Review

Systemic sclerosis: one year in review 2024

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ABSTRACT

Systemic sclerosis (SSc) is a rare and chronic connective tissue disease of unknown aetiology and characterised by three main pathogenetic events represented by endothelial damage, inflammation with activation of the immune system leading to production of specific autoantibodies and finally fibrosis. SSc is a heterogeneous disease and the classification in two subsets, the limited cutaneous (lcSSc) subset and the diffuse cutaneous one (dcSSc), is not capable of capturing the broad and different phenotypic expression of the disease. In the last years progress has been made in the knowledge of SSc pathogenesis, in its early diagnosis and new therapeutic strategies have been proposed, however, the management of SSc still represents a challenge for the clinician. For this reason, every year several studies investigate new insights of disease pathogenesis, internal organ involvement and therapeutic approaches. The purpose of this review is to provide an overview of the literature published in 2023.

Introduction

Systemic sclerosis (SSc) is a rare and chronic connective tissue disease characterised by three main pathogenetic events represented by microvascular damage (I), inflammation with activation of the immune system (II) and fibrosis (III). The aetiology of the disease still remains unknown. SSc is a heterogeneous disease as patients may present different clinical manifestations at different times during the course of the disease. For this reason, the disease management still represents a challenge for the clinician. Following the previous editorial initiatives of *Clinical and Experimental Rheumatology* (1, 2), this review aims to provide narrative critical digest of the most relevant contributions to the medical literature in 2023. A MedLine search has been performed using the term "systemic sclerosis" (MeSH terms and semantic search), focusing on the pathogenesis, organ involvement, treatments and patient-reported outcomes (PROs), published between January 1st, 2023 and December 31st, 2023. We only included studies published in English and on human subjects; case reports, case series, congress abstracts, reviews, meta-analysis and editorials were excluded.

Pathogenesis

Genetics and epigenetics

The role played by genetic background in SSc continues to attract the attention of researchers. Among the recent studies, it was found that Fms Related Receptor Tyrosine Kinase 3 (FLT3) gene variant rs76428106-c, which appears to be a low frequency single nucleotide polymorphism (SNP) in the general population, is instead significantly more frequent in SSc patients. FLT3 is a tyrosine kinase receptor involved in multiple immuno-related pathways and the mutation studied is a splicing quantitative trait locus associated with an effect similar to a gain of function mutation leading to an increase in blood monocyte count (3). Another classically investigated genetic susceptibility factor is HLA (Human Leucocyte Antigen). Interestingly, a study in a Northern Indian court found that the frequency of HLA-DRB1*11 was significantly higher in SSc patients compared to controls, whereas HLA-DRB1*12 was significantly less prevalent in the former. This finding strengthens the suggestion that some HLA alleles could play a role in determining protection or susceptibility to SSc (4).

Transforming Growth Factor-β (TGF-β) is considered the major profibrotic cytokine implied in the pathogenesis of fibrosis. It has been found in

a Mexican population that the C allele of the +869T>C variant, a SNP of the TGF-β gene, was associated with the risk of SSc development. The same study also found that the C allele of the +915G>C variant is overexpressed in SSc compared to controls (5).

Gonzàles-Serna *et al*. studied the correlation between genetic noncoding elements and the development of SSc. They isolated CD4+ T cells and CD14+ monocytes from SSc patients and healthy controls (HC) and processed their RNA finding different expressed genes (included some risk associated loci) among the two groups. Interestingly, they showed allele associated interactions between some SNPs loci (rs661849, SNPs around the promoter of Glutathione Peroxidase 3 - GPX3 gene, rs 685985) and some promoters of genes involved in immune response and inflammation in CD4+ T cells and between SNP rs589446 locus and the promoter of Structural Maintenance of Chromosome 4 (SMC4) in CD14+ monocytes. SMC4 is thought to be a promoter of inflammatory innate immune response, modulating Nuclear Factor-kB (NFκB). Interestingly, the study identified new possible genes interacting with SSc SNPs: DEAD-Box Helicase 6 (DDX6 -a protein involved in cell proliferation) and C-X-C Motif Chemokine Receptor 5 (CXCR5 - a chemokine receptor) loci in CD4+ T cells whereas in CD 14+ monocytes this interaction has been found solely with CXCR5 promoter (6).

MiRNAs (microRNA) and lncRNA (long non-coding RNA) are noncoding RNA molecules involved in regulation of genes expression on post transcriptional level by targeting the messenger RNAs. A recent study investigated the association between miRNA-133 and lncRNA-H19 in SSc. MiRNA-133 is implied in the production of TGF-β, lncRNA-H19 has been shown to regulate Pyruvate Kinase M2 (PKM2), a Pyruvate Kinase muscle gene isoform involved in the TGF-β pathway. This study found that MiRNA-133 expression was significantly lower in SSc patient than in controls, and at the same time the former had a higher expression of lncRNA-H19, PKM2 and TGF-β. Furthermore, serum concentration of MiRNA-133 was higher in patients treated with mycophenolate mofetil (MMF), and lncRNA-H19 was less upregulated in patient treated with methotrexate (MTX), implying a beneficial role of these drugs in SSc through their possible interplay in the downregulation of the TGF-β pathway (7). Another paper evaluated the serum levels of MiRNA-21 and MiRNA-29 in SSc patients. MiRNA-29 is involved in the downregulation of the expression of collagen type I, II and IV and in the inhibition of TGF-β, while MiRNA-21 promotes fibroblasts proliferation and accumulation of extracellular matrix (ECM) leading to fibrosis. The study found that MiRNA-21 levels were overexpressed in 50% of the SSc patients compared to controls whereas MiRNA-29 were downregulated in 44.1% of the SSc patients. Although the analysis of the single MiRNA could not discriminate the patients from the controls, a combined analysis could serve as a potential biomarker to differentiate SSc patients from HC (8).

