

One year in review 2021: systemic sclerosis

M. Di Battista¹, S. Barsotti¹, M. Orlandi², G. Lepri²,
V. Codullo³, A. Della Rossa¹, S. Guiducci², F. Del Galdo⁴

¹Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;

²Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Florence;

³Rheumatology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;

⁴Scleroderma Programme, NIHR BRC and Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, United Kingdom.

Marco Di Battista, MD

Simone Barsotti, MD

Martina Orlandi, MD

Gemma Lepri, MD

Veronica Codullo, MD

Alessandra Della Rossa, MD

Serena Guiducci, MD, PhD, PH

Francesco Del Galdo, MD, PhD

Please address correspondence to:

Alessandra Della Rossa,

U.O di Reumatologia,

Università di Pisa,

Via Roma 67,

56126 Pisa, Italy.

E-mail: a.dellarossa@ao-pisa.toscana.it

Received on April 30, 2021; accepted in revised form on June 10, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 131): S3-S12.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2021.

Key words: systemic sclerosis, pathogenesis, treatment, outcome, patient-reported outcomes

Competing interests: F. Del Galdo received consultancy fees and grant support not directly related to the content of this study from AbbVie, AstraZeneca, Boehringer-Ingelheim, Capella Biosciences, Chemomab Ltd, Kymab Ltd, Janssen, Mitsubishi-Tanabe. The other authors have declared no competing interests.

ABSTRACT

Systemic sclerosis is a rare and chronic connective tissue disease with a multifaceted pathogenesis characterised by heterogeneous multi-organ clinical manifestations. Every year, many studies contribute to enrich the knowledge on the pathogenesis, organ involvement and treatment of this complex and severe disease. We herein provide an overview on the most relevant contributions published in the literature in 2020.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterised by distinctive pathogenetic features, ultimately leading to a heterogeneous clinical profile. Following the previous editorial initiatives of *Clinical and Experimental Rheumatology* to present novel relevant insights on rheumatic diseases in the form of “One year in review” (1, 2), we here-with provide a narrative overview on the most significant contributions regarding SSc. A MedLine search was performed using the term “systemic sclerosis” (MeSH terms and semantic search), focusing on pathogenesis, clinical manifestations, patient-reported outcomes and treatment. We included articles in English regarding adult SSc patients published between January 1st, 2020 and December 31st, 2020. Among these papers, we have selected 69 as the most innovative in the field.

Pathogenesis of SSc

Genetics and epigenetics

The role played by genetic background in SSc represents an increasingly in-depth topic. Indeed, recent genetic investigations allowed the identification of novel genes closely associated with the disease, such as insulin-like growth factor binding protein 7, whose serum protein is up-regulated in SSc patients

and it is thought to contribute to fibrosis by inducing cell adhesion and activating fibroblasts (3). FLI1 is another susceptibility gene that was investigated in a large cohort of Japanese SSc patients. FLI1 gene contains a microsatellite repeat polymorphism constituted by GA dinucleotide repeat sequence, and its protein acts as a suppressor of collagen transcription. It was discovered that FLI1 alleles with many (more than 22) GA repeats determined lower FLI1 mRNA levels and were significantly associated with susceptibility to SSc (4). Since HLA genes were reported to have the strongest influence on SSc predisposition and with specific autoantibody subsets, their associations were examined in a large cohort of African-American (n. 662) and European-American (n. 723) SSc patients. In the former population, African ancestry-predominant HLA-DRB1*08:04 and HLA-DRB1*11:02 alleles were associated with overall SSc risk, the former allele being strongly related to antifibrillar antibody subset. This could partially explain the increased SSc prevalence among African-Americans. In the European-American cohort, HLA-DPB1*13:01 and HLA-DRB1*07:01 alleles were strongly associated with antitopoisomerase-1 (ATA) and anti-centromere (ACA) antibody subsets, respectively. In addition to reiterating the importance of HLA in defining SSc autoantibody subtypes, this study used HLA α/β allelic heterodimers to bioinformatically predict immunodominant peptides of the different self-antigens recognised by SSc autoantibodies. It was discovered that they are homologous to viral protein sequences from Mimiviridae and Phycodnaviridae families. Hence, it gives rise to the hypothesis that SSc-specific autoantibodies may originate through molecular mimicry, thus outlining a link between

HLA alleles, autoantibodies and specific viral triggering antigens (5).

An international multicentre study performed a whole blood transcriptome analysis on RNA (RNA-seq) collected from 162 SSc patients. Alongside a de-regulation in tumour suppressor p53 function, they found a significant de-regulation of several interferon (IFN)-related pathways, especially in the Toll-like receptor (TLR) cascade. This reinforces the pivotal pathogenic role that IFN-I, TLR and inflammasome play in SSc (6). Similar results were obtained in a study that performed RNA-seq on lung microvascular endothelial cells from SSc patients affected by interstitial lung disease (ILD). The findings revealed an over-expression of numerous IFN-related genes and of genes encoding antiviral immune response, suggesting that IFN pathway and antiviral response proteins could contribute to the pathogenesis of SSc-ILD. Moreover, the additional finding of an over-expression of mesenchymal cell-specific genes confirms the presence of endothelial to mesenchymal transition in SSc-ILD (7).

Genetic and immunofluorescence analyses were recently used to elucidate one of the most important profibrotic pathways that involves fibroblast growth factors (FGFs) and their associated receptors (FGFRs). It was clearly demonstrated that the profibrotic cytokine transforming growth factor β (TGF- β) selectively up-regulates both FGFR3 and its ligand FGF9 in SSc skin fibroblasts. FGF9 binds to FGFR3 in an autocrine/paracrine fashion, and FGFR3 consequently induces downstream multiple profibrotic pathways mediated by the transcription factor CREB. The prominent FGFR3 signature in SSc skin fibroblasts highlighted in this study, characterises aberrant FGF9/FGFR3 as an upstream regulator of a wide network of profibrotic mediators, thus making it a potential target for antifibrotic therapies in SSc (8).

A considerable part of the research efforts regarding SSc pathogenesis is lately focusing on epigenetics. Enhancer of zeste 2 (EZH2) is an enzyme known to operate the methylation of histone 3, thus silencing target genes,

ultimately leading to an epigenetically stable activation of SSc dermal fibroblasts. The EZH2 pathway in SSc was recently elucidated by Wasson *et al.*, who found that HOTAIR, a long non-coding RNA, drives the specific methylation profile of EZH2 both *in vitro* and *in vivo* SSc fibroblasts. It was demonstrated that such an epigenetic intervention leads to an activation of NOTCH pathway through down-regulation of miRNA-34a, a NOTCH suppressor (9). The HOTAIR/EZH2/NOTCH profibrotic pathway was further investigated by the same group, finding that HOTAIR overexpression in SSc myofibroblasts, through NOTCH activation, determines a stable up-regulation of GLI2, the main transcription factor of the Hedgehog pathway, hence mediating the expression of profibrotic markers. This putative interaction between Hedgehog and NOTCH pathways expands the possible molecular interactions that lead to profibrotic activation (10).

