Review

One year in review 2020: systemic sclerosis

M. Orlandi[1], G. Lepri[1], A. Damiani[1], S. Barsotti[2], M. Di Battista[2],
V. Codullo[3], A. Della Rossa[2], S. Guiducci[1], Y. Allanore[4]

[1]Rheumatology Unit, Department of
Clinical and Experimental Medicine,
University of Florence;
[2]Rheumatology Unit, Department of
Clinical and Experimental Medicine,
University of Pisa;
[3]Rheumatology Unit, Fondazione IRCCS
Policlinico San Matteo, Pavia, Italy;
[4]Service de Rhumatologie, Hôpital
Cochin, Université de Paris,
INSERM U1016, Paris, France.

Martina Orlandi, MD
Gemma Lepri, MD
Arianna Damiani, MD
Simone Barsotti, MD
Marco Di Battista, MD
Veronica Codullo, MD
Alessandra Della Rossa, MD
Serena Guiducci, MD, PhD, PH
Yannick Allanore, 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

ABSTRACT

Systemic sclerosis (SSc) is a connective tissue disease characterised by diffuse microangiopathy and immune dysregulation which ultimately results in widespread fibrosis of the skin and internal organs. This complex autoimmune disease is characterised by heterogeneous clinical manifestations and variable disease course in which the severity of pathology dictates the disease prognosis and course. Every year novel insights into the pathogenesis, organ involvement and treatment of this severe disease are published. Herewith, we provide an overview of the most significant literature contributions published last year, with the aim of helping the clinician in the understanding and management of SSc patients.

Introduction

Systemic sclerosis (SSc) is a connective tissue disorder characterised by immune dysregulation, endothelial cell dysfunction followed by defective vascular repair and neovascularisation, and progressive tissue fibrosis of the skin and internal organs. Following the previous annual reviews of the "One year in review" series (1, 2), in this paper we provide a narrative critical digest of the most relevant contributions to the medical literature regarding SSc. A MedLine search has been performed using the term "systemic sclerosis" (MeSH terms and semantic search), focusing on the pathogenesis, organ involvement, patient-reported outcome and treatment, published between January 1st, 2019 and December 30th, 2019. The initial search retrieved 625 results from PubMed. In the first round, all the reviewers reviewed titles and abstracts in terms of relevance. In the second round, full texts of the articles included during the first round were retrieved and re-assessed for eli-gibility. Possible discordance during study selections were discussed with senior supervisors (SG, ADR, YA) to reach a consensus. We only included articles published in English; case reports, case series, congress abstracts and editorials were excluded. Finally, a total of 118 were included and discussed in this review.

Pathogenesis of SSc

The pathogenetic features of SSc encompass alterations of the immune system, vascular bed and the extracellular matrix, leading to the deposition of collagen in the skin and internal organs (3, 4). Major histocompatibility complex (MHC) class II may represent one of the most significant genetic factors in the development of the disease. In particular, a recent study identified different alleles as risk factors for SSc, in particular in HLA-DRB1 and HPB1 (5).
Concerning non-HLA genes, López-Isac et al. performed a large genome-wide association study and a metanalysis. This study allowed the identification of 13 new risk loci for the disease, with a great increase in the number of association signals reported for SSc, bringing the total number of SSc risk loci up to 28. Most of the genetic variations identified belong to immune genes and are located in non-coding regions suggesting a putative role in regulatory mechanisms (6). The genes identified by the analysis also included genes implicated in pathways that may be relevant in SSc. For example, DDX6 is related with the regulation of vascular endothelial growth factor under hypoxic conditions, while RAB2A is correlated with the probable impairment of autophagy in SSc. The results of this study also confirmed the hypothesis of an important role in SSc pathogenesis of natural killer (NK) cells, which may represent a link between the vascular

damage and the immune activation in SSc, due their ability to induce endothelial activation.

Additionally, a genome-wide meta-analysis identified 27 single nucleotide polymorphisms (SNPs) associated with systemic seropositive rheumatic disease in non-HLA genes. Among them the analysis identified mutations in DGKQ, linked with cell proliferation and migration in SSc and lung involvement, and PRR12, associated with fibrinogen concentrations and consequently cardiovascular events. Ten (38%) of the genes identified had never been reported before as being associated with SSc and could represent innovative targets, but follow-up studies will be required (7). Other SNPs associated with susceptibility to SSc were identified in vitamin D receptor gene polymorphism (ApaI and BglI) (8) and MIF (− 794 CATT7 and − 173*C) genetic variants (9).

The study of skin biopsies identified a prevalence of innate and adaptative immune cell signatures in early diffuse SSc patients compared with patients with longstanding disease for macrophage, B- and T cells (10). Additionally, in skin biopsies, the tumour necrosis factor (TNF) signalling pathway was over-expressed in different tissues confirming a crucial role of the autoimmunity pathways in SSc patients (11).

Several studies also suggested the possible role of epigenetic factors (12). Recently, altered histone marks were identified in SSc monocytes that were enriched for immune, IFN and antiviral pathways (13). Long non-coding RNAs (lnc-RNAs) may play a role in the pathogenesis of SSc and a recent Italian study that analysed more than 500,000 transcripts in blood mononuclear cells identified a downregulation of lncRNA (ncRNA00201) that regulates tumour proliferation and genes related to inflammation, vascular alterations and fibrosis (14). Moreover, this lnc-RNA may represent a linkage between SSc and the relatively high prevalence of cancer found in SSc patients. Lnc-RNAs may also be up-regulated in patients in different stages of the diseases compared to healthy controls, in particular the negative regulator of the type I interferon (INF) response was found to be significantly upregulated in SSc monocytes (15).

The analysis of micro-RNA (miRNA) in patients with SSc and ILD allowed the identification of a different expression of miRNAs that may be involved in the pathogenesis of SSc-ILD and may represent potential diagnostic biomarkers (16). Different miRNA have been identified in the last year, including Epidermal Growth Factor Like-domain 7 (EGFL7) and its miR-126 (17), miRNA-4484 and the matrix metalloproteinase (MMP)-21 (18), and miRNA-542-3p and 708-5p (19).

Cytokines and chemokines
Several studies have evaluated the possible relationship between different cytokines and SSc. An Australian work conducted on a population of 105 SSc patients analysed the serum levels of the interleukin (IL)-1 superfamily of cytokines. IL-18 was significantly higher in SSc patients than in the healthy controls and inversely correlated with both DLCO and KCO, whereas IL-1α and IL-1β were directly correlated with KCO (20). Higher serum concentrations of IL-17B, IL-17E and IL-17F have also been identified in SSc subjects compared to controls (21), whereas serum IL-6 levels were associated with the severity of symptoms and low resilience, namely the ability to bounce back or recover previous levels of functioning after a stressful event (22).

Lymphocyte T-related inducible ligand that competes for glycoprotein D binding to herpes virus entry mediator on T cells (LIGHT) may be involved in tissue remodelling and development of fibrosis. SSc patients were found to have a significant overexpression of LIGHT in skin biopsies, especially in those with early disease, and higher LIGHT serum concentrations. The presence of digital ulcers (DUs) and creatine kinase elevation were independently associated with LIGHT serum concentration, which may therefore contribute to the vascular damage in SSc (23).

Among the cytokines, chemokines have been the subject of particular interest in SSc. Assuming that aberrant Toll-like receptor (TLR) activation is central in SSc pathogenesis and that type-I interferon (IFN-I) gene signature is associated with disease severity, an international multicentre study evaluated the actions of C-X-C motif ligand 4 (CXCL4), a proinflammatory chemokine already detected in SSc skin where it co-localises with plasmocytoid dendritic cells (pDCs). They found that CXCL4 forms liquid crystalline complexes with both self-DNA and microbial DNA, with inter-DNA spacings optimal for TLR9 amplification, thus enabling a strong activation of TLR9 in pDCs. CXCL4-DNA complexes are present *in vivo* and directly correlate with IFN-I levels in SSc blood (24).

IFN regulatory factor 7 (IRF7) has been identified as a fundamental regulator molecule for IFN-I. IRF7 expression is significantly upregulated and activated in the skin tissue of SSc patients compared with healthy controls. Additionally, IRF7 co-immunoprecipitated with Smad3, a key mediator of transforming growth factor (TGF)-β signalling, and may potentially increase the TGF-β mediated fibrosis (25).

As previously mentioned, pDCs play a central role in the pathogenesis of SSc. A large multicentre study conducted on 1193 SSc patients and over 1300 controls screened the expression of transcription factors known to intervene in the differentiation and regulation of pDCs. The authors found that runt-related transcription factor 3 (RUNX3) is significantly down-regulated in SSc pDCs compared with controls, and that RUNX3 protein levels are inversely correlated with skin involvement as measured by the modified Rodnan Skin Score (mRSS). Moreover, a significant reduction in the expression of RUNX3 in the skin and fibrotic lungs of SSc has been identified. This means that RUNX3 down-regulation also occurs in SSc affected tissues, suggesting its potential dysregulation in cells other than pDCs (26).

Others pathogenic factors
Adipokines may have a role in the pathogenesis of SSc. In particular SSc subjects presented significantly higher concentrations of resistin, fractalkine and endothelin-1 compared to controls,

with lower adiponectin levels. Moreover, fractalkine and galectin-3 were significantly higher in dcSSc compared to lcSSc, and both positively correlated with mRSS. These results reinforce the hypothesis that impaired levels of adipose tissue factors can influence endothelial dysfunction in SSc (27).

FcγRIIB is a receptor for the Fc fragment of IgG which is expressed on various cells including B lymphocytes. A Japanese work conducted on 76 SSc patients evaluated the expression levels of FcγRIIB on different B cell subsets and found a significant increase in naïve (IgD⁺CD27⁻) and double negative memory (IgD⁻CD27⁻) B cells in comparison with controls. Increased FcγRIIB expression on double negative memory B cells are associated with disease activity, presence of ILD, reduced lung function and heart involvement. The authors demonstrated that in patients who underwent intravenous cyclophosphamide pulse therapy for ILD, there was a significant decrease in FcγRIIB expression on all three subsets of memory B cells. Finally, FcγRIIB could serve as an activity biomarker for ILD (28).

Another mechanism potentially involved in the pathogenesis of SSc is efferocytosis, namely the clearance of apoptotic cells by phagocytic cells. SSc macrophages demonstrated a significant decreased efferocytosis capacity in comparison with healthy donors. Moreover, a down-regulation of Integrin β5 on SSc macrophages was found, an engulfing receptor whose suppression in the macrophages of healthy donors leads to an impairment of efferocytosis. Therefore, Integrin β5 down-expression could directly participate in the reduction of efferocytosis capacity observed in SSc (29).

Others pathogenic factors that may be involved in the pathogenesis of SSc included the alteration of angiotensin I / angiotensin II / angiotensin-(1-7) axis (30), tryptophan and its metabolite kynurenine (31) and trappin-2 (32).

Finally, environmental factors may be associated with SSc. Different Herpesviridae family viruses were associated with a higher prevalence of the disease (33), and in particular human herpes virus 6 (HHV-6a) in skin biopsies has been associated with disease severity and an increased pro-fibrotic action in endothelial cells (34). The immunodominant peptides of SSc autoantibodies were discovered to be homologues to viral protein sequences from the Mimiviridae and Phycodnaviridae families which therefore may represent an environmental trigger for the disease. Moreover, higher levels of aluminium, cadmium, mercury and lead were identified in the blood and urine of SSc patients compared to controls, which may represent risk factors for SSc (35).

