Review

One year in review 2018: systemic sclerosis

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ABSTRACT

Systemic sclerosis is a rare acquired systemic disease characterised by a complex pathogenesis and multi organ involvement. Every year the scientific world contributes to enrich the knowledge on the pathogenesis, clinical manifestations, diagnosis and treatment of this complex and severe disease. Herewith, we provide an overview of the most significant literature contributions published over the last year.

Introduction

Systemic sclerosis (SSc) is a chronic, multisystem disease with distinctive pathogenetic features, comprising vascular derangement, immune system activation, tissue fibrosis and heterogeneous clinical profile.

In this manuscript we will provide our annual update of the recent advances in the pathogenesis, diagnosis and treatment of SSc, analysing both the limited cutaneous form (lcSSc) and the diffuse cutaneous form (dcSSc). A systematic MedLine search has been performed using the term “systemic sclerosis” (MeSH terms and semantic search), focusing on the most relevant contributions to the medical literature published between August 2017 and June 2018.

Recent insights into the pathogenesis of SSc

Genetics and epigenetics

As mentioned in our previous review, SSc has been found to be associated with alleles of human leukocyte antigen (HLA) genes especially class II. Oka A et al. (1) recently studied the DNA from 318 unrelated SSc patients, all with anti-topoisomerase I positivity, and from 561 unrelated controls. Results confirmed that the alleles DPB1*09:01 and *13:01 had a significant association with SSc. In addition, the authors genetically identified rs17847931 in retinoid X receptor beta (RXRB) as an SSc susceptibility variant and suggested RXRB as a gene involved in antifibrotic activity in the skin. The HLA DRB1 allele group DRB1*11 that has been described in SSc Caucasian patients. It encodes for the β1 chain of the HLA-DR molecule whose its third hypervariable region (3rd HVR) seems to have an important role in T-cell recognition. Gentil et al. (2) recently investigated the DRβ1 3rd HVR, charge, and parental transmission in SSc patients compared to healthy controls enrolling a total of 306 unrelated families (121 SSc and 185 controls). Data from this study suggested a skewed parental inheritance of HLA-DRB1 alleles showing a reduction in paternal transmission of DRB1 alleles encoding a +2 charge 3rd HVR in SSc population compared to the control group. Contrarily, an increase of paternal transmission when charge was 0 was observed. According with these results, an epigenetic modulation of HLA may be assumed in SSc, but further investigations are needed. The major aetiopathogenesis hypothesis of SSc is that environmental factors may be a trigger in genetically susceptible patients leading to the beginning of the inflammatory cascade. The DNA methylation, an epigenetic mechanism, is influenced by inherited DNA and environmental factors therefore it may represent a link between the environment and the genetical predisposition. For these reasons, Hudson et al. (3) evaluated the DNA methylation signatures in SSc patients (n 19) and other rheumatic disease (13 patients with rheumatoid arthritis and 12 with systemic lupus erythematosus) compared to 8 controls using CD4+ T cells isolated from blood samples. Authors identified 33 differentially methylated and ex-
pressed genes in these autoimmune diseases when compared to controls, the gene mostly expressed in patients was CD1C. Regarding the functional analysis, they found that the lipid metabolism, molecular transport, small molecule biochemistry was the top network identified. Altogether, results from this recent study may indicate the presence of novel cellular targets of interest. Rezaei R et al. (4) suggested that hypomethylation of the interferon regulatory factor 7 (IRF7) promoter might play a role in SSc pathogenesis, probably through promoting the IRF7 expression in the peripheral blood mononuclear cells (PBMCs) of patients with SSc. In PBMCs of 50 limited cutaneous patients (lcSSc), the CpG2 hypomethylation was significantly associated with increased SSc risk and the mRNA expression of IRF7 was higher than controls. Moreover, overall promoter methylation and mRNA level of IRF7 were significantly correlated with each other. Bergmann et al. (5) reported that the expression of Jumonji domain-containing protein 3 J (MJJD3) was increased in fibroblasts in SSc skin and in experimental fibrosis in a transforming growth factor beta (TGFβ)-dependent manner. JMJD3 is capable to reverse the trimethylation of histone H3 on lysine 27 modification which is implicated in fibroblast activation. Moreover, they demonstrated that pharmacological targeted inhibition of JMJD3 ameliorated bleomycin-induced and topol-induced fibrosis in well-tolerated doses. Regarding gene profile in SSc, last year microarray experiments revealed that the matrix metalloproteinase 10 (MMP-10) gene is up-regulated in SSc-associated pulmonary hypertension (PH) endothelial progenitor cell (EPC)-derived endothelial cells (ECs); the treatment of Fia-2-Tg mice with neutralising anti-MMP10 antibodies reverse established PH and markedly reduced pulmonary vascular remodelling (6). In a small sample of limited SSc patients was demonstrated a decrease in transcriptional activity of some genes of the nuclear factor κB (NF-κB) family suggesting that a disregulation of intracellular signal transduction by NF-κB may have a central role both in the beginning and in the late stage of SSc (7). Integrative genomics has yielded powerful tissue-specific functional networks modelling the interaction of genes in each microenvironment. Taroni et al. (8) recently investigated if each SSc organ manifestation has distinct disease signatures at the molecular level. Results from this study indicated a common immune-fibrotic axis—indicative of pro-fibrotic macrophages in peripheral blood, skin, lung and esophagus but with different activated macrophages in each SSc tissue and different functional consequences. Therefore, the diversity of organ microenvironment seemed to give different stimuli to the infiltrated macrophages determining their pro-fibrotic phenotype, as suspected for skin macrophages when compared to the lung ones. P-glycoprotein (P-gp) is a product of ABCB1 gene that includes 29 exones and the activity of P-gp seems to be influenced by ABCB1 polymorphism. Recently, attention has been focused on the possible role of P-gp in immunologic processes, as the expression of ABCB1 is increased by proinflammatory cytokines. With these premises, a recent study aimed to investigate a possible relation between ABCB1 polymorphism and SSc morbidity in 61 SSc Polish patients compared with 100 healthy controls. ABCB1 genotypes and alleles for polymorphisms C1236T, G2677T/A and C3435T did not show a significant difference in the two populations. Authors detected a significant higher incidence of the haplotype 1236 C-2677 G-3435 in SSc than in controls suggesting a possible increased risk of SSc in patients with this haplotype (9). Killer immunoglobulin-like receptors (KIRs), cell surface proteins on NK cells specific for allelic forms of HLA class I molecules, have been investigated in SSc pathogenesis. A recent study investigated the possible association between KIR and HLA genes and SSc in Irian population enrolling 451 controls and 279 SSc subjects. The interaction between KIR genes and HLA seemed to modify the susceptibility to the disease and authors showed a correlation between this interaction and incidence rate of SSc. The combination of KIR3DL