Review

Systemic sclerosis: one year in review 2023

M. Di Battista[1,2], G. Lepri[3], V. Codullo[4], M. Da Rio[1], E. Fiorentini[3], A. Della Rossa[1], S. Guiducci[3]

[1]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;*
[2]*Department of Medical Biotechnologies, University of Siena;*
[3]*Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence;*
[4]*Rheumatology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.*

Marco Di Battista, MD
Gemma Lepri, MD
Veronica Codullo, MD
Mattia Da Rio, MD
Alessandra Della Rossa, MD
Serena Guiducci, MD, PhD

Please address correspondence to:
Alessandra Della Rossa
U.O di Reumatologia,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: a.dellarossa@ao-pisa.toscana.it

Received on April 15, 2023; accepted in revised form on April 29, 2023.

Clin Exp Rheumatol 2023; 41: 1567-1574.

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

Competing interests: none declared.

ABSTRACT

Systemic sclerosis is a rare and chronic connective tissue disease resulting from an intricate pathogenesis and is expressed in very heterogeneous clinical manifestations. Every year many studies try to unravel and shed new insights into the pathogenesis, organ involvement and treatment of this complex and severe disease. We herein provide an overview of the most relevant studies published in the literature in 2022.

Introduction

Systemic sclerosis (SSc) is a chronic and complex multi-faceted disease, whose early diagnosis and global management is crucial for the prognosis and quality of life of the patient. Continuing the editorial initiative of *Clinical and Experimental Rheumatology* to provide relevant recent insights on rheumatic diseases in the form of "One year in review" (1, 2), we herein present a narrative critical digest of the most significant studies on SSc published in 2022. A MedLine search was performed with the key word "systemic sclerosis" (MeSH terms and semantic search), focusing on pathogenesis, clinical manifestations, treatment and patient-reported outcomes (PROs). We included articles in English on adult SSc patients published between 1st January 2022 and 31st December 2022. Among these papers, we have selected 63 as the most relevant in the field.

Pathogenesis

Genetics and epigenetics

Environmental factors are one of the earliest pathogenetic events in SSc and, among these, infectious triggers have often been proposed. Arvia *et al*. remarked a possible role of Parvovirus B19 in SSc pathogenesis analysing the characteristics of normal human dermal fibroblasts from adult donors infected with this virus. The authors showed the presence of senescence markers in infected fibroblasts and these features, associated with the expression of some proinflammatory cytokines, were similar to what observed in SSc skin fibroblasts (3).

Fibrosis may be considered the culminating event in the pathogenesis of SSc. The activation of toll-like receptor 4 (TLR4) by damage-associated molecular patterns (DAMPs) has a profibrotic effect and leads to myofibroblast activations. Wang *et al*. evaluated radioprotective 105 kDa (RP105 or CD180) role in TLR4 responses in SSc patients through transcriptome analysis of skin biopsies from 22 patients with diffuse subset of SSc (dcSSc) and 9 controls. The authors reported a negative correlation between RP105 expression and myofibroblasts differentiation. In fibroblast, ectopic RP105 seemed able to inhibit TLR4 profibrotic process caused by DAMPs. They also evaluated the expression of TLR4 and of its coreceptors MD2 and MD1 reporting increased levels of TLR4 and MD2 in SSc. On the contrary, MD1 expression was reduced in skin biopsies of SSc patients compared to healthy controls. These data may suggest a certain role of RP105-MD1 in SSc pathogenesis being a negative regulator of TLR4-dependent fibrotic process (4).

Conventional dendritic cells (cDCs) are antigen-presenting cells that have been implicated in SSc pathogenesis and, among all cDCs, CD1c+ (cDC2s) appear to be the most interesting in SSc. The transcriptomic profiling of peripheral cDc2s cells collected from SSc and healthy subjects has been recently assessed suggesting that the nuclear receptor 4A (NR4A) family members (NR4A1, NR4A2, and NR4A3) may play a role as regulatory factors of cDC2s in SSc (5).

Gur *et al*. performed an accurate genomic analysis of skin and blood

samples of 56 healthy controls and 97 SSc patients showing a global dysregulation of the stromal compartment, particularly in a subset of LGR5+ scleroderma-associated fibroblasts in dcSSc patients. This subset appeared to be altered both in its abundance and signalling activity in SSc patients compared with healthy subjects (6).

Many studies focused on the pathogenetic role of microRNAs, and one of them reported that miR-132, -143, -145 and -155 were significantly upregulated in SSc patients. This study also suggested the potential impact of these microRNAs in SSc pathogenesis and their possible role as disease biomarkers (7). Another study reported that miR-27a was significantly downregulated in SSc patients compared to controls. Several factors contributing to SSc pathogenesis were found elevated upon the downregulation of miR-27a, especially positivity for anti-topoisomerase I autoantibodies (ATA), anti-ribonucleoprotein antibodies, Th/To autoantibody, and the presence of interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), myositis and digital ulcers (DUs), thus suggesting that its downregulation could be involved in the onset of the disease (8). In addition, miRNA-27a-3p was proposed as a possible protective factor in SSc, since it was found to be downregulated in lung and skin cells of SSc patients. When tested *in vitro*, its overexpression significantly inhibits fibrosis-related gene expression in human cell lines. The authors suggested that miR-27a-3p may affect the fibrotic process in SSc tissues by a negative regulation of secreted phosphoprotein 1 (SPP1) and that miR-27a-3p-SPP1-ERK1/2 axis may represent a potential therapeutic target for SSc lung and skin fibrosis (9). Han *et al*. reported an up-regulation of miR-155-5p expression in SSc patients, and also its negative correlation with suppressor of cytokine signalling 1 (SOCS1) levels. The expression of miR-155-5p was positively correlated with interleukin-17 (IL-17) expression in Th17 cells isolated from SSc patients as the disease progressed. These data suggest that miR-155-5p can modulate IL-17 and SOCS1 expression potentially having a key role in SSc progression (10). Bayati *et al*. observed that the relative expression of miR-138 was considerably decreased in both limited cutaneous SSc (lcSSc) and dcSSc patients in comparison to the controls. The authors proposed miR-138 expression as a novel biomarker for SSc, however this finding needs further studies (11).

