Review

One year in review 2019: systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is a complex disorder characterised by the involvement of small arteries, microvessels and connective tissue, with deposition of fibrotic tissue and microvascular obliteration in the skin and internal organs. Due to the multifaceted nature of the disease, several articles are published in the medical literature every year, aimed at exploring different aspects of the pathogenesis, internal organ involvement and clinical aspects, and possible therapeutic approaches. In this article we have reviewed the literature on SSc of the past year, with the aim of identifying novel approaches that may help the treating physician in the clinical management of patients.

Introduction

Systemic sclerosis (SSc) is a complex disorder of characterised by the involvement of small arteries, microvessels and connective tissue, with deposition of fibrotic tissue and microvascular obliteration in the skin and internal organs (1).

Following the previous annual reviews of the "One year in review" series (2, 3), in this paper we provide a narrative critical digest of the most recent literature regarding pathogenesis, skin and internal organ involvement and therapeutic approaches for systemic sclerosis. A systematic MedLine search has been performed using the term "systemic sclerosis" (MeSH terms and semantic search), focusing on the most relevant contributions to the medical literature published between July 2018 and May 2019.

Pathogenesis of SSc

As mentioned in our previous reviews, although the aetiology and pathological mechanisms of SSc have not been completely elucidated, the disease appears to be the result of a multistep and multifactorial process including immune system alterations as well as genetic and environmental factors.

Genetic factors

There is growing evidence pointing to the possible role of microRNAs (miRNAs) which may modulate the functions of the immune system and fibrotic-related genes in the pathogenesis of SSc. Recently, a deregulation of miR-483-5p and snRNA-U6 has been found in the early phase of SSc and in localised scleroderma, suggesting that this alteration is present in all conditions characterised by fibrosis of the skin. In addition, miR-483-5p could be a potential pro-fibrotic driver, as its overexpression seems to lead to a myofibroblast transition and to a lower expression of Fli-1, a suppressor of collagen transcription (4).

Some reports have indicated that the IRAK1 (interleukin-1 receptor-associated kinase 1) gene is a protein kinase with significant role in altered activation of NF-κB and regulation of many proinflammatory mediators (IL-6, TNF-α, IL-1b, and IL-17). Vreca et al. reported the association between IRAK1 gene and female predominance in SSc, non-severe skin involvement and ACA- negative autoantibodies, indicating that the gene can directly influence the predisposition and phenotypic heterogeneity of SSc. Moreover, reduced miR-146a expression is a risk factor for the development and progression of SSc, and the rs2910164 CC genotype showed a strong association with lung fibrosis and a more progressive form of the disease (5).

The environmental influence via epigenetic mechanisms, particularly altered status of DNA methylation, may

contribute to the environment-host interaction in the development of SSc. Gene network analysis revealed that the 20 methylation-regulated differentially expressed genes, MeDEGs, are involved in SSc pathogenesis. Zhu et al. identified six out of the 20 potential methylation-regulated differentially expressed genes (F2R, CXCR6, FYN, LTBR, CTSG, and ELANE), which distinguished SSc patients with 100% accuracy (6).

The recent study by Ding *et al*. focused on the analysis of whole genome DNA methylation status in CD4+ and CD8+ T cells in 48 subjects (24 SSc patients and 24 controls). SSc patients seemed to present higher serum levels of type I IFN-α/β and a correlation of these levels with DNA methylation status was described (7).

Another study investigated the mRNA expression and promoter methylation of integrin subunit beta 2 (ITG β 2) and selectin L (SELL) genes (involved in the functional pathways of the immune system) in peripheral blood mononuclear cells (PBMCs) from SSc patients, identifying an increase in the ITG β2 mRNA level and a hypomethylation of CpG 12, 13 and 14 in the SSc population. In addition, the level of methylation of these three sites of CpG was inversely associated to the disease risk (8).

The recent study by Garlova *et al*. analysed the genetic susceptibility loci in SSc at gene level in African- American (291 cases and 260 controls) and White patients (1833 patients and 3466 controls). The authors reported 4 novel candidate genes (STAT1, FCGR2C, NIPSNAP3B and SCT) with significant association with SSc in the White group but not in African Americans (9).

Previous studies have shown that polymorphisms in the IL6 gene are important in the development of SSc, in particular regarding fibrotic events and T cell proliferation. Zekovic *et al*. recently investigated the frequency of -174 C/G of IL-6 gene polymorphism in SSc patients and its correlation with disease manifestations, in particular with gastrointestinal involvement assessed by the gastrointestinal (GIT) 2.0 questionnaire; in particular those with the C-allele had a statistically significant higher expression of IL-6, higher total GIT score and higher distension scale score compared to the non-C allele carriers (10).

It has been suggested that the involvement of genetic variations in CD247, which is part of the T cell receptor (TCR)/CD3 complex, and in CD226, expressed on NK cells, T cells, NK-T cells and B cells, contributes to impaired T cell function. Abbasi et al. did not report any association of genetic variants of CD247 and CD226 with the risk of SSc or with specific clinical manifestations of the disease except for rs763361 variants that were found to be associated with the forced vital capacity (FVC) in SSc (11).

The role of the long non-coding RNAs (lnc-RNAs) has been recently studied by Messemaker et al. highlighting a deregulation of (antisense) lnc-RNAs in SSc and confirming that they might be involved in the pathogenesis of the disease (12).