Another epigenetic alteration that leads to a persistently activated pathologic phenotype of fibroblasts was recently described and involves TGF- β . In fact, it was demonstrated that TGF- β induces promoter hypermethylation, with consequent silencing, of the gene suppressor of cytokine signalling 3 (SOCS3). SOCS3 down-regulation strongly facilitates TGF- β aberrant activation of JAK2/STAT3 signalling, which ultimately leads to myofibroblasts transition (11).

ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) is a technique used to assess genome-wide chromatin accessibility, which is one of the most important epigenetic processes. ATAC-seq was recently used to analyse eight different cell types in skin biopsies from healthy controls and SSc patients. It was observed that dendritic cells (DCs) have the greatest changes in chromatin accessibility between normal, SSc unaffected and SSc affected skin. DCs also exhibited the highest enrichment of SSc-associated single nucleotide polymorphisms (SNPs). The fact that DCs possess great epigenetic differences in strong correlation with skin fibrosis, suggests that

these antigen-presenting cells could be one of the most important drivers of SSc pathogenesis (12).

RNA-seq performed on SSc skin biopsies enabled the identification of H19X, a long non-coding RNA, whose expression in fibroblasts is strongly induced by TGF- β . H19X mediates the profibrotic effects of TGF- β by promoting extracellular matrix (ECM) production and myofibroblasts survival. ATAC-seq revealed that H19X exerts its effects by changing chromatin accessibility of DDIT4L, a gene that acts as an inhibitor of the TGF- β pathway. Therefore, in SSc skin, TGF- β -induced H19X mediates a profibrotic effect by disabling the transcription of DDIT4L, thus avoiding the inhibition of TGF- β signalling (13).

Cells and cytokines

Different studies sought to investigate the mechanisms of activation of fibroblasts into myofibroblasts. In particular, the intracellular chloride channel 4 (CLIC4) is regulated by TGF- β and seems to be overexpressed in SSc fibroblasts. The inhibition of CLIC4 leads to reduced expression of the myofibroblast markers collagen type 1 and α -smooth muscle actin, probably interfering with the differentiation of fibroblasts and thus opening a novel target for therapeutic interventions (14). Additionally, the expression of dypeptidylpeptidase-4 (DDP-4) may also be linked to fibroblast activation in SSc patients. DDP-4 positive fibroblasts were found to be increased in SSc skin in a TGF- β dependent manner, expressing high levels of myofibroblast markers and collagen. The inhibition of DPP-4, a pharmacological approach already used for patients with diabetes mellitus, may therefore represent a potential therapy for fibrosis (15).

The role of mesenchymal stromal cells (MSCs) was recently investigated by Taki *et al.* in SSc skin biopsies. In those skin samples, MSC-like cells undergoing megakaryocytic division were identified in both involved and uninvolved skin, and exposure to dermal blister fluid caused MSC activation, inducing a myofibroblast phenotype. This suggests that the disease microenvironment may influence the

differentiation of MSCs toward a profibrotic phenotype, being responsible for the establishment of the disease (16). It is also likely that the microenvironment is involved in the activation of SSc macrophages toward a profibrotic pattern with overexpression of CCL2, IL-6 and TGF- β . Interestingly, when the differentiation of healthy donors' monocytes takes place in plasma from SSc patients, the resulting macrophages express the SSc immunophenotype, which suggests that soluble factors in SSc microenvironment may consistently influence different cellular phenotypes (17).

The analysis of skin biopsies also allowed the identification of a specific population of cytotoxic CD4⁺ T cells with enhanced metabolic activity, that are clonally expanded in SSc patients. These cells are able to induce the apoptotic death of several cellular subtypes, including the endothelial cells. Such cellular loss followed by exuberant tissue repair eventually leads to fibrosis and organ dysfunction (18).

Among the many studies carried out on different cell subtypes in SSc, the analysis of monocyte-derived DCs of patients with ATA positivity identified a common set of 10 topoisomerase-1 epitopes that are associated with the presence and severity of lung fibrosis, thus suggesting a role of these epitopes in SSc-ILD pathogenesis (19).

Cytokine imbalance may also be responsible for different SSc organ involvement. Cathepsin S is a lysosomal proteolytic enzyme involved in the regulation of intracellular signalling and in ECM remodelling, therefore its reduction could contribute to an aberrant fibrotic process. A recent study demonstrated that cathepsin S serum levels are significantly lower in SSc patients, especially those with diffuse cutaneous SSc (dcSSc), than in healthy controls. Moreover, reduced serum cathepsin S seems to strongly associate with SSc-ILD, since it also negatively correlated with other ILD biomarkers such as serum Krebs von den Lungen-6 (KL-6) (20).

Protein convertase subtilisin/kexin type 9 (PCSK9), a molecule linked with cholesterol metabolism, was

found downregulated in SSc patients compared to controls and its serum levels directly correlated with carotid intima-media thickness. PCSK9 could therefore represent a candidate to explain the link between subclinical atherosclerosis and SSc (21).

Take home messages

- HLA alleles strongly associate with different SSc autoantibodies and ethnic susceptibility (5).
- There is increasing evidence on the pivotal pathogenic role of the IFN pathway in SSc (6, 7).
- SSc epigenetic studies highlight the HOTAIR/EZH2/NOTCH profibrotic pathway and SOCS3 down-regulation (9-11).
- DCs may potentially represent one of the most important drivers of SSc pathogenesis (12, 19).
- ECM and soluble factors in SSc microenvironment are gaining growing importance in SSc profibrotic activation (13, 16, 17, 20).

Clinical manifestations

Although widespread microvascular impairment and tissue fibrosis of the skin and internal organs represent the clinical hallmarks of SSc, the disease is characterised by a wide clinical heterogeneity. Classically, SSc has been classified according to skin involvement in two subsets: limited cutaneous (lcSSc) and dcSSc. However, this classification does not seem to be able to capture the broad heterogeneity of disease phenotypes in its manifestations and progression. In fact, data from the EUSTAR database point out that severe organ involvements as ILD, should not be neglected in lcSSc patients, who may present an ILD as progressive as in dcSSc forms (22). In this context, data from a Spanish registry suggest that major SSc cardiopulmonary complications are more frequently attributable to the type of autoantibody rather than to the skin subset (23). Moreover, patients with similar clinical manifestation may present different disease trajectories and survival. Therefore the possibility to subset SSc patients overcoming classical cutaneous groups will likely ameliorate the disease manage-

ment and prognosis of this condition (24). Data from the Italian SPRING registry confirmed in male patients the known higher prevalence of dcSSc, severe vascular involvement and ILD. In addition, the short time between Raynaud's phenomenon onset and disease diagnosis emerged as an unfavourable prognostic factor (25). A EUSTAR analysis on more than 1700 patients, revealed that dcSSc also represents an independent risk factor for the development of severe vascular complications ultimately leading to gangrene (26). Data from the French national cohort confirmed the different individual course of skin involvement in 198 SSc patients (49.7% dcSSc) and suggested the possibility to predict mortality with the early detection of modified Rodnan skin score (mRSS) change over time. In fact, patients with a low baseline mRSS and no significant change over time were unlikely to develop major organ involvement and to die prematurely in comparison to patients with higher baseline mRSS and/or skin worsening or improving over time (27). This study highlights the importance of an early evaluation of skin involvement: in this context, attention is beginning to be focused on high frequency skin ultrasound that seems to be a valid and reproducible method for skin assessment in SSc patients. This technique is especially valuable for the detection of early subclinical involvement, given the proven correlation with histological skin thickness (28, 29).