CHI3L1 is an inflammation-associated glycoprotein that was reported to be increased in sera of SSc patients. Dichev *et al*. investigated a possible regulatory axis in the control of CHI3L1 expression confirming the increased levels of CHI3L1 in SSc compared to controls, particularly in dcSSc. Among the analysed miRNAs, miR-30e-5p and miR-30a-5p were found to be significantly downregulated in SSc white blood cells and plasma. The downregulation of these two miRNAs was suggested as responsible of the increased levels of CHI3L1. In addition, the dysregulation of two long non-coding RNAs (lncRNA), namely MALAT1 and NEAT1, may be associated to the downregulation of miR-30e-5p and miR-30a-5p. Data from this study suggest the possible presence of a regulatory axis between lncRNAs/miR30e/CHI3L1 in SSc patients (12).

A recent study investigated gene expression changes in peripheral blood mononuclear cells (PBMCs) from lcSSc and dcSSc. Among genes with increased expression levels, the predominant signal in PBMCs was for type I interferon signalling. The authors also reported decreased expression levels of SPAG17, a protein known to play an important role in the formation of primary cilia, in SSc skin samples compared to controls. However, the role of this protein in skin and immune cells remains to be clarified and it may open new perspectives in SSc pathogenesis. The authors also showed that the skin of SSc patients had enriched pathways with function in immune cell adhesion, migration and differentiation as well as in complement activation. A negative correlation between diffusing capacity of the lungs for CO (DLCO) and genes involved in type I interferon signalling was observed and the expression of genes involved in protein folding, unfolded proteins and endoplasmic reticulum stress had a negative correlation with modified Rodnan skin score (mRSS) (13).

Regarding genetic susceptibility, a recent study analysed the possible contribution of the regulatory splicing factor mRNA-binding protein serine/arginine protein 55 (SRp55) gene in influencing both the predisposition and the clinical phenotype of SSc. SRp55 mediates the alternative splicing of the exon 8 of vascular endothelial growth factor-A (VEGF-A) pre-mRNA, which is a key element in the switch from proangiogenic to antiangiogenic VEGF-A165 isoform. This study suggested that the SRp55 rs2235611 AA genotype may significantly influence the susceptibility to SSc, especially in the presence of SSc-ILD and severe peripheric vascular involvement (14). The human leukocyte antigen (HLA) can play an important role in disease development, especially in different ethnic groups. A recent study on Thai-population found that HLA-DRB1*15:02:01, DRB5*01:02:01, DQB1*05:01:24, DPB1*13:01:01; DQA1*01:01:01 and DPA1*02:01:01 alleles were significantly associated with SSc and ATA presence (15).

Cells and cytokines

Endothelial injury is a key event in SSc pathogenesis. Ross *et al*. reported that the expression levels of hemeoxygenase-1 (HO-1), an antioxidant enzyme, were reduced in early fibroblasts from lcSSc and inhibited by transforming growth factor-β (TGFβ) in SSc endothelial cells. In addition, the downregulation of HO-1/CO pathway seemed to influence intracellular Ca2+ signalling and to be correlated to impaired angiogenesis, suggesting a potential involvement of HO-1/CO signalling in the early pathophysiological events of SSc (16).

An interesting study on SSc-PAH pathogenesis analysed the role of sphingosine-1-phosphate receptor (S1PR) as a potential antigen for PAH autoimmunity, given the documented role of S1P/S1PR signalling in PAH pathogenesis. Serum samples from 158 SSc patients, 58 of whom with PAH, and 333 healthy control subjects were screened for the presence of antibodies against S1PR. In SSc patients without PAH, the prevalence of

these autoantibodies was higher than in healthy subjects, but in the subgroup of SSc patients with PAH their prevalence was even greater, thus suggesting that S1PR may act as an autoantigen in SSc patients, particularly if affected by PAH (17). Possible pathogenetic mechanisms of SSc-PAH have been investigated also by Sanges *et al*. who found that several serum B-cell biomarkers levels, namely IgG, b2-microglobulin, BAFF, sBCMA and sCD23, were associated with PAH status in lcSSc patients with no extensive ILD and without immunosuppressant or steroid treatment. In addition, they also demonstrated that B cells can produce greater quantities of angiogenic factors like angiogenin, angiopoietin 1, PDGF-AA and TIMP-1, suggesting a possible contribution of B cells in SSc microangiopathy (18).

T cells seem to be involved both in the early inflammatory response and in the late fibrotic process. A study evaluated the circulating levels of Th2 and Treg cells reporting lower levels in SSc compared to controls and an association between the decreased number of total T, Th, and Treg cells with C reactive protein. Regarding serum levels of cytokines, a positive correlation between IL-2 levels and erythrocyte sedimentation rate was suggested (19). Yang *et al*. explored the expression of IL-35 and its activity in CD4+ T lymphocytes and human skin fibroblast (HSF) in SSc patients. They analysed blood and skin biopsies from 41 SSc patients and 39 healthy controls and showed lower levels of Th1/Th2 and higher Treg levels in SSc. Patients also presented higher levels of IL-35 but lower levels of IFN-γ, IL-10, and TGF-β. After culture of CD4+ T lymphocytes with HSF, they reported that recombinant human IL-35 treatment suppressed CD4+ T lymphocyte and HSF proliferation in SSc patients compared with controls, suggesting a possible inhibitory role of IL-35 in CD4+ T lymphocyte proliferation. On the other hand, IL-35 seemed to activate STAT1 signalling, HSF proliferation and collagen expression in SSc (20).

Regarding monocytes, a study characterised the surface expression of adhesion/chemotactic molecules (CD62L, CD11b, CCR2, CCR5) on monocytes from blood samples of SSc patients and healthy controls. Soluble CD62L was increased in SSc serum samples and also on the surface of the SSc monocytes. The surface expression of CD62L was highest in patients with ATA and lowest in those positive for anti-PM/Scl autoantibodies (21). Yokoyama *et al*. provided new insights about the possible role of carcinoembryonic antigen-related cell adhesion molecule (CEACAM)-positive monocytes in the pathogenesis of SSc reporting that the proportion of CEACAM-positive classical monocytes was increased in early SSc patients, and their percentage decreased after immunosuppressive treatment. In addition, the authors reported the possibility to induce CEACAM6 expression on monocytes from healthy controls through SSc patients' serum. Furthermore, CEACAM-positive mo-nocytes were characterised by an inflammatory phenotype (22).

