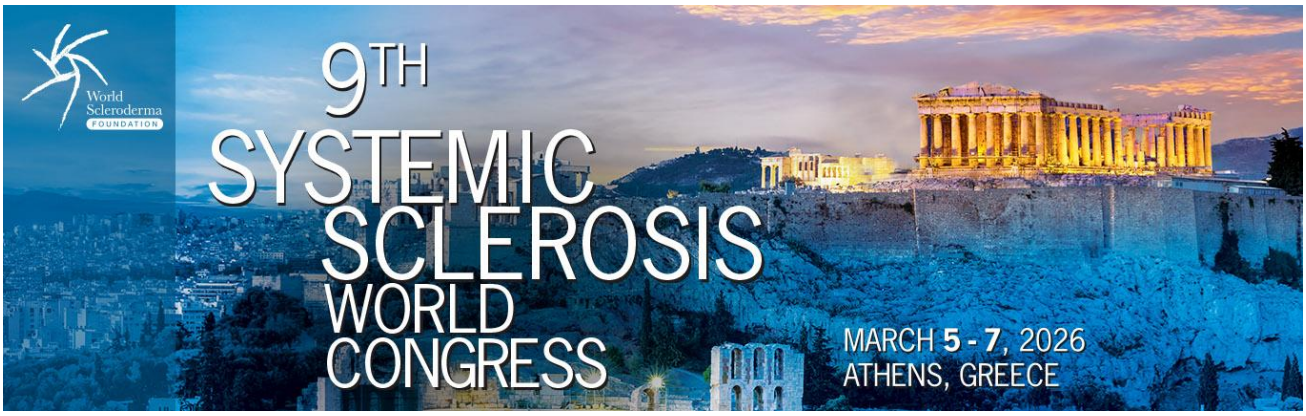

EUSTAR

Young Investigators Group (YIG)

9th Systemic Sclerosis World Congress

Highlights Brochure

Athens, Greece | 5–7 March 2026

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EDITORIAL LETTER

The 9th Systemic Sclerosis World Congress, held in Athens, Greece, from 5–7 March 2026, highlighted the rapidly evolving landscape of systemic sclerosis (SSc) research, with a strong focus on early disease mechanisms, translational immunology, vascular pathology, organ-specific complications, and emerging therapeutic strategies. This brochure, prepared by members of the EUSTAR Young Investigators Group (YIG), summarizes key scientific contributions presented during the congress and reflects the increasingly multidisciplinary and collaborative nature of the SSc field.

Several central pathogenic themes emerged throughout the meeting. Fibroblasts were consistently positioned as active orchestrators of inflammation and fibrosis rather than passive structural cells, with growing evidence supporting their role in immune modulation, tissue remodeling, and organ damage. Novel immune pathways involving type I interferon signaling, monocyte/macrophage activation, efferocytosis defects, and autoantibody-mediated innate immune activation further emphasized the complexity of immune dysregulation in SSc. Advanced single-cell and spatial transcriptomic approaches provided unprecedented insights into tissue-specific immune and stromal cell heterogeneity across skin, lung, and cardiac involvement.

Vascular disease remained a dominant topic throughout the congress. New data reinforced the concept that vasculopathy in SSc is systemic, begins early in the disease course, and affects both microvascular and macrovascular compartments. Studies presented during the congress highlighted the importance of multimodal vascular assessment, including nailfold videocapillaroscopy, Doppler ultrasound, extracellular vesicles, and circulating biomarkers, while also emphasizing the clinical significance of digital ulcers, pulmonary arterial hypertension, and early vascular dysfunction in VEDOSS patients.

Interstitial lung disease and cardiac involvement continue to represent major causes of morbidity and mortality in SSc. The congress underscored the importance of systematic screening approaches, early detection of subclinical organ involvement, and improved risk stratification using advanced imaging techniques, biomarkers, and molecular profiling. Emerging imaging modalities such as FAPI-PET/CT and cardiac magnetic resonance mapping techniques demonstrated strong potential for identifying patients at risk of progression and improving personalized management strategies.

Importantly, the therapeutic landscape of SSc is entering a new era. Beyond conventional immunosuppression, increasing attention is being directed toward combination therapies, targeted molecular approaches, and immune-reset strategies. Promising data were presented for therapies targeting B cells, plasma cells, interferon signaling, JAK/STAT pathways, and fibroblast activation. In parallel, CAR-T cell therapies and autologous hematopoietic stem cell transplantation are redefining expectations regarding long-term disease control and the possibility of treatment-free remission in selected patients.

A recurring message throughout the congress was the importance of disease interception and prevention. Lessons from rheumatoid arthritis and type 1 diabetes highlighted the growing feasibility of identifying high-risk individuals before irreversible organ damage develops, opening new perspectives for early intervention strategies in SSc.

Overall, the 9th Systemic Sclerosis World Congress demonstrated major advances in understanding SSc pathogenesis and clinical heterogeneity, while also emphasizing the transition toward precision medicine, earlier intervention, and mechanism-based therapeutic approaches. The studies and discussions summarized in this brochure illustrate both the complexity of SSc and the significant progress being made toward more personalized and effective patient care.

By Jelena Colic

Contents

PROFIBROTIC AND PROINFLAMMATORY SIGNALING PATHWAYS IN SSC

Chosen and written by:

Nikolaos Vlachogiannis

Beatrice Moccaldi

Liala Moschetti

INVITED LECTURE 2 | FRIDAY, MARCH 6

Invited Lecture 2 – Fibroblasts in Inflammation and Fibrosis | *George Kollias* (Greece)

This lecture highlighted the emerging role of fibroblasts as active innate sentinel cells, rather than passive structural elements. A key focus was the role of TNF (tumor necrosis factor). Previous mouse studies showed that TNF overexpression can induce both rheumatoid arthritis-like and Crohn's disease-like pathology. Importantly, the critical responders driving these processes were mesenchymal fibroblasts, rather than macrophages, T cells, B cells, or endothelial cells. Expression of TNFR1 on synovial and intestinal fibroblasts was shown to be both necessary and sufficient to drive TNF-dependent disease.

In the gut, TNF activation of fibroblasts was associated with loss of CD8αα+ intraepithelial lymphocytes, reduction of Paneth cells, microbial dysbiosis, increased IL-23 and IFN-γ production, and immune-cell infiltration.Distinct fibroblast subpopulations were shown to occupy specific spatial niches. Early disease involved subepithelial and lamina propria fibroblasts, whereas later progression recruited submucosal trophocytes. Myenteric fibroblasts, marked by PDGFRα and NGF, were identified by single-cell RNA sequencing as particularly relevant, as fibroblast-driven inflammation may damage the enteric nervous system and impair gut motility.

A drug-discovery pipeline aimed at deactivating pathogenic fibroblasts was also presented, combining machine learning-based drug repurposing with medicinal chemistry. A particularly promising target is HYOU1 (hypoxia up-regulated protein 1): its inhibition in fibroblasts reduces inflammatory molecule expression and may counteract oxidative stress, fibroblast activation, and mitochondrial dysfunction. HYOU1 is highly expressed in human multiorgan fibrosis (heart, liver, lung, kidney, pancreas), making it an attractive therapeutic target.