Pulmonary involvement

In 2019 a new haemodynamic definition of pulmonary arterial hypertension (PAH) was proposed, lowering the cut-off of mean pulmonary arterial pressure (mPAP) to 20 mmHg, in addition to pulmonary arterial wedge pressure \leq 15 mmHg and pulmonary vascular resistance (PVR) \geq 3 WU at right heart catheterisation. Although it should allow an increase in PAH diagnosis, an international study demonstrated that out of 55 SSc patients with mPAP between 21 and 24 mmHg, only 4 can be classified as having PAH-SSc according to the new criteria. Approximately half of the patients with mPAP 21-24 mmHg and

PVR ≥ 2 WU already presented with early functional and imaging pulmonary vascular disease. In those subjects a PVR ≥ 2 WU was significantly associated with reduced long-term survival. Data from this study point out that also the PVR cut-off should be lowered to ≥ 2 WU, since a PVR threshold ≥ 3 WU is too high to enable an early diagnosis of SSc-PAH (30).

ILD, together with PAH, still represents the most feared complication in SSc, since it is associated with a high rate of morbidity and mortality and also with a substantial increase in healthcare costs (31). The analysis of more than 800 SSc-ILD patients from the EUSTAR database demonstrated how lung involvement may present heterogeneous course and patterns, often alternating phases of stability and progression. The strongest predictive factors for forced vital capacity (FVC) decline over 5 years were found to be male sex, higher mRSS and reflux/dysphagia symptoms (32).

Given its pivotal role, SSc-ILD evaluation requires different and increasingly sophisticated methods from laboratory, instrumental and imaging fields. For example, KL-6 has increasingly established itself as the leading biomarker in ILD. A recent study on retrospective and prospective SSc cohorts highlighted that even after a multivariate analysis, KL6 was significantly and independently associated with diffusing capacity for carbon monoxide (DLCO) decline. It was then suggested a clinical utility of KL-6 in risk stratification for progressive SSc-ILD (33).

Pulmonary function tests (PFTs) are largely used in clinical practice for the assessment of ILD. However, a retrospective analysis by Bernstein *et al.* shed a light on the scarce sensitivity of PFTs in detecting ILD on high resolution chest tomography (HRCT) imaging in an early dcSSc population, confirming the fundamental role of baseline HRCT and the inadequacy of PFTs as a sole screening tool for ILD diagnosis (34). In this context, the possibility to quantify normal parenchyma, ground glass opacity, reticular alteration and honeycombing by the analysis of HRCT images through a quantitative

CT algorithm (the most widespread being CALIPER) is emerging in clinical practice. These algorithms are useful not only for quantifying lung damage, but also pulmonary vascular volume (PVV). It was recently demonstrated that in SSc-ILD patients PVV values, both absolute and normalised for lung volume (PVV/LV), positively correlated with the various ILD patterns and negatively with functional parameters in PFTs. It clearly emerged a progressive increase in PVV/LV as DLCO decreases (35). Pleuroparenchymal fibroelastosis (PPFE) is an uncommon fibrotic condition which predominantly affects upper lobe pleural and subjacent parenchyma (36). The prevalence of PPFE was recently investigated with HRCT in 359 SSc from two different cohorts. PPFE was found in 18% of them and it significantly correlated with free-standing bronchial alterations and with a worse survival, independently of ILD severity (37).

Lung ultrasound (LUS) is a helpful tool in the evaluation of ILD and B-lines are considered the main sign of an interstitial syndrome. Data from 396 SSc patients confirmed a higher number of B-lines in patients with dcSSc, ATA positivity and ILD at HRCT. At a multivariate analysis, the presence of ≥ 5 posterior B-lines was associated with onset of ILD in patients without lung involvement at baseline HRCT or with ILD worsening (38). These data suggest the utility of LUS not only in baseline screening but also as a tool able to guide the use of HRCT in the follow-up of SSc patients.

Cardiovascular involvement

Among all instrumental techniques, cardiac magnetic resonance (CMR) plays a pivotal role in SSc heart involvement detection, especially in subclinical forms where echocardiography shows normal parameters. T1 mapping is emerging as a CMR sequencethat is able to objectively distinguish normal from diseased myocardium, thus better characterising the composition of myocardial tissue. T1 lengthens with interstitium expansion caused by oedema or fibrosis, hence T1 mapping proved to be helpful in detecting SSc myocardial fibrosis. In

a study on 40 consecutive SSc patients, higher T1 values were observed more frequently in dcSSc and were associated with ILD and more frequent cardiac events during follow-up (39). Data from 24h Holter electrocardiogram and CMR on 150 SSc patients were recently compared in the multicentre Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS). The results showed an association between CMR abnormalities and ventricular rhythm disturbances, since T2 ratio and the percentage of late gadolinium enhancement are the most significant predictors of such arrhythmias (40). Taken together, these results suggest CMR not only as a fundamental tool in heart assessment, but also in the prediction of major complication in SSc patients.

In a similar way, great efforts have been made trying to predict the development of digital ulcers (DUs). In the field of nailfold videocapillaroscopy, the NEMO score evaluates the cumulative number of microhaemorrhages and microthromboses, and has already proved to be a good indicator of disease activity in SSc. In a 2-year follow-up study on 98 SSc patients, it was demonstrated that the NEMO score at baseline was significantly higher in those who developed DUs with respect to those who did not (41). When DUs are already in place, laser speckle contrast analysis (LASCA) can be of help in their prognostic stratification. A prospective study on forty SSc-DUs revealed that the ratio between the blood flow at the ulcer area and the finger base evaluated with LASCA was strictly correlated to the time of healing. The presence of infection of the wound bed greatly influenced LASCA parameters and the healing time (42). Another insidious complication of DUs is the presence of calcinosis, which was recently well characterised in 55 SSc patients with DUs. Skin calcinosis was prevalent in subjects with lcSSc and longer disease duration, mainly localised at the fingertip. Noteworthy, the healing time of DUs was significantly longer in patients with calcinosis (43).

