8th Systemic Sclerosis World Congress (SSWC)

14-16 June 2024 - Prague

Young Investigators Group (YIG) Congress highlights Travel grant awardees reports

Contents

Opening Lectures

Stefano Stano

Date and Time of session: Thursday 14th March, 19:00-20:00

Location: Forum Hall

The opening lecture focused on major cell types involved in Systemic Sclerosis (SSc) pathogenesis and their heterogeneity as a potential disease biomarker.

Dermal fibroblasts, for example, express discrete and distinct transcriptional programs. These subsets are qualitatively and quantitatively different in healthy subjects and SSc patients, correlating with SSc disease activity, clinical characteristics, and response to treatment. Dermal myofibroblast represent another relevant subset in SSc pathogenesis. They derive from specific fibroblast expressing Secreted Frizzled Related Protein 2 (SFRP2) and from endothelial cells undergoing endothelial to mesenchymal transition (EMT) driven by the Hippo pathway. In particular, this signaling cascade promotes fibrosis via stimulation of mesenchymal cells.

At least seven subtypes of endothelial cell have been identified, with specific subtypes expressed in

SSc patients. Furthermore, endothelial cells are the most important effectors of type I interferon (IFN) signaling contributing to vasculopathy and fibrosis and helping in the stratification for risk of disease progression.

A final focus of the lecture was the current development of vaccination-based immunotherapies to target profibrotic cells, with a last remark on spatial proteomics, transcriptomics, microarray and bioinformatics as new tools to investigate, as a “convex mirror”, gene expression in SSc.

The second opening lecture concerned interstitial lung disease (ILD), the primary cause of morbidity and mortality in SSc. ILD is observed in up to 90% of SSc patients, sometimes with a progressive pattern, thus demanding ILD screening in all patients with pulmonary function tests (PFT), high resolution computed tomography (HRCT) of the lungs, and antibody profile assessment. Therapeutic choices for ILD include mycophenolate mofetil (MMF), cyclophosphamide (CYC), nintedanib (NTD), tocilizumab (TCZ), and rituximab (RTX).

The most recent 2024 American Thoracic Society recommendations for SSc-ILD treatment suggest MMF use, with conditional use of CYC, RTX, TCZ, and NTD. In fact, the approval of many drugs for SSc-ILD is still an ongoing process. Evidence for combination therapy in SSc-ILD exists, but well-controlled large studies are lacking.

A goal for improving future trial design in SSc is to demonstrate drug efficacy in a short timeframe typical of clinical. The “Platform Trial Protocol Structure”, based on a Master Protocol including multiple individual subprotocols for different drugs and a common placebo, may be applied for this purpose.

The third opening lecture described the Chimeric Antigen Receptor introduced into T-cells (CAR-T) therapy use in rheumatological conditions. CAR-T therapy basic principle is that T-cells are collected and engineered via viral transfection to present anti-CD19 antibody on the cell surface, in

order to recognize and drive an immune response against self B-cells. Usually, after CAR-T infusion B cells disappear within hours and up to 100 days.

CAR-T therapy may be associated with unique toxicities, including cytokine release syndrome and immune cell associated neurotoxicity syndrome. Nevertheless, CAR- T Cell therapy has

WSC 2024 – Interstitial lung disease session

Christina Nita

This session delved into the latest advancements in systemic sclerosis-associated interstitial lung disease (SSc-ILD). Experts discussed personalized treatment approaches, identifying patient subgroups, and ongoing research on prognostic indicators.

Dr. Elizabeth Renzoni, a consultant respiratory physician at Royal Brompton Hospital and honorary senior lecturer at Imperial College London, stressed the importance of personalized treatment approaches in SSc-ILD, considering disease heterogeneity and individual patient factors. Different patient subgroups are likely to benefit from specific treatments, drawing from studies such as focuSSced (1–3) and SENSCIS (4,5), as well as post hoc analyses from Scleroderma Lung Studies I and II (6). She cautioned against generalizing group-level findings to individual patient care and suggested using a multiplier of the coefficient of variation to assess significant declines in lung function (7,8). Renzoni also highlighted ongoing research supported by the UK Scleroderma & Raynaud's and the Royal Scleroderma Foundations, focusing on deep-learning of chest CT as an imaging biomarker for risk prediction in SSc-ILD.

Helmut Prosch, associate professor of radiology at the Medical University of Vienna, discussed the role of lung high-resolution computed tomography (HRCT) in SSc. He emphasized HRCT's main role in diagnosing ILD in SSc, predicting progression and other disease manifestations, and for follow-up. In this sense, lung involvement may precede other manifestations of the disease, with connective tissue disease developing in a significant proportion of initially diagnosed idiopathic pulmonary fibrosis patients (9,10). He also emphasized the unpredictable nature of SSc-ILD progression (11), citing factors such as the pattern of ILD, extent of traction bronchiectasis, and the extent of ILD as potential predictors. Nonetheless, while HRCT imaging is pivotal, diagnosing SSc-ILD requires a comprehensive approach combining clinical and radiological information.

The following two presentations consisted of recent research studies in the field of SSc-ILD. In the first presentation, Liubov Petelytska, a postdoctoral researcher from the University Hospital Zurich, discussed a study examining the incidence and risk factors for new-onset ILD in SSc patients from the European Scleroderma Trials and Research (EUSTAR) group, initially negative for ILD on HRCT at baseline. The study found that new-onset ILD occurred in 20.2% of SSc patients who were ILD-negative at baseline, with risk factors including dyspnea, NYHA stage≥2, male sex, age, diffusing capacity of the lung for CO (DLCO), elevated inflammatory markers, hemoglobin level, anti-topoisomerase I antibody positivity, and history of digital ulcers. Surprisingly, the incidence of new-onset ILD was independent of disease duration, highlighting the importance of regular screening for ILD in SSc patients following a negative baseline HRCT.

In the second presentation, Professor Shervin Assassi from the Division of Rheumatology and Clinical Immunogenetics in Houston, USA, presented research on peripheral blood cell (PBC) expression profiling and its predictive significance for the course of ILD in SSc. The study found distinct gene expression patterns associated with cyclophosphamide (CYC) and mycophenolate mofetil (MMF) treatment. While CYC treatment led to upregulation of erythropoiesis, inflammation, and myeloid lineage-related modules, MMF treatment resulted in more modest changes including downregulation of plasmablast modules. Furthermore, in the MMF arm, higher baseline lymphoid lineage module scores predicted better subsequent lung function while higher baseline myeloid lineage and inflammation modules predicted worse lung function. The study suggests that PBC gene expression scores could serve as prognostic and predictive biomarkers for SSc-ILD.

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Summary: Heart session

Yehya Al-Adwi

Talk. 1: The management of cardiac manifestation requires a multidisciplinary approach, but it is particularly important that all Rheumatologists think as cardiologists when approaching patients with SSc and heart complications. In this way, Rheumatologists will think more about the prevention of the progression of cardiac diseases, rather than being only focused on treatment. Current literature indicates that patients with SSc have the highest risk of developing premature coronary artery disease than any other autoimmune inflammatory diseases, and even higher than type 2 diabetes mellitus. While lung complications like interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are well-recognized as the most fatal in SSc, cardiac issues represent the second leading cause of death, responsible for approximately 26% of primary deaths in SSc patients according to EUSTAR cohort data. Patients with SSc not only develop cardiovascular complications but are often affected by primary heart manifestations including among the others diastolic dysfunction, conduction defects, and cardiac fibrosis. These complications require disease activity control using immunosuppressive treatment, but the choice of the specific treatment should also consider cardiovascular risk. Finally, cardiovascular risk should be stratified and modified through lifestyle interventions through the management of arterial hypertension and dyslipidemia.