Take home messages
- The disease bears its pathogenesis on a complex interplay between vascular, immune system and ECM alterations that ultimately lead to tissue fibrosis.
- A role for MCH genes (DRB1 and DPB1) has been confirmed in predisposing to SSc.
- Non-HLA genes have been also implicated in SSc pathogenesis (especially genes involved in vascular endothelial growth under hypoxia, autophagy and NK regulation).
- A possible link between the disease and cancer has been explained through a downregulation of LncRNA, involved either in regulating genes engaged in tumour proliferation, or in tissue fibrosis and vascular alteration.
- A number of cytokines and chemokines have been linked to SSc and different disease expressions (up-regulation of IL18, IL 17, IL 6, CX CL4, down-regulation of RNX3).
- Finally, it has been confirmed that environmental factors, such as viruses (HHV6) and heavy metals contribute to the onset of the disease.

Clinical manifestations and organ involvement
The heterogeneity of SSc has long been discussed. Some limitations have been raised about the common sub-classification based on cutaneous subsets. There are clues suggesting that cutaneous subsets may indeed not capture the complete heterogeneity of the disease.

An unbiased clustering analysis has been performed using 6,927 patients and 24 clinical and serological data from the EUSTAR registry. The first analyses provided a delineation of 2 clusters showing moderate stability. In an exploratory attempt, 6 homogeneous groups that differed with regard to their clinical features, autoantibody profile, and mortality were identified. Some groups resembled usual dcSSc or lcSSc prototypes, but others exhibited unique features, such as a majority of lcSSc patients with a high rate of visceral damage and antitopoisomerase antibodies. This opens the door to revising sub-classification and improve patient stratification (36).

SSc internal organ involvement may be present from the early and asymptomatic phase of the disease, dramatically determining the prognosis. For this reason, many studies analysed possible markers of disease progression. Recently Becker *et al.* identified age, active digital ulcer (DU), lung fibrosis, muscle weakness and elevated C-reactive protein (CRP) level as predictors of severe disease worsening (defined as organ failure within a period of 12±3 months) in dcSSc patients. The factors identified in this study could be used to select patients at risk of progressive organ involvement for clinical trials (37). Another study recently supported the use of mRSS as an end point in clinical trials suggesting fibrosis short-term progression (defined as an increase in mRSS >5 and ≥25% within 1 year) associated with long-term decline in lung function and worse survival with an increase of all-cause mortality in dcSSc (38). Therefore, organ involvement represents a challenge for the clinician and prompt detection and treatment of this complication is mandatory (39). In the last decades, the survival of SSc was improved and causes of death related to SSc-internal organ involvement have drastically changed. The frequency of deaths due to scleroderma renal crisis (SRC) has significantly decreased since treatment for this has become possible (40) and lung involvement (both ILD and pulmonary hypertension (PH)) represents the leading causes of morbidity and mortality in SSc.

*Cardiopulmonary involvement
– Interstitial lung involvement and new
patterns of interstitial lung disease*

Pulmonary involvement in SSc most frequently presents as ILD with mainly a non-specific interstitial pneumonia (NSIP) or less commonly usual interstitial pneumonia pattern (UIP) on high-resolution CT (HRCT) chest scans. SSc-ILD places a large burden on the healthcare system: ILD severity and the presence of coexistent pulmonary arterial hypertension (PAH) are confirmed to be the main determinants of overall healthcare costs above the median for an SSc-ILD cohort (41). Chest HRTC still remains the gold standard for the identification of ILD. However, in the last few years lung ultrasound (LUS) has been investigated for the study of lung involvement from the early phases of the disease and in the follow-up; B-Lines have been proposed as the sonographic hallmark of connective tissue disease-associated ILD (42). Reyes-Long *et al*. recently performed LUS in 68 SSc patients without respiratory involvement showing a positive correlation between the findings of HRCT and LUS with a high sensitivity and specificity (91.2% and 88.6%, respectively). The prevalence of ILD was 41.2% and the mRSS was associated with LUS and HRCT findings (43). In addition to the early identification of lung involvement, the possibility to characterise lung lesions assessed by CT represents another challenge for the clinician to distinguish fibrotic and probably irreversible alterations from inflammatory ones. In this context, a possible role of 18F-FDG-PET/CT scan has recently been proposed. In this study the authors reported that morphologically 'positive' GGO segments presented a clear 18F-FDG uptake, suggesting the existence of an increased metabolic activity of GGO, potentially due to inflammation (44). A large, nationwide, population-based SSc study confirmed that the presence of ILD at baseline affects outcome in SSc, suggesting that all SSc patients should undergo screening for ILD (pulmonary function tests (PFTs) and HRTC) in order to diagnose ILD early. In this study, 50% of patients with SSc had ILD on HRCT

and 46% displayed ILD progression defined as pulmonary function decline. Mortality correlated with the extent of lung fibrosis and was inversely related to baseline Forced Vital Capacity (FVC)% (45). Interestingly, a recent study enrolling 8013 lcSSc and 4786 dcSSc patients, recommended systematic screening and follow-up for lung involvement both in lcSSc and in dcSSc. This suggests that lcSSc-ILD may be progressive as in dcSSc subset and supports the inclusion of lcSSc patients in SSc-ILD trials as they may benefit from anti-ILD drugs (46).

A new pattern of ILD has recently been described in 11 patients with SSc. This pattern is pleuroparenchymal fibroelastosis, defined as fibrotic thickening of the visceral pleura and subadjacent parenchymal areas of the upper lobes. This pattern seems to be rare but characterised by negative prognosis (47) and, for this reason, patients with this pattern require a close, multidisciplinary follow-up. Another distinct pulmonary manifestation in SSc is the combined pulmonary fibrosis and emphysema (CPFE) syndrome, associated with higher morbidity and mortality. Last year, two large multicentre studies on CPFE syndrome were performed. Ariani *et al*. confirmed that CPFE may increase the mortality risk in SSc together with a highly impaired lung function in 470 patients compared with SSc-ILD and other-SSc (48). Another study reported that CPFE-SSc patients more frequently developed precapillary PH, experienced more frequent unscheduled hospitalisations, and had a decreased survival rate compared to ILD-SSc controls (49). The detection of these particular pulmonary features (PPFE and CPFE) can be useful in order to select SSc patients with a more severe lung involvement, particularly when associated with a progressive course. In addition to interstitial changes, small airway dysfunction may be a feature of SSc-related lung involvement and recently small airways dysfunction has been demonstrated in 21% of 94 enrolled SSc patients, revealing a prevalence almost 5-fold higher than in controls (93 healthy subjects enrolled in the study). Bonifazi *et al*. proposed

using impulse oscillometry combined with HRCT to detect the dysfunctions of the small airways, which is not evaluable by PFTs. Approximately one-third of SSc patients (mainly lcSSc) presented with at least one feature suggestive of small airway involvement. In addition, suggestive radiological features were detected in 25% of SSc patients and mostly occurred in the absence of underlying ILD, suggesting that peripheral airways might be an early target of the SSc lung disease rather than a consequence of parenchymal architectural distortion (50). In this context, interest has increased also in the use of the nitrogen single-breath washout test for early diagnosis of small airway involvement and for the assessment of ventilation distribution heterogeneity in SSc-ILD. Andrade *et al*. recently showed heterogeneity in ventilation distribution in a group of SSc-ILD patients with limited pulmonary parenchymal involvement and without PH, suggesting that this heterogeneity is a factor that contributes to a shorter distance walked during the six-minute walking test (6MWT) (51). The presence of ILD or of initial fibrotic change may compromise gas exchange, however, SSc patients without detectable fibrosis may already present an alteration in gas transfer. Zhai *et al*. reported that impaired gas exchange is associated with alterations in pulmonary vascular morphology. Chest CT scans of 77 SSc patients without detectable pulmonary fibrosis were analysed and identified two parameters: relative contribution of small vessels compared with large vessels and vessel tree capacity. Both parameters significantly correlated with gas transfer. Moreover, systolic pulmonary artery pressure (sPAP), vessel tree capacity and forced expiratory volume in first second (FEV1%) were significant independent predictors of diffusing capacity for carbon monoxide (DLCOc%) predicted (52). Moreover, lung diffusing capacity for nitric oxide (DLNO) has been recently proposed in clinical use as it seems to be more sensitive in the detection of alveolar membrane diffusive conductance (DMCO) decrease than DLCO. A recent study on SSc pa-

tients, showed that DLNO and DLCO were significantly correlated with CT measurements of ILD but only DLNO was consistently reduced in all subjects with fibrosis extent ≥5%. However, DMCO and pulmonary capillary blood volume (VC) partitioning do not seem to be useful to establish whether different results of DLNO and DLCO are primarily due to vascular or ILD in individual subjects (53).

– *Pulmonary hypertension and*
  pulmonary arterial hypertension
As mentioned, PH and PAH together with ILD are the leading causes of mortality in SSc. In a cohort of 93 patients with SSc-associated ILD, 31.2% had RHC-proven coexisting PH, which often occurs early after SSc diagnosis. These patients often presented a diffuse subtype and had features of WHO Group III PH due to their ILD, which may warrant the use of both immunosuppressive therapies and PAH-specific therapies with a good survival rate (54). Noviani *et al*. recently reported that patients with ILD-PH had the highest risk of death, followed by PAH and ILD, but after adjustment for confounders, only PAH was an independent risk factor of mortality in SSc, but not ILD-PH or ILD (55).
Last year a descriptive study of PH-related data from the multicentre RESCLE registry was carried out. Estimated systolic pulmonary artery pressure (esPAP) was elevated (≥35 mmHg) in 43.3% of patients and this group was mostly dcSSc. RHC was performed in 114 patients with an esPAP ≥35 mmHg and PH was confirmed in 79 patients (a borderline mPAP was discovered in 9 subjects). Among these patients, 35 presented a precapillary PH, 12 a postcapillary PH and in 32 the PCWSP value was not available. However, also 9/20 patients with an esPAP <35 mmHg presented PH at the RHC (1 precapillary, 4 postcapillary and in 4 patients the PCWP value was not available). Regarding clinical and laboratory features, the group with elevated esPAP presented a greater prevalence of anti-topoisomerase-1 antibodies compared to anticentromere antibodies and a higher rate of SRC was observed (56).

Early intervention and detection of PH associated with SSc may improve its prognosis. For this reason, Ninagawa *et al*. recently proposed an algorithm to predict mean pulmonary arterial pressure (mPAP)>20 mmHg using non-invasive examinations in SSc patients by modifying the DETECT algorithm, with good sensitivity (87.5%) and specificity (92%). They reported that the elevation of FVC/ DLCO in pre- and early stages of SSc-PAH, the weighting of FVC/DLCO and the right axis deviation may improve its predictability (57). In the last year, the first prospective study to assess and compare right ventricular output reserve and pulmonary arterial compliance (PAC; ratio of stroke volume to pulse pressure) in SSc patients with mildly elevated mean PAP, with normal mean PAP, and with manifest PH was performed. The authors reported that impaired 6-MWT distance and exercise capacity in SSc patients with mildly elevated mean PAP (and normal right ventricular function at rest) might be caused by reduced PAC and reduced right ventricular output reserve (reduced right ventricular output during exercise). These findings suggest that the screening of SSc patients by RHC at rest and during exercise may lead to an identification of early pulmonary vascular disease (58). Left ventricular (LV) peak global longitudinal strain (GLS) is decreased in SSc but it is not known whether low GLS is due to SSc or PAH. Lindholm *et al*. reported that lower GLS in SSc patients is mainly determined by increased pulmonary pressure and not by SSc *per se*. Moreover, low LV and right ventricular free wall GLS on cardiac MRI are indicative of increased mPAP and pulmonary vascular resistance (PVR), which propose non-invasive methods to select patients eligible for right heart catheterisation (59).