The exact role of neutrophils in SSc pathogenesis is not fully clarified. N-formyl methionine (fMet) is a potent mitochondrial-derived neutrophil agonist that promotes neutrophil chemotaxis and activation, and it was recently assessed in plasma from two SSc cohorts. It was demonstrated that circulating fMet was significantly increased in SSc and it was directly correlated with markers of neutrophil activation (23). Another study evaluated functional and phenotypic markers of neutrophils in SSc, reporting several functional defects affecting cell migration, neutrophil extracellular traps formation, and phagocytosis of bacteria. In particular, SSc neutrophils displayed lower CD16 and CD62L on their surface, as well as a lack of the chemokine receptors CXCR1 and CXCR2, whereas a higher phosphorylation of STAT3 and STAT6 was expressed (24).

Regarding B cells, Horii *et al*. measured blood levels of IL-6-producing effector B cells (Beff) and IL-10-producing regulatory B cells (Breg) in 30 SSc patients and 21 healthy subjects. Results from this study suggested a certain role of Beff and Breg balance alteration in SSc pathogenesis: a significant increase in the frequency of IL-6-producing Beff was found in SSc patients compared to controls. On the contrary, the frequency of IL-10-producing Breg was decreased in patients with SSc compared with healthy controls. The Beff/Breg ratio was considerably increased in patients with SSc positively correlating with skin involvement and ILD extent (25).

Take home messages

- Environmental factors with the possible role of infectious triggers can act on subjects with genetic predisposition laying the fundaments for SSc pathogenesis (3, 14, 15).
- In the fibrotic process many pathways seem to interplay, among these the role of microRNAs and of long non-coding RNAs has been reported (7, 8, 10). A decrease expression of SPAG17, whose role in skin and immune cells remains to be clarified, has also been recently reported in SSc (13).
- Alteration of T-lymphocytes subset and of their serum cytokines is reported in SSc patients confirming its role in SSc pathogenesis (19). The activation of immune response also includes monocytes and neutrophils, and recent studies characterised the surface expression of adhesion and chemotactic molecules on these cells and their functional phenotype (21, 22, 24).

Organ involvement

Cardiovascular involvement

Myocardial fibrosis is believed to be the conclusion of a common process involving multiple mechanisms: recurrent episodes of ischaemia-reperfusion injury, microvascular dysfunction and myocardial inflammation. Ross *et al*. sought to clarify the extent to which fibrosis may become clinically relevant in SSc and may be a substrate for the development of arrhythmias by subjecting 34 patients without major cardiovascular involvement to evaluation with cardiac magnetic resonance (CMR) and 24-h ECG monitoring. There was no association between myocardial fibrosis and the presence of atrial or ventricular arrhythmias, also considering elevated T1-mapping or T2-mapping times or the presence of late gadolinium enhancement (26). A large British study set out to stratify cardiac involvement in SSc based on CMR retrospective data of 260 patients. They unexpectedly found that

patients with normal function with large cavity sizes have the same prognosis as patients with right ventricular failure or biventricular failure dilatation and dysfunction after adjusting for right ventricular ejection fraction (EF), native T1, and PH diagnosis. Independent CMR predictors of all-cause mortality were native T1 and right ventricular EF (27). The prognostic role of native T1 was confirmed by another study that aimed to verify the progression of myocardial damage by comparing the CMRs of healthy controls, patients with very early disease (VEDOSS), and patients with established SSc. Native T1 and extracellular volume (ECV) values were similar between VEDOSS and established SSc, a finding showing that myocardial fibrosis is already present in the early stages of disease and precedes functional impairment (28). CMR proved to be useful both in the diagnosis of SSc-myocarditis and in the evaluation of its response to treatment. A small retrospective study showed functional improvement in terms of increased EF of both ventricles after immunosuppressive therapy (mainly cyclophosphamide). T2-weight parameters were significantly reduced after immunosuppressants, unlike T1 mapping and ECV values which remained unchanged, thus representing irreversible myocardial injury. Therefore, T2 mapping seems a good parameter for assessing myocarditis progression and response to therapy (29).

Left ventricular diastolic dysfunction (LVDD) is a frequently encountered abnormality in SSc patients, even in those without apparent signs of cardiac involvement. It is not known, however, whether this dysfunction could be associated with the development of heart failure. A retrospective Australian study on 225 SSc patients reported a 15% prevalence of LVDD, without significant associations with signs of heart failure or mortality. However, LVDD was observed to progress over time (worsening of parameters of left ventricular filling pressure) (30). These findings partially contrast with those from a large American cohort of 806 SSc patients. Despite a similar LVDD prevalence of 18.6%, they found a three-fold mortality rate in patients with LVDD compared to those without. Advanced age and DLCO ≤60% were independent predictors of mortality. The strong association of DLCO with LVDD and mortality even in the absence of ILD reflects an underlying cardiovascular involvement that has to be taken into consideration (31). In this context, right atrial stiffness proved to be another echocardiographic parameter associated with SSc mortality (32). All these findings prompts to maintain a high level of attention on the cardiovascular burden of patients with SSc, which in clinical practice translates into the monitoring of useful prognostic biomarkers such as troponin (33), and above all in the promotion of early and disease-specific risk estimation strategies (34).

Vasculopathy is one of the key pathogenetic mechanisms of SSc and its clinical expression can be very heterogeneous. In this context, an interesting link with autonomic dysfunction was outlined by the reduction of baroreceptor sensitivity in SSc patients (35). Digital vasculopathy is instead a well-known complication whose study in the earliest phases of the disease still needs to be further improved. Ultra-high frequency ultrasound (UHFUS) could represent a promising tool to better characterise digital vasculopathy. UHFUS was used to assess digital palmar proper arteries (PPDA), revealing occlusions in 16.8% of SSc patients, whereas in healthy controls no alterations were detected. Considering as pathological a finger with at least one PPDA occluded, more than two-thirds of patients presented at least one pathological finger. Moreover, 73% of fingers previously affected by DUs were ultrasonographically pathological. No significant correlations emerged between nailfold videocapillaroscopy (NVC) or laser speckle contrast analysis (LASCA) findings and UHFUS features, suggesting the likely presence in SSc of non-overlapping vasculopathic processes. UHFUS can therefore detect independent subclinical vascular alterations, but the prospective value of this technique needs to be further investigated (36).

SCLEROCAP is a multicentre study aiming to validate prospectively the prognostic value of Maricq's and Cutolo's NVC classifications. It was recently demonstrated at the single finger level that capillaroscopic oedema, reduced capillary number and Cutolo's late pattern correlate with history of local DU (37). Given the importance of NVC in SSc, its use could be improved through a deep learning-based software (38). The field of non-invasive assessment of microangiopathy was recently enhanced by a novel definition of proximal-distal gradient (PDG) perfusion of fingers evaluated with LASCA. This novel LASCA-PDG definition relies on a PDG formula independent of both intra- and inter-personal factors, and thus generalisable to all kind of subjects. Its application was able to differentiate SSc and healthy controls with great sensibility and specificity; however, validation in a larger cohort is still needed (39).