Talk. 2: Dr Ross delved into the prevalence of heart involvement in SSc and discussed cardiac investigation options. Echoing the previous talk, she highlighted myocardial involvement as the second most fatal complication in SSc. Dr. Ross advocated for annual cardiac assessments for all SSc patients, emphasizing the importance of early detection of cardiac anomalies. Echocardiography serves as a primary tool for screening cardiac structures and assessing function in SSc patients. Cardiac MRIs are reserved for asymptomatic SSc patients. In a study by Dr. Ross et al., it was shown that 97% of patients have a pathological burden of fibrosis when T1 mapping times are used while subclinical edema can be detected using T2. Holter monitoring can detect rhythm abnormalities, with Ventricular ectopic beats indicating poorer outcomes in SSc.

Talk. 3: Dr. Shukla presented a study to identify protein biomarkers associated with cardiovascular MRI (CMR)-defined subclinical cardiovascular abnormalities in patients with SSc. They aimed to identify SSc patients with early subclinical heart involvement to enable early detection and to identify putative biological pathways to inform therapeutic targets. 3 panels of cardio-related proteins and 1 inflammatory panel were employed (n=355 proteins) to detect abnormal protein levels in serum of patients with SSc (n=78). 70 distinct proteins were associated with CMR

parameters of myocardial edema/fibrosis and vascular stiffness. SPON2 protein was associated with diffuse fibrosis of the heart (56%), ADAM-TS13 protein was related to focal fibrosis (10%), TFRC protein was associated with myocardial edema (16%) while MET was connected to aortic distensibility (9%). These insights provide potential underlying pathological pathways for heart involvement in SSc.

Talk. 4: Dr. Kocherova presented their multi-omics analysis to unravel cardiac fibrosis. Stress stimuli often prompt cardiac fibroblasts to release fibrotic mediators, contributing to myocardial stiffness, arrhythmias, and fibrosis. Bulk RNA-seq, scRNA-seq, and proteomics approaches were utilized on atrial cardiac fibroblasts obtained from healthy controls or heart failure donors. Results showed that FOXF1, MXRA5, and DYSF are significantly upregulated in the heart failure group, respectively. In experimental settings using human fetal cardiac fibroblasts, all three candidates were shown to be regulated by TGF-β. Further analyses showed that there is a mutual regulation between the three candidates. Finally, these results implied the potential of FOXF1, MXRA5, and DYSF to regulate cardiac fibrosis and pave the way for possible targeting.

Report session 12 – Therapy

Liala Moschetti

1) New EULAR recommendations for SSc management (F Del Galdo, UK)

The new EULAR recommendations for SSc management include 20 recommendations (as compared to 16 in 2017) and are divided in 8 disease domains (represented as columns of the Table) and 4 levels of strength (A= should be considered, B= can be considered, C= may be considered, D= expert opinion; represented as lines of the Table).

	RP	DUs	PAH	SKIN	ILD	SRC	GI	MSK
A	CCB, PDE5-I ILOP	PDE5-I, BOS ILOP	PDE5-I, ERAs ILOP	HSCT, RTX MTX	HSCT, RTX MMF, CYC NTD			
B			RIOCIGUAT SELEXIPAG	MMF	TCZ	NO ACE-I (for prevention)	PPI	
C			NO WARF	TCZ		ACE-I	PROK	
D							ATB	MTX

Abbreviations: RP=Raynaud Phenomenon, DU=digital ulcer, GI=gastrointestinal, MSK= musculoskeletal, CCB=calcium channel blockers, BOS=bosentan, WARF= warfarin, HSCT=hematopoietic stem cell transplantation, CYC= cyclophosphamide, NTD=nintedanib, PROK=prokinetic, ATB=antibiotic

Abbreviations: RP=Raynaud Phenomenon, DU=digital ulcer, GI=gastrointestinal, MSK= musculoskeletal, CCB=calcium channel blockers, BOS=bosentan, WARF= warfarin, HSCT=hematopoietic stem cell transplantation, CYC= cyclophosphamide, NTD=nintedanib, PROK=prokinetic, ATB=antibiotic

Research agenda comprises: the evaluation of the efficacy of immune suppression in the vascular and gastrointestinal manifestations of SSc, of non-pharmacologic management of digital ulcers and calcinosis, and of pharmacologic management of calcinosis; the performance of a specific comprehensive patient reported outcomes (PRO) for the overall disease burden and the expansion of the immunosuppression/anti-fibrotic portfolio.

2) EULAR/ERS guidelines for SSc ILD management (A Hoffman-Vold, Norway and O Distler, Switzerland)

This presentation described the methodology used in a systematic literature review (SLR) on appropriate screening tools, initial assessment, monitoring tools, and monitoring frequency for systemic sclerosis-associated interstitial lung disease (SSc-ILD). It covered the Task Force members, PICO framework, review of evidence, data analysis, and grading of evidence quality using the GRADE system. Publication of the guidelines is anticipated later in 2024.

3) ACR guidelines for treatment of SSc ILD (E Bernstein, USA)

ACR guidelines cover ILD screening, monitoring, and treatment in systemic autoimmune rheumatic diseases (SARD)s-ILD. The presentation was focused on SSc-ILD. First-line therapies include: MMF, TCZ, and RTX (with additional options of CYC, NTD, and Azathioprine [AZA]); treatment for progressive SSc-ILD (defined with the INBUILD criteria) include: MMF, RTX, NTD, TCZ, CYC, and hematopoietic stem cell transplantation (HSCT). Finally, rapidly progressive (RP)-ILD and its management with a combination of the above-mentioned therapies (with the addition of calcineurin inhibitors and JAKi), was reported. Of note, RP-ILD is more frequent in immune-mediated myositis (IMM, especially anti-MDA5+) than in SSc.

4) OC 45 - Rituximab retention rate (RR) in SSc: a real-life Italian multicentre study (G De Luca et al, Italy)

In the DESIRES study on RTX showed efficacy on skin and lung involvement in SSc patients. However, these data need confirmation in a real-life scenario, especially regarding long-term outcomes. This multicentre study (8 Italian centres) evaluated the RR of RTX in SSc patients with a follow- up ≥3 years, through an observational retrospective longitudinal design.

152 patients were included (80% females, 78% dcSSc, 63% anti-Topoisomerase positive, 16% ACA positive, 12% anti-RNAP3 positive, 76% ILD, 60% DUs, 41% synovitis), mean disease duration: 147 months). The main indications for RTX prescription were worsening of ILD (39%) or mRSS (37%). 93% of the patients were previously treated with immune suppressive treatments (ISTs: 48% MMF, 32% CTX) and 77% were currently on a concomitant IST (49% MMF, 47% MTX). RR of RTX was 90% at 1 year, 66% at 3 years and 55% at 5 years. Reasons for RTX discontinuations were clinical response (17% at 3 years and 20% at 5 years) that was associated with shorter disease duration and absence of anti-Topoisomerase, presence of DUs, and absence of arthritis; clinical failure (9% at 3 years, 14% at 5 years) that was associated with absence of anti-Topoisomerase and ACA+; and adverse events (9%). In conclusion, RTX showed a good RR, a satisfactory safety in a real life setting for the treatment of SSc and seems to be effective especially in the earlier stages of the disease.

5) OC 46 - Changes in treatment patterns and their influence on the outcome of SSc-interstitial lung disease (SSc-ILD) patients: an EUSTAR analysis (C Campochiaro et al, Italy)

Nowadays different therapeutic options are available for SSc-ILD: CYC showed efficacy in 2006 (SLS I trial), MMF in 2016 (SLS II trial), NTD in 2019 (SENSCIS trial) and TCZ in 2020 (FOCUSSCED trial). The aim of the study was the assessment of A) ISTs regimens over time and B) impact on ILD progression. ILD-SSc patients in the EUSTAR database with available data on PFTs and treatment at baseline and at 12 (±3) months were included. ISTs regimens were segregated into 4 periods (P) based on patients first assessment: P1) ≤2006 (pre SLS I), P2) 2007-2011 (post SLS I), P3) 2012-2016 (pre SLS II), P4) ≥2017 (post SLS II). ISTs initiation, combination, switches, and stops were evaluated.