Berkowitz *et al*. found that fibroblasts, keratinocytes and myeloid cell expression genes correlate with the severity of the cutaneous involvement measured with modified Rodnan skin score (mRSS). Interestingly, gene expression of keratinocytes and fibroblasts was significantly predictive of SSc severity, while genetic expression of myeloid cells did not correlate with disease severity. The study focuses on the role of ketatinocytes in SSc pathogenesis revealed, for example, by the overexpression of the gene KRT6A, and on their part in the cross-talk between immune pathways. Through the type-specific genetic expression, the study was able to create a set of predictive biomarkers of disease severity. The authors found that the keratinocyte biomarkers correlated better than the fibroblast biomarkers with mRSS severity implying that these cells play a significant role in the severity of skin involvement in SSc patients (9).

Investigating the correlation between autoantibody positivity (anti-topoisomerase-1 -ATA- or anti- RNA polymerase -ARA-) and gene expression, Clark *et al*. used a single cell RNA sequencing of the fibroblast gene expression having as a substrate skin biopsy from SSc patients and HC. They found differences in fibroblasts abundance by stage of the disease, identifying ten fibroblast clusters. These clusters had different gene expression pathways and the genes were also differently expressed based on the autoantibody positivity and on the stage of the disease. Early-stage ARA fibroblasts overexpressed the HIPPO signalling (SWH - a kinase cascade leading to the activation of Wnt) and Phosphoinositide 3-kinase (PI3K) – Protein kinase B (PKB or AKT) signalling, while early ATA fibroblasts had genes associated with TGF-β and IL6ST (Interleukin 6 Cytokine Family Signal Transducer) receptor, both expressed ECM-receptor pathway. These pathways were absent in late-stage SSc. In a direct comparison between early ARA and early ATA patients, the authors found that some key fibrosis associated genes such as POSTN (Periostin, a protein involved in activation of AKT pathway) and SFRP4 (Secreted Frizzled Related Protein 4, a Wnt pathway modulator) were more abundant in early ATA patients compared to early ARA patients. They also found that early ARA patients had an upregulated T cell receptor signalling and Janus Kinase (JAK) – Signal Transducer and Activator of Transcription Proteins (STATs) signalling, whereas early ATA patients had an upregulated calcium signalling pathway. Finally, there was more similarity between ARA late patients and controls, than in late ARA patients, supporting the theory of an ongoing active fibroblast phenotype in the ATA compared with the ARA late-stage patients. This study elucidated differences in the cellular basis of heterogeneity in skin involvement, finding an evolution in gene expression from an inflammatory subset to a profibrotic one during the progression of the disease (10). Another recent paper investigated the genes and molecular patterns related to interstitial lung disease (ILD) in regulatory T (T reg) cells from patients with SSc. Regulatory T cells have been found to play a crucial role in SSc-ILD through their function

of maintaining immune system homeostasis and self-tolerance. Interestingly, this study identified two hub genes expressed by T reg cells involved in ILD: LIPN (Lipase Family Member N) and CLEC4D (C-Type Lectin Domain Family 4 Member D). These two genes need further examination because their role in the pathogenesis of ILD in SSc patients is still unknown. These genes are usually upregulated in T reg cells in antimicrobial response, autoimmune disorders and downregulated in aminoacidic metabolism and other pathways. The limitation of the study was that there were no blood samples from patient with SSc without ILD (11).

Gastrointestinal (GI) manifestations are the most common internal organ manifestations in SSc suggesting a possible GI microbiota engagement in pathophysiology and progression of the disease. Tan *et al*. compared the GI microbiota and microbiome of SSc patients taking immunosuppressant drugs (IS) and those not, with HC. Interestingly they found that, regardless of IS, SSc subjects exhibited different microbial phyla when compared to HC. Acinetobacter and Firmicutes were more abundant in SSc, whereas Bacteroidetes were less represented in those patients. The study also found different gene expression pathways between the three groups, these included downregulations of DNA mismatch repair protein MutS, DNA topoisomerase III, hexosaminidase, beta-glucosidase more prominent in SSc patients versus the control group (12).

Cells and cytokines

Last year, research made it possible to reveal new roles for already known molecules and to discover new ones. Interleukin-6 (IL6) is a well-known proinflammatory cytokine that mediates pleiotropic functions in SSc immunologic response. A cross-sectional study pointed out that circulating levels of IL6 are associated with some peculiar SSc manifestations as digital ulcers (DUs) and calcinosis and above all with cardiovascular risk estimated by the SCORE2 algorithm (13). On the other hand, an American paper identified anti-gephyrin as a novel SSc autoantibody associated with bowel manifestations. Gephyrin is a protein located in the postsynaptic membrane of inhibitory synapses and is expressed by myenteric neurons that regulate gut motility. Anti-gephyrin autoantibodies were found in SSc patients in a clear and strong association with severe constipation, thus highlighting a pathogenic role for this novel autoantibody in SSc lower bowel dysfunction (14).