Gastrointestinal involvement

Gastrointestinal involvement is one of the most frequent complaints in SSc,

and it is often present from the earlier phase of the disease. It can ultimately lead to malnutrition, which strongly impairs quality of life, negatively affecting morbidity and mortality. Hence, early detection of SSc patients at risk for malnutrition becomes a crucial issue for successful early management of this condition. It was highlighted that the assessment of gastrointestinal complaints and nutritional status in SSc using symptom-based questionnaires can reflect the severity of the gastrointestinal condition and the associated malnutrition, but is frequently prone to some limitations (44). In this context, bioelectrical impedance vector analysis (BIVA) proved to be a reliable, low-cost, quick and bedside technique, emerging as a method of choice for assessing nutritional status. When applied in a SSc cohort with the clinical suspicion of malnutrition, BIVA, unlike body mass index, allowed an accurate characterisation of SSc patients at risk of malnutrition, correlating with serological malnutrition markers, with SSc-specific organ manifestations (cardiopulmonary involvement and microvascular damage), and with mortality. BIVA variables might, therefore, represent a surrogate marker of damage accrual that leads to malnutrition, thus playing a leading role in the prognostic stratification of SSc patients (45). A strong link between sarcopenia, impaired body composition and local microvascular failure characterised by a late capillaroscopic pattern with significant reduced number of capillaries was recently elucidated (46). Another aid in the assessment of malnutrition comes from laboratory analysis. It has been demonstrated that deficiencies in micronutrients (folic acid, zinc, selenium) and/or prealbumin are a frequent burden in patients with SSc, since they are present from the very early phases of the disease and become more and more significant with the worsening of the SSc clinical manifestations (47). Gut microbiota is arousing interest in all chronic conditions. Analysing stool samples from SSc patients, it was found that microbial richness was lower for patients with long-standing disease, with dcSSc and for those who reported

a recent weight loss. A deviation of the intestinal microbial composition in SSc patients compared to healthy controls, with a greater expression of *Lactobacillus* and *Streptococcus* and a depletion of *Sutterella* has been noted. Nutritional status appeared to have a marked impact on the gut microbiota (48).

Take home messages

- Although still important in the prognostic stratification of SSc, the subdivision into the classic cutaneous subsets no longer seems to have a main role but rather being complementary to the autoantibody profile and to the change over time of the cutaneous involvement (23, 24, 27).
- In addition to mPAP, also a lowering of PVR threshold was proposed in order to enable an early diagnosis of SSc-PAH (30).
- SSc-ILD evaluation requires different and increasingly sophisticated methods from laboratory (KL-6) and imaging (HRCT algorithms, LUS) fields (33, 35, 38).
- CMR is emerging as a fundamental tool for a complete evaluation of SSc heart involvement (39, 40).
- Malnutrition is a major issue in SSc, and its early detection could benefit from novel reliable and disease-specific tools as BIVA (45).

Treatment

SSc treatment is still an open challenge since older therapies gave unsatisfactory results and no novel treatments completely fulfilled the expectations. The goal of treating is stabilisation and the prevention of progressive disease. Combining therapies to address the individual SSc manifestations is a cornerstone to the comprehensive management of this condition. Controlling the complex biological network, progressive vasculopathy and fibrosis, as well as manifestations of end-organ dysfunction are all critical considerations when determining the best treatment approach for SSc.

Immunosuppressive treatments

The recent years have witnessed a great number of immunosuppressive and antifibrotic therapeutic strategies in SSc-

ILD. An analysis on 497 SSc patients from a European multicentre cohort revealed that a considerable proportion of them may be under-treated, thus making risk stratification and individualised evidence-based treatment mandatory in daily clinical practice. This study also reported that methotrexate was the most administered immunosuppressive agent, followed by cyclophosphamide (CYC), mycophenolate mofetil (MMF), and azathioprine, whereas only a small number of patients were treated with biologic agents (49). To elucidate potential differences between intravenous and oral CYC, an analysis on patients from the EUSTAR register and from Scleroderma Lung Studies I and II with a one year of follow-up was conducted. No significant differences were found between the two routes of CYC administration regarding lung function (change in FVC% and DLCO%) or cutaneous sclerosis (mRSS). Instead, discrepancies emerged with regard to side effects. Leukopenia, haemorrhagic cystitis and alopecia occurred more frequently with oral CYC, whereas in the intravenous group, more severe adverse events and need for oxygen supplementation were reported (50). Since MMF is an established therapy for SSc, a Swedish study tried to unravel its pharmacokinetics and found a considerable inter-individual variation in drug exposure. Plasma levels of MMF active metabolite were inversely related to body weight and renal function, whereas lower levels were associated with ATA positivity, male sex and strongly with chronic usage of proton-pump inhibitors. Therefore, body weight, renal function, sex, serology, gastrointestinal manifestations and concomitant therapy should be considered when using MMF for SSc (51).

Among biologic therapies, a longitudinal retrospective observational study on 24 SSc-ILD patients with ongoing lung function impairment despite treatment with CYC or MMF, evaluated the use of rituximab (RTX) as a rescue add-on therapy to MMF. After 1 year of treatment with RTX, a significant improvement in FVC and DLCO was observed in most of the patients, but a sub-analysis revealed that improvement occurred

mainly in those without a UIP pattern on HRCT. These data support the use of RTX as a rescue add-on treatment to MMF in patients with a more aggressive SSc-ILD phenotype (52). Tocilizumab (TCZ), an anti-interleukin-6 receptor antibody, showed preliminary evidence of efficacy in SSc in a phase II trial; in 2020 Khanna *et al.* reported data about a multicentre, randomised, double-blind, placebo-controlled, phase III trial in 104 dcSSc-ILD patients. At week 48, TCZ treatment was not able to significantly modify the skin fibrosis (primary endpoint) in comparison with placebo but could preserve lung function (FVC% predicted) in patients with early SSc-ILD and elevated acute-phase reactants. Safety was consistent with the known profile of TCZ (53). A phase II trial evaluated weekly subcutaneous abatacept (ABA) *versus* placebo in dcSSc. ABA was well tolerated but a change in mRSS at 12 months (primary end point) was not achieved. Secondary outcome measures, such as Health Assessment Questionnaire Disability Index (HAQ-DI) and a composite measure, showed evidence in support of ABA (54). The safety and effectiveness of ABA was analysed in 27 SSc patients from the EUSTAR database. The most frequent reason for ABA treatment was articular involvement followed by myositis. Data after 6 and 12 months of treatment showed significant improvement in the number of tender and swollen joints, in the HAQ-DI and in morning stiffness (55).

Janus kinase (JAK) inhibitors are a family of small drugs that target various possible isoforms of JAK (JAK1, JAK2, JAK3 and/or TYK2), thus blocking the signalling of pro-inflammatory cytokines. The efficacy of tofacitinib on skin fibrosis was confirmed in a pilot study on 10 dcSSc patients with skin thickening refractory to conventional immunosuppressants. The mRSS significantly improved the first month after tofacitinib treatment: these results suggest that tofacitinib may be at least as effective as intensive conventional immunosuppressants, with a quicker and higher response rate in refractory dcSSc patients with progressive skin thickness (56).

Vasoactive treatments

DeSSciper is the largest European multicentre observational real-life study with the aim of working out what the optimal management of SSc is, and its first observational trial evaluated the efficacy of different drugs for the prevention and healing of DUs. Data from 905 SSc patients with DUs (previous or ongoing) pointed to calcium channel blockers (CCB) as being the most used drug (71.6%), followed with a remarkable gap by intravenous iloprost, endothelin receptor antagonists and phosphodiesterase-5 inhibitors ($\leq 20\%$ for all of them). Noteworthy, even in the most expert centres, the proportion of patients with DUs on combination therapy with more than one vasoactive drug was quite low. Although 65% of the patients with recurrent DUs were treated with bosentan and/or sildenafil, almost one out of four patients with current and recurrent DUs was on CCB alone (57).