receptor and HLA-BW4 ligand having treonine as an 80th amino acid appeared to have a confounding effect compared to KIR3DL-HLABW4-A1 (10). In 455 Iranian SSc patients, single nucleotide polymorphisms (SNPs) of genes encoding CD247 and CD226 (whose play important roles in signalling of lymphocytes) have not been associated with the risk SSc (11). Several gene polymorphisms involved in regulatory T cell function have been identified in many autoimmune diseases, including SSc. Moreover, dysregulation of co-stimulatory and/or co-inhibitory signals, including ICOS signalling, can lead to autoimmunity. In 166 cohort of SSc patients the FOXP3 rs2294020, ICOS rs6726035 and ICOSL rs378299 SNPs were studied and no effect on SSc susceptibility was found. The occurrence of FOXP3 rs2294020 in female patients was associated with decreased time to progression from early to definite SSc so that this SNP may be considered a disease-modifying gene-variant rather than a disease-susceptibility SNP in SSc (12). Mutations of the keratin 1 gene (KRT1) were reported to associate with skin diseases. Recently in a Chinese population of 164 systemic lupus erythematosus (SLE) and 99 SSc patients the genotype of KRT1 was determined and the results showed that the mutant with G at SNP rs14024 was associated with the high risk to SLE and SSc while the deletion allele at rs26760756 was associated with the low risk to SSc. The haplo-genotype, Del/-MU+ was associated with high susceptibility to SLE and SSc but the haplotype Del+/MU- was associated with resistance to SLE and SSc (13). The crucial role of the signal transducer and activator transcription 4 (STAT4) in the pathogenesis of SSc was recently confirmed in 102 Russian SSc patients. In that pilot study STAT4 rs7574865 polymorphism is associated with SSc, the de-SSc, the presence of interstitial lung disease (ILD), cardiac injury, and anti-topoisomerase I antibodies positivity (14). Transcriptomics of SSc skin biopsies has revealed sets of pro-fibrotic genes strongly enriched in diseased as compared to normal biopsies suggesting the role of
the in vivo microenvironment in maintaining the pathological myofibroblasts phenotypes in SSc. An American group, through a novel method for quantitative image analysis of dermal collagen ultrastructure with genome-wide transcriptomic analysis, demonstrated that collagen bundle alignment is a feature of dcSSc skin and is associated with a cell migration gene signature. Moreover, these cells show increased directed migration on aligned extracellular matrix (ECM) fibers that is dependent on expression of Arhgdib (Rho GDP-dissociation inhibitor 2) (15). Studies have demonstrated the significant genetic component of SSc and genome-wide association studies (GWAS) may probably identify unknown susceptibility genes in SSc, as already happened for rheumatoid arthritis. GWAS for SSc using 716 Japanese cases,2 and 1797 controls were recently performed by Terao et al. (16) in whose study meta-analysis of GWAS using the previous GWAS from the French population was performed. Results showed two novel susceptibility loci, moreover associated with other autoimmune diseases: GSDMA and PRDM1. Gorlova OY et al. (17) published data from ImmunoChip and GWAS genotyping studies in White and African American people (1833 white sample and 3466 controls and 291 African American sample, and 260 controls). The gene-level analysis identified four novel candidate genes (STAT1, FCGR2C, NIPSNAP3B, and SCT) significantly associated with SSc in Whites and 4 genes (SERBP1, PINX1, TMEM175 and EXOC2) suggestively associated with SSc. Some of these genes (FCGR2C, SERBP1, EXOC2) have been shown to be involved in immune response. Otherwise the comparison of the results on Whites with those from African Americans demonstrated that only TNFAIP3, FCGR2C and PINX1 were nominally significant in African Americans. Recently attention has focused on exosomes, microvesicles that play a crucial role in the intercellular communication determining the target cells phenotype. They contain different macromolecules as microRNAs (miRNAs) a non-coding RNA able to regulate gene expression and for this reason, recent studies evaluated the role of miRNAs in the pathogenesis of fibrosis in SSc. The study of Wermuth et al. (18) analysed the miRNAs in exosomes of 6 SSc patients (3lcSSc and 3 dcSSc) and evaluated their ability to alter the phenotype of normal human dermal fibroblast in vitro. The results showed a significant increase of six profibrotic miRNAs level in SSc patients compared to the controls and of three others in dcSSc. On the other hand, twelve antifibrotic miRNAs were lower in SSc population, and two others in dcSSc, compared to healthy controls. Even regarding the antifibrotic miRNAs, eight were lower in lcSSc compared to dcSSc. The same study compared fibroblasts treated with exosomes from SSc patients and from controls, confirming that the first ones induce the expression of genes associated to a profibrotic phenotype and encoding interstitial collagens. miRNA-202-3p whose target is matrix metalloproteinase (MMP) is another miRNA that has been found to be increased in involved skin in SSc patients. Zhou et al. (19) suggested miRNA-202-3p as a profibrotic miRNA in SSc as it was found to be upregulated in SSc skin tissue and primary fibroblast with a consequent increase in collagen deposition. In addition, authors showed that miRNA-NA-202-3p levels were inversely related to MMP1 expression. Another recent study investigated the role of miRNAs in the SSc pathogenesis identifying six miRNAs and four miRNAs crucial in SSc pathogenesis. As indicated by authors, the identified miRNAs seem to be involved in the regulation of TGF-β, Toll-like receptor (TLR) andWant signalling pathways and these data suggested their role in the SSc pathogenesis. Five miRNAs (miR-146b, miR-130b, miR-21, miR-31 and miR34a) were higher, on the contrary miR-145 was lower, in SSc skin and fibroblasts and also in in the normal ones and in endothelial cells stimulated with SSc serum (20). miRNA-155 plays a role in pulmonary fibrosis and its expression can be induced by interleukin (IL)-1β. SSc fibroblasts have activated inflammation in circulating endothelial microvesicles that are integrally involved in the myofibroblast phenotype. Artlett et al. (21) demonstrated that microRNAs -155 (miR-155) is upregulated in SSc, especially in SSc lung fibroblasts and that its expression was dependent on inflammasome activation. Moreover, in the absence of miR-155, inflammasome-mediated collagen production is blocked confirming the key role of this miRNA in the pathogenesis of fibrosis. Plasmacytoid dendritic cells (PDCs) are a critical source of type I interferons (IFNs) and their disregulation can contribute to the persistent type I IFN signature that we can see in SSc. Rossato et al. (22) showed that miR-618 was over-expressed in PDCs from SSc patients, including those with early disease without skin fibrosis. In vitro the up-regulation of miR-618 reduced the development of PDCs from CD34+ cells and enhanced their ability to secrete IFNα and it can explain the type I IFN signature observed in SSc patients. Regarding the link between SSc and malignancies, of growing interest in recent years, to cite a recent study of Dalcino et al. (23) even regarding the possible role of miRNAs. In the PBMCs derived from patients with SSc, this study demonstrated the presence of modulated genes linked to the pathogenesis of SSc and to carcinogenesis process and the presence of miRNAs (miR-21-5p, miR-92a-3p, and miR-155-5p, miR-126-3p and miR-16-5p) that can play a predisposing role in the development of malignancies in SSc.