– *Heart involvement*
Early detection and treatment of heart involvement in SSc remains a challenge for the clinician, partly due to the wide heterogeneity of cardiac manifestations.
Heart failure with preserved ejection fraction (HfpEF) is common in SSc

and is associated with a worse prognosis. Analysing 72 patients Porpáczy *et al*. showed that left atrial stiffness has the highest diagnostic performance in predicting NT-pro-BNP I increase (>220 pg/ml), with a specificity of 89% and sensitivity of 42% (60). Interestingly, a recent study evaluated 95 SSc patients by echocardiography including multilayer speckle-tracking, and tonometry-based pulse wave analysis of the peripheral arteries in order to verify if peripheral vasculopathy influences the possible early compromise of LV. The study reported that the impairment of right ventricle (RV) and LV was independently associated with specific SSc characteristics, namely the more severe diffuse subtype and disease duration, respectively. The mechanics of RV early impairment in SSc progressed independently of the concomitant LV impairment, which, in turn, may be influenced by peripheral microvascular abnormalities in the absence of macrovascular damage (61). In a prospective study of 277 unselected SSc patients, Tennøe *et al*. described a higher prevalence of LV, RV and biventricular systolic dysfunction in SSc than expected. The study found that LV systolic function remained stable across the observation period, whereas RV systolic function deteriorated during the disease course and predicted mortality (62).
It is still debated whether SSc is specifically associated with an increased prevalence/incidence of coronary artery disease. Recently, epicardial adipose tissue (EAT) thickness was proposed to be a candidate for atherosclerotic risk assessment in these patients. EAT thickness was significantly greater in patients with SSc compared to healthy controls and correlated positively with age, erythrocyte sedimentation rate (ESR), CRP, insulin, haemoglobin A1c and total and LDL-cholesterol (assessed by Spearman's rank correlation coefficient) (63). A nationwide retrospective cohort study suggested that patients with SSc had more established cardiovascular risk factors and an increased relative risk of developing cardiovascular diseases (such as myocardial infarction, peripheral vascular disease, aortic and mitral

regurgitation) at the time of diagnosis and during follow-up (64).

In the last few years there has been increasing interest in cardiac MRI as a technique to diagnose heart oedema and/or fibrosis. In this context, a recent study confirmed the role of cardiac MRI in the evaluation of SSc patients detecting myocardial inflammation on cardiac MRI in 73%. An increased risk of myocardial inflammation was associated with young age and high mRSS at onset. Neither the SSc subset, internal organ involvement, inflammatory markers, nor cardiac and muscle enzymes were associated with myocardial inflammation in SSc (65). The identification of cardiac oedema and fibrosis might be of crucial importance in the management of patients. In fact, as indicated by a recent study, myocardial fibrosis seems to represent a predictor of cardiovascular outcomes in SSc. The authors showed an association between CRP and mortality, and also that myocardial fibrosis in middle LV segments and older age were predictors of heart failure after a follow-up of 43 months (multivariate analysis). Interestingly, the data from this study suggested the importance of higher maximum mRSS as it seemed to be associated to coronary artery disease, however, only three patients developed this complication during the follow-up. Therefore, further studies will be necessary to better understand the association of mRSS and heart disease (66). Recent efforts have been made in order to identify serological markers for the early detection of cardiac involvement and recently high-sensitive cardiac troponin T (hs-cTnT) and NT-proBNP levels have been proposed as biomarkers for heart involvement and mortality in SSc. In the study, patients positive for both markers presented a lower left-ventricular ejection fraction (LVEF) and a higher rate of right bundle branch block (RBBB) on ECG (67). Autonomic dysfunction was identified as an early marker of SSc progression and could precede cardiac fibrosis occurrence, thus helping to identify subclinical cardiac involvement. Sixty-nine SSc patients have recently been studied, the outcome of

which revealed an impaired cardiac autonomic modulation compared to healthy controls. SSc patients showed a reduced vagal and increased sympathetic modulation at rest and a blunted autonomic response to orthostatism compared to healthy subjects. Autonomic impairment was mostly detectable in the advanced and fibrotic subset of SSc and it is not an early maker of dysfunction in this population (68). Another important chapter of cardiac involvement concerns rhythm changes. An Iranian study reported that BBBs and the fragmented QRS complex were more prevalent in SSc patients (27% and 37%, respectively), without any association with the involvement of the other organs (69).

All together these recent data confirm the main role of cardiopulmonary involvement in determining the prognosis of SSc patients. A recent study suggested a more severe cardiopulmonary manifestation in SSc men than in women, with men in particular presenting a higher incidence rate of RV dysfunction and ILD compared to women, even in the early phase of the disease (70). Hsu *et al*. tried to identify predictors of mortality and cardiopulmonary hospitalisations in patients at risk for PH through the PHAROS registry. Male sex, low % DLCO, exercise oxygen desaturation, anaemia, abnormal dyspnea scores and baseline pericardial effusion were strongly associated with higher mortality. Risks for cardiopulmonary hospitalisation were associated with increased dyspnoea and pericardial effusions, although PH patients with DLCO <50% had the highest risk of cardiopulmonary hospitalisations (71).

Renal involvement
Many efforts have been made during this last year in the evaluation of kidney involvement in SSc. A retrospective study analysed the demographic, clinical and laboratory data of SSc patients who developed SRC after the disease diagnosis compared to control subjects (SSc without SRC events). The results of this study did not show a significant difference in the proportion of black race in SSc with SRC compared to controls, and the two groups showed clini-

cal differences in the frequency of PH and cardiac involvement in SRC group. Patients who developed SRC presented a higher rate of anti-Ro and anti-RNA polymerase III antibodies and control subjects were characterised by anticentromere and antinuclear antibody positivity. The authors also indicated the importance of monitoring blood pressure, proteinuria and the estimated glomerular filtration rate in order to identify patients at risk for a future SRC, showing that the presence of three or more of the following laboratory alterations (proteinuria, chronic kidney disease, elevated erythrocyte sedimentation rate, thrombocytopenia, anaemia, anti-Ro and anti-RNA polymerase III antibodies) and clinical manifestations (hypertension) was associated to SRC development (sensitivity 77% and specificity 97%) (72). Kidney involvement may be subclinical or it may occur with several clinical manifestation ranging from mild proteinuria, reduction of estimated glomerular filtration rate and high renal resistive indices (RRI). The retrospective observational study by Bruni *et al* showed a positive correlation of RRI with age and sPAP, and a negative correlation with creatinine clearance and DLCO. In addition, the authors indicated the importance of creating age-SSc adjusted pathologic RRI cut-offs which were associated with diffuse skin fibrosis, history and/or presence of digital ulcers, sPAP, presence of lung involvement with a correlation both with ILD on chest HRCT and lower FVC and DLCO by univariate correlation. The data from this study suggested the importance of RRI in the evaluation of SSc patients from the early phases of the disease: it has been suggested that the RRI value could predict mortality, thus indicating an association between a higher baseline absolute RRI and death, cardiac and renal worsening (73). Gigante *et al*. recently subjected 92 SSc patients and 40 healthy subjects to renal ultrasound (US), evaluating renal morphological variables. A significant higher renal length, parenchymal thickness and renal sinus was reported in healthy controls compared to SSc subjects. The Doppler analysis revealed a significant

difference of RRI, which was higher in SSc patients, and the glomerular filtration rate was significant lower in SSc patients. This study confirms the possible presence of a subclinical renal involvement indicating renal and Doppler US as a fundamental screening examination to perform in SSc (74).

Gastrointestinal involvement
Gastrointestinal (GI) involvement is of paramount importance because it is a key contributor of impairment and disability leading to remarkable abnormal social functioning (75). Gastrointestinal symptoms, in particular reflux and diarrhoea, are significantly more common in SSc patients compared to controls, confirming the need for early management of SSc patients complaining of GI involvement (75).

The presence of gastroesophageal reflux disease (GERD) symptoms may also affect the quality of sleep and may be associated to an increase in fatigue with a deductible impact on quality life (76). Impaired quality of life due to GI symptoms may interfere in the social life of patients and in their relationships, with depression as a possible consequence, as remarked by the study of Türki *et al*. The data from this study indicated a certain correlation between malnutrition microstomia and bowel involvement and suggested a correlation between the risk of malnutrition, skin involvement, depressive symptoms and ILD (77). GI involvement may be present from the early phase of the disease and in asymptomatic patients who may present an abnormal oesophageal manometry (78). Manometry for the study of motor disfunctions and endoscopy to investigate possible tissue alterations often consequent to dysmotility are the main diagnostic tests used in SSc patients. In addition, the study of Fraticelli *et al*. studied 55 consecutive SSc patients by videofluorography (VFG) (79) confirming the role of this examination in the morphological and functional evaluation of the swallowing phases in SSc patients. Interestingly, all patients presented an alteration of at least one of the three phases of swallowing (oral, pharyngeal, oesophageal) revealed by VFG. The oral phase was

the less frequently affected, while the pharyngeal phase presented alterations in a higher proportion of subjects. Affection of the oesophageal phase was frequent in this population, in particular an abnormal motility of the upper oesophageal sphincter (UES) (12.7%) and lower oesophageal sphincter (LES) (76.4%), inadequate primary peristalsis (52.7%), abnormal secondary peristalsis (29.1%) and non-peristaltic contractions (40%) were detected. Interestingly, patients with lcSSc and dcSSc presented some significant differences in the oesophageal phase as an inadequate primary peristalsis, and a deficit of oesophageal clearance seemed to be more frequent in dcSSc. Conversely, hiatal hernia was significantly more frequent in lcSSc. Petcu *et al*. confirmed the importance of performing upper endoscopic examination in all SSc patients as endoscopic changes may be present also in a high percentage of asymptomatic patients. In this study, 79 patients with or without gastroesophageal symptoms underwent upper GI endoscopy. The authors showed a higher frequency of hiatal hernia in symptomatic patients and a similar frequency of the other endoscopic and histopathological findings (gastric polyps, oesophageal ulcers, HP positivity, endoscopic gastritis) among symptomatic and asymptomatic subjects. Barrett's oesophagus was confirmed by histological analysis in 5 patients (2 dcSSc and 3 lcSSc) and the presence of a watermelon stomach was revealed in 2 patients (80). Adarsh *et al*. confirmed the frequent detection of oesophagitis (19 patients/21, 83%) by oesophagogastroduodenoscopy (EGDS) in SSc patients. All enrolled patients also underwent manometry which revealed the known oesophageal alterations and, in addition, the authors performed duodenal biopsies in SSc patients, and a normal histology was observed in only one patient. The most common duodenal abnormalities included an excess of mononuclear inflammatory cells in lamina propria and a partial villous atrophy. This latter alteration was more frequent in patients with a hypotensive LES, suggesting that the histological abnormality is part of the disease rather than a separate en-

tity (81). Kuribayashi *et al*. evaluated oesophageal involvement in more than 100 SSc patients by EGDs and manometry. By multivariable analysis the authors showed a relationship between oesophageal motility alterations and skin involvement. In addition, previous studies suggested a correlation between ILD and abnormal oesophageal motility suggesting a possible double aetiology of ILD: both due to the disease activity itself and to gastroesophageal reflux events. In this study, the authors did not evaluate the number of gastroesophageal events, however they did not indicate any association between ILDs and oesophageal motility abnormalities or GERD (82).