1409 pts were included (236 in P1, 558 in P2, 338 in P3, 277 in P4). Considering clinical features, over time, the percentage of SSc sine scleroderma increased (0.4% in P1, 11% in P4) and the percentage of myositis decreased (26% in P1, 12% in P4). A) Over time, the number of patients treated with ISTs significantly increased: 14% in P1, 28% in P2, 51% in P3, and 57% in P4. Among different ISTs, the use of steroids decreased (from 44% to 14%) while the use of MMF increased (22% to 42%). In P4 RTX, TCZ, and NTD were started in 15%, 18% and 4% of the patients, respectively. Additionally, the frequency of switches and stops of ISTs increased overtime (2.5% in P1, 14% in P4 and 0 in P1, 26% in P4, respectively). The most frequent combination therapies in P4 included: MMF + RTX and MMF + TCZ. ISTs initiation was associated with shorter disease duration and myositis; ISTs combination with younger age, dcSSc and lower %pDLCO at baseline; ISTs switches with dcSSc and arthritis. B) Considering the whole cohort, survival/ILD progression free time increased from P2 (46%) to P3 (65%) and to P4 (55%); deaths/ILD progression occurred in 21% of the patients in P3, 14% in P3, and 12% in P4. Similar results were observed considering anti-Topoisomerase patients (n=786/1409). In conclusion, an increasing number of SSc- ILD- patients is currently started with IST, with novel therapies being implemented; this has reduced the number of deaths/ILD progressions, but survival/ILD progression free time is still low

New strategies and developments in SSc-PAH – G. Kovacs, University of Graz, Austria

Davide Mohammad Reza Beigi

In 2022 the update of ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (PH) was published. Five groups of PH are still present:

Group 1 for pulmonary arterial hypertension (PAH),

Group 2 for PH associated with left heart disease,

Group 3 for PH associated with lung disease (ILD),

Group 4 for PH associated with pulmonary embolism, Group 5 of non-clear classification or mechanisms.

Group 2 and Group 3 are very frequent, and Group 1 and Group 4 are rarer although whit specific therapeutic options. SSc may be associated with any form of PH therefore it is important to identify

to which group each patient belong because of different therapeutic options. The prognosis is quite different: patients with SScPAH have better survival compared to those with PH with SSc-ILD.

Definitions thresholds have changed in the last guidelines from those of 2015 and 2018 world symposium. PH threshold has been lowered from a mean arterial pressure ≥25 mmHg in 2018 to 20 mmHg. In addition, the definition of pre-capillary PH was changed: in 2018 the pulmonary vascular resistance (PVR) has been included in this definition with a threshold of 3, currently lowered to 2. Accordingly, the definition of post-capillary PH was also changed. A new definition of exercise PH was also introduced with the mean pulmonary arterial pressure/cardiac output slope between rest and exercise set at 3 mm/Hg/L/min.

It is important to understand the reason for these changes. First, the previous threshold of 25 mmHg is higher than the upper limit of normal. One review performed 2009 showed that the mean PAP in the normal human subject lies around 14 mmHg±3. In addition, mortality increases from a threshold of mean PAP of 20 mmHg. Therefore, the 20-mmHg threshold is the upper limit of normal and is the lowest threshold where mortality risk is increase were strong argument driving the threshold change. Similarly, the lowest relevant threshold for increased mortality is a PVR of 2 WU, giving good reasons to decide it as a threshold for pre-capillary PH.

Regarding exercise PH, a slope proved to be better to define exercise PH as compared to a fixed value as it allows the definition of different exercise thresholds. Hence, 3 mmHg is the upper limit of normal and it is associated with worse prognosis.

The diagnostic algorithm for PH based on the current guidelines, indicates that echocardiography must be performed first, assessing the peak tricuspid regurgitation velocity and other echocardiographic signs, searching for additional risk factors such as SSc. In this case, even if the PAPs is intermediate, right hearth catheterization should be considered.

Regarding the screening of SSc-PH, the application of the DETECT algorithm to the revised definitions demonstrated marginally decreased sensitivity and slightly enhanced specificity relative to the 2014 criteria. Notably, the incidence of non-PH patients identified using the updated definitions was substantially reduced, as a larger number of patients were now classified as having PH. Despite these updated definitions, the treatment protocols remain unchanged, underscoring the necessity for new data from randomized controlled trials to address the treatment needs of patients who meet the current but not the previous PH criteria.

In terms of treatment, a pivotal aspect of the new guidelines is the recommendation to apply the same treatment algorithm used for idiopathic pulmonary arterial hypertension (IPAH) to patients with PH associated with connective tissue diseases. This algorithm begins with a risk stratification based on clinical parameters, categorizing patients into low, intermediate, or high-risk groups, and accordingly suggests initiating treatment with either a dual or triple combination therapy, followed by periodic risk reassessments.

Recent developments have also introduced new treatment options for PH affecting the lungs; notably, inhaled Treprostinil has proven effective in a 2021 trial for patients with lung-PH. Although the sample size was small, patients with connective tissue diseases showed clear benefits from this therapy, which, while available in the UK, is not yet approved in Europe.

In summary, patient classification is crucial as treatment varies depending on it. New threshold definitions for mPAP, VR, and exercise-induced PH have been proposed. Echocardiography remains the primary screening tool, while right heart catheterization continues as the diagnostic standard. Treatment paradigms for SSc-PH now also include therapeutic options for patients with ILD-PH.

Report from parallel session 4 – GI

Hilde Jenssen Bjørkekjær

The GI from the rheumatology point of view – Z McMahan (USA)

Prof. McMahan gave an excellent talk, presenting an overview of gastrointestinal (GI) manifestations in patients with systemic sclerosis (SSc). We learned that throughout the course of the disease, nearly all patients develop some form of GI manifestation; however, these manifestations are highly heterogeneous and can pose clinical challenges. The severity of GI disease correlates with high mortality, and risk factors for progression to severe GI disease are older age, male sex, black race, diffuse cutaneous subset of SSc, and baseline myopathy. The pathogenesis of GI complications is likely multifactorial; however, data suggest that the neuromuscular pathways that control GI motility are dysfunctional in SSc and that antibodies might play a role. We learned that GI motility is controlled by the autonomic (ANS) and enteric nervous systems (ENS), where the upper GI tract and the proximal colon are mainly regulated by the ANS, whereas the lower GI tract (except the proximal colon) is mainly regulated by the ENS, and the colorectum is regulated by the CNS defecation center. Dysfunction of the ANS and ENS likely contribute to the clinical diversity of GI dysmotility; however, the exact etiology of these complications is unknown. The management of GI complications is challenging, depends on the type of GI manifestation, and includes lifestyle interventions, drugs targeting the specific GI manifestation(s), screening for red flag symptoms, and the exclusion of other causes. Many agents are available to improve GI dysmotility, and they are often more effective in specific regions of the gut. The role of immunosuppression in SSc-GI disease management remains unclear. Studies are ongoing regarding microbiome and fecal transplantation, as well as neuromodulation. Finally, given the heterogeneity in SSc-GI disease, it is an important priority for patient care and clinical trials to differentiate between patients with stable disease and those with progressive disease.