Vasculopathy and endothelium

The endothelial injury and the consequent disruption of its homeostasis is one of the most important step in the SSc pathogenesis. For this reason, studies focused on the role of endothelial progenitor cells (EPCs) recruited to repair the endothelium. A population of 45 SSc patients and of 41 controls was enrolled in the study of Benyamine et al. (24) that, using flow cytometry, found CD34+CD45-EPIC mobilisation as a marker of vascular activation and disease severity. The authors also quantified circulating endothelial microparticles (EMPs) that had higher levels in plasma of SSc patients compared to controls however without a correlation with the disease severity. Between the
endothelial biomarkers, s-Fractalkine was found to be elevated in SSc compared to controls (together with vascular endothelial growth factor (VEGF) and endothenin-1 (ET-1). In addition, s-Fractalkine showed a correlation with CD34+CD45-EPCs levels suggesting new markers for the endothelial injury in SSc pathogenesis (24). In the last years, attention has been focused on endothelial-to-mesenchymal transition (EndoMT) a process for which endothelial cells (ECs) change their phenotype acquiring ECM-producing myofibroblast features. This process has been studied assuming its role in fibrotic diseases pathogenesis. For this reason, a recent study of Manetti et al. (25) suggested a potential role of EndoMT in SSc skin fibrosis pathogenesis as it seems to occur in the dermal endothelium of SSc leading to the development of fibrosis. In the study, skin section of SSc patients and of controls were immunostained for endothelial CD31 or vascular endothelial (VE)-cadherin and α-smooth muscle actin (α-SMA) myofibroblast marker. Results from this first part of their work showed that in SSc derma there were EndoMT cells that expressed both EC and myofibroblast marker, in controls this datum was detected at minimum levels. Authors also investigated EndoMT in two mouse models: mice with bleomycin-induced dermal fibrosis and uPAR-deficient mice. In these animal models EndoMT cells were assessed with both marker combination (CD31 o VE-cadherin and α-SMA) and lower levels of these cells were found in control mice compared to the higher levels detected in the bleomycin treatment group and similar results were found in the uPAR one. The angiopoietin (Ang)/Tie2 system is a key regulator of vascular biology. The expression of membrane bound (mb) Tie2 and Ang-1 ensures vessel stability, whereas Ang-2, inducible by VEGF, hypoxia, and inflammation, acts as an antagonist. Tie2 signalling is also attenuated by soluble Tie2 (sTie2), the extracellular domain of the receptor, which is shed upon stimulation with VEGF. Recently the Swiss group confirmed that peripheral microvasculopathy in SSc results from a complex dysregulation of angiogenic signalling networks including the VEGF and the angiopoietin (Ang)/Tie2. They demonstrated that dermal microvessels abundantly expressed Ang-2 and the levels of sTie2 were increased already in early disease while the percentage of the membrane bound (mb) Tie2 (mbTie2)+ microvessels was profoundly decreased. Moreover, both in skin and sera of SSc patients, the Ang1/2 ratio was reduced, especially in patients with digital ulcers (DUs) indicating vessel destabilising conditions (26). Although TGF-β plays a central role in the pathogenesis of SSc, various other growth factors, cytokines, and chemokines play a part in initiating and developing inflammation, vasculopathy, and fibrosis in SSc. IL-6 is another critical cytokine deeply associated with the development of SSc together with these cytokines and serum IL-6 levels are significantly higher in SSc patients than in healthy controls and correlate with the severity of dermal and pulmonary fibrosis. New treatment targeting the anti-IL-6 receptor antibody are showing benefit on skin sclerosis confirming the role of IL-6 in SSc fibrosis process as also evidenced by a recent review (27). In addition, Taniguchi et al. (28) showed an activation of IL-6/signal transducer in SSc cells, in particular in the endothelial ones. Leukaemia inhibitory factor (LIF) is a member of IL-6 family, which plays pleiotropic roles in vascular remodelling and angiogenesis. Taniguchi et al. (29) reported that serum LIF levels were significantly decreased in patients with SSc, especially in those with early disease and with (DUs), suggesting that decreased serum LIF levels may be associated with vasculopathy in SSc. Moreover, they hypothesize that Friend leukaemia virus integration 1 (Fli1) deficiency may contribute to the inhibition of LIF-dependent biological effects on SSc endothelial cells by suppressing the expression of LIF, LIF receptor, and gp130. Urotensin II, a potent vasoconstrictor and it is supposed to be linked to Raynaud phenomenon (RP) as it was demonstrated in SLE patients. In a small group of RP secondary to SSc, plasma UII level is decreased and maybe it is correlated to the presence of SSc and not to RP (30). Klotho is a trans-membrane protein that is involved in the control of vessel tone, reparative and fibrotic processes, for this reason it was studied in 69 SSc patients. In these patients, a significant deficit of klotho was found but no significant correlation with clinical, laboratory or instrumental features of the disease, maybe due to the small number of studied patients (31).

**Fibrosis**

SSc patients have increased collagen and extracellular matrix synthesis driven by fibroblast activation, which is characterised by transformation of fibroblasts to myofibroblasts. This event is phenotypically detected by increased α-SMA expression and synthesis of collagen type 1 (COL1A1). Several factors have been implicated in myofibroblast differentiation, including TGF-β, vascular βlial growth factor, IL-13 activation of STAT6 and TLR ligands. Fibroblasts are a key driver of the fibrotic process through deposition of extracellular matrix. The mechanisms by which fibroblasts are induced to become pro-fibrotic remain unclear. A recent study demonstrated that lcSSc- and dcSSc-derived keratocytes have pro-fibrotic effects on normal primary fibroblasts as manifested by ASMA and COL1A1 mRNA and protein expression; in a TGF-β – independent manner. Moreover, NF-kB and PPAR-g are dysregulated nodes in both lcSSc and dcSSc, indicating that inhibition of NF-kB or activation of PPAR-g may have therapeutic benefits in SSc (32). The TGF-β signalling pathway has a central role in inducing pro-fibrogenic cellular programs, as demonstrated by previous studies. The recent study of Lu et al. again focused on TGF-β that is known to be involved in the pathogenesis of skin fibrosis in SSc. The small latent TGF-β complex (SLC) forms the large latent complex (LLC) together with the latent TGF-β-binding proteins (LTBPs) that are components of themECM (33). Considering that LTBP-4 seems to be associated with fibrosis-related condition Lu et al. (34) tried to elucidate its role in SSc