Many previous studies reported monocytes and macrophages as leading actors in the SSc pathogenesis and the study by Moreno-Moral et al. recently investigated the role of monocyte-derived macrophages (MDMs) in genetic susceptibility to the disease. The study suggested a link between the risk of developing SSc and changes in macrophage transcriptome. Among cis-regulated genes associated with SSc, GSDMA showed the highest upregulation in SSc MDMs. The authors found a cis-regulation of GSDMA by the polymorphism rs3859192 and it seems to be associated to susceptibility to SSc (13).

Cells

Several studies have reported that dendritic cells (DCs) accumulate in the lungs of patients with idiopathic pulmonary fibrosis and in the skin of SSc subjects, although the role of these cells in the pathogenesis of fibrosis is still unclear. In a recent study, Kafaja et al. investigated the potential role of pDC (plasmacytoid DCs), a specialised subset of DCs that links innate and adaptive immunity in the pathogenesis of SSc. The authors reported an increase of these cells in the lung and lung-draining lymph nodes in bleomycin-induced fibrosis mice model and that pDC depletion seemed to lead to a significant lower skin fibrosis measured by dermal thickness and a reduction in collagen deposition in the skin and lung tissues. In the same work, the authors reported a correlation between the levels of pDCs in the lungs of SSc (measured by bronchoalveolar lavage, BAL) and lung disease severity at the high-resolution CT (HRCT) (14).

Another recent study focused the possible role of pDCs in promoting and/or sustaining the fibrosis in the disease. Analysing the skin biopsies from controls and SSc patients, the authors demonstrated the presence of pDcs only in those from SSc subjects, while instead, the number of circulating pDCs was lower in the SSc population that in the control subjects. In addition, pDCs seem to spontaneously secrete IFN-α and CXCL4 and the depletion of these cells seems to prevent the disease in a mice model of scleroderma or to resolve fibrosis in animals with an already established disease (15).

The study by Silvan et al. investigated the possible role of the P-selectin glycoprotein ligand-1 (PSGL-1)/ADAM8 axis in SSc. PSGL-1 deficiency in mice is associated to a disease similar to SSc and the PDGL-1 expression is regulated by the metalloproteinase ADAM8. The expression of PSGL-1 was found to be significantly higher on T cells, monocytes and DCs in SSc patients compared to controls, however, its expression on B cells was lower. The PSGL-1 signalling seemed to be altered in SSc monocytes, suggesting the possible implication of DCs in SSc, as these cells expressed high levels of PSGL-1 and were associated with the presence of interstitial lung disease in SSc patients (16).

Finally, galectin-9 (ligand of T-cell immunoglobulin and mucin domain 3), a co-inhibitory receptor for CD155, is up-regulated in dermal fibroblasts in patients with SSc and in experimental models. Recently the serum levels of galectin-9 was confirmed to be higher in SSc patients and correlated with disease severity (higher mortality and organ involvement) (17).

Fibrosis and TGF signalling

The TGF-β pathway is a potent pro-fibrotic pathway that plays a critical role in the progression and development of SSc. Studies have shown that principal influence of TGF-β on fibroblasts is based on the effects on proliferation, activation, and accumulation and stimulation of the extracellular matrix (ECM). Shi et al. reported an increase in TGF-β type II receptor (TGFBR2) expression in SSc skin and fibroblasts that may be attenuated by miR-3606-3p (18).

Milk fat globule-associated protein with EGF- and factor 8-like domains (MFG-E8) are implicated in the pathogenesis of some autoimmune disorders. Fujiwara et al. reported that MFG-E8 expression in endothelial cells and pericytes/VSMCs was reduced in the sclerotic skin lesions of SSc patients and they hypothesised that MFG-E8 inhibited TGF-β signalling and fibrosis mediated by the interaction between MFG-E8 and integrin in SSc fibroblasts, resulting in a profibrotic final effect (19).

Sawamura *et al*. recently examined the effect of IL-22 on the expression of ECM-related proteins demonstrating an increased expression of type I collagen without changing its mRNA levels. In addition, the authors found an expression of IL-22 in the infiltrated lymphocytes in skin of SSc patients but not in the controls. This expression may lead to an up-regulation of type I collagen protein in dermal fibroblasts (20).

A deceased expression of poly(ADP-ribose) polymerase-1 (PARP-1) has been identified in the SSc population compared to the controls. This study also reported the central role of TGFβ in down-regulating PARP-1 expression in fibrosis probably due to a TGFβ-induced hypermethylation of the PARP-1 promoter. In addition, the inhibition of PARP-1 seemed to foster TGFβ signalling, thus leading to collagen release and myofibroblast differentiation *in vitro* (21).

Exposure to metals

The correspondence between exposure to metals such as aluminium, cadmium, mercury, and lead and the development of SSc is suspected and studies have indicated the negative immunomodulatory role of heavy metals in cellular and humoral components of the immune system with a risk of autoimmune diseases development. Forte *et al*. reported that aluminium and lead in the blood and aluminium in the urine of SSc subjects were significantly different from controls, and a major urinary excretion of mercury was found in patients with severe disease. These results suggested that low, chronic, and multiple exposures to heavy metals – also through habits, diet, and environment – may influence the risk for SSc (22).