Patient-reported outcomes
One of the main reasons for the low applicability of patient-reported outcomes (PROs) in real-life clinical practice outside RCTs is that collecting PROs is time-consuming and represents a significant burden for patients and health operators. A novel method to shorten PROs without losing its face, content and construct validity has recently been proposed (83). In a statistical 3-step method including Optimal Test Assembly (OTA), a Generalized Partial Credit Model (GPCM) is included in the full-length PRO. A shortened set of items with low convergence is extracted and subsequently, a series of decision rules is considered until the final set of reduced items is selected with optimal discrimination. This approach has been applied to the 13-item FACIT fatigue scale in a set of patients from the Canadian Scleroderma Research Group Registry (CSRGR), obtaining a 5-item shortened FACIT with high scores of correlation and optimal reliability as measured by Cronbach's alpha and Spearman's Rho, respectively. This technique can be applied to different other PROs and indeed it has so far been applied analogously to the Social Appearance Anxiety Scale in the SPIN cohort. This approach is likely to positively impact the patient's burden and possibly increase the quality of the data collected in daily clinical practice (84). The importance of obtaining PROs in the management of SSc has been ex-

plored in a large Australian cohort in 3 crucial clinical domains by analysing the relationship between patients' subjective perception of worsening of their Raynaud's phenomenon (RP), increasing skin tightness and increasing breathlessness in the last month with the presence of digital ulcers, mRSS and worsening lung and heart objective parameters (85). The patients were followed for a mean of 4 years and between each study visit the mean time span was around 1 year. In both the uni- and multivariate analysis, all PROs were significantly associated with their respective objective measures (all $p<0.01$) except for breathlessness and new onset LVEF <50%. In particular, for each clinical domain (vascular, skin, and cardiopulmonary) the respective PRO conferred a significantly higher OR for the development of the clinical complication: worsening RP was associated with DUs (OR 1.53; 95%CI:1.34–1.74, $p<0.01$), symptoms of worsening skin were associated with higher mRSS (OR 2.10; 95%CI:1.54–2.86, $p<0.01$) and breathlessness with deteriorating PFT (OR 2.12; 95%CI:1.70–2.65, $p<0.01$), new onset ILD (OR 1.91; 95%CI:1.40–2.61, $p<0.01$) and new-onset PAH (OR 5.08; 95%CI:3.59–7.19, $p<0.01$). These relationships were equally significant in the subset of patients with <2 years of follow-up, thus strengthening the generalisability of the results to different patient populations.

RP is a prototypical clinical domain in SSc and mainly relies on the patient's subjective experience; PROs are a fundamental tool to evaluate its activity and severity. Unfortunately, as we already discussed in last year's review (1), many psychological factors might influence the patient's perception of RP. A recent cross-sectional study on Anglo-Saxon patients from the USA and UK analysed the presence of different patterns of severity and their evolution in SSc in an attempt to categorise its impact in the cross-sectional and longitudinal analysis of RP (86). Four different patterns were identified (A, B, C, D) according to the growing difficulties of patients in distinguishing between attacks and normal phases

with the last pattern, pattern D, indicating those who present with cold and discoloured fingers all the time and no perception of a recurring attack. Pattern A was more often associated to the time of symptom onset in their life. Progressive disease tended indeed to identify with more severe patterns (C, D). The patterns well associated with physician and patient VAS scores for RP and Raynaud's Condition Scores (RCS) diary parameters. The longitudinal analysis showed stable patterns in around 40% of patients while another 40% described a worsening pattern. The evolution towards pattern D indicated the difficulty of a patient in distinguishing RP from background digital ischaemia. This last consideration is crucial for the future design of RP trials and the inclusion of patterns of patients who might fail to detect an effective intervention if only evaluated with PROs such as the RCS or the SHAQ RP VAS (86).

The vascular domain of SSc PRO has been extended in 2020 with the introduction of hand disability in systemic sclerosis digital ulcers (HDISS-DU), a novel instrument adapted from the Cochin Hand Function Scale (CHFS) following FDA guidance to develop a PRO questionnaire (87). The authors have obtained a specific instrument to evaluate the impact of DUs with a PRO. Questions include domains from daily activities in private and work life and ask the patient to rate their difficulty in performing them, ranging from *no difficulties at all* to *impossible*. The final score is the mean of the responses and correlates with other PROs of workability. The authors also identify the minimally significant threshold of change, represented by 0.25–0.5 in improvement, 0.19 in worsening conditions. This offers a new contribution to the evaluation of the impact on hand function of DU in SSc with the addition of the substantial contribution from direct patients' experience, which had been lacking up to now in this specific domain of SSc. To a similar end, Hughes *et al*. have evaluated the patient experience of SSc-DU by a multicentre qualitative research study (88). The method used applied the focus group (FG) methods with qualitative analysis

in 3 different centres across the UK. A broad population of SSc-DU patients was used and after 4 FGs thematic saturation was reached for the themes that had emerged. Five themes were identified: disabling pain, emotional impact, physical and social impairment, aggravating factors and adapting to ulcers. With regards to pain, interestingly the description of its location was very variable, on the fingertips, over the small joints, under the nails or on the side of fingers, and there was also a high variability in the description of severity. Patients described a constant fear of new DU development and this led to numerous negative feelings such as anxiety, uncertainty for the future and anger. Patients also stressed their difficulties in doing simple activities that most people take for granted such as putting their hands in their pockets or purse, difficulty driving, sleeping or even shopping. Work was also affected for some patients who had to change the type of work they previously did or their job completely. Memory of the physical presence of an ulcer lasted long in patients' minds as they were able to identify the exact location of past ulcer and even tell how the ulcer looked and/or felt. Patients also kept track of the effectiveness of treatments, time to heal or recurrence. They were able to detail all the practical measures used to reduce the burden of DU and the participation of their loved ones in adapting their private life with the complication. The study (89) had therefore the strength to identify multiple domains, also interrelated, that constituted the multifaceted experience of SSc-DU, which is a fundamental part of the clinical evolution of this complication despite the fact that it is often neglected in RCTs that explore therapeutic interventions for DUs. The richness and quality of the information obtained by FG should be integrated in the methods to obtain validated and useful PROs in this domain. We have already reported the application in SSc of the PROMIS29 in SSc from the NIH initiative to improve PROs reporting across different pathologies (2). A recent study by Fisher *et al*. (90) described the responsiveness to change of

the PROMIS-29 in a cohort of SSc patients with ILD. Unfortunately, while it well correlated with other PROs and notably with SF-36, Saint George Respiratory questionnaire (SGRQ) or Leicester Cough Questionnaire (LCQ), the PROMIS-29 did not show any correlation with the severity of the restrictive disease nor the change in static volumes (FVC) or DLCO in the examined cohort, attesting the difficulty of capturing a valid PRO in SSc-ILD with enough responsiveness to change and indirectly explaining why big RCTs in this complication need to focus on better measures to demonstrate a significant change in patients quality of life, which even more recent successful trials have not attained. Implementing general measures to create a network supporting SSc patients might improve and strengthen their management. A recent RCT has investigated the use of internet-based support to improve education and self-awareness in patients (91). Regardless of the method applied, the patient population in the study was globally enthusiastic about such an initiative that needs promotion and diffusion in the scleroderma community.

Take home messages
- The heterogeneity of SSc warrants growing efforts aimed at improving the current available classification system, taking into account not only pace and extension of skin involvement, but also clinical features and serological disease subsets.
- Early major organ involvement (particularly heart and lung) remains the cardinal poor outcome feature of the disease. Thus, scientific community is engaged in making urgent efforts to improve the detection, prognostic stratification and treatment of these complications.
- Feasible, cost effective and non-invasive techniques, such as LUS and multilayer speckle tracking echocardiogram, have gained growing attention in the evaluation of the disease.
- Composite measures to assess the risk of poor outcome of disease are refining the best approach for profiling the patient affected by SSc at each assessment.

- It is important not to neglect the evaluation of the GI, kidney and vascular system, since the severity of reflux may be correlated to the extent of lung fibrosis, and kidney RRI are an early surrogate marker of more severe and poor outcome disease.
- Last but not least, PROs are an essential part of the correct evaluation of SSc subjects and should became part of the standard of care.

Treatment
EULAR recommendations for SSc treatment were updated in 2017 (92), and a recent online survey (93) highlighted a high worldwide expert agreement on their contents, considering that physicians involved in this field come from heterogeneous settings and experiences. Great progress has been made in developing effective therapeutic options in the last few years. However, efforts are still needed to delineate standardised protocols and to acquire pharmacological and non-pharmacological strategies that can control the disease progression.

Immunosuppressive treatment
A descriptive, retrospective cohort claims analysis made in a healthcare insurance database found that 30.8% of 7812 patients received immunosuppressants (IMT) during the first year after SSc diagnosis. Of them, 43.8% received at least hydroxychloroquine and 21.1% methotrexate (94). Moreover, 46.5% of the total were treated with corticosteroids (CS). Despite their widespread use, there are no controlled clinical studies evaluating the efficacy of CS as a monotherapy in SSc, whereas reports are available about an improvement or stabilisation of lung function and skin involvement in combined therapy. Furthermore, the safety of CS is controversial, since they are sometimes associated with an increased mortality and morbidity risk due to their side effects (95). An ongoing double blind RCT is investigating the effect of high dosage of methylprednisolone in thirty patients with very early SSc. The hypothesis to verify is that CS have the power to efficiently stop inflammation and arrest disease progression (96). An experimental study

(97) on 21 SS patients evaluated *in vitro* effects of dexamethasone on cytokine production in peripheral blood mononuclear cells (PBMC). The authors documented a downregulation of several cytokines of patients as well as in PBMC from healthy volunteers, apart from IL-2, which did not change significantly. A previous study of the same group evidenced a reduced effect of methylprednisolone on cytokine expression in scleroderma patients compared to healthy donors, suggesting different mechanisms of the two CS molecules and the existence of a resistance pathway to methylprednisolone in scleroderma patients.

One of the most studied immunosuppressive agents is cyclophosphamide (CYC). Although some retrospective studies enhance CYC effectiveness in reduce skin thickening (99, 100), its main application remains in ILD treatment, for which it was the first line choice, according to the latest EULAR guidelines on progressive patients. Efforts are being made to find alternative drugs, since the available data show that the duration of its benefits after suspension (101) is short and it accounts for many and severe sides effects.