Pulmonary involvement

PAH is a major complication of SSc and in most cases becomes symptomatic only in advanced stages. Therefore, the early identification of patients at risk to develop PAH becomes crucial. Favoino *et al*. had previously identified a subset of anti-centromere positive patients with higher affinity for phage clone-expressing peptide 4.2 (p4.2), who are at higher risk to develop pulmonary vascular disease. In 2022 they confirmed that this subset of patients can be identified using a synthetic p4.2 with indirect ELISA, showing an association between anti-p4.2 antibodies and reduced DLCO and pulmonary fibrosis (40). Right ventricular parameters assessed by right heart catheterisation (RHC) and echocardiogram are another source of important prognostic factors, as demonstrated by a recent study on 225 SSc patients screened for PAH. This work also underlined that, in patients without signs of pulmonary vascular disease, the only independent prognostic factor for survival was cardiac index under stress <2 L/min/m^2, thus highlighting that stress RHC can provide important information for the follow-up of apparently low-risk patients (41).

SSc-associated ILD remains a major complication and the leading cause of mortality, despite progresses in diagnosis and treatment. In this regard, an improvement in the characterisation of SSc-ILD could lead to better out-

comes. High-resolution CT (HRCT) is the pivotal investigation that every physician should use in the screening, re-screening and follow-up of SSc-ILD (42). Interesting correlations between quantitative chest tomography and SSc disease activity were proposed (43). An implementation of HRCT with radiomics, a method that extracts a large number of features from medical images using data-characterisation algorithms, was recently tried. The advantage of radiomics over other quantitative imaging techniques is the ability to create disease phenotypes by gathering information ranging from the macroscopic to the microscopic/molecular level. Schniering et al. retrospectively analysed HRCT images from two cohorts of SSc patients using an in-house-developed radiomics software and built a quantitative composite radiomic risk score to stratify patients into high- and low-risk. Such a score significantly improved the assessment of disease progression compared with the use of clinical risk factors alone (44). These results lay the foundations for a broad application of radiomics in the coming years.

Lung magnetic resonance imaging (MRI) is one of the most promising emerging techniques in the study of SSc-ILD. Several studies have already shown how lung MRI correlates with other markers of severity and can identify patients with worse pulmonary involvement. An observational study on 36 patients showed that lung MRI scores correlate with decline in forced vital capacity (FVC) and in DLCO. Moreover, MRI changed significantly between patients in stable disease and patients with ILD progression. The sensitivity, specificity, positive predictive value and negative predictive value were similar between HRCT and lung MRI (45). Lung ultrasound is another established screening tool for SSc-ILD. However, there is no standardised protocol or shared method for counting alterations detected. Results from 69 patients showed that the total number of B-lines correlates with the extent of ILD on HRCT scans. Using the 58-spaces approach, a total of >10 B-lines on the whole chest or >1 B-line on the postero-basal chest (last two intercostal spaces) showed 97% sensitivity for detecting even very early ILD signs but with a specificity of 64%. By integrating pleural changes into the analysis, the sensitivity reaches 100% but the specificity drops further (46). Dual energy CT (DECT) is a computed tomography technique that uses two separate x-ray photon energy spectra, allowing the interrogation of materials that have different attenuation properties at different energies. DECT can therefore be used to estimate lung perfusion providing complementary information to standard HRCT scans. A DECT study on 101 SSc patients described different phenotypes of perfusion changes and above all showed perfusion abnormalities even in patients with no or mild ILD (47). In consideration of all the classic and new methods exposed so far, it is essential to evaluate composite indices and not just a single parameter for a complete and correct assessment of SSc-ILD. This is also important because the importance of temporal variation has been emphasised in recent years with the definition of ILD progression based on a time delta with certain cut-offs, especially for eligibility criteria for antifibrotics. However, it has to be said that sometimes these cut-offs set restrictions, as they limit the possibility of treating patients at an early stage: this gives the input to introduce new screening methods.

Take home messages

- Cardiac magnetic resonance makes it possible to assess the actual incidence of myocardial fibrosis in SSc patients. Whether this finding is associated with the development of arrhythmias remains to be clarified. Cardiac magnetic resonance also allows to estimate the presence of subclinical myocarditis (26-29).
- Left ventricular diastolic dysfunction occurs in 15-18% of patients with SSc. The presence of this alteration is closely related to reduced DLCO and seems to result in a threefold increased mortality (30, 31).
- Ultra-high frequency ultrasound is an emerging toll for the non-invasive assessment of peripheral macroangiopathy that it is complementary to the methods already in use for the evaluation of microangiopathy (36).
- High-resolution CT remains the pivotal exam for the study of SSc-ILD, and radiomics could implement the information we can get from it (44). Next to this modality, new techniques are emerging for the study of pulmonary commitment, either for screening (lung ultrasound) or for additional information (lung MRI) (45, 46).

Treatment

Immunosuppressive therapies

Alongside data on the proven efficacy of "classic" immunosuppressants such as cyclophosphamide and rituximab, which consolidate their use in the treatment of SSc-ILD (48), in the last year the focus has been mainly on tocilizumab (TCZ). After two randomised controlled trials (RCTs), namely faSScinate and focuSSced, showed a trend in improvement of skin fibrosis and in prevention of lung function worsening in a highly enriched population of patients with early, inflammatory, diffuse and progressive SSc, the most suitable field of application for this anti-IL-6 receptor antibody has been investigated. The open-label extension of the focuSSced on 167 SSc patients reported the sustained preservation of lung function previously observed in the RCT, and confirmed the long-term safety of TCZ (49). When looking at real-life data, despite some encouraging outcomes described by a Greek centre on TCZ efficacy on refractory joint and skin involvement (50), broader multicentre cohorts get milder results. In fact, data from EUSTAR database on 93 SSc patients treated with TCZ and compared with 3180 SSc patients receiving standard of care treatment, did not show significant effectiveness of TCZ both on skin fibrosis and lung fibrosis, intended as FVC decline. However, on the other hand the trend observed in RCTs was confirmed also in a heterogeneous non-enriched real-life SSc population and with no new safety concerns (51).