There is growing evidence regarding combination therapy as a better option than monotherapy to treat SSc-PAH. A recent *post-hoc* analysis of the modified intention-to-treat population of the AMBITION study reported that initial combination therapy with ambrisentan and tadalafil provided greater benefits compared with initial monotherapy with either agent alone in patients with PAH secondary to connective tissue diseases, especially in SSc-PAH. A significant reduction of the risk of clinical failure with combination therapy was observed particularly in patients whose baseline risk was low or intermediate (at a simplified risk stratification score using non-invasive parameters from ESC/ERS guidelines) (58). The superiority of combination therapy in terms of survival rate emerged also from a retrospective analysis of the Spanish registry RESCLE (59). Taken together, these data reinforce the indication to treat the initial forms of SSc-PAH more aggressively, starting from the beginning with a combination therapy, for the sake of obtaining better outcomes.

ACE inhibitors (ACEi) are the mainstay of therapy in scleroderma renal crisis (SRC). The effect of ACEi on the incidence of this fearful complication was investigated in a retrospective anal-

ysis on 7648 patients without prior SRC from the EUSTAR database. Interesting yet controversial results emerged: ACEi in SSc patients with concomitant systemic arterial hypertension appeared as an independent risk factor for the development of SRC. Although ACEi are still the first choice in SRC treatment, these data warrant further studies in order to be clarified and to look for alternative safe antihypertensive drugs in SSc (60).

Antifibrotic treatments

After the publication of the results of the SENSICIS trial in 2019, nintedanib (NIN), a tyrosine kinase inhibitor initially approved for idiopathic lung fibrosis, received approval in many countries, also for the treatment of SSc-ILD. A *post-hoc* analysis of SENSICIS trial classified SSc patients on the basis of FVC% change and found that at week 52, in subjects treated with NIN and placebo, respectively, 13.6% and 20.1% had an FVC decline $>5\%$ - $\leq 10\%$ predicted, and 3.5% and 5.2% had an FVC decline $>10\%$ - $\leq 15\%$ predicted. The hazard ratio for an absolute decline in FVC $\geq 5\%$ predicted or death with NIN *versus* placebo was 0.83, and the hazard ratio for an absolute decline in FVC $\geq 10\%$ predicted was 0.64, supporting the clinically meaningful effect of NIN on slowing the progression of SSc-ILD (61). The adverse events profile of NIN is mainly characterised by gastrointestinal complaints, especially mild-moderate diarrhoea, which is usually managed by reducing the dose to 100 mg bid. Data from the SENSICIS trial revealed that SSc-ILD patients with gastrointestinal involvement are not more likely to have gastrointestinal adverse events from NIN than those without. Dose adjustment appears as an important strategy to minimise the impact of adverse events and to avoid treatment interruption, especially since it was demonstrated that the rate of FVC decline is similar in all NIN-treated patients irrespective of dose adjustments (62).

Other treatments

One of the most debilitating gastrointestinal complication in SSc is small intestinal bacterial overgrowth (SIBO).

Cyclic administration of antibiotics is the most widely used therapy for improving symptoms and time intervals for relapses of SIBO. An open pilot clinical trial performed in forty SSc patients with SIBO evaluated the efficacy and safety of *Saccharomyces boulardii* alone or in combination with metronidazole. This probiotic is a strain of yeast resistant to antibiotics, so it can be administered along with any antibacterial. After 2 months of treatment, the combination group reported the higher rate of SIBO eradication (55%), with a significant decrease of diarrhoea, abdominal pain, and gas/bloating/flatulence. Hence, these data indicate *S. boulardii* as the add-on probiotic of choice for the treatment of SIBO (63). Gastroesophageal reflux disease (GERD) is another gastrointestinal manifestation that sometimes can be resistant to conventional anti-acid treatments, significantly impairing the quality of life. In this context, encouraging results were obtained with vonoprazan, an H⁺/K⁺ ATPase blocker. SSc patients with GERD refractory to proton-pump inhibitors, experienced a significant improvement of symptoms after treatment with vonoprazan (64).

The efficacy and safety of autologous fat grafting for the treatment of skin and peripheral microvascular involvement in SSc was recently established in 25 patients with mouth and/or hand involvement (microstomia, xerostomia, skin sclerosis, Raynaud's phenomenon and long-lasting DUs). The surgical procedures were repeated in each patient every 6 months for a total of two or three times. The results at 6 months after the last session reported improvement of xerostomia, reduction of the skin thickness around the mouth and on the hands, reduction of the Raynaud's phenomenon and improvement of the perception of disability. DUs healed completely in 8 out of 9 patients (65).

Lenabasum is a synthetic orally administered agonist of cannabinoid receptor-2 that modulates the endocannabinoid system to activate the resolution phase of innate immune responses. Lenabasum was tested (as an add-on therapy) in 27 dcSSc patients in a phase II study for 16 weeks, proving to

be safe and well-tolerated. Compared to placebo, treatment with lenabasum determined improvements in mRSS, patient reported outcomes and, on histologic evaluation of skin biopsy specimens, an improvement in inflammation and fibrosis directly related to a reduction of their respective gene expression pathways (66). It is worth mentioning that topline data of the Phase III study for lenabasum in dcSSc, although not published in MedLine, have been disclosed by the Sponsor as not meeting the primary endpoint.

Take home messages

- Even if the therapeutic choices among immunosuppressants have greatly expanded, classic DMARDs, especially MMF and CYC, are still important first-line therapies, and their correct dosage management can make the difference in the therapeutic outcome (49, 51).
- Safety and efficacy of RTX in SSc is now well established, at the same time encouraging data are being collected on TCZ, ABA and JAK inhibitors (52-56).
- Combination vasoactive therapy should be strongly encouraged in SSc-PAH from the beginning: an aggressive early approach leads to better survival outcomes (58, 59).
- NIN proved to be effective in slowing the progression of SSc-ILD, thus dose adjustment appears as an important strategy to minimise the impact of adverse events and to avoid treatment interruption (61, 62).

Patient reported outcomes (PROs)

The importance of obtaining PROs in the management of SSc has been recognised in an important recent initiative, the Collaborative National Quality and Efficacy Registry for Scleroderma (CONQUER). This longitudinal cohort has been instituted for SSc patients with no longer than 5 years duration from first non-Raynaud's symptom. It envisages the collection of a biobank and it is intended as a validation cohort for upcoming studies. Most relevantly, biological and clinical data are paralleled by PROs questionnaires administered to participants. Questionnaires include

Patient Global Assessment, Scleroderma Health Assessment, the UCLA GIT 2.0, the PROMIS 29, patient skin assessment, dyspnoea assessment and, finally, the resource utilisation questionnaire (RUQ), which asks to report on time spent in health care, the number of healthcare professionals seen in the last period, treatments and devices used for the disease, hospitalisations, etc. The completion rate was above 88% for all questionnaires. Noteworthy, no clinical feature, age or social status prevented their finalisation (67). PROs emerged therefore as reliable variables to include patients' perspective in biological and clinical studies. A subsequent multivariate analysis of the CONQUER cohort demonstrated that the only clinical features which influenced questionnaires completion were the presence of calcinosis and acro-osteolysis. The most affected PRO was the RUQ, whereas all the others maintained high percentages of performance (68). This analysis allows two considerations. First, the RUQ is helpful in understanding healthcare policies and burden of chronic diseases but it is probably too lengthy for SSc patients and difficult to administer, especially in longitudinal cohorts. Second, hand complications deserve special and further attention when addressing intervention as specific PROs should be formulated and their completion assisted (by electronic administration of questionnaires, use of finger-friendly devices, etc).

