognostic value of cardiac magnetic resonance (CMR)-defined primary heart involvement (SSc-pHI) in SSc patients. Among 182 patients, 23% had SSc-pHI, either alone or combined with other cardiac diseases. During a median follow-up of 7 years, 30.8% experienced cardiac events and 20% died. SSc-pHI was significantly associated with increased risk of cardiac events—such as heart failure, arrhythmias, and diastolic dysfunction—but not with overall mortality. This association remained significant after adjusting for age, sex, ILD, pulmonary hypertension, and scleroderma renal crisis. SSc-pHI thus represents an independent prognostic factor for adverse cardiac outcomes in SSc.

8.8. POS0270. Major salivary glands ultrasound features in a group of patients with systemic sclerosis: a multicentric study

R. D'Alessandro et al.

This study investigated the role of salivary gland ultrasound (SGUS) in systemic sclerosis (SSc) by assessing 123 patients in France. SGUS abnormalities such as hypoechoic areas(JJ score ≥2) were found in 45.5% of patients and were significantly associated with secondary Sjögren's syndrome (72%), objective sicca syndrome, anti-SSA positivity, and longer disease duration. However, no correlation was observed between SGUS abnormalities and internal organ involvement. Fibrosis (score ≥2) was seen in 36.6% of patients and also linked to longer disease duration, but not to autoantibodies or organ involvement. These findings suggest SGUS is useful for identifying secondary SS in SSc, though fibrotic changes lack prognostic value for systemic disease severity.

8.9. POS0271. Autoantibodies and overlap syndromes: shaping the landscape of ILD risk in systemic sclerosis

M. de Pinto et al.

This prospective study analyzed 178 Italian SSc patients to investigate the role of autoantibodies and overlap syndromes in interstitial lung disease (ILD). Using a novel particle-based multi-analyte technology (PMAT), both standard and non-criteria autoantibodies, including Ro52, PM/Scl, and BICD2, were detected. ILD was present in 57% of the cohort, with overlap syndromes in 29%. Non-criteria autoantibodies like Ro52, PM/Scl, and BICD2 were frequent but not significantly linked to ILD. Multivariable analysis identified diffuse SSc, cryofibrinogen positivity, and overlap syndrome as ILD predictors. In Scl-70-negative patients, overlap syndromes increased ILD risk from 36% to 64%. The study highlights overlap syndromes as key, independent ILD risk factors.

WHAT IS NEW in Systemic Sclerosis (WIN Session)

Chosen and written by:

Sauer Gesa, MD
University of Zurich, Department of Rheumatology, Zurich, Switzerland

Prof. Dinesh Khanna

Prof. Dinesh Khanna presented on novel drug targets, innovative trial designs, and patient stratification/outcome measurements in systemic sclerosis (SSc).
Among various Phase II and III trials, data on **nerandomilast** for SSc-associated interstitial lung disease (SSc-ILD) was presented. This PDE4B inhibitor exhibits both immunomodulatory and antifibrotic properties and is currently being evaluated in a Phase IIb clinical trial.

Another compound discussed was **avenciguat**, an activator of cGMP, which is currently being tested in a Phase II trial for SSc-ILD (VITALISScE study). Its mechanism of action involves downstream effects such as smooth muscle relaxation, reduction in inflammation, and inhibition of fibroblast activation—all of which may contribute to clinical benefit in SSc.

A third promising novel therapy is **amlitelimab**, a fully human, non-depleting, non-cytotoxic anti-OX40L monoclonal antibody. By impairing the OX40–OX40L interaction, this therapy modulates antigen-dependent T-cell responses without broadly suppressing T-cell immunity.

TL1A, a member of the TNF superfamily implicated in both inflammation and fibrosis, was also discussed as a potential therapeutic target in SSc. **Tulisikibart** has demonstrated efficacy in Crohn's disease and ulcerative colitis. Further Phase II studies in SSc-ILD are currently underway.

Given that type I interferon scores are elevated in the whole blood of SSc patients—and have been associated with digital ulcers, skin severity, and even mortality—the effect of **anifrolumab** is being evaluated in the Phase III DAISY trial.