Antifibrotic therapies

The antifibrotic nintedanib (NIN) is surely the most important novelty among recent SSc therapies. Sub-analyses of the SENSCIS trial revealed that NIN is effective in reducing the decline

of FVC in all kinds of SSc patients, even in subgroups that are classically associated with the progression of SSc-ILD as ATA positivity, dcSSc and mRSS >18 (52), and that the benefit is irrespective of the extent of fibrotic ILD at baseline (53). Encouraging data comes from the open-label extension trial SENSCIS-ON which was conducted on 444 SSc-ILD patients. After 52 weeks the efficacy of NIN was proven to reduce the FVC decline previously described in SENSCIS. The long-term safety of NIN was also confirmed, with diarrhoea being the most frequently reported adverse effect in approximately two-thirds of subjects (54).

Finally, preliminary yet promising results came from a Japanese pilot study that suggested beneficial effects of NIN also on SSc cardiomyopathy. In fact, they observed a reduction of myocardial extracellular volume and an increase of right ventricular EF with CMR in NIN treated SSc patients (55).

Vasoactive therapies

Interesting findings emerged regarding vasoactive therapies during the last year. The lack of common consensus on the optimal dosage of iloprost (ILO) often results in the difficulty of integrate feasibility, cost and effectiveness of ILO infusions. In this context, a laser speckle contrast analysis (LASCA) study conducted on 27 SSc patients receiving ILO with a daily outpatient scheme highlighted how ILO has a transient vasoactive effect, losing its perfusion benefit after one month. These findings and the use of LASCA are elements to consider in the future search for the optimal ILO dosage (56).

Selexipag, an oral selective prostacyclin receptor agonist, has rapidly become one of the leading drugs in the treatment of PAH. Long-term data from GRIPHON and its open-label extension have been published. This is a cohort of 953 PAH patients, more than a quarter of whom had SSc-PAH, with a median long follow-up of 31.7 months. A strength of these long-term data is that the safety of selexipag was confirmed also as part of a combination therapy regimen with endothelin receptor antagonists and/or phosphodiesterase 5 inhibitors (57).

Other therapies

Haematopoietic stem cell transplantation (HSCT) is a treatment option for patients with severe SSc. Among the various systemic effects, HSCT also seems to improve the degree of microangiopathy as assessed by NVC (58).

Alongside pharmacological treatments, physiotherapy is also of great importance. It was recently highlighted that a short but constant physiotherapy course of 1.5 hours twice a week, determines in SSc patients after 24 weeks a significant improvement in the functionality of the hand and mouth both on a subjective and objective level (59). However, despite its proven effectiveness, physiotherapy appears to suffer from underuse. Thus, the necessity for initiatives to improve the dissemination and accessibility of physiotherapy care to address an unmet need of SSc patients (60).

Finally, it is worth reporting the results of a large survey on 932 SSc patients who received COVID-19 vaccines. The conclusions are that vaccination was safe with no serious adverse events, a side-effect profile similar to that seen in other populations, and a low rate of reported SSc flares (61).

Take home messages

- Alongside data on proven efficacy of classical immunosuppressants (48), solid evidences on safety and efficacy are also accumulating for the antifibrotic drug nintedanib (52, 54).
- Tocilizumab is a promising immunosuppressant in SSc (49), but its preferred application niche needs further elucidations (51).

Patient-reported outcomes

The impact of male sex in the perception of the disease, which is often more severe and rapidly progressive in men, has been recently investigated from the patient perspective. Besides sex-related physical concerns such as the presence of erectile dysfunction, focus groups highlighted the disease impact on masculinity as a social representation. Men tend to react with silence or dark humour and rely very infrequently on society or friends or even their partner for support. Men are also more prone to mask the full emotional burden of the disease and are reluctant to readapt their previous habits. These issues should be factored into daily practice as it is rather the physician in charge of the patient than the patient himself who should bring the sexual and emotional SSc-related challenges to the discussion (62). In focus groups, men frequently underlined a significant change in the physical activities performed and this important sphere of the daily life was recently investigated by the Scleroderma Patient-centred intervention network (SPIN) on a large cohort of 721 SSc patients. Physical exercise was reported to be significantly limited by disease barriers dependent on symptoms such as RP, joint stiffness and contractures or fatigue and difficulty in grasping objects. It was then evaluated how to overcome and facilitate exercising with disease-specific adjustments, gaining appreciation from the patients who reported that they will very likely use it in practice. These findings stress the importance of discussing limits to physical activity in a patient's daily life and the need for the physician-patient axis to overcome those SSc-specific issues that further limit the patient's quality of life (63).

Fatigue is one of the most limiting symptoms in SSc and is central to the practice of physical activity for patients, thus representing a significant barrier to conduct even normal daily activities. Management programmes with occupational therapists already exist for patients with systemic lupus erythematosus, and in 2022 a feasibility study to adapt one of them, the Fatigue and Activity Management Education (FAME), to SSc (FAME-iSS) has been conducted. Fatigue was evaluated by multiple PROs. Despite initially improving, the PROs progressively declined at 3 months after the active interventions. Despite little conclusions about the effectiveness of FAME-iSS can be drawn from this little study, it shows the multifaceted aspects of fatigue in SSc and the difficulty in overcoming it to conduct an active and healthier life (64). The SPIN-HAND, a tool developed to keep dexterity and preserve the hand function, has been recently tested in patients of the SPIN cohort with at least mild hand function limitations as evaluated by the Cochin

Hand Function Score (CHFS) ≥3. The trial enrolled 280 patients who received email invitations to connect to an online tool which offered support in promoting thumb flexibility and strength, finger bending and extension, wrist flexibility and strength. Outcome data at 3 and 6 months showed that CHFS did not differ significantly between patients undergoing SPIN-HAND and those who did not receive any online support, nor did the PROs analysed. The scarce success of this kind of intervention could be due to the method of enrolment and to the lack of guidance of a health professional (65).

Take home messages

- It is important to discuss limits to physical activity in a patient daily life; the need of the physician-patient axis to overcome those SSc-specific issues that further limit the patient quality of life could benefit from a short but constant physiotherapy (59, 63).

Conclusions

From this narrative overview of some of the most innovative studies published in 2022 clearly emerges the constant effort of all the researchers to better understand and manage such a complex disease as SSc. Progresses in unravelling the pathogenesis, deepening the organ involvement and refining the therapeutic approach, are all directed towards the goal of a diagnosis as early as possible, and a therapy as personalised as possible, with the overall aim of improving the prognosis and the quality of life of SSc patients.