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analysing the LTBP-4 expression in skin and plasma of SSc subjects. 46 SSc and 43 localised scleroderma (LSc) patients were enrolled together with a population of 46 healthy controls. The expression of LTBP-4 was higher in SSc skin patients compared to control. In addition, the ELISA assay showed that also the plasma levels of LTBP-4 was significantly increased in SSc compared to controls (no significant difference was found between LSc and controls). Similar data were detected regarding the plasma levels of TGF-β that were higher in SSc patients compared to control ones, its levels seem to positively correlate with LTBP-4 levels. The study concluded that LTBP-4 may have a crucial role in SSc fibrotic process with an increase collagen production. In fact, the authors also investigated the influence of LTBP-4 on the regulation of collagen gene and protein expression using LTBP-4 knockdown fibroblasts and showed a decrease in type I and III collagen expression. All together these results may suggest LTBP-4 as a new actor in SSc. As known, inflammation, type 2 immunity, and fibrogenic processes are involved in disease development and may be affected by sphingolipids. The sphingolipid sphingosine-1-phosphate (S1P) is elevated in the sera of SSc patients, and its receptor S1P5 is expressed in skin tissue. Schmidt et al. in a pilot study proposed that S1P5 deficiency impacts on early-stage dermal Th2 inflammatory responses by affecting longchain ceramide profiles in the skin as well as the composition of cellular infiltrates in low-dose bleomycin (BLM)–induced fibrogenesis in murine skin (35). Sir- tuin1 (SIRT1) is a deacetylase which has an anti-inflammatory and antifibrotic activity in various organs and it has already been demonstrated to play an important role in the inflammation induced by TNF-α as SIRT1 activation inhibit its production. In addition, the mammalian target of rapamycin (mTOR) whose activation has been demonstrated to have a role in inflammation is down-regulated by Sirt1. For this reason, SIRT1 may be an important target in SSc therapies as already suggested by resveratrol (Res) a Sirt1 activator. Given these premises, Zhu et al. (36) recently investigated Sirt1 role in SSc using C3H/He mice treated with bleomycin (BLM). Authors showed an up-regulation of Sirt1 in dcSSc fibroblasts, compared to controls, and in BLM-treated mice and an amelioration of cutaneous fibrosis in BLM-treated mice after administration of Res. In addition, mTOR was increased in SSc fibroblasts and in the involved skin of BLM-treated mice, in which treatment with an inhibitor of mTOR was found to inhibit the inflammation and fibrosis. In addition, authors suggested that the activation of SIRT1 by Res caused an inhibition of mTOR expression. All together, these results, confirmed a possible role of Sirt1 in SSc pathogenesis and suggested SIRT a potential therapeutic target. Recently Chu et al. (37) supposed that the loss of SIRT1 may participate in the pathogenesis of SSc-related pulmonary fibrosis, and that SIRT1 activation is an effective treatment for both the early (inflammatory) and late (fibrotic) stages of pulmonary fibrosis. They reported that the expression of SIRT1 in peripheral blood mononuclear cells of patients with pulmonary fibrosis secondary to SSc is lower than that in patients with SSc without pulmonary fibrosis. They also showed that in mice models of lung fibrosis, SIRT1 activation reduced collagen production and in human fetal lung fibroblasts, SIRT1 activation inhibited TNF-α-induced inflammatory responses. Sacchetti et al. (38) assessed the expression of all the tyrosine phosphatase (PTPs) in dermal fibroblasts of patients with dcSSc finding that PT-P4A1 (a sub-class of three prenylated PTP) mRNA and protein are significantly overexpressed in SSc dermal fibroblasts lines, especially in those derived from patients in the early stage of the disease. PTP4A1 promotes TGFβ signalling in human dermal fibroblasts enhancing the canonical pro-fibrotic TGFβ signalling in these cells and exacerbates experimental fibrosis in mice. They also propose a model of molecular mechanism in which PT-P4A1 binds directly to SRC and protects it from excessive degradation and functional inhibition. These results suggest that interfering with the interaction between PTP4A1 and SRC might represent a therapeutic strategy in fibrotic diseases where TGFβ play a pathogenic role. Metalloproteinase (MMP)-1, is the principal enzyme involved in collagen degradation and the synthesis of collagen in connective tissue. Platelet-derived growth factors (PDGFs) are important in fibrosis pathogenesis and their functions are mediated by two receptors: the PDGFRα and PDGFRβ. Studies demonstrated the role of PDGFRα in the skin and organism fibrosis development. Recently, Makino et al. (39) confirmed the role of PDGF in SSc pathogenesis evaluating the effect of crenolanib, an inhibitor of PDGFRα, PDGFRβ and demonstrating that accumulation of PDGFR-positive collagen producing fibroblasts was inhibited by crenolanib. The results from this study confirmed the role of PDGF in SSc pathogenesis showing a correlation between its receptor-α mRNA and CCN2 (connective tissue growth factor) and other profibrotic markers and a proliferation of SSc fibroblasts in response to PDGFAA, datum not detected in healthy control fibroblasts. ECs, pericytes (PC) and epithelial cells are supported by the networks formed by collagen type IV produced from ECs and PC and with a blood vassel stabilisation function. Some previous studies reported a correlation between the levels of serum collagen type IV and the disease activity of liver fibrosis in chronic hepatitis or other liver disease. For this reason, a recent study investigated the serum levels of serum collagen IV in a Japanese SSc cohort (n 127, lcSSc 72, dcSSc 55) compared these results with those obtained in a control group (n 30). Data showed higher levels of serum collagen in SSc patients compared to controls and its levels were positively correlated with the extension of skin involvement evaluate by mRSS. Serum collagen was elevated in particular in dcSSc patients with a disease duration <3 years. In addition, the same study investigated the expression of perivascular collagen type IV with immunohistochemical staining revealing a lower
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expression in SSc patients (n. 8) compared to 7 controls suggesting its potential role in the vasculopathy and/or skin fibrosis pathogenesis in SSc (40). Metalloprotease (MMP)-1, is the principal enzyme involved in collagen degradation and the synthesis of collagen in connective tissue. IL-13 which is a T helper type 2 (Th2) cytokine is a major inducer of fibrosis modulating the collagen homeostasis in fibroblasts, and stimulating the production and activation of TGF-β. Recently Brown Lobbins et al. (41) suggested that IL-13 regulates MMP-1 expression in response to TNF-α through an serine/threonine kinase B/protein kinase B (Akt)-mediated pathway. They showed that IL-13 suppresses MMP-1 in TNF-α-stimulated dermal fibroblasts and that Akt inhibitor VIII is able to block the suppressive effect of IL-13 on MMP-1 expression in fibroblasts and that Akt inhibitor increases MMP-1 protein synthesis. Previous data suggested a decrease of Fli1, a member of the Ets transcription factor family, in SSc fibroblast and endothelial cells not only in the affected skin but also in the non-involved one (42). Interestingly, Takahashi et al. recently confirmed the role of Fli1 in the SSc pathogenesis reporting a decrease of its expression in SSc keratinocytes and showing that the deficiency of Fli1 caused a SSc-like molecular phenotype. Data from the same study suggested a role of Fli1 deficiency in the disease autoimmunity and in the development of organ fibrosis. In fact, keratin 14-expressing epithelial cell-specific Fli1 knockout mice, the animal model used in this study, developed SSc fibrotic skin and esophageal involvement principally due to an epithelial activation. In the same animal model, ILD was reported, likely due to thymic abnormality with a suppression of autoimmune regulator (Aire) and the presence of lung antigens autoantibodies (43) Even regarding Fli1 deficiency, another study of Taniguchi et al. investigated the effect of Fli1 deficiency on the expression of granulocyte chemoattract protein 2 (CXCL6) known to have increased circulating levels in SSc patients and to be involved in disease vasculopathy. For this study, dermal fibroblasts were isolated from 5 dcSSc subjects and 5 controls and authors showed an increase of CXCL6 in dermal fibroblasts treated with Fli1 siRNA compared to the not treated ones. In addition, levels of CXCL6 positively correlated with mRSS and heart involvement and negatively with lung involvement (% of forced vital capacity (FVC) and % of lung diffusing capacity for carbon monoxide (DLCO)) in SSc patients. Serum CXCL6 levels were found to correlate with the presence of digital ulcers/pitting scars by multiple regression analysis. In conclusion, this study seems to confirm that Fli1 deficiency may induce a SSc-phenotype and suggest a role of CXCL6 in the process leading to fibrosis and also in the vasculopathy in SSc (44). The recent study of Saigusa et al. (45) investigated the impact of Fli1 deficiency on galectin-9 expression. Galectin-9 is a pleiotropic immune modulator interacting with a unique glycoprotein ligand TIM-3 that is highly expressed on Th1 cells and minimally on Th17 cells. The inhibition of TIM-3 signalling induces the IFN-γ, IL-17, IL-2 and IL-6. Results from this study showed that galectin-9 was overexpressed in dermal fibroblasts compared to control ones and its levels correlated with the presence of ILD and positively with mRSS. In addition, galectin-9 expression was found to be induced by Fly1 deficiency. Authors also suggested that the overproduction of galectin-9 may suppress the expression of IFN-γ that increased when Fli1+/− dermal fibroblasts were transfected with Lgals9 siRNA.