PARALLEL SESSION 11 – INFLAMMATORY CELLS/PATHWAYS | SATURDAY, MARCH 7

OC 28 – Skin macrophage subtypes and impact of tofacitinib in early diffuse cutaneous SSc | *Alain Lescoat et al.* (France)

In this study, RNA sequencing of skin biopsies from 14 healthy donors and 22 early dcSSc patients (15 from a phase I/II trial: 10 treated with tofacitinib, 5 with placebo) was used to identify macrophage subsets enriched in dcSSc and evaluate the effects of tofacitinib. This study identified a macrophage subset marked by HMOX1 and CCL13 that was enriched in early diffuse cutaneous SSc skin. These cells were linked to JAK/STAT and IL-4/IL-13 signaling, supporting their role in fibrotic inflammation.Treatment with tofacitinib reduced these macrophage markers across clinical trial biopsies, in vitro macrophage models, and ex vivo skin cultures. These findings support JAK inhibition as a potential strategy to modulate profibrotic immune pathways in early diffuse cutaneous SSc.

OC 29 – Anti-topoisomerase-1 autoantibodies induce Type I interferon through the cGAS-STING pathway | *Bent Deleuran et al.* (Denmark)

In this in vitro study ATA were shown to penetrate endothelial and immune cells, localize to intracellular compartments, and directly interfere with TOP1.This in turn activates the cGAS–STING pathway, leading to robust type I interferon production, including marked upregulation of CXCL10 and other interferon-stimulated genes. Genetic knockout experiments confirmed the central role of this pathway, with near-complete abrogation of the interferon response in STING-deficient cells. These findings add a further step toward supporting a potential pathogenetic role of autoantibodies.

OC 30 – NK cell immunotherapy reverses lung fibrosis by eliminating senescent fibroblasts | *Wolfgang Merkt et al.* (Germany)

This study uncovers a spatially defined immune evasion mechanism that sustains pulmonary fibrosis. A subset of senescent fibroblasts expressing HLA-E was found to localize at the periphery of fibrotic foci, where they directly inhibit nearby NK cells via the NKG2A checkpoint receptor, creating an immune-privileged niche. In contrast, core myofibroblasts lacked this interaction, highlighting functional heterogeneity within fibrotic lesions. Therapeutic blockade of NKG2A restored NK cell cytotoxicity, promoted clearance of senescent fibroblasts, and led to fibrosis reversal in preclinical models. Notably, the NKG2A inhibitor monalizumab reactivated NK cells from patients and enhanced killing of senescent fibroblasts in vitro, positioning the HLA-E/NKG2A axis as a compelling and translationally relevant target for NK cell-based immunotherapy in fibrotic lung disease.

OC 31 – Novel monocyte gene signatures predict progression in SSc-associated ILD | *Cristina Padilla et al.* (USA)

This study investigates new blood-based biomarkers to predict progression in SSc-ILD. Using integrated bulk and single-cell RNA sequencing of peripheral blood from patients with progressive versus stable ILD, distinct monocyte-driven molecular signatures linked to disease progression were identified. LOXHD1 and RHOB were consistently upregulated in monocyte subsets of patients with progressive SSc-ILD, alongside enrichment of inflammatory pathways. These transcriptomic findings complement established clinical and immune predictors such as male sex, elevated KL-6, and CRP levels, while highlighting the potential value of monocyte-specific progression markers.

OC 32 – Monocyte-derived macrophages in SSc: integrated single-cell analysis across tissue compartments | Sandra Maribel Lopez Garces et al. (UK)

This study examines the heterogeneity and functional roles of monocyte–macrophage populations in SSc across multiple tissue compartments using integrated single-cell RNA sequencing, spatial imaging, and in vitro modeling. The results reveal distinct, tissue-specific macrophage subsets with altered distributions in SSc, including activated CD206+CD163+ macrophages localized near blood vessels, supporting active monocyte transmigration into affected tissues. Seven macrophage clusters with coordinated disease-associated shifts were identified, reflecting processes such as apoptosis, antigen presentation, metabolic activation, and inflammatory signaling. RNA velocity analysis indicated impaired monocyte-to-macrophage differentiation in SSc. Overall, the findings demonstrate a transition from normal immune homeostasis to persistent, compartment-specific immune activation, underscoring the complex and spatially dynamic immune dysregulation underlying SSc pathogenesis.

OC 33 – IL-1β and microvascular endothelial cells synergize to favor altered macrophage efferocytosis: implication in SSc | *Cécile Contin-Bordes et al.* (France)

This study investigates the role of macrophage efferocytosis (the clearance of apoptotic cells) in SSc, focusing on its contribution to inflammation and fibrosis in the perivascular niche. Transcriptomic and imaging analyses revealed dysregulated efferocytosis-related pathways in SSc skin, alongside increased apoptosis and IL-1β signaling, particularly in patients with extensive skin fibrosis. Perivascular macrophages in SSc had decreased expression of key efferocytosis mediators such as MERTK. In vitro experiments demonstrated that IL-1β and endothelial cell-derived signals synergistically reduce macrophage phagocytic capacity. These changes promote fibroblast activation, extracellular matrix production, and endothelial-to-mesenchymal transition (EndoMT). Restoring effective macrophage efferocytosis could represent a promising therapeutic strategy to limit inflammation and fibrosis in SSc.

TAKE-HOME MESSAGES

- The type I interferon axis is a central pathogenic pathway in SSc, linking immune activation with early organ involvement, including subclinical cardiac abnormalities.
- Autoantibodies are not only biomarkers but active drivers of disease, with anti-topoisomerase I promoting type I IFN responses via the cGAS–STING pathway.
- Monocyte and macrophage compartments display disease-specific and progression-associated signatures, underscoring their key role in inflammation, fibrosis, and clinical heterogeneity.
- Fibroblasts act as central orchestrators of tissue remodelling, integrating inflammatory signals and driving fibrosis, with emerging targets (e.g., HYOU1) opening new therapeutic avenues.

Chosen and written by:

Greta Pellegrino

Carolina Teles

Cristina Andrea Vrancianu

Aslıhan Avanoglu Guler

Nikolaos Vlachogiannis

Maria Iacovantuono

PRE-CONGRESS WORKSHOP 2 | THURSDAY, MARCH 5

Pre-Congress Workshop 2 – Digital Ulcers in SSc: A Comprehensive Approach to Assessment and Management | *Michael Hughes* (UK)

Digital ulcers (DUs) are a common and serious complication in SSc, with around 50% of patients having a history of DUs and about one-third developing refractory lesions. They are considered a biomarker of severe disease course, including increased mortality. DUs most commonly occur at the fingertips where they are primarily ischemic in origin, while those on extensor surfaces are more often related to mechanical or repetitive trauma. The etiology is multifactorial, involving vasculopathy, mechanical factors, increased tissue tension due to fibrosis, and calcinosis.

Serial wound assessment should follow the TIME framework — Tissue, Infection/Inflammation, Moisture balance, and Edge of the wound — to guide treatment decisions. DUs can be classified based on pathophysiology: ulcers derived from pitting scars (small, superficial), pure DUs (irregular borders, perilesional edema), and ulcers related to calcinosis (deeper, very painful, most infection-prone, up to 40% infection rate). Pharmacological treatment focuses on three key vasoactive pathways: endothelin, nitric oxide, and prostacyclins. PDE5i and prostanoids are used for healing, while bosentan and PDE5i are used for prevention. Additional options include selexipag for severe digital ischemia. The most common infectious organisms are Staphylococcus aureus (~50% of cases).