Several mechanisms have been proposed to drive the fibrotic process in SSc. Among them, endothelial to mesenchymal transition (EndMT) is certainly one of the most investigated in the recent literature. A cross-sectional study on skin biopsies demonstrated that EndMT features were more frequent in SSc patients compared to HC but found no differences between subgroups with a different extent of clinical and histopathological fibrosis. This suggests that the contribution of EndMT to SSc pathogenesis is not strictly correlated to the severity of fibrosis. Moreover, the frequency of EndMT features increased with the abundance of senescence markers, thus highlighting an interesting interplay of these two pathogenic mechanisms (15). Another study started from the evidence that blood vascular endothelial cells can undertake EndMT and investigated whether this could also happen for the lymphatic endothelium. Differently from HC, the co-expression of both lymphatic endothelial cell markers and myofibroblast markers was found only in skin samples from SSc patients. The presence of these intermediate cells is strong evidence that lymphatic endothelium can represent an additional source of myofibroblasts in SSc through a lymphatic-EndMT process (16).

The constant search for new pathogenetic mediators has led to the identification of the S100A4 protein as a possible biomarker for fibrogenesis. S100A4 has both intracellular and extracellular functions, acting in a wide range of processes from apoptosis to mesenchymal proliferation and acts as a damage-associated molecular pattern (DAMP) protein, thus stimulating pro-inflammatory pathways and extracellular matrix remodelling. In a recent study, it was demonstrated that S100A4 concentrations were significantly higher in both serum and culture supernatants of fibroblasts from SSc than HC. A clear association was also found with the presence of ILD. Moreover, recombinant S100A4 promoted a fibrotic phenotype in normal fibroblasts and a monoclonal antibody targeting S100A4 was able to revert the fibrotic phenotype exhibited by SSc fibroblasts. All these findings point towards a profibrotic role for S100A4 in SSc and suggest that its serum level may be used as a biomarker for organ involvement and disease severity, making this protein a potential treatment target for future trials (17).

Given that ILD and pulmonary arterial hypertension (PAH) are the leading causes of death in SSc patients, several efforts have been made to unravel their pathogenesis. A recent article put the spotlight on the role of extracellular vesicles (EVs) in SSc-ILD pathophysiology. Transmission electron microscopy made it possible to demonstrate that the number of EVs found in SSc lung tissue and in cultures of SSc lung fibroblasts was significantly higher than that observed in lung and fibroblasts from HC. Moreover, the EVs from SSc lung samples showed higher fibrotic content, namely fibronectin and collagen type I. The authors then incubated lung fibroblasts from HC with SSc-EVs and found a greater expression of fibrotic protein like collagen type I and III, thus suggesting that EVs can actively propagate fibrosis in SSc lung. This hypothesis was strengthened by the fact that EVs derived from TGFβ-stimulated lung tissues are able to induce fibrotic gene expression and secretion in healthy lung fibroblasts (18). Instead, other studies focused on the identification of reliable biomarkers for ILD and PAH secondary to SSc. In this context, C-X-C motif chemokine ligand 10 (CXCL10) and soluble receptor for advanced glycation end products (sRAGE) emerged as two interesting molecules given that their serum levels were found to be significantly higher in SSc patients with ILD or PAH, respectively, compared to those without. However, the most relevant aspect is their predictive value.

In fact, SSc patients with high baseline CXCL10 levels had a 2.74-fold increased risk of developing new onset ILD during the follow-up. Moreover, baseline sRAGE levels in the highest quartile were predictive of new-onset PAH and PAH-related mortality (19, 20). Similarly, serum proteome analysis on more than one thousand candidates identified chemerin as a promising biomarker in SSc-PAH, given that its serum levels were found significantly higher in SSc patients with PAH compared to those without. There is evidence that chemerin induces pulmonary arterial smooth muscle cell proliferation in culture and that this effect is lost when adding the inhibitor of chemerin receptor. Furthermore, chemerin levels were in direct correlation with pulmonary vascular resistance as assessed by right heart catheterisation (RHC), thus suggesting a possible role for this biomarker for the non-invasive assessment of haemodynamic severity in SSc-PAH (21). Another attempt was made by Jee *et al*. who started from 28 serum biomarkers selected by a comprehensive literature review and measured them in 640 patients (438 SSc of whom 179 SSc-ILD, 172 with idiopathic pulmonary fibrosis and 30 HC), ultimately identifying surfactant protein-D, Ca 15.3 and ICAM-1 as the most accurate for SSc-ILD classification. The composite score calculated on the empirical thresholds of these three biomarkers was able to discriminate with great accuracy between the presence and absence of ILD and between SSc-ILD and SSc without ILD. Moreover, a higher index was associated with worse baseline ILD severity, thus making it helpful not only for the identification but also for the risk stratification of ILD in SSc patients at baseline (22). A similar study was conducted by Alotaibi *et al*. who started from the hypothesis that the worse outcome of SSc-PAH compared to idiopathic PAH may depend in part on a different alteration of circulating bioactive metabolites. They analysed more than 700 bioactive lipid metabolites from 400 SSc-PAH patients and more than one thousand idiopathic PAH and ultimately identified five metabolites able to accurately distinguish between the two forms as well as associate with markers of disease severity, thus highlighting that patients with SSc-PAH are characterised by an unfavourable bioactive metabolic profile (23).

Take home messages

- HLA alleles and SNPs play a role in determining a protection or a susceptibility to SSc (3-6).
- MiRNAs are deeply involved in the modulation of the TGF-β-mediated fibrosis production (7-8).
- EndMT is one of the most important factors for the fibrotic process in SSc, with several interplays still to be elucidated (15-16).
- Constant effort is made to find and characterise reliable biomarkers for the prediction course of ILD and PAH (19-23).