Immunity and inflammation

Regulatory B cells (Bregs) may prevent the autoimmunity secreting IL-10 which have anti-inflammatory functions suppressing different pro-inflammatory immune cells. Because some results reported a hyperactivation of B cells but a decreased secretion of IL-10 in SSc, a recent study evaluated TIM-1+ B cells in SSc (39 SSc patients and 53 controls). TIM-1 is the T cell Ig and mucin domain protein that some studies demonstrated to be a marker for IL-10+ Bregs in mice (46). The study of Aravena et al. (47) confirmed TIM-1 as a marker to identify Bregs producing IL-10 and showed a great ability of TIM-1+ B cells to suppress the differentiation and the activation of pro-inflammatory cells in the control group (inhbition of IFN-γ, TNF-α and IL-17 production). On the other hand, this capacity was lower in the 39 SSc patients remarking the importance of B cells in the SSc pathogenesis and characterising a subpopulation of B cells that seem to have a crucial role. Another recent study focused on IL-10+ B cells analysing peripheral blood isolated from 12 controls and 26 SSc patients. The authors did not find any correlation between B cells and specific antibodies levels. However, investigating also IL-17+ ant IFNγ T cells an inverse correlation of these cells and B cells was described, for IFN-γ+ CD3+ cells only in deSSc and not in lcSSc (48). It is thought that the cytokine production by T cells influences the function of fibroblasts and endothelial cells playing a central role in vascular disease and fibrosis development. There is a strong evidence in literature for altered T-cell activation and T helper cells abnormalities in SSc. Several authors have reported higher frequency of Th17 lymphocytes in the peripheral blood of SSc patients and have pointed out the role of these cells as a factor engaged in the pathogenesis of the disease. Th17 cells, firstly described in 2005, produce IL-17A, IL-17F, IL-21, IL-22, and IL-26. Krasimirova et al. (49) investigated the T-cell activation in small sample of 24 SSc patients demonstrating that Th 17 cells are up-regulated in patients, especially in the lcSSc and an increased percentage of CD4+CD25 Foxp3+ in deSSc patients. This group also analysed the circulating cytokine profile in SSc describing raised levels of IL-6, TGF-β1 (increased in early stage), IL-10 and IL-17A. Because Treg abnormalities have been found in the SSc pathogenesis, a recent study analysed Treg subpopulations and their cytokine (IL-10 and TGF-β) in the peripheral blood of SSc patients with an early stage of the disease. Results suggested an imbalance of Treg subsets and abnormalities in their cytokines in SSc. The enrolled population was composed
by 26 SSc patients, 7 lcSSc and 19 dcSSc. Authors described a significant elevation of CD4+CD25+Foxp3+ Treg cells with a diminished IL-10 production in dcSSc subjects and in SSc patients with anti-topoisomerase I/anti-RNApolIII antibodies and lung fibrosis. CD62L+ Treg cells, that represent a population with an active recirculation into lymph nodes, with less TGF-β production were present in all SSc groups. In addition, authors described a reduced methylation of Treg specific FOXP3 enhancer regions (50). Gugino et al. (51) suggested that T helper 9 (Th9) cells and IL-9 are implicated in the pathogenesis of SSc because they found an overexpression of IL-9, IL-9R, IL-4, thymic stromal lymphopoietin (TSLP) and TGF-β in skin tissues of patients (both limited and diffuse SSc). IL-9 is overexpressed in the context of skin infiltrating mononuclear cells and in renal biopsies of patients with SSc and the major source of IL9 was found in Th9 cells in the skin and in PBMCs. The expression of IL9 and Th9 correlated with the modified Rodnan skin score (mRSS) and the stimulation with IL-9 induced the production of anti-systemic scleroderma 70 (ScI70) by B cells. Mekinian et al. (52) demonstrated a reduction of the absolute numbers and frequencies of the mucosal-associated invariant T cells (MAIT) and γδ T cells in blood samples from patients with SSc. They failed to prove any correlation between this data with different disease clinical subsets. A Japanese group demonstrated that the serum levels of soluble forms of programmed death 1 (sPD-1) and one of its ligands, soluble PD ligand 2 (sPD-L2) were elevated in SSc T cells, B cells, and macrophages of 91 patients and correlated with the development and the severity of fibrosis. They proposed that PD-L2 acts as a regulator of T cell cytokine production via cognate interactions with T cells and B cells (53).

After an inflammatory reaction has been initiated, rapid innate immunity effector mechanisms have notable potential to cause damage to host tissues. Proteases, enzymes produced mainly by inflammatory phagocytes, provide a perfect example of such action. Recent evidence highlights how innate immune defense can promote autoimmunity and cause damage to host tissues by excessive release of proteases being its effectors. In response to these enzymes, antiproteases belonging to a group of either “alarm” or “systemic” inhibitors, are secreted. Alarm antiproteases include secretory leukocyte protease inhibitor (SLPI) and elafin are produced in response to the activation of innate immunity response, mainly in response to IL-1 and TNF and integrate innate and adaptive immunity systems. In 28 patients with SSc Olewicz-Gawlik et al. (54) demonstrated SLPI high levels those correlated with lung involvement in SSc (reduction of DLCO and TLC). Xu et al. (55) recently suggested that also TNF-like ligand 1A, a member of the TNF superfamily, might have a role in the pathogenesis of SSc. In fact, it has effects on proliferation and activation of immune cells, including helper and regulatory T cells and results from this study showed that SSc patients had higher serum levels of TLA1 compared with controls, in particular patients with an active disease. In addition, TLA1 levels has a positive correlation with cytokines produced by Th17 cells (IL-17 and IL-21). The function of the indoleamine 2,3-dioxygenase (IDO1) enzyme is that to transform tryptophan (TRP) into kinurenins (KYN) a family of molecules whose effects on immune system cells has been reported leading to a suppression of effector T cells and a facilitation of their differentiation to regulatory T cells. B7 costimulatory molecules are expressed on antigen-presenting cells (APCs) and seem to influence the IDO intracellular expression. Legány et al. (56) in their recent work studied the expression of B7 molecules and the expression of IDO in patients with SSc (n. 9), Sjögren’s disease (pSS) (n. 15) and in healthy controls (n. 20) supposing that differences in B7 molecules expression might have a role in the diversities of the two diseases pathogenesis. Regarding the CD28 receptors expression, the authors showed that it was lower in SSc as well as in p(SS), similarly in both disease a decreased frequency of PD-1 expressing T cells were found. On the other hand, the frequency of some receptors, like CTLA-4 and ICOS were increase in pSS but not in SSc.