DUs are a common SSc feature whose emotional burden comprises a complex interplay of experiences associated with significant pain and morbidity. Existing PROs fail to capture this in full. In a recent qualitative study, focus groups of patients were asked to describe their personal experience of DU-related pain. It emerged quite unanimously that describing their experience through figurative images, comparisons to other relatable physical events or detailing strategies for coping was extremely effective in communicating with partners and healthcare professionals (69). Descriptive tools (metaphors, graphic contents, similitudes, etc) captured the burden of DUs in SSc patients better than semi-

qualitative or multidimensional scales (70). Therefore, this modality should be taken into consideration to improve the approach to something as multifaceted as DUs.

Finally, in the year of the pandemic from Sars-Cov-2 infection, an international mental health survey investigated whether this situation could differently affect patients with a pre-existing condition such as SSc, which is considered to be more at risk of complication from COVID-19. The results obtained with the PROMIS anxiety scale and the Patient Health Questionnaire (focused on depression) in the same cohort of SSc patients in the pre-COVID period were compared with those in the COVID period. Symptoms of depression did not change significantly, whereas quite homogeneously in all the participating countries an increase in anxiety exceeding the minimal clinically important difference in the PROMIS anxiety scale was noted. It was mainly influenced by time since diagnosis and revealed higher percentages in Anglo-Saxon countries (UK, US) with respect to France or Canada (71). Mental health status is an aspect not to underestimate when assessing the vulnerability of SSc patients to the current pandemic.

Conclusions

This brief, not exhaustive narrative overview of some of the most innovative studies published in 2020 clearly indicates a considerable step forward in understanding and managing an extremely complex pathology such as SSc. More and more refined studies are allowing us to unravel its pathogenesis, providing insights into hitherto unknown mechanisms and often opening the path for new therapeutic approaches. From a clinical point of view, a common theme has been the effort to obtain an increasingly early diagnosis and early treatment, with the overall aim of improving the prognosis and the quality of life of SSc patients. Advances in understanding this pathology and disease outcome heterogeneity will help to better design future trials, following the winning path of precision medicine.

Abbreviations

(in order of appearance):

- SSc: systemic sclerosis
- ATA: antitopoisomerase-1
- ACA: anticentromere
- IFN: interferon
- TLR: toll-like receptor
- ILD: interstitial lung disease
- FGF(R): fibroblast growth factor (receptor)
- TGF- β : transforming growth factor- β
- EZH2: enhancer of zeste 2
- SOCS3: suppressor of cytokine signalling 3
- ATAC-seq: Assay for Transposase-Accessible Chromatin using sequencing
- DC: dendritic cell
- SNP: single nucleotide polymorphism
- ECM: extracellular matrix
- CLIC4: intracellular chloride channel 4
- DDP-4: dypeptidylpeptidase-4
- MSC: mesenchymal stromal cell
- dcSSc: diffuse cutaneous SSc
- KL-6: Krebs von den Lungen-6
- PCSK9: protein convertase subtilisin/kexin type 9
- lcSSc: limited cutaneous SSc
- mRSS: modified Rodnan skin score
- PAH: pulmonary arterial hypertension
- mPAP: mean pulmonary arterial pressure
- PVR: pulmonary vascular resistance
- FVC: forced vital capacity
- DLCO: diffusing capacity for carbon monoxide
- PFT: pulmonary function test
- HRCT: high resolution chest tomography
- PVV/LV: pulmonary vascular volume / lung volume
- PPFE: pleuroparenchymal fibroelastosis
- LUS: lung ultrasound
- CMR: cardiac magnetic resonance
- DU: digital ulcer
- LASCA: laser speckle contrast analysis
- BIVA: bioelectrical impedance vector analysis
- CYC: cyclophosphamide
- MMF: mycophenolate mofetil
- RTX: rituximab
- TCZ: tocilizumab
- ABA: abatacept
- HAQ-DI: Health Assessment Questionnaire Disability Index
- JAK: janus kinase
- CCB: calcium channel blockers
- ACEi: ACE inhibitors
- SRC: scleroderma renal crisis
- NIN: nintedanib
- SIBO: small intestinal bacterial overgrowth
- GERD: gastroesophageal reflux disease
- PRO: patient reported outcome
- RUQ: resource utilisation questionnaire

References

1. BARSOTTI S, ORLANDI M, CODULLO V *et al.*: One year in review 2019: systemic sclerosis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S3-14.
2. ORLANDI M, LEPRI G, DAMIANI A *et al.*: One year in review 2020: systemic sclerosis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S3-17.
3. YAN Y-M, ZHENG J-N, LI Y, YANG Q-R, SHAO W-Q, WANG Q: Insulin-like growth factor binding protein 7 as a candidate biomarker for systemic sclerosis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 131): S66-76.
4. YAMASHITA K, KAWASAKI A, MATSUSHITA T *et al.*: Association of functional (GA)_n microsatellite polymorphism in the FLI1 gene with susceptibility to human systemic sclerosis. *Rheumatology* 2020; 59: 3553-62.
5. GOURH P, SAFRAN SA, ALEXANDER T *et al.*: HLA and autoantibodies define scleroderma subtypes and risk in African and European Americans and suggest a role for molecular mimicry. *Proc Natl Acad Sci USA* 2020; 117: 552-62.
6. BERETTA L, BARTUREN G, VIGONE B *et al.*: Genome-wide whole blood transcriptome profiling in a large European cohort of systemic sclerosis patients. *Ann Rheum Dis* 2020; 79: 1218-26.
7. PIERA-VELAZQUEZ S, MENDOZA FA, ADDYA S, POMANTE D, JIMENEZ SA: Increased expression of interferon regulated and antiviral response genes in CD31+/CD102+ lung microvascular endothelial cells from systemic sclerosis patients with end-stage interstitial lung disease. *Clin Exp Rheumatol* 2020 Nov 17; PMID: 33253099 [Online ahead of print].
8. CHAKRABORTY D, ZHU H, JÜNGEL A *et al.*: Fibroblast growth factor receptor 3 activates a network of profibrotic signaling pathways to promote fibrosis in systemic sclerosis. *Sci Transl Med* 2020; 12.
9. WASSON CW, ABIGNANO G, HERMES H *et al.*: Long non-coding RNA HOTAIR drives EZH2-dependent myofibroblast activation in systemic sclerosis through miRNA 34a-dependent activation of NOTCH. *Ann Rheum Dis* 2020; 79: 507-17.
10. WASSON CW, ROSS RL, WELLS R *et al.*: Long non-coding RNA HOTAIR induces GLI2 expression through Notch signalling in systemic sclerosis dermal fibroblasts. *Arthritis Res Ther* 2020; 22: 286.
11. DEES C, PÖTTER S, ZHANG Y *et al.*: TGF- β -induced epigenetic deregulation of SOCS3 facilitates STAT3 signaling to promote fibrosis. *J Clin Invest* 2020; 130: 2347-63.
12. LIU Q, ZABA L, SATPATHY AT *et al.*: Chromatin accessibility landscapes of skin cells in systemic sclerosis nominate dendritic cells in disease pathogenesis. *Nat Commun* 2020; 11: 5843.
13. PACHERA E, ASSASSI S, SALAZAR GA *et al.*: Long noncoding RNA H19X is a key mediator of TGF- β -driven fibrosis. *J Clin Invest* 2020; 130: 4888-905.
14. WASSON CW, ROSS RL, MORTON R, MANKOURI J, DEL GALDO F: The intracellular chloride channel 4 (CLIC4) activates systemic sclerosis fibroblasts. *Rheumatology* 2020; 4: 1-6.