Ferri *et al*. identified significantly higher serum silica levels in SSc patients with previous occupational exposure compared to non-exposed patients and healthy controls. Moreover, a significant correlation of serum silica levels with diffuse cutaneous SSc variant, myositis, and/or the presence and severity of the interstitial lung involvement (23). Data from a Belgian cohort of male SSc patients, confirmed a history of occupational exposure to silica in 70/96 patients, and the association between the exposure and anti-Scl70 antibodies positivity and higher disease activity. In addition, they observed an important difference in male prevalence between the two populations, with a higher prevalence in patients with a history of occupational exposure (24).

Others pathogenic factors

Persistent/latent viral infections such as human cytomegalovirus (HCMV) infection and the consequent unbalanced anti-viral immune responses have been proposed as being possibly involved in the pathogenesis of SSc. A recent study described greater HCMV-specific CD8+ T cell responses in SSc patients, especially in those with a longer disease duration and higher mRSS (25).

The role of oxidative stress in SSc has been highlighted by many studies in animal models and in patients. The transcription factor NRF2 is a key player in antioxidant defence, as it can induce the transcription of antioxidant genes, including glutathione GSH. Kavian et al. reported a downregulation of the NRF2 pathway in fibroblasts from fibrotic skin in SSc patients and in lungs from mice with HOCl-induced SSc (26).

It is known that fibroblasts production of collagen and fibrotic cytokine connective tissue growth factor (CTGF) are activated by hypoxia, for example in Raynaud's phenomenon. In this scenario, hypoxia-inducible factor 1 alpha (HIF-1a) seems to play a crucial role in the induction of collagen I under hypoxic conditions and this datum suggests that HIF-1a-mediated hypoxia pathways may be a novel target in SSc. Recently, Zhou et al. investigated how 2-methoxyestradiol (2-ME) (a inhibitor of HIF-1a) inhibits the proliferation of fibroblasts in SSc patients and suggested a possible role of PI3k/Akt/mTOR/HIF-1a signalling in the antifibrotic effect of 2-ME in these subjects. Through this pathway 2-ME seems to be able to reduce the production of CTGF (27).

Recently, Raschi *et al*. demonstrated that sera from scleroderma patients contains immune complexes (ICs) and, using fibroblasts from skin biopsies (*in vivo* and *in vitro*), they reported that SSc-ICs can trigger proinflammatory and profibrotic mediators. In particular, the incubation with SSc-ICs modulated several molecules involved in the three cardinal scleroderma pathophysiologic processes: vascular dysfunction (ET-1 and IL-8), inflammation (ICAM-1, IL-6, IFNs and MCP-1) and fibrosis. Moreover, they proposed that these effects might be mediated by Toll-like receptors via interaction with nucleic acid fragments embedded in SSc-ICs (28).

Clinical aspects

In addition to the skin involvement, SSc is characterised by the involvement of several internal organs, in particular the heart, the lungs and the gastrointestinal apparatus.

SSc vasculopathy may result in significant morbidity and mortality as in the case of DUs and pulmonary hypertension (PH) (29). A prospective cohort study followed up 300 SSc patients for at least 5 years, during which 10% developed PH (all causes) and 23% DUs. Analysing the baseline characteristics, the authors found that the patients who

developed PH were more likely to have diffuse cutaneous involvement, a baseline forced vital capacity (FVC)/ diffusing capacity of the lungs for carbon monoxide (DLCO) ratio >1.6, and a higher right ventricular pressure at baseline assessed by echocardiography, whereas male sex and a previous history of DUs were reliable predictors for the development of new DUs (30).

Nailfold video-capillaroscopy (NVC) has recently proved to have also a reliable prognostic role in very early disease onset (VEDOSS) cases, helping to differentiate subjects that are more likely to progress into established disease by those who are going to be not progressors (31). Given the growing evidence of correlations between microangiopathy and the involvement of other organs, a thorough evaluation of capillary alterations is very important. Among 134 SSc Spanish patients evaluated with NVC, in patients with interstitial lung disease (ILD) a lower median capillary density and a higher median number of neoangiogenesis was identified (p=0.005) compared with those without ILD. A correlation between neoangiogenesis and decreased FVC was established (32).

Microangiopathy is considered to be the earliest pathological process in SSc, but larger vessels can also be involved. A cross-sectional multicentre study performed Doppler ultrasonography on both hands in 204 SSc patients identifying presence of ulnar artery occlusion (UAO) in 37.3% of the patients, bilateral in 24%. A significant association between UAO and a history of DUs, mRSS, lower DLCO values and positivity of anti-centromere antibodies was identified (33).

In a recent study, Gigante *et al*., correlated the autonomic nervous system function using heart rate variability (HRV) analysis with vascular endothelial growth factor (VEGF). The authors identified an increased autonomic nervous system activity in patients with DUs and a correlation between autonomic nervous system function and VEGF (p<0.01, r=0.55). These results suggested that parasympathetic activity increases with digital microvascular damage and promotes VEGF release (34). Interestingly, in patients without clinical evidence of cardiopulmonary involvement, the better exercise tolerance has been correlated to compensatory sympathetic autonomic system activation. This activation may led to a compensatory cardiovascular response, which may be present also in early stage of the disease and that may improve the exercise tolerance and cardiac function during physical effort (35).

Cardiac affection in SSc is more common than was previously thought and may represent a major cause of mortality. In this perspective left ventricular diastolic dysfunction (DD), a parameter easily assessed by echocardiography, has gained growing attention, as it is considered a precursor of heart failure with preserved ejection fraction (EF). An interesting study by Tennøe *et al*. reported that DD is a stronger predictor of death (HR 3.7) than PH assessed by right heart catheterisation (RHC) (HR 2.0). Since DD is the hallmark of heart failure with preserved EF, SSc patients presenting DD surely require a closer follow-up (36).