SESSION 4 – VASCULAR | FRIDAY, MARCH 6

The complex world of Extracellular Vesicles as markers of vascular injury | *Jelena Colic* (Serbia)

Extracellular vesicles (EVs) are membrane-bound particles released by multiple cell types and comprise several distinct subtypes. They reflect cellular activation and injury while also actively modulating recipient cells, functioning as important mediators of intercellular communication. In SSc, endothelial injury, an early and central pathogenic event, triggers inflammation, dysregulated angiogenesis, and ultimately fibrosis. Within this context, EVs lie at the intersection of inflammation, coagulation, and angiogenesis. They may impair nitric oxide signaling, alter vascular reactivity, activate inflammatory pathways, and promote coagulation. In addition, EVs contain proangiogenic molecules that may further influence angiogenic processes.

In SSc, defective clearance mechanisms and reduced inhibitory signaling contribute to increased platelet activation, resulting in enhanced shedding of platelet-derived EVs. These vesicles are abundant in SSc and may carry molecules such as high-mobility group box 1 (HMGB1). HMGB1 expression on platelet-derived EVs appears to play a critical role in promoting neutrophil extracellular trap (NET) formation. Furthermore, platelet-derived EVs have been shown to alter fibrin clot architecture, thereby contributing to thromboinflammation.

Clinical studies have shown that endothelial EVs may contribute to the development of SSc-PAH by inducing oxidative stress. In addition, ICAM-positive EV levels are elevated in the early stages of SSc, including VEDOSS, and have been associated with SSc-ILD.

In conclusion, EVs exhibit several important functional properties in SSc. They capture dynamic aspects of vascular biology, reflect endothelial activation and injury, actively drive immunothrombosis and thromboinflammation, and may help distinguish early-stage from more advanced disease.

ORAL COMMUNICATIONS | FRIDAY, MARCH 6

OC 08 – Unmasking lower limb peripheral arterial disease in SSc through Doppler waveform analysis | *Begonya Alcacer-Pitarch et al.* (UK)

Peripheral arterial disease (PAD) of the lower limbs is underrecognized in SSc, and the ankle-brachial index (ABI) may lack sensitivity, making Doppler waveform analysis a useful alternative. In a study of 116 SSc patients (~80% lcSSc) and 51 healthy controls, the dorsalis pedis and posterior tibial arteries were assessed bilaterally, with monophasic or absent flow considered pathological. Abnormal Doppler findings were more common in SSc (19% vs 3%), with 37% having at least one affected artery (vs 6% of controls) and 24% showing bilateral involvement. In contrast, pathological ABI values did not differ substantially between SSc and controls (12% vs 6%). Doppler-detected PAD was associated with smoking, a history of digital ulcers (DUs), and lack of immunosuppressive therapy. Overall, Doppler ultrasound reveals a high prevalence of subclinical PAD in SSc that is often missed by ABI, supporting its role in vascular risk assessment.

OC 09 – Risk factors of progression of calcinosis and acro-osteolysis in the hands of patients with SSc: a longitudinal observational study | *Alain Lescoat et al.* (France)

SSc-related hand involvement significantly impairs quality of life, but predictors of progression of calcinosis and acro-osteolysis remain unclear. This longitudinal study included SSc patients with baseline power Doppler ultrasound and serial hand X-rays. Among 84 patients (67% lcSSc), 63% had calcinosis and 52% acro-osteolysis at baseline. One third of patients showed progression of acro-osteolysis, independently associated with a history of DUs and anti-centromere antibodies, while 38% had worsening calcinosis, predicted by longer disease duration, telangiectasia, higher mRSS, and abnormal finger pulp blood flow. Overall, markers of severe vasculopathy emerged as key drivers of progression, supporting the role of multimodal vascular assessment for risk stratification.

OC 11 – Points to consider for reporting outcomes measures in SSc interventional studies on digital ulcers: an initiative from the World Scleroderma Foundation DU Ad Hoc Committee | Corrado Campochiaro et al. (Italy)

This initiative from a WSF ad-hoc committee of leading experts aimed to establish standardized guidelines for defining and measuring DUs in SSc for research purposes, to improve consistency across studies and inform future clinical trial design.

The collaborative effort resulted in 7 points to consider:

1. Uniform definition of DUs and classification based on pathophysiology and chronicity (DU on pitting scars, pure DU, DU on calcinosis, DU derived from gangrene).
2. Inclusion criteria are limited to patients with defined ulcer duration and stable background therapy.
3. Standardized outcome measures: 50% healing of the cardinal ulcer and functional improvement assessed by HIDSS-DU; secondary outcomes include pain and patient-reported outcomes.
4. Accurate reporting of previous and concomitant medications including their duration.
5. Harmonization of wound care procedures across centers.
6. Prespecified timing and frequency of assessments, with long-term follow-up for ulcer recurrence.
7. Consideration of climate and seasonal variations in trial design.

SESSION 5 – VERY EARLY DISEASE | FRIDAY, MARCH 6

OC 12 – Early progression of SSc: a longitudinal cohort study on disease evolution and microvascular changes | *Dieneke Haverkort et al.* (The Netherlands)

The VEDOSS criteria help identify patients at increased risk for SSc progression but also include patients with mild or non-progressive disease. This study evaluated progression in patients with refined VEDOSS criteria (Raynaud's phenomenon - RP, puffy fingers <3 years, SSc-specific autoantibodies, and an early or active scleroderma pattern on NVC, but no prior organ or skin involvement). Outcomes included incidence of disease progression, clinical characteristics, and microvascular changes evaluated by nailfold videocapillaroscopy.

More than 40% of the 30 patients included developed clinically meaningful disease progression within 3 years, most commonly presenting as DUs or skin thickening. Anti-RNP antibodies were strongly associated with progression (hazard ratio 32.5), suggesting they could serve as a potential screening tool. Microvascular deterioration was also documented, with over half of patients showing worsening scleroderma patterns within two years. These findings emphasize that the window between early suspicion and irreversible damage is narrow and may inform the design of future disease interception trials.

SESSION 6 – JOURNALS | FRIDAY, MARCH 6

Exploiting a unified vascular framework to predict organ-specific complications and accomplish disease modification in SSc | *John Pauling et al.* (UK) – The Lancet Rheumatology 2025

This paper proposes a unified vascular framework for SSc, based on the hypothesis that SSc vascular damage occurs simultaneously across multiple organ systems from the very beginning of the disease, yet remains clinically silent in most organs for years. The framework highlights the strong inter-relationship between four domains: cutaneous vascular features (RP, DUs, telangiectasia); internal organ complications (primarily PAH and cardiac disease); macrovascular involvement; and nailfold capillaroscopy changes, which serve as a window into systemic microangiopathy progression.

The authors propose a binary disease endotype: an early reversible vasospastic phase transitioning into a fixed obliterative microvasculopathy. Two main proposals are particularly relevant for future research: first, a composite vascular risk score incorporating quantifiable metrics to predict future major vascular events (DUs, PAH, MACE); second, a unified vascular composite endpoint for clinical trials of disease-modifying vascular interventions in SSc. The central message is clear: by recognizing and exploiting these inter-relationships, we may finally move from reactive treatment to true preventive disease modification in SSc.