References

1. DI BATTISTA M, BARSOTTI S, ORLANDI M *et al*.: One year in review 2021: Systemic sclerosis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 131): S3-12. https://doi.org/10.55563/clinexprheumatol/izadb8
2. LEPRI G, ORLANDI M, DI BATTISTA M *et al*.: Systemic sclerosis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40: 1911-20. https://doi.org/10.55563/clinexprheumatol/3401fl
3. ARVIA R, ZAKRZEWSKA K, GIOVANNELLI L *et al*.: Parvovirus B19 induces cellular senescence in human dermal fibroblasts: putative role in systemic sclerosis-associated fibrosis. *Rheumatology* 2022; 61: 3864-74. https://doi.org/10.1093/rheumatology/keab904
4. WANG W, BALE S, YALAVARTHI B *et al*.: Deficiency of inhibitory TLR4 homolog RP105 exacerbates fibrosis. *JCI Insight* 2022; 7: e160684. https://doi.org/10.1172/jci.insight.160684
5. SERVAAS NH, HIDDINGH S, CHOURI E *et al*.: Nuclear receptor subfamily 4A signaling as a key disease pathway of CD1c+ dendritic cell dysregulation in systemic sclerosis. *Arthritis Rheumatol* 2022; 75: 279-92. https://doi.org/10.1002/art.42319
6. GUR C, WANG SY, SHEBAN F *et al*.: LGR5 expressing skin fibroblasts define a major cellular hub perturbed in scleroderma. *Cell* 2022; 185: 1373-88.e20. https://doi.org/10.1016/j.cell.2022.03.011
7. WAJDA A, WALCZYK M, DUDEK E *et al*.: Serum microRNAs in systemic sclerosis, associations with digital vasculopathy and lung involvement. *Int J Mol Sci* 2022; 23: 10731. https://doi.org/10.3390/ijms231810731
8. BAYATI P, KALANTARI M, ASSAREHZADEGAN MA, POORMOGHIM H, MOJTABAVI N: MiR-27a as a diagnostic biomarker and potential therapeutic target in systemic sclerosis. *Sci Rep* 2022; 12: 18932. https://doi.org/10.1038/s41598-022-23723-7
9. CHENG Q, CHEN M, WANG H *et al*.: MicroRNA-27a-3p inhibits lung and skin fibrosis of systemic sclerosis by negatively regulating SPP1. *Genomics* 2022;114:110391. https://doi.org/10.1016/j.ygeno.2022.110391
10. HAN L, LV Q, GUO K, LI L, ZHANG H, BIAN H: Th17 cell-derived miR-155-5p modulates interleukin-17 and suppressor of cytokines signaling 1 expression during the progression of systemic sclerosis. *J Clin Lab Anal* 2022; 36: e24489. https://doi.org/10.1002/jcla.24489
11. BAYATI P, POORMOGHIM H, MOJTABAVI N: Aberrant expression of miR-138 as a novel diagnostic biomarker in systemic sclerosis. *Biomark Insights* 2022; 17: 1-8. https://doi.org/10.1177/11772719221135442
12. DICHEV V, MEHTEROV N, KAZAKOVA M, KARALILOVA R, BATALOV A, SARAFIAN V: The incRNAs/miR-30e/CHI3L1 axis is dysregulated in systemic sclerosis. *Biomedicines* 2022; 10: 496. https://doi.org/10.3390/biomedicines10020496
13. ROBERSON EDO, CARNS M, CAO L *et al*.: Alterations of the primary cilia gene SPAG17 and SOX9 locus noncoding RNAs identified by RNA-sequencing analysis in patients with systemic sclerosis. *Arthritis Rheumatol* 2023;75:108-19. https://doi.org/10.1002/art.42281
14. ROMANO E, ROSA I, FIORETTO BS *et al*.: A candidate gene study reveals association between a variant of the SRp55 splicing factor gene and systemic sclerosis. *Clin Exp Rheumatol* 2022; 40: 1921-5. https://doi.org/10.55563/clinexprheumatol/mpgq0y
15. LOUTHRENOO W, KASITANON N, WONGTHANEE A *et al*.: Association of HLA-DRB1*15:02:01, DQB1*05:01:24 and DPB1*13:01:01 in Thai patients with systemic sclerosis. *HLA* 2022; 100: 563-81. https://doi.org/10.1111/tan.14793
16. ROSS RL, MAVRIA G, DEL GALDO F, ELIES J: Downregulation of Vascular Hemeoxygenase-1 leads to vasculopathy in systemic sclerosis. *Front Physiol* 2022; 13: 900631. https://doi.org/10.3389/fphys.2022.900631
17. GLUSCHKE H, SIEGERT E, MINICH WB *et al*.: Autoimmunity to sphingosine-1-phosphate-receptors in systemic sclerosis and pulmonary arterial hypertension. *Front Immunol* 2022; 13: 935787. https://doi.org/10.3389/fimmu.2022.935787
18. SANGES S, GUERRIER T, DUHAMEL A *et al*.: Soluble markers of B cell activation suggest a role of B cells in the pathogenesis of systemic sclerosis-associated pulmonary arterial hypertension. *Front Immunol* 2022; 13: 954007. https://doi.org/10.3389/fimmu.2022.954007
19. GUO RH, CHENG H, ZHANG XY *et al*.: Changes in peripheral T-lymphocyte subsets and serum cytokines in patients with systemic sclerosis. *Front Pharmacol* 2022; 13: 986199. https://doi.org/10.3389/fphar.2022.986199
20. YANG C, LEI L, PAN J *et al*.: Altered CD4+T cell and cytokine levels in peripheral blood and skin samples from systemic sclerosis patients and IL-35 in CD4+T cell growth. *Rheumatology* 2022; 61: 794-805. https://doi.org/10.1093/rheumatology/keab359
21. BREZOVEC N, PERDAN-PIRKMAJER K, KURET T *et al*.: Increased L-selectin on monocytes is linked to the autoantibody profile in systemic sclerosis. *Int J Mol Sci* 2022; 23: 2233. https://doi.org/10.3390/ijms23042233
22. YOKOYAMA K, MITOMA H, KAWANO S *et al*.: CEACAM 1, 3, 5 and 6 -positive classical monocytes correlate with interstitial lung disease in early systemic sclerosis. *Front Immunol* 2022; 13: 1016914. https://doi.org/10.3389/fimmu.2022.1016914
23. KULEY R, STULTZ RD, DUVVURI B *et al*.: N-formyl methionine peptide-mediated neutrophil activation in systemic sclerosis. *Front Immunol* 2022; 12: 785275. https://doi.org/10.3389/fimmu.2021.785275
24. IMPELLIZZIERI D, EGHOLM C, VALAPERTI A, DISTLER O, BOYMAN O: Patients with systemic sclerosis show phenotypic and functional defects in neutrophils. *Allergy* 2022; 77: 1274-84. https://doi.org/10.1111/all.15073
25. HORII M, FUSHIDA N, IKEDA T *et al*.: Cytokine-producing B-cell balance associates with skin fibrosis in patients with systemic sclerosis. *J Dermatol* 2022; 49: 1012-9. https://doi.org/10.1111/1346-8138.16495
26. ROSS L, COSTELLO B, BROWN Z *et al*.: Myocardial fibrosis and arrhythmic burden in systemic sclerosis. *Rheumatology* 2022; 61: 4497-502. https://doi.org/10.1093/rheumatology/keac065
27. KNIGHT DS, KARIA N, COLE AR *et al*.: Distinct cardiovascular phenotypes are associated with prognosis in systemic sclerosis: a cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 2023; 24(4): 463-71. https://doi.org/10.1093/ehjci/jeac120
28. GOTSCHY A, JORDAN S, STOECK CT *et al*.: Diffuse myocardial fibrosis precedes subclinical functional myocardial impairment and provides prognostic information in systemic sclerosis. *Eur Hear J Cardiovasc Imaging* 2023; 24: 373-82. https://doi.org/10.1093/ehjci/jeac094
29. PANOPOULOS S, MAVROGENI S, VLACHOPOULOS C, SFIKAKIS PP: Cardiac magnetic resonance imaging before and after therapeutic interventions for systemic sclerosis-associated myocarditis. *Rheumatology* 2023; 62(4): 1535-42. https://