Rituximab (RTX), a monoclonal antibody targeting CD20, was compared to CYC in an open RCT evaluating both skin and lung outcomes (102). The study enrolled 60 patients with skin and lung involvement, randomly receiving monthly pulses of CYC 500 mg/m^2 or RTX 1000 mg at baseline and after 15 days. At 6 months, FVC in the RTX group significantly improved, while it declined in the CYC; moreover, mRSS improved significantly more in the RTX group. Also, the safety profile was in favour of RTX, with major adverse events observed only in patients receiving CYC. However, a longitudinal cohort by Elhai *et al*. (103) did not highlight significant improvements on lung fibrosis in patients treated with RTX.

As already known, mycophenolate mophetil (MMF) is being considered as an alternative to CYC. In the SLS II study, the two treatments produced similar improvements in FVC% predicted at 24 months, with better tolerability and safety given by MMF. The only sig-

nificant between-treatment differences were that the DLCO %-predicted and DL/VA %-predicted decreased less during treatment in the MMF arm than in the CYC arm. The authors hypothesised a benefit of MMF in moderating the destructive effects of SSc-ILD on gas transfer (104). Moreover, Volkmann *et al*. (105) dosed CCL-18 and KL-6 – two pneumoproteins considered as predictors of ILD progression – at baseline and after 24 months in the two SLS II arms and they found that their level in patients assigned to MMF experienced the greatest decline. This could be a consequence of adherence difference or it may be explained by different mechanisms of action in the two molecules. Finally, volumetric HRCT scans were performed at baseline and at the 2-year follow-up in the two groups and transitional radiographic changes in patterns of ILD have been analysed by Kim *et al*. (106). The authors calculated the differences in the probabilities of changes from one ILD pattern to another by using voxel-by-voxel transitional scores on paired HRCT scans – considering as patterns lung fibrosis, ground glass (GG), honeycombing (HC), and normal lung – and they observed changes in the extent of ILD patterns, indicating comparably significant net transitions from both fibrotic reticulation and GG opacity to a pattern of normal lung. They found no difference between the two treatment arms, thus indicating a comparable efficacy of CYC and MMF in improving radiological evident lung damage.

IL-6 promotes fibrosis, causing activation of the transcription factor STAT3, and stimulating the differentiation of naïve T lymphocytes to Th17 cells, which in turn secrete IL-17. This suggested the use of tocilizumab (TCZ), a monoclonal antibody targeting IL-6 receptor, in treating the disease. Results from a multicentric, double-blind, randomised, placebo-controlled study (the faSScinate study) involving TCZ evidenced a decrease in mRSS although significant between-group differences were not observed. A significant lesser reduction in FVC was also evident in the treated group at week 24 but it was not maintained at week 48. The results of a recently completed phase III trial of

TCZ (focuSSced trial) (107) in 212 SSc patients suggest that while TCZ therapy did induce a trend of efficacy similar to the one of the phase 2 trial, there is potential retardation of the progression of lung fibrosis in these patients. It must be pointed out that these patients were early active DcSSc at risk of ILD but selected for skin disease (some were free of ILD, while others had early ILD). The interpretation is that in these at-risk patients, tocilizumab offered some lung preservation. Finally, a randomised parallel group study was conducted comparing 6 patients maintained on conventional therapy with 7 patients who received an additional 8mg/kg/month infusion of TCZ. The observation lasted 6 months and it revealed a non-significant reduction of mRSS in the TCZ-receiving patients. Nevertheless, the authors were able to identify in patients with short disease duration, high CRP, low IL-13 and low CCL5, a possible SSc endotype responsive to TCZ therapy (108).

Intravenous immunoglobulins (IVIg) have immunomodulatory properties and their use is gaining attention in several autoimmune conditions as well as in many SSc manifestations (skin fibrosis, ILD, GI involvement). Although consistent clinical studies are still lacking and IVIg are not yet included in recommended treatments, the available data are promising, showing clinical benefits with few adverse events (109). A recent retrospective study on 52 patients with SSc-associated myopathy was conducted. Having a significantly higher maximal CS dose at baseline, IVIg-treated patients showed a greater decrease of CS at 3 months, and a lower CS dose at one year and at the end of follow-up so that, in presence of an acceptable tolerance profile, this study supports the use of IVIg as a CS-sparing agent (110).

Vasoactive treatment
Vascular alterations play a key role in SSc pathogenesis of PAH, RP, DUs and renal crisis. Vasoactive pharmacologic molecules targeting different pathways are available (111). Nevertheless, from the DeSScipher study (112) it emerged that 33.8% of patients with previous or current DU were treated with CCBs

alone. According to the PROSIT study (113), iloprost, a synthetic analogue of prostacyclin PGI2, is the first-line choice for the management of severe RP and DUs, when oral therapy fails. It represents an effective and quite well-tolerated option, as it also emerged from the treatment satisfaction questionnaire scores analysed in the study. Schioppo *et al*. (114) also assessed the patient's point of view through HRQoL by comparing two different infusion protocols with no evidence of differences. A standardised posology in terms of infusion velocity and frequency is still needed to uniform different centres' practice. An Expert Consensus based on a systematic literature review (115) suggests a 1–3-day monthly regimen for RP and DU healing, while 1 day monthly for DU prevention. Riociguat is an elective soluble guanylate cyclase stimulator, currently approved for treatment of PAH and PH due to chronic thromboembolism. A multicentre randomised, double-blind, placebo-controlled pilot study (116) evaluated the effect of riociguat on DU burden, but with no evidence of efficacy during the 16-week FU period. Nevertheless, during the open-label extension, the patients treated saw the complete healing of their DUs, suggesting that a longer duration of therapy is needed to obtain results.

An observational study (117) aimed to assess the role of bosentan in functional impairment, RP and DU-related symptoms, reported an improvement in HAQ-DI, VAS-R and VAS-DU scores in response to bosentan therapy over the 1-year follow-up period. However, 2 of the 41 patients had to stop treatment due to elevated liver enzymes, with rapid normalisation after suspension of the therapy. Baseline QoL scores were lower and they showed less improvement in patients with dyspnea, confirming that PAH-related symptoms have a high functional impact and are difficult to treat. EDITA, a randomised, controlled, double-blind, parallel group study, investigated the efficacy of early use of ambrisentan in patients with mildly elevated mPAP did not significantly differ in treated patients and the control group, but the authors found

significant improvements in the cardiac index and pulmonary vascular resistance (PVR) at rest and during exercise (118).

Antifibrotic treatment
Fibrosis represents the ultimate phase of the SSc pathologic pathway; pharmacological agents against fibrosis are poor in number and lack validated studies. Recently, nintedanib, a tyrosine kinase (TK) inhibitor approved for idiopathic lung fibrosis, is being investigated also in ILD related to scleroderma with favourable results, as the SENSCIS study (92) has shown. In particular, 576 patients with SSc-related ILD were 1:1 randomised to receive 150 mg bid nintedanib or placebo. In both groups, patients with diffuse and limited cutaneous SSc were equally represented, and about half of the entire population was taking MMF. The outcomes were evaluated after 52 weeks, evidencing a lower rate of decline in FVC in the nintedanib group (*p*=0.04). Differences between groups were fewer than expected also because FVC in the placebo groups showed a minor decrease with respect to the one observed in the placebo group of the study performed in IPF (132) The authors speculated that the presence of patients with limited cutaneous SSc, as well as the use of MMF, may constitute bias in SENSCIS. The study did not demonstrate any efficacy of this molecule in other scleroderma-related fibrosis such as skin.
Nintedanib interacts with the ATP-binding pocket of many TK receptors including PDGFR, fibroblast growth factor receptors (FGFR), and vascular endothelial growth factor (VEGFR) (119). An *in vitro* study (120) using this molecule on lung fibroblasts derived from scleroderma patients demonstrated the ability of nintedanib to reduce lung fibroblast proliferation and migration. Moreover, it can reduce extra-cellular matrix (ECM) molecule expression and the transition of LF to activated and contractile myofibroblasts which are correlated to the progression of the fibrotic process. This phenomenon has been previously observed in fibroblasts from patients with ILF but

at higher concentrations. In the present study the *in vitro* exposition amount of drug needed to reach the outcome is consistent with the *in vivo* therapeutic range of nintedanib, suggesting that this drug could have a stronger antifibrotic effect for scleroderma patients.

Cell transplantation
Autologous haematopoietic stem cell transplantation (auto-HSCT) is shown to be effective in severe and rapidly progressive form of the disease, regarding cutaneous and pulmonary involvement (121-123). A standard protocol in terms of induction phase, transplanted cell typology and successive immunosuppression is not still available. A *post-hoc* analysis (124) on a phase I/II clinical trial conducted on 19 patients with severe SSc was performed to evaluate whether the transplantation of CD34-selected cells (11 patients) instead of unmanipulated HSCs (8 patients) is more effective in improving disease activity and in maintaining the obtained results. The group treated with CD-34 selected cells experienced a higher benefit in mRSS and in FVC and its duration was longer (8 years *vs*. 3 years). Even if studies on the mechanisms by which HSCT halts disease progression are scarce, it is possible that CD-34 selected cells prevent the reinfusion of autoreactive lymphocytes that may be associated with SSc pathogenesis. Recently, Assassi *et al*. (125) published an analysis of the global molecular changes at the whole blood transcript and serum protein levels of 62 participants (27 HSCT and 35 CYC) of the SCOT study, as well as of 62 matched unaffected controls. The authors found that individuals with SSc, compared to controls, have a marked IFN, neutrophil, and inverse cytotoxic/NK cell transcript signatures which were corrected by HSCT but not by CYC. These changes correlated with improvement in the lung volumes and skin fibrosis. This gave a molecular basis on sustaining the immune system "resetting" power of the HSCT.
Autologous adipose stem cell (ADSC)-enriched lipotransfer is a surgical intervention proposed in the treatment of SSc-related oro-facial fibrosis and has recently been evaluated in a cohort of

62 SSc patients (126). The enrolled subjects achieved a significative improvement in all domains of mouth function assessed by the MHISS score. Also, aesthetical and psychological benefits were observed following the treatment. In 3 patients, an *in vitro* analysis of fibroblasts extracted and cultured with ADSC was also performed, resulting in a reduced expression of proinflammatory and profibrotic mediators.

Physiotherapic treatment
Physiotherapy, occupational therapy, local treatment and electromedical devices are gaining attention in the management of SSc, on top of pharmacological options. Self-administered stretching programmes have been created for both face and hands trying to help maintain function. Although some data regarding the efficacy of these interventions are available, the importance of patients' adherence is crucial as well as a careful training process (127), often requiring dedicated professional figures (128). Moreover, long-term maintenance of the results obtained is scarce, as it has been evaluated in a 9-year follow up study performed on a Japanese cohort, in which the improvement of ROM in the fingers was lost in 14% of the participants at the end of the follow-up (129). Another area of investigation is low-level light therapy (LLLT) (130), the interest of which comes from the treatment of refractory skin (diabetic, pressure, and venous) ulcers. Its action consists in increasing local perfusion, oxygenation, neoangiogenesis, as well as in an antimicrobic effect. A recent feasibility study was performed to assess the safety, tolerability and benefit in the management of DUs in SSc. At the end of the 46 applications, good tolerability was appreciated in the 8 enrolled patients, together with a reduction in pain and an improvement of the vascularisation measure by laser Doppler perfusion imaging.
A physical medicine regimen provides benefits also in the management of RP in SSc2. Carbon dioxide (CO_2) hand immersion has proven its efficacy in increasing distal digital blood flow in patients with peripheral arterial occlusive disease and it has also been considered

in primary and secondary Raynaud's syndrome. Lange *et al.* (131) evaluated the effect on acral perfusion of CO_2 enriched hand bath in 12 SSc patients and in 12 healthy volunteers; a control group of 12 patients instead received a hot water bath. Doppler ultrasound with measurements of the resistance index (RI) of digital arteries was performed with evidence of significant reduction of the RI in the CO_2-receiving patients but not in the patients treated with hot water or in the healthy controls.