PARALLEL SESSION 12 – ORAL PRESENTATION CLINICAL | SATURDAY, MARCH 7

OC 34 – From first symptom to diagnosis: initial symptoms and delays in SSc from the SOLAR Registry | *Aslihan Avanoglu Guler et al.* (Turkey)

This study described the initial symptoms leading to first hospital presentation, key diagnostic intervals, and factors associated with diagnostic delay in patients with early SSc using data from the Early Systemic SclerOsis Longitudinal Assessment Registry (SOLAR). Only patients diagnosed within the previous three years were included to minimize recall bias. The study evaluated three major time intervals: from first symptom to first hospital admission, from first symptom to diagnosis, and from first hospital admission to diagnosis.

RP was the most frequent initial symptom leading to hospital admission, followed by arthralgia, dyspnea or cough, and puffy hands. The median number of consultations before diagnosis was three. Rural residence was independently associated with a higher number of pre-diagnostic consultations and longer diagnostic delay. Patients with RP as an initial symptom had significantly longer times to hospital admission and to diagnosis. The median time from first symptom to hospital admission was 4.07 months, from first symptom to diagnosis 13.7 months, and from hospital admission to diagnosis 2.9 months. Overall, 61.8% of patients reported experiencing diagnostic delay, most commonly due to underestimation of symptoms by patients, lack of referral by healthcare providers, and difficulty accessing rheumatology care.

OC 41 – Cross-trait genetic analysis reveals MEOX2 as a novel susceptibility locus shared between primary Raynaud's phenomenon and SSc | *Carlos Rangel-Peláez et al.* (Spain)

Given the shared vascular and immune mechanisms involved in both primary Raynaud's phenomenon (RP) and SSc, this study aimed to investigate their common genetic architecture. The authors performed a cross-trait meta-analysis combining GWAS data from large cohorts of patients with primary RP and SSc, analyzing approximately 8.6 million genetic variants. A significant genetic correlation between the two conditions was identified, supporting the presence of a shared genetic background. Five non-HLA pleiotropic loci associated with both diseases were detected, with MEOX2 emerging as a novel association for both traits.

Notably, MEOX2-associated variants showed a protective effect for primary RP but increased risk for SSc. Functional analyses also highlighted genes involved in vascular and inflammatory pathways, including IL12A, NFKB1, TNIP1, and ADRA2A. Classification in the highest-risk polygenic risk score (PRS) group was significantly associated with the risk of developing SSc among primary RP individuals. These findings provide new insights into the shared genetic basis of primary RP and SSc, identifying MEOX2 as a potential contributor to disease pathogenesis and supporting the role of genetic markers in early risk stratification

SESSION 15 – THERAPY | SATURDAY, MARCH 7

OC 55 – RECONNOITER-1: A phase 2, prospective, blinded, randomized, parallel-group and crossover clinical trial evaluating AISA-021 (cilnidipine) in subjects with SSc-associated Raynaud's phenomenon | *Francesco Del Galdo et al.* (UK)

RP affects over 95% of SSc patients. While calcium channel blockers (CCBs) are commonly used, marginal efficacy, side effects, and intolerance limit their use. This trial evaluated AISA-021 (cilnidipine), a dual N- and L-type CCB, as a potential new treatment for SSc-associated RP. In the initial dose-finding phase, 20 mg demonstrated the best balance between efficacy and safety and was then assessed versus placebo in a crossover design.

Treatment with AISA-021 was associated with improvements in several RP-related outcomes, including reductions in attack frequency, duration, and severity, as well as improvements in the proportion of attack-free days and higher responder rates than placebo. Patient-reported pain and functional impairment also improved, and the treatment was generally well tolerated with mostly mild adverse events. These preliminary results suggest that cilnidipine may provide symptomatic benefit in SSc-associated RP, although larger studies are needed to confirm its therapeutic potential.

POSTER SESSION- PULMONARY ARTERIAL HYPERTENSION (PAH) | SATURDAY, MARCH 7

P 076 – Micro- and macro-vascular damage in SSc: an observational prospective cohort study (VASSC study) | *Vincenzo Zaccone et al.* (Italy)

This study addressed a knowledge gap regarding the interplay between microvascular and macrovascular components in SSc. Three groups of patients (SSc, VEDOSS, and primary RP) were included, with clinical, laboratory, and imaging assessments aimed at assessing micro- and macrovascular function. The atherosclerotic burden was similarly elevated in both SSc and VEDOSS patients (~50-53% in both groups), compared to just 21% in primary RP, although there were no significant differences in the 10-year risk of fatal and non-fatal CVD events assessed by SCORE2. Patients with atherosclerosis also presented more severe capillaroscopic findings.

Markers of vascular activation such as VCAM-1 and ICAM-1 were significantly elevated only in established SSc, not in VEDOSS, suggesting an uncoupling between macro- and microvascular damage in early disease. The authors conclude that macrovascular injury appears to be an early and underappreciated feature of the SSc disease continuum, preceding overt endothelial dysfunction. Larger multicenter studies are necessary to confirm these findings.

TAKE-HOME MESSAGES

- Vasculopathy in SSc is systemic, early, and clinically silent, affecting both micro- and macrovascular compartments from the earliest disease stages, including VEDOSS.
- Digital ulcers are a hallmark of advanced vasculopathy, associated with disease progression, increased morbidity and mortality and macrovascular manifestation. Their standardized assessment is essential for trials and clinical care.
- Multimodal vascular assessment (clinical, imaging, and biomarker-based) improves detection of subclinical disease and enables more accurate risk stratification.
- Disease progression begins early and may be rapid, with a substantial proportion of VEDOSS (40%) patients progressing within a few years, highlighting a narrow therapeutic window for intervention.
- A unified vascular framework integrating cutaneous, microvascular, macrovascular, and organ-specific features may enable a shift from reactive management to preventive, disease-modifying strategies.

LUNG INVOLVEMENT IN SSC

Interstitial Lung Disease (ILD)

Chosen and written by:

Liala Moschetti

Francesco Benvenuti

Gesa Sauer

SESSION 1 – LUNG | THURSDAY, MARCH *5*

The patient perspective was presented by Ilaria Galetti, focusing on access to oxygen therapy worldwide. Particular emphasis was placed on the stigma patients often experience when relying on oxygen in public. Nevertheless, access to portable oxygen supplies remains crucial for enabling social participation and allowing patients to travel. Prof. *Anna Maria Hoffmann-Vold* (Norway) and Prof. *Vincent Cottin* (France) discussed ILD from both rheumatology and pulmonology perspectives. ILD is frequent and remains the leading cause of death among patients with SSc. The 2025 ERS/EULAR guidelines for CTD-ILD were summarized. Key messages included the recommendation to perform HRCT at the time of SSc diagnosis in all patients, in addition to evaluating respiratory symptoms and pulmonary function tests, particularly FVC and DLCO. From the pulmonology perspective, there has been a shift from diagnosing ILD primarily in symptomatic patients toward systematic screening approaches, recognizing the importance of detecting lung involvement at an early stage. BAL and lung biopsy are now reserved for diagnostically uncertain cases or when malignancy is suspected. The CT pattern may also be associated with prognosis, as a UIP pattern might be linked to impaired survival (Raghu et al..., 2022). Regarding therapy, the choice of specific drugs in the context of ILD was presented based on ERS guidelines, further supported by the 2023 ATS guidelines. New data from the FIBRONEER trial were presented: this placebo-controlled study showed an extended time to exacerbation of ILD, hospitalization, or death with Nerandomilast, which also significantly contributed to survival benefits. *Corrado Campochiaro* (Italy) new EUSTAR data on treatment regimens since 2007, showing an increase in immunosuppressive therapies from 14% before 2007 to 57% after 2016. Increasing use of biologics was observed, while MMF remained the cornerstone of therapy, particularly in combination regimens. Clinical factors such as disease duration, myositis, dyspnea, arthritis, and skin fibrosis were independently associated with treatment choices. *Antonio Tonutti* (Italy) subsequently focused on the often-underrecognized limited cutaneous subtype. Limited cutaneous SSc (lcSSc) represents the most prevalent disease subset, with ILD occurring in more than one third of patients. Despite this, lcSSc remains underrepresented in clinical trials. Particular attention was given to antibody profiles: anti-topoisomerase I antibodies were associated with an increased risk of ILD, whereas anti-centromere antibodies appeared to confer a protective effect in lcSSc.

ORAL COMMUNICATIONS | FRIDAY, MARCH 6

OC 16 – Pulmonary function and ILD in juvenile SSc: insights from the largest single-site pediatric scleroderma registry | *Kathryn Torok et al.* (USA)

This longitudinal observational study (NRCOS registry) characterized ILD in pediatric SSc using the lower limit of normal (5th percentile) and GLI equations, rather than the adult 80% threshold, to define pulmonary function abnormalities.

From the Pittsburgh cohort (NRCOS), the epidemiological, functional, and radiological characteristics of 93 patients with SSc and SSc-ILD were examined, the majority diagnosed after 2022. Patients with SSc-ILD exhibited HRCT abnormalities including UIP, and NSIP, the latter often with an apical-anterior or basal-posterior distribution. 73% of patients were female, with a mean disease duration of approximately 2 years. The most frequent clinical phenotype was overlap (SSc-myositis), and the most common antibodies were anti-Scl-70 and anti-PM/Scl. The mean mRSS was 5.5; the most frequent organ involvements were digital ulcers, myositis, and gastrointestinal dysmotility. 40% of patients experienced weight loss and 43% had a diagnosis of ILD. The presence of ILD was associated with esophageal dysmotility (GERD) and pulmonary arterial hypertension. In patients with ILD, the use of MMF and bDMARDs (rituximab and tocilizumab) increased.

ORAL COMMUNICATIONS | SATURDAY, MARCH 7

OC 25 – Prevalence of organ involvement and baseline predictors of disease progression in lcSSc | *Alain Lescoat et al.* (France)

The data were derived from the CONQUER database, a multicenter US-based cohort of patients with early SSc (less than 5 years after first non-Raynaud symptom), including patients with lcSSc or sine scleroderma. The CRISTAL composite index was used to assess overall response. Patients were defined as progressors if they experienced one or more of the following: new renal crisis, ILD progression, new heart failure, PAH detection, digital ulcers or gangrene, need for enteral/parenteral nutrition, or death.

A total of 275 patients were included (85.5% female, 34.2% ACA+, 24.4% ATA+, 29.5% with digital ulcers and 34.9% with ILD at baseline). The most frequent new events during follow-up were reflux (19.3%), other gastrointestinal manifestations (18.9%), dyspnea (16.4%), joint involvement (14.2%), and progression to dcSSc (13.8%). During the first 12 months, 5% of patients showed disease progression; by 24 months, 11%. The main drivers of progression were worsening ILD (55.2%), digital ulcers or gangrene (17.2%), new heart failure (13.8%), and newly diagnosed PAH (10.3%). Baseline predictors of progression included ATA positivity (OR 3.2), dyspnea (OR 3.05), ILD (OR 4.1), FVC <80% (OR 2.44), and DLCO <80% (OR 3.26).

OC 27 – Clinical characteristics associated with ILD in MCTD and SSc: insights from an EMR-derived cohort | *Alana Haussmann et al.* (USA)

This study identified and compared the clinical factors associated with ILD in both MCTD and SSc using an EMR-based cohort of adult patients assessed between 2005 and 2025. A total of 3,988 patients with SSc were included, of whom 2,042 had ILD, while 970 patients had MCTD, including 301 with ILD. ILD was more common in SSc than in MCTD (51% vs 31%). In both diseases, ILD was associated with pulmonary hypertension, GERD, dysphagia, anti-SSA positivity, ATA positivity, and Hispanic ethnicity. In SSc specifically, ILD was additionally associated with Black ethnicity, Asian ethnicity, and male sex.

OC 38 – 68Ga-FAPI PET/CT for tracking disease trajectory in SSc-related ILD | *Panagiotis Garantziotis et al.* (Germany)

FAP (fibroblast activation protein) is expressed by activated fibroblasts; FAPI compounds labeled with 68Ga allow its detection by PET imaging. This single-arm prospective observational cohort study enrolled 84 patients with SSc (62% female, mean age 57 years, mean disease duration 6.1 years, 50% ATA-positive, mean ILD extent on HRCT of 19%). The primary endpoint was annual change in FVC (mL/year); secondary endpoints included annual FVC decline (%), annual DLCO change, and time to ILD-related hospitalization or treatment change.

Baseline 68Ga-FAPI uptake volume normalized to lung volume was independently associated with accelerated FVC decline. Patients with higher FAPI uptake had a greater risk of hospitalization. A machine-learning model integrating FAPI

metrics with traditional clinical and serological risk factors achieved an AUC of 0.808 for predicting 5-year ILD progression (FVC decline ≥5%), compared to 0.596 without FAPI. FAPI-PET/CT metrics outperformed established risk factors as predictors of ILD progression, supporting a more personalized risk stratification.

TAKE-HOME MESSAGES

- SSc-ILD is still the leading cause of mortality in SSc, mandating systematic screening at diagnosis in all patients, including HRCT and pulmonary function tests.
- Early detection has shifted from symptom-driven to screening-based approaches, enabling timely intervention before irreversible lung damage occurs.
- ILD affects all SSc subsets, including lSSc, which is often underrepresented in clinical trials despite its prevalence.
- In juvenile SSc, ILD is frequent and associated with specific clinical features (e.g., overlap phenotype, esophageal involvement), requiring tailored assessment strategies.
- Treatment strategies are evolving toward earlier and combined approaches, with MMF remaining the backbone, increasingly complemented by biologics and emerging antifibrotic agents.
- Novel imaging and biomarker tools (e.g., FAPI-PET/CT) improve prediction of disease progression, supporting more personalized management.

Pulmonary Arterial Hypertension (PAH)

Chosen and written by:

Devis Benfaremo

William Berthelot

Francesco Benvenuti

ORAL COMMUNICATIONS | THURSDAY, MARCH 5

OC 03 – Initial therapy in SSc-PAH improves outcomes across haemodynamic thresholds and risk stratification: insights from the EUSTAR database | *Hilde Jenssen Bjørkekjær et al*. (Norway)

This study explored treatment patterns and clinical outcomes in SSc-PAH using data from the EUSTAR database. Patients fulfilled the 2022 ESC/ERS diagnostic criteria for PAH and were stratified according to two haemodynamic thresholds and the four-strata risk model. The primary outcomes were all-cause mortality and PAH progression (composite: death, lung transplantation, initiation of parenteral prostanoids, or clinical worsening).