In this regard, echocardiographic speckle-tracking strain analysis has recently aroused interest, as it seems to be able to identify also subtle myocardial dysfunction. In particular, left ventricular systolic function can be reliably assessed by global longitudinal strain (GLS). A recent Dutch work sought to compare GLS and EF in the assessment of left ventricular systolic dysfunction in 234 SSc patients followed for a median of 2.3 years. At follow-up they found significant worsening in GLS (p<0.001), while left ventricular EF had not changed (p=0.124). Moreover, patients with a GLS reduction >15% were more likely to develop proximal muscle weakness, lung fibrosis, renal impairment and to have an increased risk of all-cause mortality (37).

According to the PHAROS registry data, PAH accounts for more than half of the deaths in SSc, 93% of which occurs within four years of diagnosis, which suggests the importance of a correct and rapid management of this complication (38). The most important novelty in this field is the haemodynamic redefinition of PH. In fact, during the 6th World Symposium on PH, it was decided to lower the cut-off of the mean pulmonary arterial pressure (mPAP) measured by RHC from 25 to 20 mmHg (39). One of the most recent studies on SSc patients with borderline mPAP showed in fact that this particular subgroup of patients actually has a significant performance reduction, exhibiting a lower 6-minute walking distance, a lower cardiac index and a greater pulmonary vascular resistance during exercise (40). Respiratory impairment is one of the most relevant pathological aspects in SSc and it is often due to pulmonary involvement which can manifest as ILD or as PH or as both of them, since it was found that more than 30% of SSc-ILD patients present coexisting PH (41). The 6-minute walk test (6MWT) represents one of the most important test for the evaluation and monitoring of changes in lung function in SSc patients (42). In this regard, all newly diagnosed SSc patients should initially undergo a 6MWT. Its proven stability over a 5-year follow-up in SSc subjects without ILD or PAH, makes this test a useful reference for the management of those who will develop one of these complications (43).

Several efforts have been made to try to predict in a reliable and early manner the possible progression of SSc-ILD. A study by Wu *et al*. evaluated 215 SSc patients divided into two independent cohorts presenting mild ILD (extent of <20% pulmonary fibrosis on HRCT at baseline). They sought to identify predictive clinical characteristics of ILD progression (decrease in FVC >15% or FVC >10% combined with decrease in DLCO >15%) at the 1-year follow-up. After a multivariable logistic regression analyses on both cohorts, they found that lower peripheral oxygen saturation (SpO_2) after a 6-minute walking test (6MWT) and the presence of arthritis ever were independent predictors of mild ILD progression at 1 year. A prediction model was therefore developed, which is able to stratify the risk of mild ILD progression with a positive predictive value of 91.7% and a specificity of 98.6% (44).

Data from 300 SSc patients with ILD who participated in the Scleroderma

Lung Studies I and II were analysed to identify predictors of long-term survival. It was demonstrated that, in addition to the already known mortality risk factors in SSc (mRSS and older age), a decline in FVC and DLCO over 2 years is a better predictor of mortality than baseline FVC and DLCO (45). This means that short-term progression of ILD, as assessed by spirometry, is an extremely important element that can influence long-term survival, and therefore changes in FVC and DLCO should guide therapeutic decisions.

Skin fibrosis is a hallmark of SSc and the focus on this aspect of the disease is still very high in all clinical trials. For example, research on a cohort of 1021 dc-SSc patients from the EUSTAR database highlighted how progressive skin fibrosis, defined as an increase in mRSS >5 and <25% from baseline within 1 year, is independently associated with a decline in lung function and all-cause death during follow-up (HR 2.58) (46).

Numerous studies are recently flourishing about methods able to assess skin involvement in a very accurate way. High-frequency ultrasound proved to be an instrument capable of measuring skin thickness, showing how this parameter offers a valid estimate of disease activity (47). Furthermore, a work on shear wave elastography in SSc has recently been published. This non-invasive technique makes it possible to estimate skin stiffness and can be considered operator-independent because, thanks to its ultra-fast imaging technique, it can reduce the risk of artifacts due to patients' or investigators' movements. Shear wave elastography turned out to be more sensitive in detecting subtle skin changes than B-mode ultrasound, as also skin stiffness better reflects the degree of skin involvement in SSc patients than skin thickness (48).

Nearly 90% of SSc patients have gastrointestinal involvement, but in some this may be severe, and become a source of serious complications. A large inception cohort on 556 SSc subjects reported that the probability of developing severe gastrointestinal disease, defined as malabsorption, need for hyperalimentation, episodes of pseudo-obstruction, weight loss in association with the use of antibiotics for small intestinal bacterial overgrowth or oesophageal stricture, was 9.1% at 2 years and 16% at 4 years and was associated with myositis, telangiectasias, higher mRSS, and above all with a 2-fold increase in mortality (HR 2.27) and worse health-related quality of life (49). Patients who require supplemental nutrition, enteral or parenteral, are more likely to be male and present with myopathy and sicca symptoms (50).

The possible relationship between esophageal disease and involvement of other organs in SSc, especially ILD, is a debated topic. A study by Winstone *et al*. evaluated HRCT scans from 145 SSc-ILD patients and found that every 1 cm increase in esophageal diameter is associated with 1.8% higher fibrosis score on HRCT and with 5.5% lower FVC. Esophageal diameter is independently associated with ILD severity and mortality, but not with ILD progression or asymmetry, thus making esophageal dilation an unlikely driver of SSc-ILD progression (51).