Clinical manifestations and organ involvement

Classification and prognosis

SSc is a heterogeneous disease and the binary classification in limited (lcSSc) and diffuse cutaneous subset (dcSSc) may not encompass a wider spectrum of clinical phenotypes. The classification and stratification of SSc patients represent the next challenge for physicians, allowing them to identify patients at higher risk of progression and in this context serum and tissue proteomics seem to play an important role. The proteomic analyses of serum proteins performed by Motta *et al*. identified different concentration of 33 proteins between SSc patients and HC. In addition, significant different levels of 9 proteins were detected in SSc patients with ILD who showed serum higher levels of a vascular growth factor (angiopoietin-2) and IL-22B (24). The need for biomarkers leads to investigate the possible role of proteins involved in vasculopathic processes such as semaphorine 3A whose levels have been found to be decreased in SSc patients compared to controls, particularly in those with vascular disease complications such as DU, PAH and scleroderma renal crisis (SRC) (25).

Mismetti *et al*. investigated plasma protein expression to evaluate their correlation with survival in patients with the coexistence of pulmonary hypertension (PH) and diffuse ILD, reporting a different expression of 7 proteins comparing patients with long and short survival. In particular, the authors reported that a decreased level of 5 proteins (prostaglandin D2 synthase, noelin, complement component C7, insuline-like growth factor-binding protein 7 and fibrillarin-1) and an increased level of 2 proteins involved in blood coagulation (ADAMTS13 and heparin cofactor 2) were associated with survival status. All these data again emphasise a possible role of proteomics in tracing the survival and prognosis of SSc patients (26).

The role of auto-antibodies remains important in the disease diagnosis and classification and consequently also in trying to define their prognosis (27). Yu *et al*. reported the association of ARA with a rapid progressive phenotype of SSc evaluating 75 SSc patients, and showed that some disease and demographic features such as disease duration, skin involvement, male gender, SSc subset and malignancies presented a different prevalence between patients with a rapid phenotype and those with a non-rapidly progressive SSc (28). Analysing 140 patients, a correlation between antibodies and specific clinical manifestations has been reported: anti-centromere (ACA) antibodies were associated with PAH and ATA with ILD. Anti-NOR90 and Th/To correlated with renal involvement. These data point to the importance of serological profile in tracing a possible trajectory of patient evolution (27).

In addition, SSc patients with specific autoantibodies seem to present a higher risk of cancer, such as those presenting ARA positivity. The impact of antibodies against Sjögren's syndrome/scleroderma autoantigen 1 (anti-SSSCA1 or anti-p27) has been evaluated in a case-control study analysing the serum of 209 SSc patients with malignancy and of 205 SSc subjects without. Anti-SSSCA1 presented a prevalence of 7% (31/414 patients) and their frequency was higher in patients with cancer. Breast and lung cancers were the most common cancers in patients positive for

anti-SSSCA1, and considering only patients with cancers, those anti-SSSCA1 positive showed a longer cancer-SSc interval (29).

Knowing the impact of the antibody profile in SSc, recent efforts have been made to evaluate whether the presence of additional antibodies, other than ACA, ATA and ARA, could be associated with specific clinical manifestations. In this context, Liem *et al*. reported a higher prevalence of anti-carbamylated protein (CarP) IgG antibodies in SSc patients compared to controls, particularly in ATA patients, but did not report a correlation of these antibodies with age or skin involvement (30).

Skin involvement

Skin involvement certainly represents a distinctive feature of SSc, particularly finger and hand involvement. For this reason, the possibility of SSc to affect fingerprints has been investigated by a study on 100 SSc patients, underlining a certain difficulty in their acquisition, in particular in patients who experienced loss of the fingertip fat pad, joint contracture or acro-osteolysis. However, the disease did not seem able to change the fingertips in the identification of subjects (31).

The extension of skin involvement may vary among patients and its severity often correlates with the presence of specific antibody profiles. Skin involvement is clinically evaluated by the mRSS which is unfortunately burdened by some limitations such as a low reproducibility. Also, for this reason, more objective assessment techniques, such as skin ultrasound (US), have been investigated showing promising results. In this context, it is important to remark that also the evaluation with skin US may be influenced by contextual factors. Investigating the impact of temperature, phase of menstrual cycle and time of day, Santiago *et al*. suggested that only the latter (particularly the performance of US in the morning *versus* afternoon) may influence some parameters such as dermal thickness and stiffness in the legs and feet. Therefore, this result requires particular attention in designing future clinical studies and trials (32).

A cross-sectional study on 34 patients with SSc (13 dcSSc and 21 lcSSc) and 31 HC reported an excellent intra- and inter-examiner reproducibility of myotonometre in the assessment of skin tone and stiffness. The evaluation of skin involvement by myotonometre correlated with mRSS and showed an increase in tone and stiffness parameters in dcSSc patients both compared to controls and lcSSc subjects, suggesting that myotonometre is a potential technique in the assessment of SSc patients (33).

Calcinosis is a frequent clinical manifestation in SSc patients. The revision of the medical records of 3388 patients classified as SSc revealed a prevalence of 29.4% of calcinosis and 13.5% of these had a heavy burden. Comparing patients with calcinosis and those without, the data from this study also reported a higher frequency of female gender, severe GI manifestations, skin and musculoskeletal involvement, cardiac comorbidities and vascular complications [PAH, telangiectasia and severe Raynaud's phenomenon (RP)] in the first group. The authors also described demographical and clinical characteristics comparing patients with a light burden of calcinosis or no calcinosis with those with a heavy burden, the latter being younger at diagnosis and with a longer disease duration. In addition, in patients with a heavy burden of calcinosis, musculoskeletal involvement and anti-PM/Scl antibodies were more frequent (34).