Previous studies (DESIRE, RECITAL) have shown improvement in lung and skin scores through B-cell depletion. Building on this, the effects of **belimumab** (a BLyS/BAFF inhibitor) and **ianalumab** (a monoclonal antibody targeting the BAFF receptor) are currently being investigated. Additionally, **tibulizumab**, which combines anti-IL-17A and anti-BAFF activity, may offer an exciting new approach.

The rationale for **CAR T-cell therapy** in autoimmune disease was emphasized as a method of achieving deep B-cell depletion in tissue, aiming for a long-lasting immune system reset. Particularly in SSc patients with progressive ILD, diffuse cutaneous subset, high mRSS, and poor therapeutic response, CAR T-cell therapy may emerge as a potential

strategy for selected patients, especially at highly specialized centers in close cooperation with haematology departments.

As SSc is a rare disease, randomized controlled trials (RCTs) face challenges due to limited patient numbers. Prof. Khanna introduced **CONQUEST**, a new placebo-controlled Phase IIb **platform trial** for SSc-ILD. It includes multiple interventional arms with a shared placebo group. A 2:1 randomization scheme is used to increase the number of patients receiving active treatments.

Finally, the role of **autoantibodies** as key prognostic markers in SSc was emphasized. For example, patients with anti-Scl-70 antibodies tend to experience a more rapid decline in forced vital capacity (FVC), while anti-U1RNP-positive patients show rapid deterioration in skin score, peaking at 2 years, followed by a period of spontaneous improvement, reflecting the natural course of the disease.

Prof. Khanna also highlighted the disconnect between research and patient perspectives, reinforcing the importance of **holistic outcome measures**. The **CRISS index**, a composite outcome score, has already been integrated into many recent trials (e.g., DAISY, CAR T-cell trials).

SSc heterogeneity continues to present a significant challenge for both treatment and trial design.

EULAR DEBATE: COMBINATION THERAPY FOR FIBROSIS IN SSC?

Chosen and written by:

Gehad Gamal Maghraby, MD
Rheumatology and Clinical Immunology, Alainy Hospitals
Cairo University, Cairo, Egypt
Faculty of Medicine, Kasr Alainy Hospitals,

Beatrice Moccaldi, MD
Rheumatology Unit, Department of Faculty of Medicine, Kasr
Medicine-DIMED Padova
University Hospital, Padova, Italy.

This session focused on a pivotal and timely question: **Should combination therapy with antifibrotic and anti-inflammatory agents be the standard initial approach in SSc-ILD?**

Yes

Prof. Anna-Maria Hoffman-Vold

In this debate, Professor Hoffmann-Vold presented the case in favor of initiating combination therapy for patients with SSc-ILD. Her argument was grounded in the recognition that a complex interplay of inflammatory and fibrotic mechanisms drives SSc-ILD. She emphasized that monotherapy may leave critical pathogenic pathways insufficiently addressed. Instead, combination therapy allows for simultaneous targeting of multiple disease drivers, offering a more comprehensive treatment strategy.

She further highlighted that current immunosuppressive monotherapies including mycophenolate mofetil (MMF), cyclophosphamide, and tocilizumab have yielded only modest improvements in FVC and have not translated into meaningful survival benefits, reinforcing the need for more robust therapeutic approaches.

Emerging data have shown promising additive effects when antifibrotics are used in conjunction with immunosuppressives. In the SENSCIS trial, nintedanib significantly reduced the annual FVC decline compared to placebo (-52.4ml/year, -93.3 ml/year respectively) in SSc-ILD patients. Further analyses revealed that adding nintedanib to background MMF yielded a greater reduction of the annual decline of FVC (-40.2 ml/year for MMF and nintedanib versus -66.5 ml/year for MMF and placebo). Similarly, a combination of rituximab and MMF demonstrated enhanced stabilization of FVC and improved progression-free survival in patients with idiopathic and connective tissue associated ILD. Subgroup analyses suggested particularly strong efficacy in patients with autoimmune-related ILDs. In the FIBRONEER-ILD trial, the addition of nerandomilast to standard background therapy (including selected immunosuppressive drugs and/or nintedanib) was associated with a slower decline in FVC in patients with progressive autoimmune ILD (23.1% of whom had SSc).