OC 8 – Distinct clinical trajectories of gastrointestinal progression among patients with SSc – J Perin et al (USA)

Jamie Perin, PhD, MS, presented a study aiming to characterize GI phenotypes in SSc patients. The severity of GI symptoms was assessed using the Modified Medsger GI Severity Score, and patients were included if they had at least two measured Medsger GI scores. 2696 SSc patients from Johns Hopkins Scleroderma Center were included in the analyses, with an average disease duration of 4 years at the start of the observation period, an average observation time of 4 years, and a median of 6 visits per patient. The overall mortality in the study cohort was 35%. The authors identified four characterizing trajectories/phenotypes: (A) early progressive; (B) early severe; (C) stable; and (D) late progressive. The “early progressive phenotype” consisted of 142 (5%) patients and was characterized by severe GI symptoms and fibrosis. They had the second highest proportion of males (21%), the highest proportion of diffuse cutaneous subset (61%), the shortest

disease duration, a high prevalence of black race, most myopathy (36%), and the second worst survival. The “early severe phenotype” consisted of 114 (4%) of the patients and was characterized by the most severe GI symptoms. They had the highest proportion of males (25%), the oldest age, the second highest proportion of diffuse subset (44%), and the worst survival. The “stable phenotype” consisted of 2325 (86%) of the patients and was characterized by mild GI symptoms. They had a higher proportion of women (83%), a younger age, the highest proportion of limited cutaneous subset (63%), least cardiac manifestations, and the best survival. The “late progressive phenotype” consisted of 115 (4%) patients and was characterized by moderate GI symptoms in addition to vascular symptoms. They had the highest proportion of females (88%), youngest age, worst Raynaud’s, worst cardiac manifestations, most teleangiectasias, most calcinosis (65%), most sicca (85%), worst FVC and DLCO, and the and the highest proportion of anti-centromere antibodies (35%). The investigators conclude that clinically distinct GI subgroups in SSc are strongly supported, that refined subgroups may present an opportunity for mechanistic research, and that early cluster identification may allow for the targeting of therapy and the identification of optimal patients for clinical research.

OC 9 – Faecal microbiota transplantation in patients with systemic sclerosis and lower GIT symptoms: a phase two, randomised, double-blind, placebo-controlled trial – H Fretheim et al (Norway)

Finally, Dr. Fretheim, MD, PhD, presented the ReSScue trial, a phase 2 randomized controlled clinical multicenter trial in Norway. Based on the knowledge of intestinal dysbiosis in SSc patients, the study rationale was to manipulate the gut microbiome using fecal microbiota transplantation (FMT) with ACHIM, a standardized anaerobic microbiota culture. The study aimed to assess the efficacy and safety of repeated intestinal infusions of ACHIM in SSc patients with moderate to severe symptoms of bloating and diarrhea. 70 patients were randomized 1:1 to ACHIM or placebo, infused intestinally through gastroscopy at weeks 0 and 2, with the primary endpoint analyzed at week 12. At week 12, both arms received an infusion of ACHIM, and the participant was followed to week 20 in an open label extension period. The primary endpoint was the change from baseline to week 12 in the UCLA GIT score item diarrhea or bloating, depending on which was the worst symptom at the baseline evaluated separately for each patient. Secondary endpoints were safety and tolerability, as well as the change from baseline to week 12 in the total UCLA GIT score. The study was unfortunately negative with respect to the primary outcome. There were no adverse events related to the study drug. The investigators conclude that fecal microbiota transplantation with ACHIM was well tolerated, but there was no significant improvement in bloating or diarrhea. Despite a negative trial, the study brings valuable knowledge for the planning of future randomized trials.

Very early SSc & pre SSc

Veronica Batani

Friday 15 March 2024

The session, focused on early systemic sclerosis (SSc), acknowledged its significance for future preventive strategies.

Professor Kuwana, from the Nippon Medical School in Japan, addressed the complexity of early SSc pathogenesis, highlighting the lack of comprehensive studies specifically targeting the pathogenesis of pre-scleroderma. He emphasized that the three primary pathogenetic features of systemic sclerosis (SSc)—namely excessive fibrosis, vasculopathy, and autoimmunity with inflammation—are typically and uniquely observed in patients with manifest SSc, yet the dynamics of their interplay remain unclear. The recent proposal of the conceptual framework of pre-scleroderma has facilitated a better observation of early clinical signs in scleroderma patients, suggesting that vascular involvement precedes inflammation and progression to fibrosis. Following this hypothesis, endothelial damage—which may be contributed to by autoantibodies, infectious stress, and oxidative stress among others—in the presence of defective vascular repair machinery (impairment in vasculogenesis mediated through endothelial progenitor cells) leads to the recruitment of immune and inflammatory cells and promotes the transformation of various cell types (endothelial cells, bone marrow-derived fibroblasts, adipocytes, and others) into pro-fibrotic myofibroblasts. Thus, identifying drugs that can prevent vascular injury or damage and manage subsequent upstream pathogenic processes may provide the rationale for developing more effective therapies for patients with SSC.

Professor S. Bellando-Randone from the University of Florence, Italy, discussed the clinical aspects of systemic sclerosis (SSc), emphasizing the challenges in early diagnosis over the past 50 years despite the important advancements due to the introduction on VEDOSS criteria. These criteria have significantly aided in recognizing very early stages of the disease and helped to understand more about the risk of progression in overt systemic sclerosis in patients with Raynaud's phenomenon and puffy fingers. However, recent studies have highlighted that VEDOSS patients with rapidly progressive disease during follow-up did not differ from VEDOSS patients with long-standing mild disease evolution in terms of their clinical features at first presentation. Therefore, the VEDOSS group represents a mixture of patients with early diagnosis of scleroderma but with potentially different prognoses, and further studies are necessary to better stratify these patients to establish different follow-up protocols, risk stratifications, and treatments based on predictive factors of prognosis.

The session continued with the presentation of recent data from studies on VEDOSS populations.

Kim et al. from Leeds University explored the role of metabolic serum biomarkers in identifying rapid disease progression in systemic sclerosis (SSc) patients by comparing the global metabolic profiles of VEDOSS, progressing diffuse cutaneous SSc (pDcSSc), stable DcSSc (sDcSSc), and limited cutaneous SSc (LcSSc). Specific metabolic patterns correlated respectively with disease progression from VEDOSS to established SSc, and with early disease progression in the lung and skin. These results suggest the potential of these biomarkers to stratify SSc patients according to the risk of severe clinical manifestations.

N. Massey et al. from the UK conducted a study to evaluate the implementation of the VEDOSS criteria by physicians in the US, Europe, and Japan for patients suspected of having systemic sclerosis (SSc). The study revealed that, despite the established predictive value of these criteria,

only slightly more than one-third of physicians consistently apply the VEDOSS tests or assessments in their clinical practice. Furthermore, the application of these criteria showed significant variation across different countries, suggesting variable levels of awareness and adoption of the VEDOSS criteria globally.

Based on recent evidence of the presence of interstitial lung disease (ILD) in VEDOSS patients, M. Neto et al. from Portugal explored the prevalence and trajectory of ILD in a cohort observed in a tertiary systemic sclerosis unit for 10 years. They found that a subset of patients remaining in a VEDOSS state over time continues to show significant subclinical pulmonary involvement.

At the conclusion, Iudici et al. presented the results of an observational EUSTAR trial comparing the effectiveness of immunosuppressive treatment alone versus combined with oral glucocorticoids in managing skin fibrosis over a one-year follow-up in patients with early diffuse SSc. The data revealed no significant difference in skin fibrosis between patients treated with or without low to moderate doses of oral glucocorticoids."