Vascular manifestations

RP represents the first SSc symptom in the majority of patients reinforcing that SSc is primarily a vascular disease. The evaluation of 25 SSc patients (12 dcSSc and 13 lcSSc) by flow-mediated dilation (FMD) revealed lower values in SSc patients than in 25 HC showing that patients with SSc presented a significant decrease in brachial artery diameter after its occlusion. In addition, the authors demonstrated a certain association between the decrease in FMD and lung involvement at HRCT and a negative correlation of FMD values with mRSS and disease duration, suggesting this non-invasive technique as a useful instrumental examination to evaluate endothelial function in SSc (35).

DUs are a frequent complication in SSc, burdened by high healthcare costs as also demonstrated by data from the Canadian registry reporting an increased number of rheumatology and internal medicine visits in patients with DU (36). Asadourian *et al*. confirmed a predominance in the involvement of ulnar artery evaluating hand vasculature in 21 SSc patients by magnetic resonance angiography as already shown by conventional angiography (37) and Doppler ultrasound of the arterial vessels.

Magnetic resonance imaging (MRI) in the evaluation of hand vasculopathy has recently been investigated by another study which suggests the possibility of differentiating between SSc patients with present or history of DU and those without by a MRI time-of-fight based technique, the DAVIX (digital artery volume index) (38).

Renal involvement

RP and DU are not the only manifestations of SSc vasculopathy, in fact endothelial involvement and damage are responsible for some of the most fearsome manifestations such as SRC and PAH. Fortunately, SRC is now a rare event in SSc patients, however, a subclinical renal vasculopathy may be detected in SSc patients. Kinuretic acid serum levels have been found decreased in 52 SSc patients compared with 20 controls, particularly in SSc patients with increased atrophy index. Contrarily, the presence of an increase in renal resistive index was associated with higher level of kinuretic acid. The data from this study suggested that serum levels of kinuretic acid could be used as a potential marker of renal involvement in SSc (39).

PAH and cardiopulmonary involvement

PAH is considered one of the most feared complications in SSc patients. In fact, data from an Italian study investigating the principal factors linked to SSc survival confirmed that PH group 1 and 3 was associated with an increased mortality risk and reported older age at SSc diagnosis, male gender, dcSSc sub-

set, steroid treatment and again PAH or PH due to ILD as significant negative prognostic factors (40).

Fairley *et al*. described the clinical phenotypes of patients with PAH and ILD from the Australian Scleroderma Cohort Study and out of 1561 enrolled patients, PAH and ILD were diagnosed in 107 patients. 112 patients only presented PAH and 372 ILD alone. The authors described a higher prevalence of male gender and dcSSc subset in the PAH-ILD group, while patients with PAH were more likely to have lcSSc and ACA positivity. In addition, regarding autoantibodies, ATA positivity was uncommon in patients with PAH and ILD and more prevalent in the group with ILD alone. Also, ANCA were more frequent in patients with only ILD and anti-Ro60, antiphospholipid antibodies and ARA more prevalent in those with PAH and ILD. Among clinical manifestations, the authors also reported that ILD was more extensive in patients with PAH-ILD than in those with ILD alone, and DU as well as a greater cutaneous involvement and myositis were more common in patients with PAH-ILD or ILD alone. The presence of both PAH and PAH-ILD were burdened by a reduced survival and extensive ILD and PAH were the conditions with the worst prognosis (41).

ILD is very common in SSc patients and lung HRCT represents the gold standard technique for its diagnosis. In a retrospective study enrolling 101 SSc patients (37 without ILD, 56 with ILD and 8 with pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis), Dupont *et al*. reported that dual-energy CT (DECT) may give additional information to standard HRCT, providing morphological and functional lung information in a single contrast-enhanced examination. In fact, the authors detected alterations of lung perfusion also in patients without lung involvement or with mild ILD and these patients complained of severe dyspnoea and lower exercise tolerance at the 6-minute walking test (6MWT). Therefore, this technique could unmask the presence of lung microvasculopathy involvement in those patients with mild or absent ILD at HRCT (42).

Patients with SSc showed a reduction of exercise tolerance compared to HC and one study reported that skin involvement, DU, reduction in forced vital capacity (FVC), and treatment with IS drugs and prednisolone, were associated with a reduced exercise capacity. In addition, the presence of myocardial fibrosis and oedema and skeletal muscle oedema correlated with a significant functional impairment (43).

Knowing that cardiac involvement and ILD are main determinants of patient prognosis, it is mandatory to investigate heart and lung status in all SSc patients. In this regard, a retrospective study enrolling 40 patients evaluated by cardiac MRI reported a correlation between right atrial functional and mortality, again highlighting the need to study SSc patients with MRI (44). The importance to evaluate cardiac function and morphology by MRI has been noted also by Knight *et al*., who reported 5 cardiac phenotypes in their analysis of heart MRI in 260 SSc patients: normal function and small cavity (I), normal function and average cavity (II), normal function and large cavity (with preserved systolic function) (III), biventricular failure (with dilatation and poor function of biventricular chambers) (IV) and right ventricular failure (V). The first and the second phenotype presented the more favourable prognosis and the other 3 phenotypes had a similar prognosis. All these data reinforce the use of cardiac MRI in clinical practice, also suggesting its possible role in the prognosis stratification of SSc patients (45).