Infectious agents

As know monocytes/macrophages and TLR pathway seem to be involved in the SSc pathogenesis. In the study of Farina et al. (57) monocytes from 53 dcSSc and from 34 controls peripheral blood were isolated and infected by Epstein-Barr virus (EBV) in order to investigate if this infection contribute to innate immune activation in SSc. Authors showed an activation of TLR8 by viral lytic genes in monocytes. In addition, EBV seems to be associated with an IFN proinflammatory activation in cells isolated from dcSSc patients suggesting its potential role in the innate immune response. Human cytomegalovirus (HCMV) has been proposed an infectious trigger for SSc, however the definition of its role in the disease pathogenesis is still unknown. Marou et al. (58) recently aimed to investigated about immunoreactivity against this virus in SSc enrolling a population composed of 84 SSc, 30 subjects with multiple sclerosis (MS) and 28 controls. In order to conduct their study, authors tested IgG anti-HCMV directed against UL83 epitope founding higher levels in SSc population compared both to MS patients and controls. In addition, anti-UL83 levels were associated to lung fibrosis in SSc patients confirming HCMV possible role in SSc pathogenesis. Different results have been found about UL57, in fact even regarding HCMV, the same group recently investigated the prevalence of antibodies anti-HCMV UL44 and UL57 in SSc patients (n 60), MS subjects (n 40) and controls (n 17). The SSc group was composed by 30 lcSSc and 30 dcSSc patients. Anti-UL 57 was present in all three populations (SSc, MS, control group) without significant differences and its levels did not correlate with disease clinical, immunological and demographic characteristics in SSc population. Authors concluded that these results suggest that the role of HCMV UL57 epitope in SSc pathogenesis has to be investigated and further new studies will be needed (59).
Clinical features
Serological profile
Since SSc is a chronic, multisystem disabling disease with no definite cure, the efforts of the scientific community are targeted at the early diagnosis and treatment. It is clear that diagnosis and classification should be based on clinical grounds, but also serological characterisation is a useful adjunct to improve diagnostic power and to better refine prognosis. In this respect, the usefulness of autoantibody profile has been confirmed in a Spanish registry, where it was established the role for autoantibodies anti-RNA polymerase III (RNAP) in increasing the risk of SSc renal crisis, while Scl-70 strongly associate with ILD (61). Autoantibody specificity might be also a biologic filter for cancer risk stratification in SSc patients, as it was demonstrated in Johns Hopkins scleroderma cohort, confirming the role of RNAP for cancer risk definition. Moreover, cancer specific risk may vary depending on scleroderma subtype: patients with RNAP positivity and dCSSc had an increased risk for breast cancer, while those with lcSSc had a higher lung cancer risk (62). Alongside traditional autoantibodies, there is a growing interest in novel biomarkers which could help both in diagnosis and in understanding of the pathogenesis. For example, it was found that serum CD163, a well-accepted marker for activated M2 macrophages, levels are significantly (p<0.001) higher in SSc patients than in controls; suggesting a possible role of M2 macrophages' signalling in SSc pathogenesis (63). It was recently demonstrated that plasma concentrations of resistin, a protein thought to be involved in the inflammatory process, are higher in SSc patients than in controls; moreover, resistin showed a significant association with lung disease, arthralgia, oesophageal involvement and increased C-reactive protein (64). Another study revealed a lower concentration of the protein Klotho in SSc patients’ serum as compared with healthy controls, although there is no significant association with clinical, laboratory or instrumental findings (65). It was also found that free light chains (FLC) of immunoglobulins, and specifically isotype K serum levels are elevated in SSc, more in detail is 1-k-FLC are significantly increased in subjects with restrictive lung disease and correlate with IL-6 levels, namely with a higher degree of inflammation. This finding supports a possible role for B cell activation in the pathogenesis of the disease (66).

Classification of the disease is based on 2013 criteria, which take into account a number of clinical features specific for the disease and include nailfold videocapillaroscopy (NVC) and serological characterisation. However, semi-structured interviews randomly assigned to SSc experts have pointed out a series of limitations of the existing view of the disease: the classical division in limited and diffuse subset is almost universally accepted, but this definition may be misleading, since it could lead to misclassification or false prognostic definition, furthermore the limit of above or below the elbows is considered arbitrary. Most of researchers involved in this disease add other classification criteria, such as sine scleroderma SSc (ssSSc), divisions based on autoantibody profile, overlap and juvenile disease. This work has raised the question of some limitations in content validity of the existing criteria and the need of a more modern classification system based not only on clinical and cutaneous subset, but also on novel knowledge on autoantibodies and on the evolution rapidity of the disease (67).