Data from the EUSTAR database on 1027 subjects with early SSc revealed important clinical differences dependent on the gender. In early stages of SSc in fact, men showed more frequently than women signs and symptoms of more severe disease, such as elevated acute phase reactants, muscular and pulmonary involvement. This gender imbalance was confirmed in lcSSc, but not in dcSSc (52). Interestingly, also the hormonal modification that are pharmacologically induced as part of male to female sex transition, may be relevant in the development of SSc (53). Although the contribution of autoantibodies in risk-stratification and clinical subsetting in SSc has been reconsidered as less crucial than previously thought (54).

Investigating cancer risk in a large cohort of more than 2300 SSc patients, the significant association with the presence of RNA polymerase III autoantibodies (standardised incidence ratio 2.84) was confirmed. Among anti-RNA polymerase positive subjects, cancer-specific risk may vary by SSc subtype: breast cancer is prevalent in dc-SSc, whereas lung cancer is more prevalent in lcSSc (55).

Articular involvement in SSc was recently assessed in a cohort of 103 patients who underwent power Doppler ultrasonography of both hands. This work reported that ultrasonographic synovial/tenosynovial involvement concerns about one-third of SSc patients. The two main power Doppler ultrasonography features were Doppler-positive/inflammatory synovitis (17.5%) and sclerosing tenosynovitis (18.4%). They were both significantly associated with inflammatory arthralgia, and the former also with high C-reactive protein (CRP) levels and pericarditis, whereas the latter was correlated with male sex, RNA polymerase III autoantibodies, dc-SSc and ILD (56).

The impaired hand function is one of the primary causes of disability and reduction of the quality of life in SSc patients. In a very large cohort of 1193 SSc patients, using the Cochin hand function scale (CHFS), the hand function was reduced in particular in those with DUs, severe Raynaud's phenomenon, diffuse SSc, arthritis and small joint contractures (57).

As far as the prognostic factors are concerned, the widely available erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) confirmed their role in the stratification of the patients with SSc, as elevated ESR and CRP values are associated to worst lung function and decline of respiratory function, and to more severe skin, vascular and musculoskeletal manifestations (58). Additionally, a recent study identified a possible role in the assessment and prognostic stratification of SSc patients for growth differentiation factor-15 (GDF-15), placenta growth factor (PlGF), endostatin, vascular endothelial growth factor (VEGF), and pentraxin 3 (PTX3) (59).

Patient-reported outcomes in systemic sclerosis

In SSc, patient-reported outcomes (PROs) are a fundamental part of the global patient evaluation both in RCT and in real practice albeit most of them in SSc are still poorly validated and performing.

A recent study from South Korea further remarked on the impact of SSc on health-related quality of life as compared to other rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) (60). Park *et al*. compared all 8 components of the SF36 and the EuroQOL 5D descriptive system (EQ-5D-3L) in a total of 480 patients (120 subjects for each disease group). Patients in the SSc cohort had a mean HAQ-DI score of 0.99 and a mean SHAQ of 0.87, indicating an average moderate disability. The univariate analysis found scores for the Mental Component Summary (MCS) of the SF-36 in SSc lower than in RA (43±0.9 *vs*. 48.9±0.9, $p<0.001$), and also for the global health (GH) domain in the physical component scores (41.4±1.8 *vs*. 51.3±0.9, $p<0.001$). Further multivariate and sensitivity analyses confirmed lower scores in GH, MH and MCS domains versus RA and SLE patients. EQ-5D-3L scores were significantly lower in SSc than in RA, were also lower than in patients with SLE and SS but did not reach statistical significance. Low BMI, longer disease duration, high mRSS, elevated scores in the digestive and pulmonary domains and disease severity VAS were the major contributors to the SF36 scores. EQ-5D-3L was also associated to mRSS and disease severity VAS (60). Despite some limitations of the study, especially the lack of application of a disease activity score for SSc patients, it is remarkable how low the perception of general health is. Analogously, health related quality of life (HRQoL) was analysed in the International Systemic Sclerosis Inception Cohort (INSYNC) harmonised platform, which is a multicentric international database of SSc patients including incident cases of SSc with a disease duration of less than 2 years (61). In this setting with a relatively early disease both the physical and the mental components of the SF-36 were significantly lower than what had been expected. In particular the diffuse cutaneous involvement and PAH emerged as a predictor of lower PCS. Age was a predictor of lower scores in both domains. Very interestingly, in this study, a disparity between Physical component scale (PCS) and MCS scores was noted (61). Scores of PCS were substantially lower than their mental components indicating the potential capacity to better adapt mentally than physically to the presence of the disease, the plasticity of the psychological assessment and the need to address it in clinical interventions alongside the physical counterpart, which unfortunately may be less responsive. When mental status is impacted it generates high levels of anxiety and depression in SSc as compared to the general population and other chronic rheumatic diseases such as RA and SLE for which the burden of depression is more commonly recognised (62). There is an increasing need to address this comorbidity in SSc and it is time that mental health outcomes were incorporated in the care of patients alongside the treatment of internal organ complications.