Gastrointestinal manifestations

GI involvement still remains a challenge for the clinician being present in the majority of patients, often from the earlier phases of the disease. Patients with SSc and GI involvement may complain different symptoms depending on the affected tract, but they can also be asymptomatic and for this reason all SSc patients should be investigated to evaluate GI involvement and function also in the absence of specific symptoms. Among instrumental examinations, oesophageal and intestinal manometry, surface electrogastrography and hydrogen breath test have been used to evaluate 30 SSc patients revealing an intestinal manometric compromise in 80% of patients. 76% of patients presented alterations at the oesophageal manometry and electrogastrography was compromised in one third of the enrolled patients. In addition, evaluation by hydrogen breath test revealed a bacterial overgrowth in two-thirds of the patients and among these 23% also presented an oesophageal, gastric and intestinal involvement. In this population, oesophageal and GI involvement did not correlate with the presence of symptoms again reinforcing the need to investigate the presence of a gastrointestinal involvement also in asymptomatic SSc patients (46). To know whether GI involvement is present is of primary importance as it may lead to malnutrition as recently reported by Rivet *et al*. showing an association between severe malnutrition and interincisal distance <35 mm in 120 SSc patients, 71 (59.2%) of whom malnourished according to 2020 French recommendations. In addition, the authors reported a correlation of malnutrition and cardiac involvement (47).

Neurological involvement

Neurological involvement is rarely investigated in scleroderma patients and therefore often unrecognised. Ivanova *et al*. evaluated the prevalence of small- and large-fibre neuropathy in 67 patients (54 females and 13 males) by nerve conduction studies (NSC) of bilateral upper and lower extremities. The authors reported a large-fibre neuropathy in 32/67 patients and in the remaining a high prevalence of small-fibre neuropathy was found (27 patients). Out of 59 patients with neuropathy (both small- and large-fibre), a possible secondary cause was found in 21 (treatment with cyclophosphamide, chemotherapy, diabetes mellitus or thyroid and renal diseases), however, there were no differences in the prevalence of these same conditions in patients without neuropathy. The authors also reported an association of the Health Assessment Questionnaire-Disability Index and the severity of neuropathy and neuropathic pain (48).

Take home messages

- Stratifying the prognosis of SSc patients represents the next challenge and recent studies confirm the importance of autoantibodies together with serum and tissue proteomics that seem to play a prominent role (25-28).
- Skin involvement is a distinctive feature of the disease and new evaluation methods, such as US, have confirmed promising data (32).
- Characterising cardiac involvement remains of fundamental importance in SSc. MRI is an essential method to study heart involvement allowing the identification of different phenotypes characterised by a different prognosis (40-45).
- GI involvement is often asymptomatic and all SSc patients should be screened for GI involvement by semi-invasive methods (46, 47).

Treatment

Treatment of SSc is still particularly complex since the disease is frequently characterised by heterogenous internal organ involvement. Therapies need to be carefully tailored according to the clinical presentation and comorbidities of the patient.

ILD and PH

To date, SSc-ILD is the main cause of morbidity and mortality in SSc patients. Keyes-Elstein *et al*. showed that haematopoietic stem cell transplantation (HSCT) significantly improved pulmonary function, mRSS and quality of life in SSc patients compared to cyclophosphamide (CYC), particularly benefiting those with inflammatory and fibroproliferative disease. The study emphasised the importance of considering early treatment failures in clinical trend analyses, revealing long-term benefits of HSCT (49). Similarly, in a single-centre cohort study on 29 SSc patients, rituximab treatment was associated with notable improvements in skin and lung fibrosis in SSc-ILD, with reductions in serum immunoglobulins indicating a stronger response to treatment (50).

Nintedanib, the only antifibrotic approved to date, emerged as a key treatment for SSc-ILD, showing efficacy in slowing disease progression across various patient subgroups, regardless of the extent of fibrotic ILD at baseline (51), proving a better response rate among patients with risk factors for rapid progression (52). Real-world data further supported nintedanib use despite gastrointestinal side effects (53).

The association between oesophageal involvement and ILD has been well investigated even though the casual relationship between the two factors is still ill-defined. A retrospective analysis on patients with SSc and SSc-ILD from the German Network for Systemic Sclerosis (DNSS) database found no link between gastroesophageal reflux disease (GERD) and SSc-ILD survival outcomes but suggested a potential survival benefit from proton pump inhibitor (PPI) use, highlighting diverse therapeutic strategies in managing Ssc-ILD (54).

Skin and musculoskeletal involvement

A Phase 3 study on lenabasum, a cannabinoid type 2 receptor agonist, failed to demonstrate efficacy in dcSSc, showing no significant improvements on the American College of Rheumatology combined response index in dcSSc (CRISS), nor on mRSS compared to placebo (55). Similarly, the PRedSS trial, a Phase II study, on the impact of low-dose prednisolone on dcSSc, showing no significant difference in primary endpoints (HAQ-DI and mRSS) at 3 months (56). However, prednisolone use resulted in significantly less pain, anxiety, and feelings of helplessness, suggesting potential benefits in symptom management despite the small sample size. To notice, there were no renal crises.

A single-centre phase 1 trial in Japan found that brodalumab (57), an anti-IL-17 receptor A monoclonal antibody, reduced mRSS in SSc patients at 4 and 52 weeks, indicating potential efficacy of brodalumab in skin involvement in SSc, despite drug-related adverse events such as oral and vulvovaginal candidiasis.

The NOVESA study, a phase IIa trial, reported the efficacy of ziritaxestat, a selective autotaxin inhibitor, on skin involvement in early dcSSc with a significant reduction of mRSS compared to placebo at 24 weeks. The treatment was well tolerated, with headache and diarrhoea as the most frequent adverse events (58).