15. SOARE A, GYÖRFI HA, MATEI AE *et al.*: Dipeptidylpeptidase 4 as a marker of activated fibroblasts and a potential target for the treatment of fibrosis in systemic sclerosis. *Arthritis Rheumatol* 2020; 72: 137-49.
16. TAKI Z, GOSTJEVA E, THILLY W *et al.*: Pathogenic activation of mesenchymal stem cells is induced by the disease microenvironment in systemic sclerosis. *Arthritis Rheumatol* 2020; 72: 1361-74.
17. BHANDARI R, BALL MS, MARTYANOV V *et al.*: Profibrotic activation of human macrophages in systemic sclerosis. *Arthritis Rheumatol* 2020; 72: 1160-9.
18. MAEHARA T, KANEKO N, PERUGINO CA *et al.*: Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis. *J Clin Invest* 2020; 130: 2451-64.
19. TINIAKOU E, FAVA A, MCMAHAN ZH *et al.*: Definition of naturally processed peptides reveals convergent presentation of autoantigenic topoisomerase I epitopes in scleroderma. *Arthritis Rheumatol* 2020; 72: 1375-84.
20. TOYAMA S, YAMASHITA T, SAIGUSA R *et al.*: Decreased serum cathepsin S levels in patients with systemic sclerosis-associated interstitial lung disease. *J Dermatol* 2020; 47: 1027-32.
21. FERRAZ-AMARO I, DELGADO-FRÍAS E, HERNÁNDEZ-HERNÁNDEZ V *et al.*: Pro-protein convertase subtilisin/kexin type 9 in patients with systemic sclerosis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S18-24.
22. FRANTZ C, HUSCHER D, AVOUAC J *et al.*: Outcomes of limited cutaneous systemic sclerosis patients: Results on more than 12,000 patients from the EUSTAR database. *Autoimmun Rev* 2020; 19: 102452.
23. ARANDIA NI, ESPINOSA G, VILELLA CT *et al.*: Serodiscordant patients with systemic sclerosis: When antibody does not correspond to skin involvement. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S106-14.
24. JOHNSON SR, VAN DEN HOOGEN F, DEVAKANDAN K, MATUCCI-CERINIC M, POPE JE: Systemic sclerosis: To subset or not to subset, that is the question. *Eur J Rheumatol* 2020; 7: 222-7.
25. FERRI C, GIUGGIOLI D, GUIDUCCI S *et al.*: Systemic sclerosis progression INvestiGation (SPRING) Italian registry: Demographic and clinico-serological features of the scleroderma spectrum. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S40-7.
26. MIHAI C, DISTLER O, GHEORGHIU AM *et al.*: Incidence and risk factors for gangrene in patients with systemic sclerosis from the EUSTAR cohort. *Rheumatology* 2020; 59: 2016-23.
27. LEDOULT E, LAUNAY D, BÉHAL H *et al.*: Early trajectories of skin thickening are associated with severity and mortality in systemic sclerosis. *Arthritis Res Ther* 2020; 22: 30.
28. CHEN C, CHENG Y, ZHU X *et al.*: Ultrasound assessment of skin thickness and stiffness: The correlation with histology and clinical score in systemic sclerosis. *Arthritis Res Ther* 2020; 22: 197.
29. NAREDO E, PASCAU J, DAMJANOV N *et al.*: Performance of ultra-high-frequency ultrasound in the evaluation of skin involvement in systemic sclerosis: A preliminary report. *Rheumatology* 2020; 59: 1671-8.
30. XANTHOULI P, JORDAN S, MILDE N *et al.*: Haemodynamic phenotypes and survival in patients with systemic sclerosis: The impact of the new definition of pulmonary arterial hypertension. *Ann Rheum Dis* 2020; 79: 370-8.
31. MORRISROE K, STEVENS W, SAHAR J *et al.*: The clinical and economic burden of systemic sclerosis related interstitial lung disease. *Rheumatology* 2020; 59: 1878-88.
32. HOFFMANN-VOLD AM, ALLANORE Y, ALVES M *et al.*: Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021; 80: 219-27.
33. STOCK CJW, HOYLES RK, DACCORD C *et al.*: Serum markers of pulmonary epithelial damage in systemic sclerosis-associated interstitial lung disease and disease progression. *Respirology* 2021; 26: 461-8.
34. BERNSTEIN EJ, JAAFAR S, ASSASSI S *et al.*: Performance characteristics of pulmonary function tests for the detection of interstitial lung disease in adults with early diffuse cutaneous systemic sclerosis. *Arthritis Rheumatol* 2020; 72: 1892-6.
35. OCCHIPINTI M, BRUNI C, CAMICIOTTOLI G *et al.*: Quantitative analysis of pulmonary vasculature in systemic sclerosis at spirometry-gated chest CT. *Ann Rheum Dis* 2020; 79: 1210-7.
36. ORLANDI M, LANDINI N, BRUNI C *et al.*: Pleuroparenchymal fibroelastosis in rheumatic autoimmune diseases: a systematic literature review. *Rheumatology* 2020; 59: 3645-56.
37. BONIFAZI M, SVERZELLATI N, NEGRI E *et al.*: Pleuroparenchymal fibroelastosis in systemic sclerosis: prevalence and prognostic impact. *Eur Respir J* 2020; 56: 1902135.
38. GARGANI L, BRUNI C, ROMEI C *et al.*: Prognostic value of lung ultrasound B-lines in systemic sclerosis. *Chest* 2020; 158: 1515-25.
39. TERRIER B, DECHARTRES A, GOUYA H *et al.*: Cardiac intravoxel incoherent motion diffusion-weighted magnetic resonance imaging with T1 mapping to assess myocardial perfusion and fibrosis in systemic sclerosis: association with cardiac events from a prospective cohort study. *Arthritis Rheumatol* 2020; 72: 1571-80.
40. MAVROGENI S, GARGANI L, PEPE A *et al.*: Cardiac magnetic resonance predicts ventricular arrhythmias in scleroderma: The Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS). *Rheumatology* 2020; 59: 1938-48.
41. DEL PAPA N, PIGNATARO F, MAGLIONE W *et al.*: High NEMO score values in nailfold videocapillaroscopy are associated with the subsequent development of ischaemic digital ulcers in patients with systemic sclerosis. *Arthritis Res Ther* 2020; 22: 237.
42. BARSOTTI S, D'ASCANIO A, VENTURINI V *et al.*: Is there a role for laser speckle contrast analysis (LASCA) in predicting the outcome of digital ulcers in patients with systemic sclerosis? *Clin Rheumatol* 2020; 39: 69-75.
43. BARSOTTI S, VENTURINI V, DI BATTISTA M *et al.*: The impact of skin calcinosis on digital ulcers in patients with SSc: clinical and prognostic stratification using the "wound bed score". *Int Wound J* 2020; 17: 1783-90.
44. YALCINKAYA Y, ERTURK Z, UNAL AU *et al.*: The assessment of malnutrition and severity of gastrointestinal disease using symptom-based questionnaires in systemic sclerosis: Is it related to severe organ involvement or capillary rarefaction at microcirculation? *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S127-31.
45. DI BATTISTA M, BARSOTTI S, MONACO A, ROSSI A, DELLA ROSSA S, MOSCA M: Bioelectrical impedance vector analysis for nutritional status assessment in systemic sclerosis and association with disease characteristics. *J Rheumatol* 2021; 48: 728-34.
46. PAOLINO S, GOEGAN F, CIMMINO MA *et al.*: Advanced microvascular damage associated with occurrence of sarcopenia in systemic sclerosis patients: Results from a retrospective cohort study. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S65-72.
47. LÄUBLI J, DOBROTA R, MAURER B *et al.*: Impaired micronutrients and prealbumin in patients with established and very early systemic sclerosis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S120-6.
48. NATALELLO G, BOSELLO SL, STERBINI FP *et al.*: Gut microbiota analysis in systemic sclerosis according to disease characteristics and nutritional status. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S73-84.
49. PANOPOULOS S, CHATZIDIONYSIOU K, TEKTONIDOU MG *et al.*: Treatment modalities and drug survival in a systemic sclerosis real-life patient cohort. *Arthritis Res Ther* 2020; 22: 56.
50. BRUNI C, TASHKIN DP, STEEN V *et al.*: Intravenous versus oral cyclophosphamide for lung and/or skin fibrosis in systemic sclerosis: An indirect comparison from EUSTAR and randomised controlled trials. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S161-8.
51. ANDRÉASSON K, NERINGER K, WUTTGE DM, HENROHN D, MARSAL J, HESSELSTRAND R: Mycophenolate mofetil for systemic sclerosis: Drug exposure exhibits considerable inter-individual variation—a prospective, observational study. *Arthritis Res Ther* 2020; 22: 230.
52. NARVÁEZ J, LLUCH J, MOLINA-MOLINA M *et al.*: Rituximab as a rescue treatment added on mycophenolate mofetil background therapy in progressive systemic sclerosis associated interstitial lung disease unresponsive to conventional immunosuppression. *Semin Arthritis Rheum* 2020; 50: 977-87.
53. KHANNA D, LIN CJF, FURST DE *et al.*: Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020; 8: 963-74.
54. KHANNA D, SPINO C, JOHNSON S *et al.*: Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol* 2020; 72: 125-36.
55. CASTELLVÍ I, ELHAI M, BRUNI C *et al.*: Safety and effectiveness of abatacept in systemic sclerosis: The EUSTAR experience. *Semin Arthritis Rheum* 2020; 50: 1489-93.