Take home messages

- SSc treatment is still an open challenge since older therapies gave unsatisfactory results and no novel treatments completely fulfilled the expectations; furthermore, the number of well-conducted clinical trials is still too low.
- Several immunosuppressive drugs are available to treat the disease and its complications (mainly ILD), such as CYC, MMF, rituximab and tocilizumab.
- HSCT is a promising treatment for skin and lung involvement, however, there is still uncertainty regarding the best protocol and the subsequent maintenance treatment. Therefore, HSCT remains a treatment that should be managed only in centres of high expertise.
- Iloprost, bosentan and other vasoactive drugs remain the mainstay for the treatment of vascular involvement.
- Nintedanib, an anti-fibrotic drug, has recently been approved in Europe for the management of SSc-ILD and has proven to slow down the decline of forced vital capacity in treated patients as compared with placebo.
- An unmet need is the profiling of standardised multicentre protocols in order to define the best therapeutic regimen, targeted to the stage of the disease and the type of organ involvement. Furthermore, in the future it would be desirable to define the right timing for immunosuppressive and antifibrotic treatments – particularly for ILD –, finding the best combination and sequence of drugs aimed at maximising effectiveness and tolerability.

Conclusions

Knowledge in this appalling condition, SSC, is rapidly growing. Genetics and epigenetics are providing insights into potential targets for innovative therapies and precision medicine. The interplay between various players is starting to be better understood, helping to design future trials. The heterogeneity of the disease remains a challenge for research and management. Several attempts have been published this last year to try to improve patient stratification and risk prediction. The prognosis has been clarified and it is now clear that the heart and lungs are the leading causes of disease-associated deaths. In this field also, subsets are becoming better delineated and news tools available for stratification. One key question that remains is the balance between inflammation and fibrosis for heart and lung involvement, which needs to be carefully measured to guide the management. If major organ involvement is still a concern, for a large proportion of patients, quality of life impairment and disability are the primary consequences of the disease. The 2019 publications of oesophageal involvement must be highlighted because it is in this part of the disease that improvements are needed. Finally, with a better understanding of the pathogenesis and the availability of targeted therapies, it is hoped that the management will improve soon. The recent results have also allowed the labelling of a new drug in scleroderma for associated interstitial lung disease, which opens avenues for many patients and for the stimulating field of new therapeutic strategies with future upfront or sequential combinations of therapies which should enable a better fight against scleroderma.

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, BARSOTTI S, LEPRI G *et al.*: One year in review 2018: systemic sclerosis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 113): S3-23.
3. RAMOS PS: Epigenetics of scleroderma: Integrating genetic, ethnic, age, and environmental effects. *J Scleroderma Relat Disord* 2019; 4: 238-50.
4. ČOLIĆ J, MATUCCI CERINIC M, GUIDUCCI S, DAMJANOV N: Microparticles in systemic sclerosis, targets or tools to control fibrosis: This is the question! *J Scleroderma Relat Disord* 2020; 5: 6-20.
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. LÓPEZ-ISAC E, ACOSTA-HERRERA M, KERICK M *et al.*: GWAS for systemic sclerosis identifies multiple risk loci and highlights fibrotic and vasculopathy pathways. *Nat Commun* 2019; 10: 4955.
7. ACOSTA-HERRERA M, KERICK M, GONZÁLEZ-SERNA D *et al.*: Genome-wide meta-analysis reveals shared new loci in systemic seropositive rheumatic diseases. *Ann Rheum Dis* 2019; 78: 311-9.
8. LI J, CHEN S-Y, LIU H-H, YIN X-D *et al.*: Associations of vitamin D receptor single nucleotide polymorphisms with susceptibility to systemic sclerosis. *Arch Med Res* 2019; 50: 368-76.
9. BAÑOS-HERNÁNDEZ CJ, NAVARRO-ZARZA JE, BUCALA R *et al.*: Macrophage migration inhibitory factor polymorphisms are a potential susceptibility marker in systemic sclerosis from southern Mexican population: association with MIF mRNA expression and cytokine profile. *Clin Rheumatol* 2019; 38: 1643-54.
10. SKAUG B, KHANNA D, SWINDELL WR *et al.*: Global skin gene expression analysis of early diffuse cutaneous systemic sclerosis shows a prominent innate and adaptive inflammatory profile. *Ann Rheum Dis* 2020; 79: 379-86.
12. KARIMIZADEH E, SHARIFI-ZARCHI A, NIKAEIN H *et al.*: Analysis of gene expression profiles and protein-protein interaction networks in multiple tissues of systemic sclerosis. *BMC Med Genomics* 2019; 12: 199.
13. MAZZONE R, ZWERGEL C, ARTICO M *et al.*: The emerging role of epigenetics in human autoimmune disorders. *Clin Epigenetics* 2019; 11: 34.
14. VAN DER KROEF M, CASTELLUCCI M, MOKRY M *et al.*: Histone modifications underlie monocyte dysregulation in patients with systemic sclerosis, underlining the treatment potential of epigenetic targeting. *Ann Rheum Dis* 2019; 78: 529-38.
15. DOLCINO M, TINAZZI E, PUCCETTI A, LUNARDI C: In systemic sclerosis, a unique long non coding RNA regulates genes and pathways involved in the three main features of the disease (vasculopathy, fibrosis and autoimmunity) and in carcinogenesis. *J Clin Med* 2019; 8: 320.
16. MARIOTTI B, SERVAAS NH, ROSSATO M *et al.*: The long non-coding RNA NRIR Drives IFN-response in monocytes: implication for systemic sclerosis. *Front Immunol* 2019; 10: 100.
17. HE Y, LIU H, WANG S, CHEN Y: In silico detection and characterization of microRNAs and their target genes in microrna microarray datasets from patients with system-

ic sclerosis-interstitial lung disease. *DNA Cell Biol* 2019; 38: 933-44.

18. LIAKOULI V, CIPRIANI P, DI BENEDETTO P *et al.*: Epidermal Growth Factor Like-domain 7 and miR-126 are abnormally expressed in diffuse systemic sclerosis fibroblasts. *Sci Rep* 2019; 9: 4589.

19. RUSEK M, MICHALSKA-JAKUBUS M, KOWAL M, BEŁTOWSKI J, KRASOWSKA D: A novel miRNA-4484 is up-regulated on microarray and associated with increased MMP-21 expression in serum of systemic sclerosis patients. *Sci Rep* 2019; 9: 14264.

20. VAHIDI MANESH P, FARAZMAND A, GHA-RIBDOOST F *et al.*: Downregulation of miR-542-3p contributes to apoptosis resistance in dermal fibroblasts from systemic sclerosis patients via survivin overexpression. *Iran J Allergy Asthma Immunol* 2019; 18: 173-81.

21. LIN E, VINCENT FB, SAHHAR J *et al.*: Analysis of serum interleukin (IL)-1alpha, IL-1beta and IL-18 in patients with systemic sclerosis. *Clin Transl Immunol* 2019; 8: e1045.

22. ROBAK E, GERLICZ-KOWALCZUK Z, DZIANKOWSKA-BARTKOWIAK B, WO-ZNIACKA A, BOGACZEWICZ: Serum concentrations of IL-17A, IL-17B, IL-17E and IL-17F in patients with systemic sclerosis. *Arch Med Sci* 2019; 15: 706-12.

23. ROJAS M, RODRIGUEZ Y, MONSALVE DM *et al.*: Cytokine imbalance in patients with systemic sclerosis and resilience: the key role of interleukin-6. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S15-22.

24. GINDZIENSKA-SIESKIEWICZ E, DISTLER O, RESZEC J *et al.*: Increased expression of the TNF superfamily member LIGHT/TNFSF14 and its receptors (HVEM and LTssR) in patients with systemic sclerosis. *Rheumatology* (Oxford) 2019; 58: 502-10.

25. LANDE R, LEE EY, PALAZZO R *et al.*: CXCL4 assembles DNA into liquid crystalline complexes to amplify TLR9-mediated interferon-alpha production in systemic sclerosis. *Nat Commun* 2019; 10: 1731.

26. WU M, SKAUG B, BI X *et al.*: Interferon regulatory factor 7 (IRF7) represents a link between inflammation and fibrosis in the pathogenesis of systemic sclerosis. *Ann Rheum Dis* 2019; 78: 1583-91.

27. AFFANDI AJ, CARVALHEIRO T, OTTRIA A *et al.*: Low RUNX3 expression alters dendritic cell function in patients with systemic sclerosis and contributes to enhanced fibrosis. *Ann Rheum Dis* 2019; 78: 1249-59.

28. STOCHMAL A, CZUWARA J, ZAREMBA M, RUDNICKA L: Altered serum level of metabolic and endothelial factors in patients with systemic sclerosis. *Arch Dermatol Res* 2019 Oct 30.

29. YAGI-NUMATA N, MATSUSHITA T, TAKE-HARA K, HAMAGUCHI Y: Increased expression levels of FcgammaRIIB on naive and double-negative memory B cells in patients with systemic sclerosis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S23-31.

30. BALLERIE A, LESCOAT A, AUGAGNEUR Y *et al.*: Efferocytosis capacities of blood monocyte-derived macrophages in systemic sclerosis. *Immunol Cell Biol* 2019; 97: 340-7.

31. MIZIOŁEK B, BERGLER-CZOP B, KUCHARZ E *et al.*: Significance of the angiotensin I/angiotensin II/angiotensin-(1-7) axis in the pathogenesis of systemic sclerosis. *J Eur Acad Dermatology Venereol* 2020; 34: 558-64.

32. CAMPOCHIARO C, LYTTON S, NIHTY-ANOVA S, FUCHS D, ONG VH, DENTON CP: Elevated kynurenine levels in diffuse cutaneous and anti-RNA polymerase III positive systemic sclerosis. *Clin Immunol* 2019; 199: 18-24.

33. MIYAGAWA T, ASANO Y, SAIGUSA R *et al.*: A potential contribution of trappin-2 to the development of vasculopathy in systemic sclerosis. *J Eur Acad Dermatol Venereol* 2019; 33: 753-60.

34. STERNBAEK L, DRABORG AH, OSTER-LUND MT *et al.*: Increased antibody levels to stage-specific Epstein-Barr virus antigens in systemic autoimmune diseases reveal a common pathology. *Scand J Clin Lab Invest* 2019; 79: 7-16.

35. CASELLI E, SOFFRITTI I, D'ACCOLTI M *et al.*: HHV-6A infection and systemic sclerosis: clues of a possible association. *Microorganisms* 2019; 8: 39.

36. FORTE G, FADDA C, BOCCA B, ERRE GL, PASSIU G, MADEDDU R: Association between exposure to heavy metals and systemic sclerosis: the levels of Al, Cd, Hg, and Pb in blood and urine of patients. *Biol Trace Elem Res* 2019; 190: 1-10.