Radić *et al*. showed how eradicating Helicobacter pylori even in SSc patients without dyspeptic symptoms improved skin condition and inflammatory markers, indicating potential therapeutic value, though further research is needed (59).

Gastrointestinal involvement

GI involvement is still one of the main comorbidities in SSc patient with very limited therapeutic approaches. A multicentre retrospective study on the use of intravenous immunoglobulin (IVIG) in SSc patients highlighted its positive impact on gastrointestinal symptoms, muscle strength, and skin tightness, with minimal adverse effects (60). Interestingly, benefits on GI involvement were not see in patients with ARA positivity, suggesting IVIG's varying effectiveness based on specific SSc manifestations.

PPIs are still one of the mainstay symptomatic treatments for GI symptoms. In a cross-over study, Alex *et al*. investigated the effects of acid-reducing agents on the bioavailability of MMF in SSc patients, showing how acid-reducing medications decreased the bioavailabity of MMF, hence reducing its effectiveness (61).

Vascular involvement

The RISE-SSc trial's extension phase, involving 87 participants from the initial study, indicated that long-term use of riociguat in SSc patients, including those with ILD, was safe with no new pulmonary concerns, despite lacking a control group (62).

Senet *et al*. found that botulinum toxin was ineffective in reducing the frequency of RP episodes in SSc patients, indicating it may not be an effective treatment option (63).

Conversely, preliminary findings from phase IIa study on angiotensin II type 2 receptor agonist, C21, suggest it might reduce symptoms of RP in SSc (64), warranting further research.

A multicentre study by Watanabe *et al*. reported that continuous heating of the arm near the elbow significantly alleviated RP in SSc patients, suggesting a potential non-pharmacological treatment method (65). Scaturro *et al*. revealed that combining manual and ultrasound therapy were more effective in improving pain and healing of SSc ischaemic DU than manual therapy alone (66).

Other treatments and future perspectives

Karaaslan *et al*. compared real-time telerehabilitation (RTT) and asynchronous telerehabilitation (AT) on SSc patients with a single-blinded randomised clinical trial (67). Over 8 weeks, both RTT and AT groups saw improvements in finger and wrist range of motion, upper extremity functions, and activities of daily living, with RTT showing additional benefits.

With a similar intent, Sahin *et al*. investigated in a randomised controlled trial the impact of upper extremity home exercises on grip strength, range of motion, and overall functionality in individuals with SSc, showing a positive effect and suggesting the inclusion of these exercises in rehabilitation programs (68).

Iglesias *et al*. found that fat micrograft combined with the adipose-derived stromal vascular fraction significantly alleviated pain and reduced DU in SSc compared to standard medical treatments (69). Focusing on pain reduction, Bellocchi *et al*. observed that transcutaneous auricular vagal nerve stimulation (tVNS), a non-invasive treatment for SSc, significantly reduced pain and downregulated inflammatory markers compared to control, suggesting its potential as a complementary treatment for SSc (70).

Take home messages

- Haematopoietic stem cell transplantation, rituximab, and nintedanib significantly benefit SSc- ILD patients' pulmonary function and quality of life (49, 50, 53).
- PPI use, not GERD, correlates with better survival in SSc-ILD, indicating therapeutic potential (54).
- Treating *Helicobacter pylori* infection can improve skin involvement and reduce inflammation (59).
- IVIG effectively targets gastrointestinal, skin, and musculoskeletal symptoms in SSc (60).
- Innovative methods like continuous heating and combined manual and ultrasound therapies show promise in treating RP and DU (65, 66).
- Telerehabilitation and home exercises improve functionality and quality of life in SSc, endorsing their inclusion in treatment plans (67, 68).

Patient-reported outcomes

There are few longitudinal studies examining the predictors of perceived functional status in SSc by systemic patient-reported outcomes (PROs). Modified health assessment questionnaire (M-HAQ) score is a validated measure and recently it has been tested in a large multicentre prospective trial of early SSc patients established in North America, the GENISOS cohort (71). This study assessed M-HAQ changes over time, factors associated to its course and the effect on mortality. At enrolment, African American and Hispanic ethnicity, older age, single marital status, current smoking, dcSSC involvement, higher mRSS, and ARA were significantly but univariately associated with higher M-HAQ scores, on the contrary higher levels of education and income, higher FVC% predicted, ACA or high haemoglobin levels associated with lower scores. These associations persisted in the longitudinal analysis, and multivariate models showed that only education and income levels, mRSS, and age at enrolment were the only baseline independent predictors of longitudinal M-HAQs. The positive relationship between M-HAQ and mRSS was maintained also in the longitudinal analysis and equally higher FVC% corresponded with persistently low M-HAQ scores. Lastly, but most importantly, M-HAQ was an independent predictor of survival in a multivariable model that included all variables predictive of survival in the simple models, together with (as expected) age at enrolment, and baseline FVC%.

The newly described EULAR Systemic sclerosis Impact of Disease (ScleroID), already validated and tested on SSc general manifestations has been further investigated for its correlation with musculoskeletal and internal organ involvements in a large tertiary care SSc European cohort (72). The authors found that in general ScleroID scores were similar across different disease subgroups but that a significant correlation existed with Eustar revised AI, GI scores assessed by MHISS and the UCLA GIT 2.0 questionnaires and with all articular disease activity scores (DAS28-CRP, DAS28- ESR, CDAI and SDAI) or other PRO related to musculoskeletal function such as M-HAQ, the HAMIS, the Cochin hand score, and in a similar fashion across dc- and lc-SSc subgroups, with both early and longstanding disease. On the negative side, the ScleroID in this cohort did not perform well in distinguishing different degrees of cardiopulmonary involvement as assessed by NYHA scores or 6MWT distance or else low FVC% (72).