Among 889 patients who underwent right heart catheterisation, 301 formed the study cohort. Overall survival at three years was 66%. Approximately two-thirds received PAH-targeted therapy at diagnosis, while 27% were treated with initial combination therapy. After adjustment for baseline characteristics, initiation of PAH-specific therapy was associated with a lower risk of mortality for both monotherapy and combination therapy, and with a significant reduction in PAH progression risk. Among patients with milder haemodynamic impairment, the mortality benefit was less clear. Overall, early initiation of PAH-targeted therapy in SSc-PAH may improve survival and reduce disease progression, particularly in patients with more severe haemodynamic involvement.

SESSION 4 – VASCULAR | FRIDAY, MARCH 6

OC 10 – Association between vasoactive-vasodilating therapy and reduced detection of PAH in SSc: evidence from a EUSTAR study | *Cosimo Bruni et al.* (Switzerland)

This EUSTAR analysis included 944 SSc patients, 53% of whom were diagnosed with precapillary pulmonary hypertension (pPH) via right heart catheterization (RHC). Medication exposure to vasoactive-vasodilating drugs (VVD) - endothelin receptor antagonists (ERA), PDE5 inhibitors, and prostanoids - was assessed both at the time of RHC and during the preceding three years. Although patients exposed to ERAs appeared to have higher pPH detection rates, marginal-effect estimates revealed a non-significant protective association between ERA exposure and pPH detection in patients with current digital ulcers.

Focusing on Bosentan specifically, a protective association with pPH detection was observed regardless of digital-ulcer status when considering ever exposure. For ongoing bosentan exposure, a protective association was confirmed in patients with current digital ulcers. These findings provide a novel basis for understanding disease mechanisms and the potential preventive effects of VVD therapy on pulmonary involvement in SSc.

OC 42 – PAH susceptibility in SSc patients with DNASE1L3 rs35677470 variant | *Brian Skaug et al.* (USA)

This study examined whether the DNASE1L3 (R206C) loss-of-function genetic variant, previously associated with ACA positive SSc, influences disease outcomes. Using data from over 1,200 patients across U.S. and U.K. cohorts, carriers of the variant had significantly higher mortality, particularly among patients with ACA-positivity (n=366) (HR: 1.23 for all SSc; HR: 1.43 for ACA-positive SSc), with the greatest risk in homozygous individuals, suggesting a dose-dependent effect. The variant was also associated with a higher risk of pre-capillary pulmonary hypertension, especially PAH (risk ratio 1.69 for all SSc; 1.81 for ACA-positive SSc), an association not explained by severe ILD, which was rare in these patients.

TAKE-HOME MESSAGES

- Early SSc-PAH-targeted therapy improves survival and delays progression, with upfront combination therapy providing additional benefit in higher-risk patients.
- Genetic determinants (e.g., DNASE1L3 variant) contribute to PAH susceptibility, enabling earlier risk stratification and precision approaches.
- Endothelin receptor antagonists, particularly bosentan, may have a protective role in pulmonary vascular involvement, especially in patients with digital ulcers.
- Tight, integrated risk stratification remains central to management, guiding treatment intensity and improving long-term outcomes.

CARDIAC INVOLVEMENT IN SSC

Chosen and written by:

Devis Benfaremo

William Berthelot

Francesco Benvenuti

SESSION 2 – HEART | THURSDAY, MARCH 5

Session 2 – HEART: Unmasking and managing primary heart involvement (pHI) in SSc | *Giacomo De Luca* (Italy)

Primary cardiac involvement in SSc (SSc-pHI) is one of the most severe and complex disease manifestations. The true prevalence remains uncertain, ranging from 7% to 39%, but cardiac disease represents a major cause of mortality, accounting for nearly 30% of deaths in the EUSTAR cohort. A standardized definition proposed in 2021 emphasizes the need to distinguish primary myocardial involvement directly related to SSc from secondary cardiac complications due to pulmonary hypertension, renal crisis, or coronary artery disease.

The pathogenesis of SSc-pHI is multifactorial, including coronary microvascular dysfunction, recurrent ischemia–reperfusion injury, myocardial inflammation, and progressive fibrosis, leading to ventricular stiffening and impaired function. The inflammatory phase may represent a potentially reversible stage if recognized early. Risk factors include inflammatory myopathy, impaired pulmonary function, and older age. Possible red flags include the presence of interstitial lung disease, arrhythmias, and elevated troponin levels.

Diagnosis remains challenging as many patients are asymptomatic. Biomarkers such as troponins and natriuretic peptides may detect myocardial injury but lack specificity. Echocardiography is the most widely used first-line tool, though it cannot characterize myocardial tissue. EUSTAR data indicate that only about 5% of patients show reduced left ventricular ejection fraction, while diastolic dysfunction appears more frequent and may occur earlier. Holter ECG monitoring is important for detecting arrhythmias: polymorphic ventricular ectopic beats may suggest active inflammation, whereas monomorphic beats are more often associated with fibrotic disease.

Cardiac magnetic resonance (CMR) has emerged as the most informative non-invasive imaging modality, providing detailed information on cardiac structure, function, and tissue characteristics. Newer T1 and T2 mapping techniques improve detection of diffuse myocardial abnormalities and have prognostic value for arrhythmias and progressive dysfunction. Currently, no specific recommendations for SSc-pHI are included in the EULAR SSc guidelines. Management combines standard cardiovascular care with attempts to target vasculopathy, inflammation, and fibrosis. Immunosuppressive therapy may improve symptoms and CMR parameters in selected patients, underscoring the importance of early detection before irreversible fibrotic damage develops.

ORAL COMMUNICATIONS |THURSDAY, MARCH 5

OC 04 – High Type I interferon associates with subclinical myocardial involvement in SSc | *Maya Buch et al.* (UK)

This study evaluated type I interferon activity in SSc patients with subclinical myocardial involvement. Thirty-six SSc patients from the CONVAS cohort without known heart disease underwent cardiac magnetic resonance (CMR) imaging. Abnormal CMR findings (non-ischemic LGE, native T1 >1050ms, ECV >30%) were detected in 23/36 individuals. A serum type I interferon score was calculated. A higher proportion of patients with CMR abnormalities showed high interferon activity (52.1% vs 23.1%) compared to those without, although IFN activity was not associated with individual quantitative CMR parameters. In a secondary analysis, 59 SSc patients from STRIKE and CONVAS cohorts, without evidence of myocardial involvement, underwent assessment of interferon activity at baseline and CMR imaging after 12 months. Patients with high baseline interferon activity were more likely to develop CMR abnormalities compared to those with lower IFN activity (70.8% vs 45.4%). These findings suggest that high type I interferon activity is associated with myocardial tissue alterations and injury in SSc and may serve as a prognostic biomarker for myocardial involvement in asymptomatic SSc patients.