doi.org/10.1093/rheumatology/keac504
30. ROSS L, PATEL S, STEVENS W *et al*.: The clinical implications of left ventricular diastolic dysfunction in systemic sclerosis. *Clin Exp Rheumatol* 2022; 40: 1986-92. https://doi.org/10.55563/clinexprheumatol/irc0ih
31. HINZE AM, PERIN J, WOODS A *et al*.: Diastolic dysfunction in systemic sclerosis: risk factors and impact on mortality. *Arthritis Rheumatol* 2022; 74: 849-59. https://doi.org/10.1002/art.42054
32. NÓGRÁDI Á, VARGA Z, HAJDU M, CZIRJÁK L, KOMÓCSI A, FALUDI R: Prognostic value of right atrial stiffness in systemic sclerosis. *Clin Exp Rheumatol* 2022; 40: 1977-85. https://doi.org/10.55563/clinexprheumatol/3vdmeh
33. PAIK JJ, CHOI DY, MUKHERJEE M *et al*.: Troponin elevation independently associates with mortality in systemic sclerosis. *Clin Exp Rheumatol* 2022; 40: 1933-40. https://doi.org/10.55563/clinexprheumatol/fytfmy
34. DI BATTISTA M, BARSOTTI S, DELLA ROSSA A, MOSCA M: Cardiovascular burden in systemic sclerosis: QRISK3 versus Framingham for risk estimation. *Mod Rheumatol* 2022; 32: 584-8. https://doi.org/10.1093/mr/roab011
35. COLACI M, ZANOLI L, LA MALFA L *et al*.: Reduction of carotid baroreceptor sensitivity in systemic sclerosis. *Clin Exp Rheumatol* 2022; 40: 1964-9. https://doi.org/10.55563/clinexprheumatol/4j6028
36. DI BATTISTA M, VITALI S, BARSOTTI S *et al*.: Ultra-high frequency ultrasound for digital arteries: improving the characterization of vasculopathy in systemic sclerosis. *Semin Arthritis Rheum* 2022; 57: 152105. https://doi.org/10.1016/j.semarthrit.2022.152105
37. BOULON C, VELARDO F, BLAISE S *et al*.: Correlation of nailfold capillaroscopy findings with history of digital ulcer on same finger: results of SCLEROCAP study. *Microvasc Res* 2022; 142: 104365. https://doi.org/10.1016/j.mvr.2022.104365
38. GRACIA TELLO B, RAMOS IBÁÑEZ E, FANLO MATEO P *et al*.: The challenge of comprehensive nailfold videocapillaroscopy practice: a further contribution. *Clin Exp Rheumatol* 2022; 40: 1926-32. https://doi.org/10.55563/clinexprheumatol/6usce8
39. DI BATTISTA M, MORGANTI R, TANI E, DA RIO M, DELLA ROSSA A, MOSCA M: Definition and application of proximal-distal gradient finger perfusion in systemic sclerosis by laser speckle contrast analysis. *Microvasc Res* 2022; 140: 104307. https://doi.org/10.1016/j.mvr.2021.104307
40. FAVOINO E, CATACCHIO G, MININNI A *et al*.: Novel biomarker for pulmonary vascular disease in systemic sclerosis patients. *Clin Exp Rheumatol* 2022; 40: 1956-63. https://doi.org/10.55563/clinexprheumatol/0exnav
41. XANTHOULI P, MIAZGOWSKI J, BENJAMIN N *et al*.: Prognostic meaning of right ventricular function and output reserve in patients with systemic sclerosis. *Arthritis Res Ther* 2022; 24: 173. https://doi.org/10.1186/s13075-022-02863-1
42. BRUNI C, CHUNG L, HOFFMANN-VOLD AM *et al*.: High-resolution computed tomography of the chest for the screening, re-screening and follow-up of systemic sclerosis-associated interstitial lung disease: a EUSTAR-SCTC survey. *Clin Exp Rheumatol* 2022; 40: 1951-5. https://doi.org/10.55563/clinexprheumatol/7ry6zz
43. SAMBATARO D, SAMBATARO G, BATTISTI S *et al*.: Quantitative chest tomography indexes are related to disease activity in systemic sclerosis: results from a cross-sectional study. *Clin Exp Rheumatol* 2022; 40: 1970-6. https://doi.org/10.55563/clinexprheumatol/7q5gkz
44. SCHNIERING J, MACIUKIEWICZ M, GABRYS HS et *al*.: Computed tomography-based radiomics decodes prognostic and molecular differences in interstitial lung disease related to systemic sclerosis. *Eur Respir J* 2022; 59: 2004503. https://doi.org/10.1183/13993003.04503-2020
45. HOCHHEGGER B, LONZETTI L, RUBIN A *et al*.: Chest MRI with CT in the assessment of interstitial lung disease progression in patients with systemic sclerosis. *Rheumatology* 2022; 61: 4420-6. https://doi.org/10.1093/rheumatology/keac148
46. GARGANI L, ROMEI C, BRUNI C *et al*.: Lung ultrasound B-lines in systemic sclerosis: cut-off values and methodological indications for interstitial lung disease screening. *Rheumatology* 2022; 61: SI56-64. https://doi.org/10.1093/rheumatology/keab801
47. DUPONT A, KOETHER V, LABREUCHE J *et al*.: Dual-energy CT lung perfusion in systemic sclerosis: preliminary experience in 101 patients. *Eur Radiol* 2023; 33: 401-13. https://doi.org/10.1007/s00330-022-09016-7