Basic Science

Antonio Tonutti

Saturday 16th March (8 AM)

The Basic Science session commenced with a lecture delivered by Prof. Robert Lafyatis, elucidating the role of TGF-beta in SSc, wherein he delineated the current understanding and prospective insights into the pivotal involvement of this cytokine in disease pathogenesis and targeted therapies, encompassing pulmonary arterial hypertension and calcinosis. However, emphasis was also placed on the imperative need to acknowledge the potential side effects of TGF-beta inhibition in the early stages of cancer pathogenesis. Hence, it is paramount to elucidate the roles and distinct signalling pathways of various TGF-beta isoforms. Sara Fakhouri (University of Erlangen) presented an intriguing study focusing on the molecular changes occurring in SSc-affected skin. The study delved into the anatomic-molecular correlates of skin reticulation, characterized by the loss of papillary derma typical of scleroderma and associated with altered perfusion. The study delineated a loss of the physiological WNT/β-catenin gradient in SSc compared to healthy controls, correlating with the loss of papillary dermal structures. A fresh perspective on fibroblast dysfunction was explored by Prof. Del Galdo's group and presented by Rebecca Wells (University of Leeds). The study investigated alterations in the primary cilium, an organelle implicated in intercellular signalling, which was found to be stably shortened in SSc fibroblasts. This observation is anticipated to contribute to the profibrotic aspects of the disease. Notably, these structural cilia alterations were not linked to aberrant TGF-beta signalling but rather to the downregulation of Caveolin-1 and altered Aurora-kinase A activity, warranting further exploration as novel fibrogenic pathways in the disease. Two distinct yet correlated research endeavours were presented by Jacqueline Wax and Afsaneh Mehrpouyan (University of Lubeck), investigating the role of the cytokine milieu in the pathogenesis of pulmonary vascular disease in SSc. Wax's study focused on IL-13 in a mouse model, revealing that transgenic IL-13-hyperexpressing mice manifested inflammation and occlusive vascular disease of the lungs compared to controls, with changes correlating with IL-6 levels and neutrophils in bronchoalveolar lavage fluid. Notably, neutralization of IL-13 activity inhibited the development of pulmonary vascular disease. Mehrpouyan's study explored the role of IL-6 inhibition in similar circumstances, unexpectedly finding that IL-6 inhibition was associated with low IL-6 levels in the blood but not in the lung of mouse models. Furthermore, IL-6 inhibition increased the incidence of pulmonary vascular disease, prompting speculation regarding a possible protective role of IL-6 in the development of pulmonary arterial hypertension, as demonstrated by the IL-13- hyper expressing mouse model. The session concluded with Cristina Padilla (University of Pittsburgh) presenting the results of a study dissecting the role of NK cell populations in lung tissue from SSc-ILD patients. Results were obtained through single-cell RNA sequencing of explanted lung specimens from patients with SSc-ILD and healthy controls. Interestingly, increased levels of NK CD16+CD56dim cells with an activated phenotype were observed in patients with SSc-ILD compared to controls. These cells expressed high levels of cytotoxic enzymes and molecules, such as granzyme and interferon-beta, and were likely responsible for alveolar epithelium damage contributing to the pathogenesis of pulmonary fibrosis in SSc patients. The authors called for further characterization of these cells in the processes of alveolar bronchiolization and the formation of honeycombing.

Basic Science Parallel Session 6

Blaz Burja

Dysregulation of interferon signaling as a prominent hallmark of SSc pathogenesis

The Basic Science Parallel Session 6 at the World Scleroderms Congress in Prague showcased groundbreaking insights into cutting-edge technologies, pathogenesis, and novel drug targets in systemic sclerosis. Prof. Franck J Barrat (USA) opened the session, emphasizing the pivotal role of plasmacytoid dendritic cells (pDCs) and interferon signaling in autoimmune diseases, including systemic sclerosis. Plasmacytoid DCs, known as type I interferon-producing cells, synthesize significant amounts of IFN-I in response to ligands engaging endosomal TLR7 or TLR9. In systemic lupus erythematosus (SLE), specific targeting of these cells using humanized IgG1 against BDCA2 led to substantial inhibition of IFN-I and chemokine production by pDCs, resulting in reduced immune infiltration in SLE skin lesions and disease activity. Further evidence of their role in SSc was provided, showing increased IFN signature in PBMCs of SSc patients, particularly in those with early diffuse subtype. Depleting pDCs prevented skin fibrosis and reduced IFN-I response in a bleomycin-induced skin fibrosis model, suggesting a potential novel treatment strategy. Dr. Stefano di Donato (UK) provided additional evidence for the significance of IFN in SSc, demonstrating elevated expression of Interferon-stimulated genes (ISGs) in PBMCs from systemic sclerosis patients compared to healthy controls. This elevated expression was successfully mitigated by STING inhibition. Furthermore, in vitro cell culture experiments revealed that coculturing SSc fibroblasts with THP1 monocytes induced an Interferon-Signature in a cGAS/STING dependent manner, leading to the activation of ISRE transcription via pIRF3 signaling.

Multi-omics techniques reveal novel cellular populations and their crosstalk in fibrotic environment

Prof. R. Kramman (Germany) presented the utilization of scRNAseq, ATAC-seq and spatial transcriptomics in human kidney fibrosis to study the cellular origins of human kidney myofibroblasts. The findings indicated that mesenchymal cells (pericytes and fibroblasts) serve as the primary cellular sources of scar-forming myofibroblasts during human kidney fibrosis, with only a minor contribution from epithelial cells. In a second presented study focusing on fibrotic remodeling after heart infarction using scRNAseq and spatial transcriptomics, authors observed strong spatial cellular dependencies between TGFB and NFkb fibroblast signaling, as well as JAK-STAT and NFkb immune signaling. Through investigation of fibro-myeloid signaling interaction using spatial transcriptomics, a unique interaction between SPP1+ macrophages and myofibroblasts was revealed. CXCL4 was identified as essential for SPP1+ profibrotic macrophage activation and fibrosis, as depletion of Cxcl4 both in vivo and in vitro lead to the abrogation of profibrotic Spp1 macrophage differentiation and the amelioration of fibrosis after heart and kidney injury. Using scRNAseq to investigate endothelial cell composition in SSc, Dr. M Huang (USA) presented the results revealing a decreased proportion of arterial endothelial cells in SSc, which were characterized by higher expression of interferon signaling genes and markers of cell death, such as IGFBP3. The study identified two new minor populations exclusively present in SSc: Tip+ and proliferating cells. Tip+ cells, whose proportion correlated with more severe disease, were primarily implicated in angiogenesis and migration of endothelial cells (EC). Receptor-ligand analysis suggested that Tip+ cells might directly communicate with fibrotic signaling through the TGFB receptor and secretion of extracellular matrix markers such as FN1 and COL. These findings indicate the presence of increased angiogenic activities in SSc endothelial cells as a compensatory response to EC injury.

Novel therapeutic strategies to combat fibrosis in SSc

Dr. C Wenglen (Sweden) introduced a novel approach to target fibrosis by inhibiting the 5-HT2B receptor, which is expressed and upregulated in dermal and lung fibrosis. It is believed that 5-HT is released from platelets upon tissue injury and activates myofibroblast differentiation. Treatment with a 5-HT2B receptor antagonist resulted in the inhibition of fibroblast and macrophage activation through Dkk1-WNT signaling, leading to the amelioration of fibrosis. Dr. Elena Pachera (Switzerland) presented a study focusing on identifying potential novel drug targets in SSc. In collaboration with Novartis, they employed a fully automated system for pharmacological screening of targetable molecules to prevent TGFβ-triggered myofibroblast differentiation. Utilizing an extensive mode of action library containing 3,000 different compounds, they conducted immunohistochemical staining of TGFβ-activated myofibroblasts as their experimental readout. Through this screening process, 82 compounds were identified that significantly reduced the myofibroblast area compared to the average of the TGFβ-only control. Furthermore, they identified 176 target genes, among which 36 were inhibited by different compounds. Notably, members of the PI3K/AKT/mTOR signaling pathway emerged as top targets, suggesting their important relevance for the inhibition of TGFβ-activated myofibroblasts.

Parallel Session 9 – Oral Presentation

Claudia Iannone

09:30-10:30 Forum Hall PARALLEL SESSION 9 - ORAL PRESENTATIONS

Chairpersons: M Inanc (Turkey), E Kucharz (Poland), U Kumar (India)

09:30-09:40 OC 33 - Evaluating the robustness of 2D and 3D deep learning models for diagnosing idiopathic pulmonary fibrosis in ILD patients across different CT imaging protocols

Presented by G Hyun Kim from USA

- This study evaluated how well 2D and 3D deep learning models could diagnose idiopathic pulmonary fibrosis within a population of patients with interstitial lung disease (ILD), and tested the robustness of the models across different CT imaging protocols. The rational behind this lays in that CT-scans across different centres may be collected under different machines: indeed, several factors can influence the results of this exam (i.e. slice thickness, CT manufacturer model name (mAS), reconstruction kernels, patient position, effective tybe current-time product.