OC 05 – Arrhythmic burden, myocardial markers, and long-term survival in distinct cardiac MRI subsets of SSc | *Davide Patti Gaspare et al.* (Italy)

This observational multicenter study validated the cardiac magnetic resonance (CMR)-based Knight clustering technique in a cohort from 3 Italian referral centers with 10-year follow-up. The technique analyzed biventricular volume and function values, identifying 5 risk groups (right ventricular dysfunction, biventricular dysfunction, enlarged right ventricular cavities, reduced left ventricular cavities, normal left ventricular cavities) correlated with different 5-year survival rates.

Patients with right ventricular dysfunction, biventricular dysfunction, and enlarged right ventricular cavities showed lower 10-year survival, with right ventricular dysfunction carrying the greatest concern. Patients with right ventricular and biventricular dysfunction were more frequently male, with lower predicted FVC% and DLCO% values. Right ventricular dysfunction and enlarged right ventricular cavities were associated with higher electrophysiological abnormality rates and elevated nt-proBNP. CMR clustering therefore enables mortality risk stratification independently of classic prognostic disease factors.

ORAL COMMUNICATIONS| SATURDAY, MARCH 7

OC 46 – Spatial transcriptomic-based phenotyping of fibroblast niches in SSc-associated primary heart involvement | *Alexandru Micu et al.* (Germany)

This study used spatial transcriptomics to analyze heart tissue from SSc patients with primary heart involvement and compare it with other cardiac conditions (chronic: postviral myocardial fibrosis, hypertrophic cardiomyopathy, ischemic cardiomyopathy; acute: myocardial infarction). Six distinct fibroblast subpopulations were identified (GSN/DCN+, AP1+, TIMP1+, COL1A1/POSTN+, NOTCH3+, and myofibroblasts). In SSc-pHI and other chronic fibrotic conditions, GSN/DCN+ fibroblasts and myofibroblasts were more abundant, particularly in areas of perivascular and subendocardial fibrosis, whereas TIMP1+, COL1A1/POSTN+, and NOTCH3+ fibroblasts were more prominent in acute myocardial injury. These findings show that SSc-related heart disease has a unique fibroblast landscape with distinct cell populations, tissue localization, and interactions, shedding new light on the pathophysiology of fibrotic myocardial remodeling and highlighting potential therapeutic targets.

TAKE-HOME MESSAGES

- pHI in SSc is common, often silent, and a major driver of mortality (~30%), requiring a high index of suspicion even in asymptomatic patients.
- Early myocardial injury may be reversible, making timely detection critical before progression to fibrosis.
- CMR is the key tool for early diagnosis and risk stratification, outperforming conventional methods in detecting subclinical disease.
- Type I interferon activity and CMR-based phenotypes help identify patients at risk and predict outcomes, including development of myocardial involvement and survival.
- Right ventricular dysfunction and arrhythmic burden signal poor prognosis, emphasizing the need for integrated cardiac assessment.
- Understanding disease-specific fibrotic pathways opens the door to targeted therapies, but management still relies on early detection and a multimodal approach.

Chosen and written by:

Beatrice Moccaldi

Karla Chácon

Greta Pellegrino

Marloes Verstappen

SESSION 5 – VERY EARLY DISEASE AND PREVENTION OF DAMAGE | FRIDAY, MARCH 6

Prevention of autoimmune diseases is emerging as a major research goal, shifting focus from treating established disease to earlier intervention in at-risk individuals. Dr. Ana Llego-Delgado and Dr. Kulveer Mankia highlighted how this paradigm is already becoming a reality, presenting type 1 diabetes and rheumatoid arthritis as two models of early detection and disease interception.

Delaying the onset of Type I Diabetes: a model and a new opportunity | *Ana Llego-Delgado* (USA)

Type 1 diabetes (T1D) currently represents the most advanced model of disease prevention. It develops through a prolonged pre-symptomatic phase characterized by the emergence of multiple islet autoantibodies, followed by dysglycemia before clinical onset. Screening strategies that combine autoantibody testing with genetic risk assessment are increasingly used to identify high-risk individuals and facilitate enrollment in prevention trials. A breakthrough is teplizumab, an anti-CD3 monoclonal antibody approved by the FDA to delay progression from stage 2 T1D (defined by dysglycemia and multiple autoantibodies) to clinical disease in individuals aged 8 years and older. In randomized trials, a single treatment course delayed progression to stage 3 disease by a median of approximately two years compared with placebo. Ongoing research is focused on combination immunotherapies, antigen-specific tolerance approaches, and interventions targeting β-cell stress and inflammation

The APIPPRA study in RA | *Kulveer Mankia* (UK)

RA is increasingly understood as a continuum. The earliest stage consists of asymptomatic autoimmunity in genetically predisposed ACPA-positive individuals. Several prevention trials have recently been reported: the TREAT EARLIER trial (methotrexate + glucocorticoid injection in patients with arthralgia and MRI-detected subclinical inflammation) did not prevent progression to clinical arthritis but significantly improved symptoms and physical functioning over two years. The STOP-RA trial (hydroxychloroquine in high anti-CCP individuals without inflammatory arthritis) found no reduction in RA progression and was terminated early for futility.

More promising results were observed in the APIPPRA trial (phase 2b), which assessed Abatacept in ACPA-positive individuals with inflammatory joint pain. Treatment for 12 months reduced progression to RA and delayed disease onset, an effect confirmed to persist up to four years in the ALTO study, particularly in those with broader autoantibody profiles.

Overall, these studies support the concept that individuals with ACPA positivity and subclinical inflammation represent a key population for disease interception.

PARALLEL SESSION 10 - ORAL PRESENTATION CLINICAL | SATURDAY, MARCH 7

OC 24 – Real-world evidence of patients meeting the inclusion criteria of the DAISY trial (anifrolumab in SSc): a EUSTAR cohort study | *Lesley Anne Bissell et al.* (UK)

Using real-world data from the EUSTAR cohort, investigators evaluated how many patients with SSc would meet eligibility criteria for the DAISY Phase III trial evaluating anifrolumab, and how often they would achieve the Revised Composite Response Index in SSc (CRISS-25) outcome. Among 13,139 patients with available data, 1,632 (12.4%) fulfilled simplified DAISY inclusion criteria. Eligible patients had a median mRSS of 19, 68% had ILD, and 14% had limited cutaneous disease. Compared to non-eligible patients, eligible individuals were younger, more often male, had shorter disease duration, and higher CRP levels.

Twelve-month follow-up data were available for 771 patients. Of 416 with sufficient outcome data, 65 (16%) achieved the CRISS-25 response, defined as ≥25% improvement in at least two domains without worsening in more than one. These results highlight challenges in trial recruitment and generalizability, while underscoring a substantial unmet clinical need in SSc.

SESSION 15 – THERAPY | SATURDAY, MARCH 7

Evidence to support combination therapies in SSc | *Yannick Allanore* (France)

Systemic sclerosis involves multiple pathogenic pathways, making targeted therapy challenging. The strongest evidence for combination therapy comes from SSc-PAH: the AMBITION trial showed upfront combination of tadalafil and ambrisentan significantly outperformed monotherapy, and selexipag studies confirmed similar benefits. EUSTAR data further suggest combining immunosuppressants with vasoactive therapies may improve outcomes and reduce mortality.