48. BENAD M, KOSCHEL D, HERRMANN K, WIEFEL K, KLEYMANN A, ARINGER M: Effects of cyclophosphamide and rituximab in patients with connective tissue diseases with severe interstitial lung disease. *Clin Exp Rheumatol* 2022; 40: 483-8. https://doi.org/10.55563/clinexprheumatol/o5t1f7
49. KHANNA D, LIN CJF, FURST DE *et al*.: Long-term safety and efficacy of tocilizumab in early systemic sclerosis–interstitial lung disease: open-label extension of a phase 3 randomized controlled trial. *Am J Respir Crit Care Med* 2022; 205: 674-84. https://doi.org/10.1164/rccm.202103-0714OC
50. PANOPOULOS ST, TEKTONIDOU MG, BOURNIA VK, ARIDA A, SFIKAKIS PP: Anti-interleukin 6 therapy effect for refractory joint and skin involvement in systemic sclerosis: a real-world, single-center experience. *J Rheumatol* 2022; 49: 68-73. https://doi.org/10.3899/jrheum.210273
51. KUSTER S, JORDAN S, ELHAI M *et al*.: Effectiveness and safety of tocilizumab in patients with systemic sclerosis: a propensity score matched controlled observational study of the EUSTAR cohort. *RMD Open* 2022; 8: e002477. https://doi.org/10.1136/rmdopen-2022-002477
52. KUWANA M, ALLANORE Y, DENTON CP *et al*.: Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: subgroup analyses by autoantibody status and modified Rodnan skin thickness score. *Arthritis Rheumatol* 2022;74:518-26. https://doi.org/10.1002/art.41965
53. DENTON CP, GOH NS, HUMPHRIES SM *et al*.: Extent of fibrosis and lung function decline in patients with systemic sclerosis and interstitial lung disease: data from the SENSCIS trial. *Rheumatology* 2023; 62(5): 1870-6. https://doi.org/10.1093/rheumatology/keac535
54. ALLANORE Y, VONK MC, DISTLER O *et al*.: Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. *Ann Rheum Dis* 2022; 81: 1722–9. https://doi.org/10.1136/ard-2022-222564
55. NINAGAWA K, KATO M, TSUNETA S *et al*.: Beneficial effects of nintedanib on cardiomyopathy in patients with systemic sclerosis: a pilot study. *Rheumatology* 2023; 62(7): 2550-5. https://doi.org/10.1093/rheumatology/keac674
56. DI BATTISTA M, DA RIO M, LOGIACCO A, BARSOTTI S, DELLA ROSSA A, MOSCA M: Kinetics of response to iloprost evaluated by laser speckle contrast analysis in systemic sclerosis. *Scand J Rheumatol* 2023; 52: 302-5. https://doi.org/10.1080/03009742.2022.2099630
57. GALIÈ N, GAINE S, CHANNICK R *et al*.: Long-term survival, safety and tolerability with selexipag in patients with pulmonary arterial hypertension: results from GRIPHON and its Open-Label Extension. *Adv Ther* 2022; 39: 796-810. https://doi.org/10.1007/s12325-021-01898-1
58. BOONSTRA M, CIAFFI J, NOORDHOEK DC *et al*.: Improvement of microangiopathy after haematopoietic stem cell transplantation in systemic sclerosis. *Clin Exp Rheumatol* 2022; 40: 1993-8. https://doi.org/10.55563/clinexprheumatol/5rjvkc
59. ŠPIRITOVIĆ M, ŠMUCROVÁ H, HEŘMÁNKOVÁ B *et al*.: The effect of a 24-week physiotherapy and occupational therapy programme in systemic sclerosis: A monocentric controlled study with follow-up. *Clin Exp Rheumatol* 2022; 40: 1941-50. https://doi.org/10.55563/clinexprheumatol/0njr37
60. LIEM SIE, VAN LEEUWEN NM, VLIET VLIELAND TPM *et al*.: Physical therapy in systemic sclerosis: the patient perspective. *Arthritis Care Res* 2023; 75: 145-51. https://doi.org/10.1002/acr.24741
61. GORDON JK, SHOWALTER K, WU Y *et al*.: Systemic sclerosis and COVID-19 vaccines: a SPIN cohort study. *Lancet Rheumatol* 2022; 4: e243-6. https://doi.org/10.1016/S2665-9913(21)00416-1
62. FLUREY CA, PAULING JD, SAKETKOO LA *et al*.: 'I turned in my man card': a qualitative study of the experiences, coping styles and support needs of men with systemic sclerosis. *Rheumatology* 2023; 62(6): 2160-7. https://doi.org/10.1093/rheumatology/keac585
63. HARB S, PELÁEZ S, CARRIER ME *et al*.: Barriers and facilitators to physical activity for people with scleroderma: a scleroderma patient-centered intervention network cohort study. *Arthritis Care Res* 2022; 74: 1300-10. https://doi.org/10.1002/acr.24567
64. CARANDANG K, POOLE J, CONNOLLY D: Fatigue and activity management education for individuals with systemic sclerosis: adaptation and feasibility study of an intervention for a rare disease. *Musculoskeletal Care* 2022; 20: 593-604. https://doi.org/10.1002/msc.1617
65. KWAKKENBOS L, CARRIER ME, WELLING J *et al*.: Randomized controlled trial of an internet-based self-guided hand exercise program to improve hand function in people with systemic sclerosis: the Scleroderma Patient-centered Intervention Network Hand Exercise Program (SPIN-HAND) trial. *Trials* 2022; 23: 994. https://doi.org/10.1186/s13063-022-06923-4