37. SOBANSKI V, GIOVANNELLI J, ALLANORE Y *et al.*: Phenotypes determined by cluster analysis and their survival in the prospective European scleroderma trials and research cohort of patients with systemic sclerosis. *Arthritis Rheumatol* 2019; 71: 1553-70.

38. BECKER M, GRAF N, SAUTER R *et al.*: Predictors of disease worsening defined by progression of organ damage in diffuse systemic sclerosis: a European Scleroderma Trials and Research (EUSTAR) analysis. *Ann Rheum Dis* 2019; 78: 1242-8.

39. WU W, JORDAN S, GRAF N *et al.*: Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort. *Ann Rheum Dis* 2019; 78: 648-56.

40. BELLANDO-RANDONE S, MATUCCI-CERIN-IC M: Very early systemic sclerosis. *Best Pract Res Clin Rheumatol* 2019; 33: 101428.

41. STEEN VD, MEDSGER TA: Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; 66: 940-4.

42. MORRISROE K, STEVENS W, SAHHAR J *et al.*: The clinical and economic burden of systemic sclerosis related interstitial lung disease. *Rheumatology* (Oxford) 2020; 59: 1878-88 .

43. WANG Y, CHEN S, LIN Z *et al.*: Imaging and serum biomarkers in connective tissue disease-associated interstitial lung diseases: correlation between lung ultrasound B-lines and KL-6 levels. *Ann Rheum Dis* 2019; 78: 573-5.

44. REYES-LONG S, GUTIERREZ M, CLAVIJO-CORNEJO D *et al.*: Subclinical interstitial lung disease in patients with systemic sclerosis. a pilot study on the role of ultrasound.

Rheumatol Clin 2019 Aug 7 [Online ahead of print].

45. BELLANDO-RANDONE S, TARTARELLI L, CAVIGLI E *et al.*: ¹⁸F- fluorodeoxyglucose positron-emission tomography/CT and lung involvement in systemic sclerosis. *Ann Rheum Dis* 2019; 78: 577-8.

46. HOFFMANN-VOLD AM, FRETHEIM H, HALSE AK *et al.*: Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med* 2019; 200: 1258-66.

47. 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.

48. BARGAGLI E, MAZZEI MA, ORLANDI M *et al.*: Pleuroparenchymal fibroelastosis in patients affected by systemic sclerosis: What should the rheumatologist do? *Medicine* (Baltimore) 2019; 98: e16086.

49. ARIANI A, SILVA M, BRAVI E *et al.*: Overall mortality in combined pulmonary fibrosis and emphysema related to systemic sclerosis. *RMD Open* 2019; 5: e000820.

50. CHAMPTIAUX N, COTTIN V, CHASSAGNON G *et al.*: Combined pulmonary fibrosis and emphysema in systemic sclerosis: A syndrome associated with heavy morbidity and mortality. *Semin Arthritis Rheum* 2019; 49: 98-104.

51. BONIFAZI M, SVERZELLATI N, NEGRI E *et al.*: Increased prevalence of small airways dysfunction in patients with systemic sclerosis as determined by impulse oscillometry. *Rheumatology* (Oxford) 2020; 59: 641-9.

52. ANDRADE FM, OLIVEIRA AD, LOPES AJ: Ventilation distribution as a contributor to the functional exercise capacity in patients with systemic sclerosis-associated interstitial lung disease without pulmonary hypertension. *Braz J Med Biol Res* 2019; 52: e8513.

53. ZHAI Z, STARING M, NINABER MK *et al.*: Pulmonary vascular morphology associated with gas exchange in systemic sclerosis without lung fibrosis. *J Thorac Imaging* 2019; 34: 373-9.

54. BARISIONE G, GARLASCHI A, OCCHIPINTI M, BAROFFIO M, PISTOLESI M, BRUSAS-CO V: Value of lung diffusing capacity for nitric oxide in systemic sclerosis. *Physiol Rep* 2019; 7: e14149.

55. YOUNG A, VUMMIDI D, VISOVATTI S *et al.*: Prevalence, treatment, and outcomes of coexistent pulmonary hypertension and interstitial lung disease in systemic sclerosis. *Arthritis Rheumatol* 2019; 71: 1339-49.

56. NOVIANI M, SAFFARI SE, TAN JL *et al.*: Mortality and hospitalization outcomes of interstitial lung disease and pulmonary hypertension in the Singapore systemic sclerosis cohort. *Semin Arthritis Rheum* 2020; 50: 473-9.

57. GARCÍA-HERNÁNDEZ FJ, CASTILLO-PALMA MJ, TOLOSA-VILELLA C *et al.*: Pulmonary hypertension in Spanish patients with systemic sclerosis. Data from the RES-CLE registry. *Clin Rheumatol* 2019; 38: 1117-24.

58. NINAGAWA K, KATO M, NAKAMURA H *et*

al.: Reduced diffusing capacity for carbon monoxide predicts borderline pulmonary arterial pressure in patients with systemic sclerosis. *Rheumatol Int* 2019; 39: 1883-7.

59. NAGEL C, MARRA AM, BENJAMIN N *et al.*: Reduced right ventricular output reserve in patients with systemic sclerosis and mildly elevated pulmonary artery pressure. *Arthritis Rheumatol* 2019; 71:805-16.

60. LINDHOLM A, HESSELSTRAND R, RÅDEGRAN G, ARHEDEN H, OSTENFELD E: Decreased biventricular longitudinal strain in patients with systemic sclerosis is mainly caused by pulmonary hypertension and not by systemic sclerosis per se. *Clin Physiol Funct Imaging* 2019; 39: 215-25.

61. PORPÁCZY A, NÓGRÁDI Á, VÉRTES V *et al.*: Left atrial stiffness is superior to volume and strain parameters in predicting elevated NT-proBNP levels in systemic sclerosis patients. *Int J Cardiovasc Imaging* 2019; 35: 1795-802.

62. TOUNTAS C, PROTOGEROU AD, BOURNIA VK *et al.*: Mechanics of early ventricular impairment in systemic sclerosis and the effects of peripheral arterial haemodynamics. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S57-62.

63. TENNØE AH, MURBRÆCH K, ANDREASSEN JC *et al.*: Systolic dysfunction in systemic sclerosis: prevalence and prognostic implications. *ACR Open Rheumatol* 2019; 1: 258-66.

64. TEMIZ KARADAG D, SAHIN T, TEKEOGLU S, OZDEMIR ISIK O, YAZICI A, CEFLE A: Epicardial adipose tissue thickness in systemic sclerosis patients without overt cardiac disease. *Rheumatol Int* 2019; 39: 1191-200.

65. BUTT SA, JEPPESEN JL, TORP-PEDERSEN C *et al.*: Cardiovascular manifestations of systemic sclerosis: a Danish nationwide cohort study. *J Am Heart Assoc* 2019; 8: e013405.

66. TIPPAROT T, FOOCHAROEN C, MAHAKKANUKRAUH A *et al.*: Clinical and laboratory predictions of myocardial inflammation as detected by cardiac magnetic resonance imaging in patients with systemic sclerosis: A pilot study. *Int J Rheum Dis* 2019; 22: 2125-33.

67. RODRÍGUEZ-REYNA TS, ROSALES-UVERA SG, KIMURA-HAYAMA E *et al.*: Myocardial fibrosis detected by magnetic resonance imaging, elevated U-CRP and higher mRSS are predictors of cardiovascular complications in systemic sclerosis (SSc) patients. *Semin Arthritis Rheum* 2019; 49: 273-8.

68. BOSELLO S, DE LUCA G, BERARDI G *et al.*: Cardiac troponin T and NT-proBNP as diagnostic and prognostic biomarkers of primary cardiac involvement and disease severity in systemic sclerosis: A prospective study. *Eur J Intern Med* 2019; 60: 46-53.

69. RODRIGUES GD, TOBALDINI E, BELLOCCHI C *et al.*: Cardiac autonomic modulation at rest and during orthostatic stress among different systemic sclerosis subsets. *Eur J Intern Med* 2019; 66: 75-80.

70. JAVINANI A, JAVADY NEJAD Z, GHARIBDOOST F *et al.*: Bundle branch blocks and fragmented QRS complex in Iranian patients with systemic sclerosis. *J Tehran Heart Cent* 2019; 14: 6-11.

71. WANGKAEW S, TUNGTEERABUNDITKUL S, PRASERTWITTAYAKIJ N, EUATHRONGCHIT J: Comparison of clinical presentation and incidence of cardiopulmonary complications between male and female Thai patients with early systemic sclerosis: inception cohort study. *Clin Rheumatol* 2020; 39: 103-12.

72. HSU VM, CHUNG L, HUMMERS LK *et al.*: Risk factors for mortality and cardiopulmonary hospitalization in systemic sclerosis patients at risk for pulmonary hypertension, in the PHAROS Registry. *J Rheumatol* 2019; 46: 176-83.

73. GORDON SM, STITT RS, NEE R *et al.*: Risk factors for future scleroderma renal crisis at systemic sclerosis diagnosis. *J Rheumatol* 2019; 46: 85-92.

74. BRUNI C, ROSATO E, MAESTRIPIERI V *et al.*: The Renal Resistive Index in systemic sclerosis: Determinants, prognostic implication and proposal for specific age-adjusted cut-offs. *Eur J Intern Med* 2019; 70: 43-9.

75. GIGANTE A, BARBANO B, GASPERINI ML, ZINGARETTI V, CIANCI R, ROSATO E: Renal parenchymal thickness in patients with systemic sclerosis is related to intra-renal hemodynamic variables and Raynaud renal phenomenon. *J Rheumatol* 2020; 47: 567-71.

76. TONSAWAN P, TALABTHONG K, PUAPAIROJ A, FOOCHAROEN C: Renal pathology and clinical associations in systemic sclerosis: a historical cohort study. *Int J Gen Med* 2019; 12: 323-31.

77. YANH H, XU D, LI MT *et al.*: Gastrointestinal manifestations on impaired quality of life in systemic sclerosis. *J Dog Dis* 2019; 20: 256-61.

78. HORSLEY-SILVA JL, UMAR SB, VELA MF *et al.*: The impact of gastroesophageal reflux disease symptoms in scleroderma: effects on sleep quality. *Dis Esophagus* 2019; 32.

79. TÜRK İ, CÜZDAN N, ÇIFTÇI V, ARSLAN D, DOĞAN MC, UNAL İ: Malnutrition, associated clinical factors, and depression in systemic sclerosis: a cross-sectional study. *Clin Rheumatol* 2020; 39: 57-67.

80. ARANA-GUAJARDO AC, BARRERA-TORRES G, VILLARREAL-ALARCÓN MÁ, VEGA-MORALES D, ESQUIVEL-VALERIO J: Esophageal symptoms and their lack of association with high-resolution manometry in systemic sclerosis patients. *Rheum Clin* 2019; 15: 165-9.

81. FRATICELLI P, PISANI AM, BENFAREMO D *et al.*: Videofluorography swallow study in patients with systemic sclerosis: correlation with clinical and radiological features. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S108-14.

82. PETCU A, GHIB LJ, GRAD SM *et al.*: Upper gastrointestinal involvement in systemic sclerosis: Findings in a real-life setting. *Exp Ther Med* 2019;18: 5095-100.