The psychological impact of SSc is a major determinant that increases the impact of many disease manifestations in SSc. Perhaps Raynaud's is the symptom which conditions SSc patients in their daily life because of its frequency, severity, pain and aesthetics. Quantifying its impact is very difficult and it may be assessed in clinical practice mainly by PROs such as the Raynaud Condition Score (RCS). Recently, in analysing which factor influences the reporting of RCS, Pauling *et al*. (63) found a significant association between coping strategies and lower scores, while patients with a catastrophising behaviour (according to the coping strategies questionnaire, - CSQ, and pain catastrophisation score - PCS) tended towards higher scores of RCS. In this study of 107 patients, other factors influencing RCS reporting were also related to the VAS pain scale, SHAQ GI involvement and RP VAS, indicating the need to intervene in PROs to ameliorate PROs and general health in SSc. The importance of behavioural and resilience strategies could result in better control of one the most common symptoms of the disease (RP, reflux, etc.).

The psychological involvement of the disease in patients who are most commonly female and still in their working age reflects in appearance anxiety. In a recent review Gholizadeh *et al*. (64) encompass a series of an often neglected area of psychological involvement specific to SSc and the changes it induces in a patient's appearance and social aspects (*e.g*. Raynaud's and sclerodactily in the handshake). This sort of issue may induce avoidance of social situations and social isolation. In a vicious circle this may lead to poorer mental health, which is a risk factor for physical symptom exacerbation. Measures of appearance anxiety are relatively scarce: among them there is the Social Appearance Anxiety Scale (SAAS), a self-report scale that is able to predict depression, social anxiety and negative body image (65). The SPIN cohort served in a validation study which demonstrated excellent consistency and large positive and negative correlations respectively between depression, social interaction anxiety, fear of negative evaluation and appearance dissatisfaction (65). Analogously, the Brief Fear of Negative Evaluation Scale (BNFE) was validated in the SPIN cohort (66). It is an 8-item measure of worries about being negatively evaluated with a straightforward wording construct (*e.g*. "When I am talking to someone, I worry about what they may be thinking of me"). A negative correlation has been shown between age and BNFE scores but no specific disease features emerged (66). Similarly, the Social Interaction Anxiety Scale (SIAS), in a short 6-question format, was tested in the SPIN cohort for validation in SSc (67) as well as the Body Concealment Scale (BCSS) in two North American SSc cohorts (68). All these measures were conceived in a psychiatry environment thus scores and cut-offs must be further validated to meet the challenge of identifying patients who need specific interventions and a different kind of support than that provided by targeting internal organ or vascular manifestations.

Emotional difficulties are one of the strongest challenges that patients and their informal caregivers are experiencing. An international study (69) recently reported the results of the

submission of a questionnaire obtained with the nominal group technique conducted with 13 SSc caregivers. They previously generated survey items that reflected challenges faced by informal SSc caregivers and also identified the preferred types of support demanded (70). The survey was submitted to an international sample of SSc caregivers identified through SSc patient associations in North America and Europe (69). The item that was rated highest was "providing emotional support to my care recipient on challenging days" while lowest percentages of importance was given to "feeling ashamed to think about my own well-being or needs" (69). In other medical settings such as oncology, targeting patient information and involvement of their caregiver has shown to improve the ability, confidence and satisfaction of patients themselves (71). Once again, the emotional and social spheres of the disease emerge as an essential complement to symptom evaluation and the medical approach.

Treatment

Despite the complexity of the disease and the lack of well-defined therapeutic approaches, in the last year several steps forward have been made with improvements of the use of existing drugs and novel therapeutic approaches. Moreover, innovative approaches, including the possibility of interacting with epigenetic targets are under investigation (72).

Despite the potential benefits of these new therapies, the efficacy of the treatment may be greatly influenced by adherence of the patients to the treatment, that may be low, particularly in patients with chronic disease (73).

Immunosuppressive treatment

Immunosuppressive treatment continues to maintain a central role for the treatment of SSc (74). According to EULAR recommendations, cyclophosphamide (CYC) remains the first choice for treatment of SSc-ILD (75). In a recent retrospective study on 75 SSc patients, 12 monthly pulses with CYC were successful in stabilising FVC and respiratory functions and the effects are not influenced by disease duration, proportion of ground glass, extent of ILD and baseline DLCO (76). Despite the efficacy of CYC in the treatment of SSc-ILD, a pooled analysis of 148 patients included in the Scleroderma Lung Study I and II, demonstrated a high number of side effects and that the benefits are not maintained after the cessation of CYC, suggesting the need for long-term therapy for these patients (77). Although the maintenance treatment with other mild immunosuppressive agents may preserve the beneficial effects after CYC treatment, no clear differences between methotrexate, azathioprine and mycophenolate mophetil (MMF) have been identified (78).

The response to treatment with CYC may be predicted by a rapid reduction of interleukin-6 (IL-6) serum levels after three CYC pulses in patients with SSc-ILD (79). In a study from a Japanese centre, other parameters of good response to CYC at baseline included higher DLCO values, lower levels of Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) and CRP (80).

CYC may be useful also for the treatment of gastric antral vascular ectasia, a major gastrointestinal complication in SSc patients (81).

Other chemical immunosuppressants, such as tacrolimus, may represent an option for the treatment of SSc-ILD. A recently published study from Konma *et al*. retrospectively analysed a monocentric cohort of patients treated with prednisone associated with tacrolimus, and reported a decline in lung function only in 1/11 patients and a stabilisation or improvement in the others (82).