While concerns about additive toxicity exist, data suggest no major increase in adverse events with combination regimens. For example, the combination of MMF and rituximab (RTX) had similar safety profiles to MMF alone, except for a modest increase in infection risk.

Ultimately, patients with SSc-ILD often progress and die. While the evidence supporting combination therapy is not perfect, the available data provide compelling rationale to advocate for its use. It is not a matter of black and white but of leveraging the best available evidence to optimize patient outcomes.

No

Prof. Oliver Distler

Prof. Distler subsequently outlined arguments against the use of upfront combination therapy in all patients with SSc-ILD.

During his presentation, he emphasized that every therapeutic decision should take into account not only the efficacy of the treatment but also its potential toxicity, recalling Hippocrates' principle of “first, do no harm” (*primum non nocere*). The patient should remain at the center of the decision-making process, which ideally involves a shared, collaborative approach between physician and patient. At the same time, the cornerstone of any treatment recommendation must be high-quality evidence supporting both its efficacy and safety.

Specifically, in the management of patients with SSc-ILD, rheumatologists are often challenged with balancing the potential benefits and risks of combination therapy. While recent RCTs provide robust evidence for the use of several immunosuppressants and nintedanib in SSc-ILD, data supporting the efficacy and safety of combination therapy remain limited. To date, the body of literature examining the potential role of combination therapy in SSc-ILD derives from three RCTs.

The Scleroderma Lung Study (SLS) III trial evaluated the efficacy and safety of upfront combination therapy with MMF and pirfenidone compared to MMF monotherapy in patients with SSc-ILD. Although the trial was underpowered due to recruitment challenges during the COVID-19 pandemic, it demonstrated no added benefit from the combination approach, with higher adverse event rates in the combination group. The subgroup analysis from the SENSCIS trial, that has been previously mentioned, indicates that patients receiving combination therapy experienced a slower decline in FVC compared to those on monotherapy, but this effect did not appear to be driven only by MMF use. Furthermore, the SENSCIS trial was not designed to allow for adequate stratification based on MMF use, limiting the interpretability of these findings. Nonetheless, in this case, safety profiles were overall similar between the combination and the monotherapy groups. Lastly, the EVER-ILD trial, evaluating efficacy and safety of the upfront combination therapy with RTX and MMF compared to MMF monotherapy in a group of patients with CTD-ILD and idiopathic interstitial pneumonia with NSIP pattern, found limited efficacy of the combination therapy compared to monotherapy, without adequate stratification by CTD subtype. Moreover, combination therapy was associated with an increased risk of viral infections, and treatment discontinuation.

Taken together, these findings highlight the current uncertainty surrounding the role of combination therapy in SSc-ILD and do not allow us to formulate any specific recommendation supporting its routine use in clinical practice. Further high-quality studies are needed to clarify SSc-ILD patients might benefit from combination strategies without compromising safety.

Take-home messages

The therapeutic landscape for SSc-ILD is constantly evolving. While guidelines are increasingly supportive of combination therapy, especially in patients at high risk of progression, the evidence base remains incomplete. The absence of head-to-head trials and uncertainty around optimal combination strategies underscore the need for

future high-quality research. In particular, the development of future trials should focus on understanding the molecular pathogenic pathways involved in the disease.

Nevertheless, given the high early mortality risk, poor outcomes with progression, and multi-faceted disease biology, many clinicians now view early combination therapy as a rational and justified approach, particularly in patients with markers of likely progression and with aggressive disease.

EUSTAR Young Investigator Group (YIG)
EULAR 2025 Systemic Sclerosis Highlights Brochure

Edited and reviewed by:

Jelena Čolić*, MD, PhD*

PD Researcher at Department of Rheumatology, Karolinska Institutet, Stockholm, Sweden
Internal medicine specialist, Clinical Assistant at the Institute of Rheumatology, Belgrade, School of Medicine, University of Belgrade, Serbia