Severe and progressive ILD is a major determinant of SSc patients' quality of life (HRQoL). In SSc, PRO, especially those focused on lung-related outcomes, are very hard to change even in successful registrational trials where clinical endpoints are significantly attained, as is the case of nintedanib in the SENSCIS trial (73), or tocilizumab in the Focussed trial (74). There are more factors than just strictly respiratory determinants in SSc-ILD to influence PROs such as St. George's Respiratory Questionnaire (SGRQ), Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea, or the VAS breathing problems included in the modified SHAQ. A recent *post-hoc* analysis of the SENSCIS trial has investigated possible peculiarities of SSc-ILD patients and whether SSc/SSc-ILD severity and great changes in lung function correlate with HRQoL (75). Aggregating treatment arms from baseline to week 52, the authors have demonstrated that baseline PRO measure scores were generally worse in patients with dcSSc, with more advanced lung function impairment (FVC <70%

predicted), greater extent of fibrosis on HRCT (>30%), worse skin disease (mRSS >18), higher ILD-GAP (gender age and physiology) stage, presence of GERD, and presence of upper GI symptoms in those who were receiving MMF. After the 52 weeks of the trial, those patients with a preserved (>70%) FVC showed significantly favourable mean scores of SGRQ, FACIT-Dyspnoea HAQ-DI and SHAQ VAS breathing problems. Similar results were observed when categorising patients into those who required oxygen support already at baseline, those with cough or those with a tomographic extent of fibrotic changes >30%. In general, PRO scores in patients, albeit not reaching statistical significance, followed trends in FVC: they improved in those experiencing an increase (>5%) and worsened in patients who showed declining lung function (>10%), thus meaning that PROs are well representative of the direction of the biologic process underlying symptoms and signs of SSc-ILD. The lack of a significant effect in the treatment group, however, stresses the need to identify therapeutic strategies ensuring a true DMARD effect on various SSc manifestations, in particular the cardiopulmonary ones.

Manifestations prognostically less severe than ILD but with a significant impact on a poor health- related quality of life (HRQoL) are calcinosis and ulcers/infections with consequent pain and functional impairment. There is no standard treatment for SSc-calcinosis and no standardised measures to assess potential therapeutic responsiveness in clinical trials. Patients often rely on self- report and self-management but the presence of calcinosis influences the evaluation of general PROs in SSc thus contributing to the lack of their sensitivity to change in clinical studies not specifically targeted to calcinosis. A study by Saketkoo *et al*. (76) has recently proposed the development of the Mawdsley Calcinosis Questionnaire (MCQ) by conducting a study in North American and UK centers via in-person focus groups (FG). The questions asked were just 2: 1. 'Since developing calcinosis, how has your life changed over time?' and '2. How has the calcinosis changed over time?'. With the help of the 40 patients enrolled, questions that could help the clinician determine changes in the calcinosis manifestation were formulated and assessed by a Likert scale from 0 to 5. Seven themes emerged: qualities, physical sensation, functional impairment, influencing factors, self-management, emotional impact and uncertainty, and 4 major PRO domains: Quantity/Frequency of Calcinosis (4 items), Pain/Sensation (5 items), Physical Function/Functional Impairment (4 items), and Psychological Impact (6 items). During discussions, interesting features emerged of living and dealing with calcinosis but also some issues such as cognitive slowing and fatigue emerged as especially difficult to be attributable to calcinosis alone as opposed to other SSc features such as lung involvement, and would not be valuable PRO elements for SSc-calcinosis. The MCQ is not yet fully validated but is already being used in multicentre clinical studies alongside further validation steps (and translations), which are anticipated to finalise a scoring and weighting system (76).

Three studies (77-79) have focused on one of the key debilitating symptoms in SSc, unique in the way PROs reflect to the clinician the essence of the symptom, RP. At the crossroad between PRO and telemedicine, Domsic *et al*. have described the construction and content validity of the Raynaud Diary, and tested the usability of a tablet and their smartphone to complete the survey. Results were varied as patients verbalised the RP experience in different ways, but themes emerged that are common ground of studies on RP, *e.g*., pain, triggers and hand activity limitations. No feasibility issues emerged from the device evaluation, generally well accepted and straightforward to use by the majority of participants. A large study of 420 SSc patients determined the validity and reliability of the Assessment of Systemic Sclerosis-Associated RP (ASRAP) questionnaire and its recently described short form (39 *vs*. 27 items) (78), showing good and significant correlation with disability indexes, hand function, pain and global health assessment and with vascular complication such as DU and calcinosis; the minimally important clinical difference was also identified (4.17 (95% CI 0.53, 7.81, p=0.029)) (79).

Take home messages

- PROs in SSc are being validated for different aspects of the pathology, ILD, RP, general impact on QoL, but are still very difficult to improve with current therapeutic strategies in the disease (72-75).
- Direct involvement of patients in establishing validated PROs has proven helpful to understand the subjective perception of multiple clinical domains of SSc and aspects of the management that need most improvement (76-79).

Conclusions

Our narrative review provides an overview of the most innovative studies published in 2023. Many efforts have been made to better understand the pathogenesis of the disease and its clinical manifestations and currently available therapeutic approaches offer new perspectives in the management of the disease. The next goal will be to achieve the concept of precision medicine also in SSc tailoring the best therapeutic strategy for each patient. Achieving this objective need to early diagnose the disease and to classify all patients trying to trace their trajectory in order to know their prognosis with the aim to improve patients' survival and quality of life.

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