For the treatment of SSc-ILD, also rituximab (RTX), a B-cell depleting treatment, has been widely investigated in particular in patients refractory to CYC (74). In 2018, the first head-to-head randomised trial between CYC and RTX was published in an open-label study. A similar efficacy of the two treatments was identified but RTX was associated to fewer major adverse events than CYC (83). The good safety profile of RTX has also been confirmed in a prospective cohort of 254 patients with SSc from the European Scleroderma Trials and Research (EUSTAR) network; in particular, only six deaths were recorded after RTX and only two of them were possibly related (respiratory insufficiencies). In this study, the majority of patients had an improvement regarding skin fibrosis, while the effects on ILD, although less evident, may be increased by a concomitant MMF treatment (84). The potential benefit of the combination therapy of MMF and RTX has been also investigated in a small Italian monocentric cohort, which also confirms the good safety profile (85).

In addition to the possible effect on skin and lung involvement, some studies suggest a possible role of RTX for the treatment of vascular abnormalities (86) and for cutaneous calcinosis in SSc patients (87).

Tocilizumab (TCZ), a monoclonal antibody targeted against IL-6, has been investigated in the treatment of diffuse systemic sclerosis. Results derived from the phase II and III trials showed that the treatment was associated to a substantial stabilisation of skin and lung involvement (88). The influence of IL-6 on SSc seems to be greater in patients with early disease and in those with lung involvement (89). The poor effect on skin fibrosis already evaluated in the randomised controlled trial (90), has been recently confirmed in a small case series even if the skin response seems to be better in patients with higher C-reactive protein (CRP) at baseline (89). According to these data, TCZ may represent an interesting opportunity also for patients with SSc-RA overlap disease syndrome (91).

Although not directly immunosuppressive, the treatment with intravenous immunoglobulins (IvIg) may interfere with the immune system in several ways and has been used in SSc patients since 2000. Although no RCT has been conducted, the treatment may be relatively safe for muscle, skin and gastrointestinal involvement of SSc patients (92).

Cellular therapies

Autologous haematopoietic stem cell transplantation (AHSCT) may represent a good therapeutic choice for patients with signs of rapidly progressive SSc and has been proposed as an authorised indication for SSc (93). Al-

though the treatment has been associated with improved prognosis with a good effect on skin fibrosis, lung involvement and a reduction of the disease activity (94), there are still many open questions to address, including the optional therapeutic protocol, the lack of biomarkers that may help in selecting patients and the necessity of maintenance immunosuppressive treatment (94, 95).

Data from a retrospective French cohort of patients treated with AHSCT for autoimmune diseases included in the analysis 56 patients with SSc and reported good overall survival and the stabilisation of the disease (96).

Vasoactive treatment

Vascular abnormalities in patients with SSc are responsible for some of the main burdens for patients including digital ulcers, pulmonary arterial hypertension (PAH) and scleroderma renal crisis. Although only few drugs have been approved for the treatment of vascular involvement in patients with SSc, treatments directed at the endothelial dysfunction may have a positive impact on the SSc prognosis (97).

PAH has a very bad impact on the SSc patients' outcome and prognosis. In the treatment of PAH, although monotherapy with endothelin receptors antagonists (ERA), phosphodyesterase-5 (PDE5) inhibitors, prostacyclin analogues and riociguat may be considered (75), recent data suggest that combination therapy may represent a better therapeutic option (98). A retrospective cohort study performed using data from the Spanish Scleroderma Registry identified that combination therapy was superior to monotherapy as a long-term protective factor against mortality (99). Combination therapy with vasoactive drugs may also have an impact on reducing the onset and accelerating the healing of digital ulcers (100), however, as described in a recent article by the EUSTAR group, the number of patients treated with more than one vasodilator is lower than 50% and a great number of patients continue to present recurrent DUs (101).

Among vasodilating agents, one of the most important treatments is intravenous Iloprost (ILO) that is used for the treatment of severe Raynaud's phenomenon when oral treatment is insufficient (75). From a systematic literature review, ILO is usually prescribed for RP in SSc patients who are unresponsive to oral treatment but also to prevent DUs and promote DU healing (102). Despite the potential benefits, the optimal regimen for ILO in SSc is not clearly defined, and among different tertiary centres, dissimilar therapeutic ILO administration schemes are frequently used (103). In addition, therapeutic approaches with elastomeric pumps may be used in order to improve the patient's treatment acceptance and optimise the adherence to the treatment (104).

The determination of an optimal scheme of the ILO regimen would be very important, as the vasodilator effect of this drug is very short and the increase of vascular flow is generally not maintained until the following administration (105). In particular, a laser Doppler flowmetry study demonstrated an increase of blood flow three days following ILO infusions that rapidly decrease in the subsequent days (106).

Antifibrotics

Recently, encouraging data have been published on antifibrotic treatment with nintedanib. This drug, approved for the treatment of idiopathic pulmonary fibrosis, and targeted against the receptors for fibroblast growth factor, vascular endothelial cell growth factor and platelet-derived growth factor (PDGF), demonstrated a very good effect in the stabilisation of ILD in SSc patients. In particular, in the SENSCIS trial, which recruited 576 SSc patients, the drug reduced the annual rate of decline of FVC by 44% with similar results across patients with different baseline characteristics and with overall good safety and tolerability (107); gastrointestinal manifestations, including diarrhea, is the most common adverse event. Unfortunately, nintedanib seems to be ineffective for other disease fibrotic manifestations including skin fibrosis. The results appear to be improved when associated with an immunosuppressant such as MMF.