83. ADARSH MB, SHARMA SK, PRASAD KK, DHIR V, SINGH S, SINHA SK: Esophageal manometry, esophagogastroduodenoscopy, and duodenal mucosal histopathology in systemic sclerosis. *JGH Open* 2019; 3: 206-9.

84. KURIBAYASHI S, MOTEGI SI, HARA K *et al.*: Relationship between esophageal motil-

85. HAREL D, BARON M: Methods for shortening patient-reported outcome measures. *Stat Methods Med Res* 2019 ;28: 2992-3011.

86. HAREL D, MILLS SD, KWAKKENBOS L *et al.*: Shortening patient-reported outcome measures through optimal test assembly: application to the Social Appearance Anxiety Scale in the Scleroderma Patient-centered Intervention Network Cohort. *BMJ Open* 2019; 9: e024010.

87. ROSS L, STEVENS W, WILSON M *et al.*: Can patient-reported symptoms be used to measure disease activity in systemic sclerosis? *Arthritis Care Res* (Hoboken) 2019; acr.24053.

88. PAULING JD, REILLY E, SMITH T, FRECH TM: Evolving symptom characteristics of Raynaud's phenomenon in systemic sclerosis and their association with physician and patient-reported assessments of disease severity. *Arthritis Care Res* (Hoboken) 2019; 71: 1119-26.

89. MOUTHON L, POIRAUDEAU S, VERNON M, PAPADAKIS K, PERCHENET L, KHANNA D: Psychometric validation of the Hand Disability in Systemic Sclerosis-Digital Ulcers (HDISS-DU®) patient-reported outcome instrument. *Arthritis Res Ther* 2020; 22: 3.

90. HUGHES M, PAULING JD, JONES J *et al.*: Multi-centre qualitative study exploring the patient experience of digital ulcers in systemic sclerosis. *Arthritis Care Res* (Hoboken) 2020; 72: 723-33.

91. HUGHES M, PAULING JD: Exploring the patient experience of digital ulcers in systemic sclerosis. *Semin Arthritis Rheum* 2019; 48: 888-94.

92. FISHER CJ, NAMAS R, SEELMAN D *et al.*: Reliability, construct validity and responsiveness to change of the PROMIS-29 in systemic sclerosis-associated interstitial lung disease. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S49-56.

93. DISTLER O, HIGHLAND KB, GAHLEMANN M *et al.*: Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease. *N Engl J Med* 2019; 380: 2518-28.

94. KOWAL-BIELECKA O, FRANSEN J, AVOUAC J *et al.*: Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327-39.

95. DE VRIES-BOUWSTRA JK, ALLANORE Y, MATUCCI-CERINIC M, BALBIR-GURMAN A: A. Worldwide Expert Agreement on Updated Recommendations for the Treatment of Systemic Sclerosis. *J Rheumatol* 2020; 47: 249-54.

96. GALE SL, TRINH H, MATHEW N, JAHREIS A, LIN CJF, SARSOUR K: Characterizing disease manifestations and treatment patterns among adults with systemic sclerosis: a retrospective analysis of a US healthcare claims population. *Rheumatol Ther* 2020; 7: 89-99.

97. IUDICI M, VAN DER GOES MC, VALENTINI G, BIJLSMA JWJ: Glucocorticoids in systemic sclerosis: weighing the benefits and risks - a systematic review. *Clin Exp Rheumatol* 2013; 31 (Suppl. 76): S157-65.

98. VAN DEN HOMBERGH WMT, KERSTEN BE,

KNAAPEN-HANS HKA *et al*.: Hit hard and early: analysing the effects of high-dose methylprednisolone on nailfold capillary changes and biomarkers in very early systemic sclerosis: study protocol for a 12-week randomised controlled trial. *Trials* 2018; 19: 449.

99. DE ALMEIDA AR, DANTAS AT, PEREIRA MC *et al*.: Dexamethasone inhibits cytokine production in PBMC from systemic sclerosis patients. *Inflammopharmacology* 2019; 27: 723-30.

100. KERSTEN BE, DEN BROEDER N, VAN DEN HOOGEN FHJ, KNAAPEN-HANS HAK, VAN DEN ENDE CHM, VONK MC: Treatment with cyclophosphamide i.v. pulse therapy is an option for effective treatment of skin fibrosis in patients with early systemic sclerosis. *Rheumatology* (Oxford) 2020; 59: 1550-55.

101. NAMAS R, TASHKIN DP, FURST DE *et al*. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post hoc analyses from two randomized placebo-controlled trials. *Arthritis Care Res* 2018; 70: 439-44.

102. VOLKMANN ER, TASHKIN DP, SIM M *et al*.: Cyclophosphamide for systemic sclerosis-related interstitial lung disease: a comparison of Scleroderma Lung Study I and II. *J Rheumatol* 2019; 46: 1316-25.

103. SIRCAR G, GOSWAMI RP, SIRCAR D, GHOSH A, GHOSH P: Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. *Rheumatology* 2018; 57: 2106-13.

104. ELHAI M, BOUBAYA M, DISTLER O *et al*.: Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. *Ann Rheum Dis* 2019; 78: 979-87.

105. TASHKIN DP, ROTH MD, CLEMENTS PJ *et al*.: Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708-19.

106. VOLKMANN ER, TASHKIN DP, KUWANA M *et al*.: Progression of interstitial lung disease in systemic sclerosis: the importance of Pneumoproteins Krebs von den Lungen 6 and CCL18. *Arthritis Rheumatol* 2019; 71: 2059-67.

107. KIM GHJ, TASHKIN DP, LO P *et al*.: Using transitional changes on high-resolution computed tomography to monitor the impact of cyclophosphamide or mycophenolate mofetil on systemic sclerosis-related interstitial lung disease. *Arthritis Rheumatol* 2020; 72: 316-25.

108. KHANNA D, LIN CJF, KUWANA M *et al*.: (2018) Efficacy and safety of tocilizumab for the treatment of systemic sclerosis: results from a phase 3 randomized controlled trial [abstract]. *Arthritis Rheumatol* 2018; 70 (suppl 10): abstract 898.

109. SHIMA Y, KAWAGUCHI Y, KUWANA M: Add-on tocilizumab versus conventional treatment for systemic sclerosis, and cytokine analysis to identify an endotype to tocilizumab therapy. *Mod Rheumatol* 2019; 29: 134-9.

110. GOMES JP, SANTOS L, SHOENFELD Y: Intravenous immunoglobulin (IVIG) in the vanguard therapy of Systemic sclerosis. *Clin Immunol* 2019; 199: 25-8.

111. CHAIGNE B, RODEIA S, BENMOSTEFA N *et al*.: Corticosteroid-sparing benefit of intravenous immunoglobulin in systemic sclerosis-associated myopathy: A comparative study in 52 patients. *Autoimmun Rev* 2020; 19: 102431.

112. FERNÁNDEZ-CODINA A, CAÑAS-RUANO E, POPE JE: Management of Raynaud's phenomenon in systemic sclerosis—a practical approach. *J Scleroderma Relat Disord* 2019; 4: 102-10.

113. 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.

114. NEGRINI S, MAGNANI O, MATUCCI-CERINIC M *et al*.: Iloprost use and medical management of systemic sclerosis-related vasculopathy in Italian tertiary referral centers: results from the PROSIT study. *Clin Exp Med* 2019; 19: 357-66.

115. SCHIOPPO T, SCALONE L, COZZOLINO P *et al*.: Health-related quality of life burden in scleroderma patientstreated with two different intravenous iloprost regimens. *Reumatismo* 2019; 71: 62-7.

116. INGEGNOLI F, SCHIOPPO T, ALLANORE Y *et al*.: Practical suggestions on intravenous iloprost in Raynaud's phenomenon and digital ulcer secondary to systemic sclerosis: Systematic literature review and expert consensus. *Semin Arthritis Rheum* 2019; 48: 68693.

117. NAGARAJA V, SPINO C, BUSH E *et al*.: A multicenter randomized, double-blind, placebo-controlled pilot study to assess the efficacy and safety of riociguat in systemic sclerosis-associated digital ulcers. *Arthritis Res Ther* 2019; 21: 202.

118. REZUS E, BURLUI AM, GAFTON B *et al*.: A patient-centered approach to the burden of symptoms in patients with scleroderma treated with Bosentan: A prospective single-center observational study. *Exp Ther Med* 2020; 19: 1739-46.

119. PAN Z, MARRA AM, BENJAMIN N *et al*.: Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: a randomized, controlled, double-blind, parallel group study (EDITA study). *Arthritis Res Ther* 2019; 21: 217.

120. WOLLIN L, DISTLER JH, DENTON CP, GAHLEMANN M: Rationale for the evaluation of nintedanib as a treatment for systemic sclerosis–associated interstitial lung disease. *J Scleroderma Relat Disord* 2019; 4: 212-8.

121. ATANELISHVILI I, AKTER T, NOGUCHI A *et al*.: Antifibrotic efficacy of nintedanib in a cellular model of systemic sclerosis-associated interstitial lung disease. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S115-24.

122. BURT RK, SHAH SJ, DILL K *et al*.: Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* 2011; 378: 498-506.

123. VAN LAAR JM, FARGE D, SONT JK *et al*.: Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. *JAMA* 2014; 311: 2490-8.

124. SULLIVAN KM, GOLDMUNTZ EA, KEYES-ELSTEIN L *et al*.: Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med* 2018; 378: 35-47.

125. AYANO M, TSUKAMOTO H, MITOMA H *et al*.: CD34-selected versus unmanipulated autologous haematopoietic stem cell transplantation in the treatment of severe systemic sclerosis: a post hoc analysis of a phase I/II clinical trial conducted in Japan. *Arthritis Res Ther* 2019; 21: 30.

126. ASSASSI S, WANG X, CHEN G *et al*.: Myeloablation followed by autologous stem cell transplantation normalises systemic sclerosis molecular signatures. *Ann Rheum Dis* 2019; 78: 1371-8.

127. ALMADORI A, GRIFFIN M, RYAN CM *et al*.: Stem cell enriched lipotransfer reverses the effects of fibrosis in systemic sclerosis. *PLoS One* 2019; 14: e0218068.

128. LANDIM SF, BERTOLO MB, MARCATTO DE ABREU MF *et al*.: The evaluation of a home-based program for hands in patients with systemic sclerosis. *J Hand Ther* 2019; 32: 313-21.

129. URAS C, MASTROENI S, TABOLLI S *et al*.: A comparison between two educational methods in the rehabilitation of the microstomia in systemic sclerosis: a randomized controlled trial. *Clin Rehabil* 2019; 33: 1747-56.

130. MUGII N, MATSUSHITA T, OOHATA S *et al*.: Long-term follow-up of finger passive range of motion in Japanese systemic sclerosis patients treated with self-administered stretching. *Mod Rheumatol* 2019; 29: 484-90.

131. HUGHES M, MOORE T, MANNING J *et al*.: A feasibility study of a novel low-level light therapy for digital ulcers in systemic sclerosis. *J Dermatolog Treat* 2019; 30: 251-7.

132. LANGE U, BOGENSPERGER S, TARNER, MÜLLER-LADNER U: The effects of a single carbon dioxide and hot water hand bath on acral perfusion in systemic sclerosis: A randomized, clinical study. *J Scleroderma Relat Disord* 2019; 4: 160-2.

133. RICHELDI L, DU BOIS RM, RAGHU G *et al*.: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071-82.