- Study population: N=343 and 271 subjects of 2D and 3 D deep learning models, respectively. Given the limited study protocol, only non-IPF ILD subjects were included in the model evaluation stage.

- Results: three models performed well on reference conditions, with model specific >= 0,97.For two out of three models, the model performance decreased when applying to evaluation conditions (P<0.05). In conclusion, when applying three high-performing IF deep learning diagnosis models to CT series collected under different imaging protocols, specificity decreased for all three models. Effective mAs is a key factor that leads to the lack of robustness for two out of three

models, which may due to the inconsistent level of effective As in the training set among IF and non-IPF population.

09:40-09:50 OC 34 - **Recommendations for execution and reporting of skin ultrasound in systemic sclerosis from the World Scleroderma Foundation skin ultrasound group**

Presented by T Santiago from Portugal

• This study presents the first evidence-based recommendations for the execution and reporting of skin ultrasound studies in systemic sclerosis (SSc), developed by a 16-member international multidisciplinary task force under the World Scleroderma Foundation.

The recommendations were formulated based on:

- A systematic literature review evaluating the current evidence on ultrasound and elastography for assessing skin involvement in SSc

- Expert opinion through a consensus process involving two rounds of voting

Five overarching principles highlight that while ultrasound and elastography are promising tools, their role in SSc management is not yet defined. Standardization of technical aspects, training, and appropriate equipment are critical needs.

Seven specific recommendations are provided:

- For execution:

1. Include both B-mode ultrasound for thickness/echogenicity and elastography for stiffness
2. Examine standardized skin sites used for modified Rodnan Skin Score
3. Use ≥18 MHz linear probes, perpendicular to skin, with generous gel and minimal pressure
4. Do not use stand-offs
5. Only allow well-trained examiners

- For reporting:

6. Specify quality criteria, skin layers, locations, number of images per site
7. Specify number/location of measurements per image, elastography region details, how measures were combined

• The recommendations aim to improve standardization to advance interpretability, reliability and validation of skin ultrasound for assessing and monitoring skin disease in SSc patients.

09:50-10:00 OC 35 - **Differentiation between scleroderma and non-scleroderma patterns in nailfold capillary microscopy using artificial intelligence**

Presented by V Korendovych from Germany.

- This study explored whether artificial intelligence models could effectively distinguish between scleroderma and non-scleroderma patterns visualized on nailfold capillary microscopy, which is used to evaluate microvascular changes in scleroderma patients.

- Methods: NVC was performed using the Optilla Digital Capillaroscope®. A total of 1176 images from 80 patients were collected and classified into two groups: "scleroderma" and "nonscleroderma" patterns. Of these images, 976 were randomly assigned to a training set, while the remaining 200 were allocated to a test set. A deep learning model based on a 2D convolutional neural network was trained on the training set using 5-fold cross-validation. Additionally, software was developed to classify capillaroscopy pictures with and without the support of the trained deep learning model, which served as a 'second opinion'.

For evaluation, capillaroscopy pictures from the test set were classified by three physicians with practical experience in nailfold videocapillaroscopy (NVC) and three doctors without NVC experience, after a 10-minute tutorial.

- Results: despite the relatively small number of images, the researchers successfully developed a deep learning model for differentiating between 'scleroderma' and 'non-scleroderma' NVC patterns.The use of such a model may help physicians achieve better inter-rater reliability, especially for inexperienced providers in interpreting NVC results.The study demonstrated the potential application of AI-based technologies in medical image analysis and diagnosis.

10:00-10:10 OC 36 - **Comparing Deep Neural Network Analysis to Modified Rodnan Skin Score in a Trial of Belumosudil for SSc Patients**

Presented by B Gunes from USA

- This study compared the performance of a deep neural network analysis of skin imaging to the modified Rodnan Skin Score (mRSS) in assessing skin involvement in systemic sclerosis (SSc) patients enrolled in a clinical trial of belumosudil. The researchers evaluated using deep learning/neural network models analyzing skin images as a potentially more objective and sensitive method compared to the standard mRSS for assessing skin thickening in SSc patients treated with the study drug belumosudil.

- Methods: validation cohort included 60 SSc patients, 164 skin biopsies, and 16 controlsvData was split into 70% training set and 30% test setvRecruited 12 adults with early diffuse cutaneous SSc (disease duration ≤ 6 years, mRSS < 35). mRSS and 4mm dorsal arm skin biopsies collected at baseline, 24 and 52 weeksvDNN analysis performed on skin images.vPatients received belumosudil 200mg twice daily orally

- Results: multivariate analysis using a DNN-fibrosis score and linear ridge regression.vDNN model predicted mRSS with R=0.70 on training set cross-validation and R=0.55 on test set. The deep learning model showed reasonable performance in predicting the clinical mRSS score from skin images in this trial, suggesting potential for AI-based skin assessment in SSc clinical studies

10:10-10:20 OC 37 - Validation of a Lung Ultrasound Interpretation Criteria for Interstitial Lung

Disease Screening in SSc, Mixed Connective Tissue Disease and Inflammatory Myopathy

Presented by R Fairchild, from USA

- The aim of this study was to validate specific ultrasound criteria to reliably detect ILD, which is a major complication in SSc and other connective tissue diseases, using lung ultrasound as a screening tool. Aimed for criteria that are simple, highly sensitive, with good inter-reader reliability.
- Methids: x14 lung zones per patient (6 anterior, 2 axillary, 6 posterior) were examined. Highresolution CT (HRCT) was used as the gold standard for ILD. The study included 100 patients (71% SSc/MCTD, 29% IM). LUS was performed using GE Logiq E with 12 MHz linear probe, capturing 4-second videos at 14 positions. 3 blinded readers (1 expert, 1 intermediate, 1 rheumatology ultrasound experience)
- Results: 41 patients had possible ILD on HRCT. Free marginal kappa for 3 readers was 0.92 (excellent agreement).Overall agreement between readers was 95.8%
- Conclusions: the revised LUS-ILD criteria showed high sensitivity and specificity for ILD detection. LUS severity correlated with CT imaging severity and %DLCO on PFTs. Combining LUS and PFTs increased sensitivity without losing specificity.

10:20-10:30 OC 38 - Detection of Scleroderma Facial Features by Artificial Intelligence: A Pilot Study

Presented by Y Suliman from United Arab Emirates

- This was a pilot study which aimed to develop an AI model to automatically detect scleroderma facial manifestations from photographs
- Methods: facial photographs from 40 scleroderma patients and 40 healthy controls were used. Applied state-of-the-art computer vision techniques to train the AI model.
- Results: specific facial features like tight skin, lips, and nose changes were detected
- Conclusions: the model was able to distinguish between scleroderma and healthy faces with reasonable accuracy. This preliminary study demonstrates the potential of leveraging AI and computer vision to aid in identifying the facial involvement and manifestations characteristic of scleroderma.

Parallel Session 8 - Oral Presentations

João Oliveira

March 16th, 8h30-9h30

OC 27: “Interferon Score as a novel trial enrichment tool to predict clinical trial outcomes in patients with Limited Cutaneous SSc” By Stefano Di Donato et al (UK)

Donato and colleagues examined serum Type I IFN levels’ predictive value in lcSSc outcomes, using the MINIMISE combined morbi-mortality endpoint. Analyzing 149 lcSSc patients from a national, multicenter cohort, they stratified patients using the IFN score. Their findings revealed a robust association between high IFN scores and increased risk of reaching the combined endpoint, with a hazard ratio of 5.5 compared to low IFN scores. This association persisted even when considering IFN score as a continuous variable. Thus, evaluating serum Type I IFN activity holds promise as a valuable tool for predicting severe outcomes in lcSSc.

OC 28: “Results from outcome selection for an FDA- and EMA acceptable Combined Response Index for Limited Cutaneous SSc: The CRISTAL Project” By Alain Lescoat et al (France)

The CRISTAL project, supported by several scleroderma organizations, aims to develop the CRISTAL index as an outcome measure for lcSSc clinical trials. Through qualitative analysis based on patient focus groups and literature reviews, pertinent domains were identified. Expert input was gathered via a Delphi exercise and nominal group technique, resulting in 19 draft items for observational studies. The project progresses steadily, and next steps include a prospective study to assess the psychometric properties of the items.