A recent report also investigated the possible effect of imatinib as an antifibrotic agent in SSc with a possible effect on organic cation transporters and Notch pathway activation in SSc fibroblasts (108). Although these mechanisms may have an antifibrotic role, given the lack of further in-vivo studies, the use of imatinib should be reserved only for selected cases.

As preclinical *in vivo* and *in vitro* studies suggest a role for lysophosphatidic acid (LPA1) receptor in the pathogenesis of SSc, the possibility of using a selective oral antagonist of LPA1 (product name SAR100842) has been recently investigated in a phase 2 double blind RCT on 32 SSc patients. Although the preliminary report did not reach statistical significance, the drug was well tolerated and the effects on gene signature analysis suggested a possible role of SAR100842 in the treatment of skin involvement in SSc patients (109).

Treatment for specific organ involvements

As SSc may affect many different organs, also the treatment of specific internal organ manifestations should be part of the therapeutic approach for patients (110). A recent study in 31 SSc patients with gastrointestinal symptoms showed how treatment with pyridostigmine may improve the clinical pattern in 51.6% of the patients treated, and the major improvement was for patients with severe constipation (111). Another GI manifestation, frequently developed by SSc patients, is represented by a small intestinal bacterial overgrowth that may lead to malnutrition and poor quality of life. Despite there is a lack of high quality studies, a recent systematic review pointed out that antibiotic therapy may be useful for some patients (112). Moreover, dietary intervention may improve the gastrointestinal involvement in systemic sclerosis, in particular, the supplementation with probiotic and a low-fermentable oligosaccharides, disaccharides, monosaccharides and polyol (low-FODMAP) diet (113). For upper gastrointestinal involvement the surgical approach may be a useful opportunity for patients refractory to the medical treatment;

among the different surgical possibilities the laparoscopic gastric bypass may represent a good choice compared to fundoplication to improve or resolve the gastroesophageal symptoms (114).
Although the incidence of Scleroderma renal crisis (SRC) has decreased in the last few years, it may represent a very severe and life-threatening manifestation. The treatment is mainly based on ACE-inhibitors and, to improve blood pressure control, the addition of calcium-channel blockers and alpha blockers (115). In patients in whom medical treatment is not sufficient and who develop end stage renal disease (ESRD), kidney transplantation may be an option as the survival rate after transplantation was similar to that observed among patients with ESRD due to other conditions, while the survival of patients who receive dialysis was worse than for those with other causes of ESRD (116).
DUs, when present, may represent another important cause of impairment for patients with SSc and a combination of pharmacological and local treatment is recommended (100). In a proof of concept study performed by Hughes *et al*., they suggested the possible use of low-level light therapy as a well-tolerated, safe method that can be proposed for the local treatment of SSc-DUs with some promising data on the efficacy (117). Additionally, a non-invasive oxygen-ozone therapy has been studied for the treatment of SSc-DUs with encouraging results in terms of reduction of wound dimension and higher healing rate. The process of ozone-induced wound healing is probably mediated by the expression of VEGF and ET-1 type A receptor (118).

Non-pharmacologic approach
Of note, in addition to pharmacological treatment, an adjunctive advantage may be obtained with physical exercise and should be recommended for all patients with SSc (119). In addition, an occupational therapy treatment, in particular with a combination of thermal modalities, tissue mobilisation, and upper extremity mobility exercises for 8 weeks, may improve the hand and upper extremity function in a statistical and clinically meaningful way (120). On the contrary, in a cohort of 36 SSc patients the addition of a daily home wax bath to hand exercises for 9 weeks did not demonstrate any statistically significant improvement compared to hand exercises alone (121).
A very curious complementary approach for SSc patients may be pet therapy. The interaction between patients and dogs during ILO infusions may benefit patients by decreasing their anxiety and pain perception and improving their social interaction, thus providing better compliance to the treatment (122).

Ongoing studies
As only few data derived from RCTs are available, several clinical trials are ongoing for the treatment of patients with SSc. In particular, a recently registered trial is aimed at studying the effects on the vascular aspect of steroid pulse therapy for patients with early SSc, in order to verify whether an early, aggressive and relatively safe treatment may modify the clinical course of the disease (123). Despite the possible benefit of this treatment, high dose steroid treatment has been associated to the occurrence of scleroderma renal crisis which may represent a limitation of this trial (115, 124).
Moreover, a trial on the use of infusions of mesenchymal stromal cells (MSCs) for the treatment of SSc-DUs is ongoing (125). Several other clinical trials on the use of MSCs in SSc are also ongoing (126).
Lastly, very promising results in the treatment of SSc have been anticipated for lenabasum, a small molecule that acts as an agonist to cannabinoid receptor type 2 (CB2) (127). A phase III study on patients with SSc will probably be published in 2020 (128).

Conclusions
In the last year a great number of significant contributions have been made to the clinical management of patients with SSc; it is evident how an early diagnosis and an early aggressive therapeutic approach may greatly improve the prognosis of the patients. Moreover, the in-depth study of this complex disease and in particular the ongoing studies on the pathogenesis have opened the path for new therapeutic opportunities. In particular, promising results have been published on antifibrotic drugs, especially nintedanib, but also therapies with immunosuppressants, such as tocilizumab and rituximab; these medications may modify the long-term outcome for SSc patients. Hopefully, available and ongoing studies will be able to define specific patterns of the disease and move towards a personalised approach for each patient.

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