Vascular involvement
One of the hallmarks of SSc is vascular involvement: an intriguing hypothesis is that the disease may be a primitive vascular disorder, with the loss of angiogenic and vasculogenic potential representing a major driver of most of the clinical events during the natural course of the disease. For example, serum endostatin levels, an angiogenesis inhibitor, which raises in severe vascular damage, were found significantly elevated in SSc patients presenting a progressive peripheral microvascular damage, so that endostatin can be considered a reliable marker of skin perfusion and digital arteries damage (68). Vascular complications affect not only capillary bed, but also larger vessels, with oblitative involvement of ulnar and tibial artery. This warrants a thorough assessment involving both micro and macrovascular system in SSc patients (69). In any case, although vascular abnormalities in SSc could represent a plausible risk factor for the development of venous thromboembolism (VTE), a recent study revealed a VTE cumulative incidence comparable between SSc patients and the general population. This suggests that, unlikely RA and SLE, SSc is not an independent risk factor for VTE (70). Microvascular involvement is exploited for the early diagnosis of the disease and NVC represents a milestone in the definition and prognostication of the disease (71). More recently, computed methods to enhance image quality and to standardise quantification of capillary measurements are emerging (72). NVC, in expert hands, is a valid, reliable, reproducible and inexpensive tool which has gained rightfully its place in clinical practice as indispensable diagnostic test for disease definition. In order to provide an idea on how NVC has become a priceless tool, during last year several studies were published regarding its prognostic role in SSc. A Portuguese paper revealed that NVC changes, as capillary loss and avascular areas, have a significant association with the presence of ILD (p=0.008 and p=0.015, respectively). Moreover, avascular areas and capillary loss were associated with a worse pulmonary function, consisting
Regarding lower-limb ulcers in SSc patients, a recent multicentre retrospective case-control study pointed out how approximately half of them is related to venous insufficiency while the other half is due to ischaemic causes with poorer outcomes. Past or concomitant DU and cutaneous sclerosis of the feet were found to be independent risk factors for ischaemic lower-limb ulcers (81). High frequency ultrasound is a feasible and tolerated technique in most SSc patients which may prove useful in better characterising DUs (82). Microvascular alteration is a prominent feature for several organs affected in SSc, in particular kidney, lung and heart. Intransahe vascular resistance is an early sign of vascular involvement that, no less than NVC, could predict the evolution of the disease and its outcome (83). Scleroderma heart involvement, an ominous as well as insidious manifestation of the disease, stems its origin on myocytes band necrosis due to microvascular damage. A number of efforts addressed at the early recognition of this complication, has outlined the need of more sensitive screening methods than standard echocardiography. In this respect, cardiac magnetic resonance imaging (MRI), although with some limitations due to the method of elaboration, maintains its primacy in detecting early SSc heart involvement (84). In fact, apart from the assessment of ventricular volumes and EF, it is reconfirmed to be the gold standard technique to detect myocardial inflammation, early perfusion defects and myocardial fibrosis (85). A recent study evaluated with cardiac MRI eighty-two SSc patients without any clinical cardiac symptom. Interestingly, according to Lake Louis criteria (positivity if at least 2 on 3 of the examined indices are pathological: T2 ratio, early and late gadolinium enhanced images), nine of them (10.9%) were found positive for myocarditis. Remarkably, no correlation between MRI results and blood inflammatory indices, cardiac troponin T or SSc subgroups was identified. This leads to hypothesise a routinely assessment of SSc patients with cardiac MRI in order to reveal silent heart involvement. An early diagnosis in asymptomatic patients opens new perspectives in the management of a silent and often ominous clinical manifestation, although at present it is not completely clear the correct timing of screening and the prognostic significance of these findings (86). Newer techniques, such as speckle-tracking echocardiography (STE) analysis are promising but still under scrutiny. One of the most studied STE-parameters is the right ventricular longitudinal systolic strain (RVLSS), a deformation index useful in the assessment of regional myocardial contractility. On the basis of an already established RVLSS reduction of both global right ventricular and its lateral wall in SSc patients compared to healthy controls, it was recently detected a RVLSS deterioration in all myocardial layers, with an increasing worsening from the epicardial layer to the mid-myocardial and subendocardial ones. This finding clarifies that all myocardial layers are affected in this connective tissue disease, and not only the subendocardial one (even if it is the most affected), as it would be expected in patients with microvascular involvement (87). STE was also used to demonstrate differences between subgroups of pulmonary arterial hypertension (PAH). In fact, apart from the evidence that global RVLSS is markedly diminished in PAH compared to controls, it was showed that, at similar afterloads, this parameter is significant (p=0.03) worse in SSc-related PAH than in idiopathic PAH. Notably, right ventricular contractile deficit as detected by RVLSS were present despite shorter PAH disease duration in SSc-related PAH patients (88). Another work revealed that global longitudinal strain is impaired in SSc both in right and left ventricles, strengthening the hypothesis that contractility worsening is a direct consequence of primary myocardial involvement rather than a result of PAH. It was also showed how SSc patients with no clinical or traditional echocardiographic parameters of heart involvement, has global longitudinal strain reduction in over 60% of cases, revealing a subclinical right and left systolic impairment. This data lead to reconsider the prevalence of cardiac involvement in SSc and propose STE as a low-cost, non-invasive and reliable tool in order
to detect early cardiac impairment in SSc patients, who would be otherwise underdiagnosed with traditional echocardiographic parameters (89). PAH assessment and Recognition of outcomes in Scleroderma (PHAROS) registry is a multicentre prospective cohort of patients with SSc at high risk of developing PAH or with definitive right heart catheter pulmonary hypertension (90). 160 incident group I PAH patients were analysed, and Kaplan-Meier survival curves were generated for the overall cohort and for those who died of PAH. When restricted to PAH-related deaths, 93% of those occurred within 4 years from diagnosis. Male sex (hazard ratio [HR] 3.11), dcSSc (HR 2.12), systolic pulmonary artery pressure (PAP) on echocardiography (HR 1.06), mean PAP on right heart catheterisation (HR 1.03), 6MWD (HR 0.92); and DLCO (HR 0.65) significantly affected survival on multivariate analysis. Although overall survival in PHAROS was higher than in other SSc-PAH cohorts, PAH accounted for more than one-half of deaths and primarily within the first few years after PAH diagnosis. This warrants a close follow-up of SSc patients to screen for this complication (91).

In this respect, DETECT algorithm has demonstrated higher utility as a screening tool in SSc subjects in comparison to other screening instruments (92). Evaluating the prevalence of PAH diagnosed by heart catheterisation before and after the institution of DETECT algorithm, a Norwegian study outlined that PAH frequencies were similar (18% in the DETECT cohort and 21% in the previous one). However, in the newer cohort the proportion of patients with borderline hypertension was increased when comparing with patients recruited before DETECT (31% vs. 17%), as well as the proportion of patients divided by risk stratification. In fact, in the DETECT group 27% of the patients were classified at low risk (19% in the previous cohort), while 27% at high risk (44% previously). These findings open new scenarios for earlier PAH diagnosis and treatment (93). Simple clinical features at enrolment, such as male sex, prior history of DUs, diffuse subset, FVC/DLCO ratio >1.6 might be useful to predict future vascular complications in unselected SSc patients (94).

It was also found that serum levels of adipsin, which is an adipokine, namely a peptide secreted by adipose tissue with recently identified effects in modulating fibrosis, inflammation and vascular homeostasis, are significantly (p<0.0001) elevated in patients with lcSSc and strongly associate with PAH (p=0.02) (95). In a prospective bicentric cohort of SSc patients included in the DETECT study, Coghlan et al. evaluated the incidence and determining factors of PH. Patients without PH at initial catheterisation were systematically followed-up by clinical examination and repeated catheterisation. High pulmonary vascular resistance at baseline, elevated tricuspid regurgitation velocity, low DLCO and enlarged size of inferior vena cava were independent predictors for PH development during follow-up. However, it should be underlined that due to the DETECT inclusion criteria, this cohort is preselected for SSc patients with DLCO <60%, which can limit its generalisability to an unselected SSc population. These patients in fact have a higher prevalence of PH (25%), while PAH seem to be similar (7%) in comparison with other series. Since low DLCO population shows a decline in pulmonary function test, a progression of haemodynamic alterations and a high incidence of PH, it seems reasonable to perform regular clinical assessment including right heart catheterisation in this population until more reliable methods of screening are available (96).

Since PAH in SSc is a heterogeneous condition, as patients may present a spectrum ranging from pure PAH without ILD to PAH due to extensive ILD, Launay et al. evaluated 200 SSc patients with PAH and classified them in homogeneous subgroups according to relevant and simple criteria in order to predict different future survivors. They just split PAH in severe (≥35 mmHg) and in mild-moderate (<35 mmHg), and divided ILD in extensive and in absent-limited on the basis of the staging system proposed by Goh et al. (97). A first consideration that can be done is that the presence of a limited ILD has to be considered in the same group of patients without ILD, where the severity of PAH drives the prognosis. They eventually found four simple homogeneous subgroups. The first important distinction concerns patients with extensive ILD, representing a cluster with the worst 3-years survival rate (49.9%). This means that the presence of an extensive ILD, whatever the PAH, is associated with a very severe outcome. All the other patients with absent or limited ILD can be divided according to the presence of severe PAH, individuating a cluster which accounts for a 61.9% 3-years survival, consistent with the poor prognostic features of high pulmonary vascular resistances and low cardiac indexes. Patients with mild-moderate PAH and no extensive ILD represent the most common presentation in SSc and can be further differentiated on the basis of low or normal DLCO, representing two clusters that carry a 3-year survival prognosis of 81.5% and 87.1%, respectively. An unanswered question is whether the last three clusters are distinct subgroups, or a same cluster diagnosed at a different stage of the disease (98).