For skin involvement, in a romilkimab trial (anti-IL-4/IL-13), patients receiving the drug alongside immunosuppressants showed greater skin improvement than those on romilkimab alone. For SSc-ILD, the SENSCIS trial provided robust evidence: patients on nintedanib who continued background MMF achieved better outcomes. Real-world EUSTAR data support these findings: rituximab plus MMF may slow lung function decline, and tocilizumab combined with MMF has been associated with favorable lung trajectories over 24 months. Overall, combination therapy is increasingly becoming standard practice, particularly in the vascular field, and similar strategies are emerging for immunosuppressive and targeted treatments.

New horizons in the treatment of SSc | *Dinesh Khanna* (USA)

This presentation highlighted emerging therapies in SSc across three key areas: B-cell–directed agents, targeted molecular therapies, and immune-reset strategies aimed at drug-free remission. Current treatments largely address inflammation or organ-specific complications without altering disease trajectory. Ongoing Phase II and III trials include B-cell–targeted approaches such as rituximab (DESIRES, RECITAL, head-to-head versus cyclophosphamide in early diffuse SSc–associated lung disease), BAFF/BLyS inhibitors (belimumab, ianalumab), tibulizumab (dual BAFF and IL-17A blockade), FcRn inhibitors, and CAR-T cell therapy for profound B-cell depletion and immune reset. Additional emerging targets include TL1A (tulisokibart), OX40L (amlitelimab), PDE4B (nerandomilast), IL-31RA (nemolizumab), and type I interferon blockade with anifrolumab (Phase III DAISY trial). Collectively, these advances signal a shift toward personalized, multi-pathway strategies designed to achieve long-term disease control and remissin.

ORAL COMMUNICATIONS | SATURDAY, MARCH 7

OC 52 – Targeting the plasma cell niche in SSc: a case series about the bispecific anti-BCMA×CD3 antibody teclistamab in severe, treatment-refractory patients | *Andrea-Hermina Györfi et al.* (Germany)

Long-lived plasma cells are believed to sustain autoantibody production in SSc. Targeting the BCMA pathway with teclistamab, a BCMA×CD3 bispecific antibody, may help eliminate pathogenic plasma cells. In this case series of severe, treatment-refractory SSc patients, key findings included marked reduction of plasma cells in affected tissues, significant decreases in anti–Scl-70 antibody titers, and clinical improvement. Observed adverse effects included cytokine release syndrome (CRS), hypogammaglobulinemia, and infections. These results suggest that targeting the plasma cell niche is a promising therapeutic strategy in refractory SSc, though larger studies with longer follow-up are needed to confirm efficacy and establish optimal maintenance protocols.

OC 53 – Use of the CD19/CD3 T-cell engager blinatumomab in refractory systemic sclerosis: a case series | *Yannick Allanore et al.* (France)

This case series evaluated blinatumomab, a CD19/CD3 T-cell engager, in 5 patients with anti-topoisomerase I–positive SSc refractory to multiple therapies (≥3 DMARDs failed), with recent disease (≤6 years) and ongoing inflammatory activity or objective progression. Treatment consisted of premedication followed by continuous IV blinatumomab (9 µg/day for 7 days, escalated to 28 µg/day for another 7 days), with concomitant immunosuppressives discontinued. Key findings included rapid peripheral B-cell depletion, acceptable safety, and clinical benefit in patients achieving complete B-cell aplasia; B-cell repopulation (predominantly naïve and transitional subsets) occurred at approximately 1 month. CD19-directed T-cell engager therapy may represent a novel immunologic strategy in refractory SSc, though controlled clinical trials are needed.

SESSION 15 – THERAPY: CAR-T AND AHSCT | SATURDAY, MARCH 7

UPSIDE Trial | *Julia Spierings* (The Netherlands)

The UPSIDE trial is a randomized controlled trial comparing upfront autologous hematopoietic stem cell transplantation (AHSCT) with immunosuppressive medication (cyclophosphamide + MMF) in patients with early progressive dcSSc. The optimal timing of AHSCT — rescue therapy versus upfront use — remains unclear. Inclusions have been completed with 60 patients enrolled. Preliminary results showed that in the CYC+MMF group, 40% required rescue treatment with AHSCT, while in the AHSCT group only 7% currently require post-transplant DMARD therapy. Infections were more frequent in the AHSCT group (27% vs 10%), mostly airway infections. Three patients died (one in each arm from progressive disease or adverse events), resulting in a treatment-related mortality of 3.3%. Efficacy data from the primary outcome (global rank composite score at 2 years) are awaited.

AUTOGRAPH-SSc (Cohort 1) – CD19-targeted CAR-T therapy with rabcabtagene autoleucel | *Dinesh Khanna* (USA)

This multi-part, five-year randomized open-label phase 2 study enrolled 6 SSc patients with severe progressive skin, lung, or cardiac involvement and inadequate response to previous systemic treatments in Cohort 1. The safety profile was favorable; cytokine release syndrome was the most common adverse event, uniformly grade 1. At 20 weeks, the absolute reduction in mRSS from baseline was 16 points (range 4–23), a relative reduction of 46%. In patients with a history of ILD, FVC% predicted improved by 8%. Patient Global Assessment, Physician Global Assessment, and HAQ-Disability Index decreased by 52%, 46%, and 47%, respectively. Cohort 2 will randomize similar patients to CAR-T therapy or rituximab to provide comparative data.

BREAKFREE-1 Trial – CD19-targeted CAR-T therapy (Zola-cel) | *Dinesh Khanna (USA)*

This basket study included 31 patients with dcSSc and progressive skin or pulmonary disease refractory to more than one immunosuppressive therapy. Lymph node biopsy at day 20 confirmed complete tissue-level B-cell depletion. At six months, FVC increased by 6.7% from baseline and mRSS improved by 23.7%. Future comparative studies between AHSCT and CAR-T therapy will be of great interest.

Cilnidipine for Raynaud's phenomenon in SSc | *Francesco Del Galdo* (UK)

Professor Del Galdo highlighted cilnidipine, a novel fourth-generation calcium channel blocker, for the treatment of Raynaud's phenomenon. Treatment with cilnidipine resulted in a significantly greater increase in the proportion of attack-free days compared with placebo (21% vs 12%, p=0.015). Cilnidipine was concluded to be a safe and effective treatment option, although a head-to-head study comparing it with conventional calcium channel blockers would be valuable.

TAKE-HOME MESSAGES

- Early identification of at-risk individuals is key to disease interception in SSc, marking a shift from managing established disease toward prevention and early intervention.
- Insights from other autoimmune diseases support the feasibility of preventive strategies, particularly when high-risk populations are clearly defined.
- Targeted therapies (e.g., JAK inhibitors, B-cell and plasma cell–directed agents, type I interferon blockade) are expanding treatment options and may modify disease course.
- Combination and immune-reset strategies (AHSCT, CAR-T) are emerging as key approaches to achieve deeper and more durable disease control, with the potential for treatment-free remission.

Clinical topics reviewed by Coordinators of EUSTAR YIG Clinical Educational group

Marco Di Battista

Claudia Iannone

Gonçalo Boleto

Basic topics reviewed by Coordinators of EUSTAR YIG Basic Educational group

Blaz Burja

Veronica Batani

Nikolaos Vlachogiannis

Conceptualization, editing and final review done by

Jelena Colic, Head of EUSTAR YIG Group