OC 29: “DecreaSSc: an observational study to assess the validity of home monitoring to detect progression of interstitial lung disease in systemic sclerosis.” By Arthiha Velauthapillai et al (The Netherlands)

This interim analysis of the ongoing DecreaSSc study investigates the validity of home spirometry for detecting progressive ILD in SSc. Forty-three SSc patients conducted weekly home spirometry for six months alongside hospital pulmonary function tests semi-annually. Preliminary findings from 25 patients show strong correlation between home and hospital measurements. Home spirometry demonstrated a sensitivity of 75% and specificity 81% for identifying progressive SSc-ILD. These results suggest that home spirometry could be a valuable tool for monitoring lung function in SSc patients.

OC 30: “Best clinical practice in the treatment of juvenile systemic sclerosis: expert panel guidance - the result of the international Hamburg consensus meeting December 2022” By Ivan Foeldvari et al (Germany).

The current treatment guideline for juvenile SSc, jSSc SHARE, is based on data up to 2014. Therefore, a multidisciplinary expert workshop at the Hamburg Symposium for jSSc aimed to update this guideline. Treatment options were reviewed and a consensus meeting held to achieve >80% agreement. Discussions, moderated by Dr. Dan Furst, covered various aspects of jSSc treatment, including general management and specific organ involvement. The consensus supports a treat-to-target strategy to prevent cumulative disease damage in jSSc. Recommendations draw from expert opinion and literature, primarily based on adult SSc. The presentation ended with an invitation to participate in the Juvenile Inceptions Cohort Project.

OC 31: "Cigarette exposure in systemic sclerosis: impact on autoantibody expression and disease manifestations: an analysis of the EUSTAR cohort" By Jacopo Ciaffi et al (Italy)

This study investigates the relationship between smoking and anti-topoisomerase antibodies (ATA) expression in SSc. Utilizing data from the EUSTAR database, the analysis revealed a significant difference in ATA expression between never-smokers and ever-smokers, particularly in females. Additionally, a dose-response relationship was observed, with higher smoking exposure correlated with lower ATA expression. Conversely, smoking correlates with increased risk of being anti-centromere antibody (ACA) positive in females. Interestingly, smoking exposure had different impact on disease manifestations depending on ATA/ ACA status.

OC 32 "Incident interstitial lung disease in systemic sclerosis in the EUSTAR database: increased risk of mortality despite less functional progression" By Liubov Petelytska et al. Presented by Cosimo Bruni (Italy).

This study investigated the prognosis of incident and prevalent ILD in SSc. Using the EUSTAR database, 9003 SSc patients were categorized based on ILD status: ILD-prevalent, ILD-incident and ILD-negative. ILD-incident cases showed milder baseline impairment but had higher mortality risk compared to ILD-negative cases and lower risk compared to ILD-prevalent cases. The findings emphasize the importance of ongoing screening for SSc-ILD after a negative baseline, to enable early detection and treatment.

Parallel Session 10 – Oral Presentation

Marcelo Neto

OC 39 Drivers of disease burden in patients with SSc reported by the ScleroID Questionnaire – a cross-sectional analysis across clinical and demographic subgroups

Sinziana Muraru1 et al.

1Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, SWITZERLAND

A cross-sectional analysis of 471 patients from the ScleroID validation cohort explored the clinical drivers drives of disease burden in SSc patients. Higher educational, female sex, worker/student status were associated with higher ScleroID scores. Among clinical manifestations, digital ulcers, dyspnoea, ILD and oesophageal disease emerged as significant contributors to disease burden.

ScleroID correlated strongly with patient-reported disease activity (measured by VAS), but not with the physicians' assessment. The authors highlight the importance of including patient-reported outcomes in clinical care and research.

OC 40 Early characterization of renal impairment in patients with systemic sclerosis by multiparametric magnetic resonance imaging

Xinyu Tong1, Huilin He2 et al.

1School of Clinical Medicine, Tsinghua University, Beijing, CHINA, 2Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Beijing, CHINA

This cross-sectional study compared multiparametric MR renal imaging features between 46 SSc patients and 22 healthy controls. SSc patients with normal eGFR had significantly lower T2*, longer T1, and lower renal blood flow. dcSSc patients had significantly lower renal blood flow when compared with lcSSc. The authors conclude that multiple parametric MR might be a sensitive and non-invasive modality to characterize early impairment of renal microstructure.

OC 41 Efficiency of annual pulmonary arterial hypertension screening by echocardiography in patients with systemic sclerosis

Yuichiro Shirai1 et al.

1Nippon Medical School, Tokyo, JAPAN

A retrospective analysis of a cohort of 651 SSc patients was performed to determine the incidence of PAH and predictors of its development. Serial PAH screening was conducted, guided by a 2-step algorithm: 1) identification of suspected cases based on tricuspid regurgitant velocity (TRV), other echocardiographic features of PH and the presence of dyspnoea; and 2) right heart catheterization of suspected patients. A total of 1600 screenings were performed (median 3/patient, mean interval 1.3 yrs.). PAH incidence rates were 2.5%, 1.2% and 0.3% at 1st, 2nd and 3rd screenings, respectively. In 3 patients, PAH was diagnosed prior to the next screening. In multivariate analysis, initial lower DLCO and higher TRV predicted PAH diagnosis. ROC analysis revealed TRV ≥ 2.3 m/s and DLCO ≤53% as optimal cut-offs. The authors suggest that the intervals of PAH screening need to be adjusted based on initial risk, and parameters such as TRV and DLCO might be useful for stratification.

OC 42 Clinical significance of anti-Ro/SSA antibodies in patients with systemic sclerosis: a study from the EUSTAR database

Blaz Burja1 et al.

1Center of Experimental Rheumatology, Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, SWITZERLAND

In this analysis of 4421 patients from the EUSTAR cohort, the 15.2% (n=661) with positive anti-SSA antibodies had more frequent muscular involvement, PAPs>45 mmHg on echocardiography and

lung fibrosis. In patients with lung fibrosis, anti-SSA positivity was associated with lower DLCO. Data on 3060 patients was analysed over a median follow-up of 2.4 years; anti-SSA did not predict lung fibrosis progression or death. The authors conclude that anti-SSA may be useful for better risk stratification in SSc.

OC 43 Treatment regimens and mortality in systemic sclerosis-associated pulmonary arterial hypertension in light of the 2022 ESC/ERS guidelines

Hilde Jenssen Bjørkekjær1,2 et al.

1Hospital of Southern Norway, Kristiansand, Department of Rheumatology, Kristiansand, NORWAY, 2University of Oslo, Institute of Clinical Medicine Oslo, NORWAY

This longitudinal study included 359 SSc-PAH patients from the EUSTAR database to access currently used initial treatment regimens. Upfront combination therapy (dual or triple) was used more frequently in patients with higher mPAP and PVR, and in the high-risk group (COMPERA stratification). Up-front monotherapy was associated with lower mortality in multivariable analysis (vs. no therapy), but upfront combination treatment was not. The authors also noted that few patients have received the currently recommended upfront combination treatment.

OC 44 Predictors of systemic sclerosis related primary heart involvement at cardiac magnetic resonance: a monocentric retrospective study

Veronica Batani1 et al

1UnIRAR, Vita-Salute San Raffaele University & San Raffaele Hospital, Milan, ITALY

The authors retrospectively studied a cohort of 259 SSc patients, 56 of which underwent cardiac MR for suspected primary heart involvement (pHI) which was confirmed in 37. In multivariate analysis, increased troponin T, increased C-reactive protein and ILD emerged as predictors of pHI-SSc. In the subgroup that underwent MR, the presence of an arrhythmic event at 24h-Holter was the only predictor of pHI. In the subgroup with positive MR, an arrhythmic event emerged at univariate analysis as a predictor of fibrotic changes; no other clinical features associated with signs of pHI in MR.