56. YOU H, XU D, HOU Y *et al.*: Tofacitinib as a possible treatment for skin thickening in diffuse cutaneous systemic sclerosis. *Rheumatology* 2021; 60: 2472-7.
57. BLAGOJEVIC J, ABIGNANO G, AVOUAC J *et al.*: Use of vasoactive/vasodilating drugs for systemic sclerosis (SSc)-related digital ulcers (DUs) in expert tertiary centres: results from the analysis of the observational real-life DeSScIpher study. *Clin Rheumatol* 2020; 39: 27-36.
58. KUWANA M, BLAIR C, TAKAHASHI T, LANGLEY J, COGHLAN JG: Initial combination therapy of ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) in the modified intention-to-treat population of the AMBITION study: Post hoc analysis. *Ann Rheum Dis* 2020; 79: 626-34.
59. PESTANA-FERNANDEZ M, RUBIO-RIVAS M, TOLOSA-VILELLA C *et al.*: Longterm efficacy and safety of monotherapy versus combination therapy in systemic sclerosis-associated pulmonary arterial hypertension: A retrospective RESCLE registry study. *J Rheumatol* 2020; 47: 89-98.
60. BÜTIKOFER L, VARISCO PA, DISTLER O *et al.*: ACE inhibitors in SSc patients display a risk factor for scleroderma renal crisis - A EUSTAR analysis. *Arthritis Res Ther* 2020; 22: 59.
61. MAHER TM, MAYES MD, KREUTER M *et al.*: Effect of nintedanib on lung function in patients with systemic sclerosis-associated interstitial lung disease: further analyses of the SENSICIS trial. *Arthritis Rheumatol* 2021; 73: 671-6.
62. SEIBOLD JR, MAHER TM, HIGHLAND KB *et al.*: Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSICIS trial. *Ann Rheum Dis* 2020; 79: 1478-84.
63. GARCÍA-COLLINOT G, MADRIGAL-SANTILLÁN EO, MARTÍNEZ-BENCOMO MA *et al.*: Effectiveness of *saccharomyces boulardii* and metronidazole for small intestinal bacterial overgrowth in systemic sclerosis. *Dig Dis Sci* 2020; 65: 1134-43.
64. TABUCHI M, MINAMI H, AKAZAWA Y *et al.*: Use of vonoprazan for management of systemic sclerosis-related gastroesophageal reflux disease. *Biomed Rep* 2021; 14: 25.
65. PIGNATTI M, SPINELLA A, COCCHIARA E *et al.*: Autologous fat grafting for the oral and digital complications of systemic sclerosis: results of a prospective study. *Aesthetic Plast Surg* 2020; 44: 1820-32.
66. SPIERA R, HUMMERS L, CHUNG L *et al.*: Safety and efficacy of lenabasum in a Phase II, randomized, placebo-controlled trial in adults with systemic sclerosis. *Arthritis Rheumatol* 2020; 72: 1350-60.
67. SHANMUGAM VK, FRECH TM, STEEN VD *et al.*: Collaborative National Quality and Efficacy Registry (CONQUER) for Scleroderma: outcomes from a multicenter US-based systemic sclerosis registry. *Clin Rheumatol* 2020; 39: 93-102.
68. FRECH TM, VANBUREN JM, STARTUP E *et al.*: Does hand involvement in systemic sclerosis limit completion of patient-reported outcome measures? *Clin Rheumatol* 2021; 40: 965-71.
69. JONES J, HUGHES M, PAULING J, GOBERMAN-HILL R, MOORE AJ: What narrative devices do people with systemic sclerosis use to describe the experience of pain from digital ulcers: A multicentre focus group study at UK scleroderma centres. *BMJ Open* 2020; 10: e037568.
70. HUGHES M, PAULING JD, JONES J *et al.*: Multicenter qualitative study exploring the patient experience of digital ulcers in systemic sclerosis. *Arthritis Care Res* 2020; 72: 723-33.
71. THOMBS BD, KWAKKENBOS L, HENRY RS *et al.*: Changes in mental health symptoms from pre-COVID-19 to COVID-19 among participants with systemic sclerosis from four countries: A Scleroderma Patient-centered Intervention Network (SPIN) Cohort study. *J Psychosom Res* 2020; 139: 110262.