Biomarkers in SSc, input for clinical practice and RCT

Marius Cadar

Prof. S Assassi (United States)

Biomarkers can be related to disease course (prognostic) or to response to a certain treatment (predictive) Anti-Topoisomerase I (ATA) in SSc-ILD could be considered as the first biomarker, as it is highly specific for the development of ILD and functional decline in early cohorts. A study from GENISOS cohort showed that, among different laboratory methods, only positivity at immunodiffusion was predictive of predicted FVC decline >5%. In SLS II and SENSCIS trials, ATA did not predict functional decline, while in FocuSSced trial predicted the response to Tocilizumab among early patients with high inflammatory markers. In conclusion,

ATA could be considered as a biomarker of accelerated FVC decline in unselected cohorts with the predictive significance depending on the detection method.

Elevated C-reactive protein (CRP), as showed in the GENOSIS cohort, was associated with decreased survival and accelerated FVC decline, thus representing a useful prognostic biomarker for a poor ILD outcome in early SSc. It could also be useful as an enrichment criterion, but not as a mandatory criterion because it is decreased by Mycophenolate Mofetil and only less than 20% of ILD patients on stable treatment has elevated CRP levels.

Interferon (IFN) signature is detected in about 50% of SSc patients and seems a promising strategy for the identification of a biomarker. In SLS II trial, patients with higher interferon chemokine score at baseline had a lower FVC decline at 3 and 12 months both in cyclophosphamide (CYC) and MMF arms but not in the placebo arm, suggesting that interferon signature could represent a biomarker predictive of immunosuppressive treatment response. The levels of The CXC chemokines interferon-gamma-inducible protein-10 (IP-10) and the monokine induced by interferon-gamma (Mig) measured at the baseline and at 12 months were associated to a better response to MMF treatment. Importantly, the predictive significance of the IFN chemokine score was independent of the baseline CRP levels and clinical predictors.

New biomarkers were found while investigating the circulating extracellular collagen neo-epitopes, with different concentration at baseline and one year follow-up when comparing progressive and non-progressive ILD.
Moreover, high levels of the lung specific protein KL-6 seem to represent a prognostic biomarker of worse ILD course regardless of treatment status, when analyzing data from several studies including clinical trials.

Data from SLS II and SENSCIS trials highlighted another possible prognostic biomarker in ILD: baseline PBC gene expression involved in myeloid lineage predicted accelerated FVC decline, regardless of MMF background treatment.

When considering biomarkers associated to skin involvement, the identification of biomarkers becomes even more challenging. Skin gene expression profiling in dcSSc was shown to have a possible predictive significance for response to immunosuppression, while no role as predictive biomarker of mRSS course over time in observational cohorts. Importantly, disease duration is an important determinant of gene expression profile: in early stages of the disease, fibrosis and inflammation can co-exist; afterward the inflammatory gene profile decreases over time with a trend toward normalization. Data from observational study and from the ASSET trial showed that patients with anti-RNA polymerase III (ARA) positivity, as compared to negative ones, have a higher peak of mRSS and a shorter interval for reaching the peak. Data from skin of ARA+ patients showed a highly inflammatory profile corresponding to a rapidly progressive clinical course, and thus requiring early immunosuppressive treatment. In clinical trials focused on skin involvement, it would be useful to stratify patients according to ARA status.

Top of SSc Science (Session 11)

Ana Rita Prata

Date and Time of session: Saturday 16th March, 14:00-15:30; Location: Forum Hall

Chairpersons: S Onuora (Nature), A Clarke (Lancet Rheumatology), M Trojanowska (Arthritis & Rheumatology), M Matucci-Cerinic (Journal of Scleroderma and Related Disorders).

For the session Top of Systemic Sclerosis (SSc) Science, four lecturers were chosen to present recent significant contributions to the Scleroderma field (best from journals).

In the first communication, Prof Cosimo Bruni presented the results of a project published in two different papers1,2 concerning SSc-Primary Heart Involvement (SSc-pHI). A first systematic review was conducted to generate statements of what was considered SScpHI. Finally, seven overarching principles and ten guidance statements for SSc-pHI screening, diagnosis and follow-up included the importance of integrating signs and symptoms with specific test results, the relevance of patient education for reporting symptoms, the need for SSc-pHI screening at diagnosis and annually (together with pulmonary arterial hypertension surveillance), and the consideration of performing cardiac magnetic resonance if suspicion of SSc-pHI remains after core tests.

In the second part of the session, Prof Francesco Del Galdo focused on the results of a recently published study on MRI Digital Artery Volume Index (DAVIX®) as a surrogate outcome measure of digital ulcer disease in patients with SSc3. This publication follows a project started in 2014 pursuing the unmet need of detecting vascular disease progression in SSc. For this purpose, the authors used MRI with a specific hand sequence to quantify the volume of the digital arteries and the volume of the finger and determine their ratio (DAVIX®). After a first pilot study in 2017, an observational cohort study including two independent SSc cohorts was started, and automated DAVIX® determination was developed parallelly. Among the most interesting results of this study are: (i) the significantly lower DAVIX® found in patients with digital ulcer disease and in patients developing new digital ulcers during 12 months of follow-up; and (ii) the finding that DAVIX® was positively correlated with the DLCO and negatively correlated with the nailfold capillaroscopy pattern and the FVC/DLCO ratio.

Dr. Alexandru-Emil Matei then presented the results of a study based on biophysical phenotyping of cells given its importance in understanding cell dysfunction in SSc4. Raising the hypothesis that mechanical cell phenotyping can be used as a clinical tool in rheumatic diseases, the authors performed a study including SSc, Rheumatoid Arthritis and ANCA-associated vasculitis patients using real-time fluorescence and deformability cytometry to determine biophysical properties of monocyte subsets. After adjusting for potential confounders, SSc-specific changes in the biophysical properties of monocyte subsets were associated with disease activity and the extent or progression of fibrosis.

Finally, Dr. Janet Pope shared the most relevant results of a 2023 review on SSc treatment, focusing on evidence for the treatment of skin involvement in diffuse SSc patients with immunosuppressive drugs. The main challenges of using modified mRSS as a primary outcome in clinical trials were highlighted, and the ACR Combined Response Index in diffuse SSc was presented as a score that better captures the complex and dynamic nature of early diffuse SSc. The lecture also stressed the importance of considering testing an oncology model (multidrug treatment) and improving equity, diversity, and inclusivity in clinical trials.

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SWC 2024, Prague session 3 – Vascular/ Raynaud/ Skin

Rucsandra Dobrota

Friday, March 15th

This very interesting session presented an update on the assessment of vascular and skin manifestations in systemic sclerosis (SSc).

From the first presentation by John Pauling, we've learned that the various vascular manifestations are interrelated and likely share common pathogenic mechanisms. Prof. Vanessa Smith further offered a thorough illustration of capillaroscopy and other modern tools for assessment of the microcirculation in SSc. Prof. Denton continued with a presentation focused on assessment of skin fibrosis, from the wellknown modified Rodnan skin score and its application as an outcome measure in clinical trials, to more modern techniques, like durometry, skin ultrasound or shear weave elastography. Further, patient reported outcome measures for assessment of skin fibrosis, as well as biomarkers, were discussed. Maria Grazia Lazzaroni followed, with a presentation on multidisciplinary management for evaluation of lower extremities arterial disease in SSc in an Italian single centre. Another original presentation by Marco Di Battista followed, introducing an artificial intelligence-based Raynaud quantification index (ARTIX) based on mobile phone images, which was validated against clinical diagnosis, cold challenge and thermography. The last presentation of the session was by Judith Potjewijd, who reported on a new potential biomarker for vascular calcification and inflammation, the Plasma dephosphorylateduncarboxylated Matrix Gla-Protein, which correlated with inflammation and was associated with an increased risk of cardiovascular disease or death in the presented study.