Lung involvement
Pulmonary involvement is another frequent SSc complication, usually combined the presence of ILD with pulmonary vascular involvement. As previously said, the extremes of the spectrum are represented by pure ILD and pure pulmonary vascular involvement with isolated PAH, but most of the times a combination of the two conditions is present in the same patient (92). Lung function tests are not a sensitive screening tool for lung involvement in SSc, therefore using only this exam in the follow-up, a relevant number of patients with consistent ILD can be missed. Ultrasound B-lines are an excellent non-invasive method for the assessment of ILD in SSc subjects. In a single-centre study of 40 consecutive SSc patients, the US B-lines number and the Warwick score confirmed excellent correlation (Spearman rho: 0.958, p=0.0001). The receiver operating characteristic (ROC) curve analysis revealed that 10 US B-lines are the cut-off point with
the greatest positive likelihood ratio (12:52) for the presence of significant SSc-ILD. Thus, the detection of at least 10 B-lines is highly predictive for the high resolution CT (HRCT) presence of SSc-ILD. In SSc patients, lung US assessment as first imaging tool, may represents an effective model to improve the correct timing of chest HRCT (99). However, in order to assess the severity of lung involvement and the individual risk of progression to end stage disease, it is necessary to perform HRCT scan, which remains the gold standard for the definition of the extension and type of lung involvement. Indeed, in the context of an ILD, the affection of more than one third of lung parenchyma and the presence of reduced FVC at an early stage of the disease, classifies the patient at higher risk of disease progression, thus identifying a subgroup of patients with higher potential advantage from immune suppression (100). In patients with milder disease, however, it is more difficult to establish a cut off point for risk of progression. In this context a recent study assessed the risk of progression in unselected SSc patients with mild lung involvement and found that the presence of arthritis and reduced SpO₂ after 6MWD might represent red flags that independently predict the risk of evolution at follow-up. Outcome measures was derived from a prospective dataset of patients from University centre in Zurich and validated on cohort from 3 different centres across Europe (Oslo, Paris; Berlin). SpO₂ <94% after 6MWD associated with arthritis during the follow-up, predicted the progression of ILD at follow-up both in the derivation and in the validation cohort (101). Whilst reduced saturation is intuitively correlated with worsening of lung involvement, it is less clear how the presence of arthritis could represent a link with the risk of future lung impairment in these patients, and possible biases related to concomitant treatments, pattern of ILD or recurrent infections have been claimed (102). As far as 6MWD is concerned, although it has demonstrated several limitations in SSc subjects and may reflect not only parenchymal but also vascular aspects of lung involvement, it is feasible in the majority of SSc patients and represents a good reference by comparing the single patient values at different time points, rather than rest upon the reference standards at a single observation, since the general population cannot represent a reliable comparison in these subjects (103-104). A study conducted repeating 6-MWT twice, within a minimum 3 months interval among 56 SSc patients, showed strong reproducibility (p<0.0001) of this test and pointed out that factors like mRSS, arthralgias and tendon friction rubs, FVC, DLCO, left ventricular EF are independently associated with a lower 6MWD. Considering that 6MWD at first referral was found to be an independent predictor of overall mortality and SSc related mortality, this test is confirmed as a useful tool to assess the overall prognosis in SSc patients (105). To detect progression of ILD, slice reduced sequential HRCT (reduced HRCT) may be an alternative to standard HRCT. In a retrospective study conducted on 60 SSc subjects, reduced HRCT was non-inferior to standard HRCT, with the only exception for the detection of intrapulmonary bronchiectasis, which was significantly lower in reduced HRCT than in standard HRCT (p=0.039). No differences were found comparing visual scores for fibrosis severity and extension from standard and reduced HRCT. Hence, reduced HRCT might be used to detect early disease progression of lung fibrosis in SSc patients (106).

**Skin involvement**

Skin involvement is a prominent feature of the disease. Numerous data have pointed out a significant prognostic role not only for the extension but also for the pace of skin involvement progression. It is therefore pivotal to predict the pace of progression, in order to timely start treatments and also for the purpose of trial enrichment. Scleroderma Observational Study has set a study to identify patterns and predictors of skin score change in early dcSSc, recording mRSS every 3 months in 326 SSc patients. ‘Progressors’ were defined as those experiencing a 5-unit and 25% increase in mRSS score over 12 months. Logistic models were fitted to predict progression and, using ROC curves, were compared on the basis of the area under curve (AUC) accuracy and positive predictive value (PPV). 22.5% of the patients progressed, while 77.5% did not. Progressors had shorter disease duration (median 8.1 vs. 12.6 months, p=0.001) and lower mRSS (median 19 vs. 21 units, p=0.03) than non-progressors. Skin score was highest, and peaked earliest, in the RNAP subgroup. A first predictive model (including mRSS, duration of skin thickening and their interaction) had an accuracy of 60.9%, with AUC of 0.666 and PPV of 33.8%. Adding a variable for RNAP positivity, the model reached an accuracy of 71%, with AUC of 0.711 and PPV of 41% (107). Another common skin feature in SSc patients is the presence of telangiectasias. Telangiectasia (TA) is a capillary dilatation located over different skin surfaces and several previous reports have correlated the number and extension of TAs to the severity of vascular involvement. Recently, a single-centre study has investigated the distribution and clinical significance of TAs in 106 consecutive SSc patients. The authors pointed out that TAs were predominantly located on the face, hands, and the upper part of the trunk. TAs appeared to be associated with vasculopathy features of SSc, particularly with PAH and soluble endoglin levels (108).

**Gastrointestinal involvement and nutrition**

GI tract involvement is present in up to 90% of SSc patients, with the esophagus the most frequently affected. It is not correlated to the entity of skin harassment and can be severe and disabling in up to 8–10% of SSc subjects, where it portends a poor outcome. Gastroesophageal reflux is a frequent complaint, however there is no strict association between symptoms and the severity of the organ involvement. Reflux aetiology in SSc is likely multi-factorial with both inheritance and exposures playing a role in the pathogenesis (109-110). Severe GI dysmotility (upper and lower bowel dysfunction till the requirement of enteral or parenteral nutrition) is a life-threatening condition with 85% mortality rate. McMahan et al. re-
revealed that SSc patients with severe GI
dysmotility are more likely than those
with mild symptoms to be male, to have
myopathy and sicca symptoms, while
baseline features associated with future
severe GI dysmotility include male sex
and myopathy (111). Malnutrition is a
frequent finding in SSc patients: it can be
related to GI involvement, to diffi-
culties in correct feeding due to disabili-
ty, to increased energy expenditures for
systemic involvement and eventually
it can be related to treatments. While
body mass index is not a good indicator
of malnutrition, body composition by
electric impedance analysis is a more
reliable method for its identification.
In a single-centre study involving 129
SSc patients, sarcopenia was a common
finding, affecting 22.5% of the subjects
and was associated with a physical im-
pairment that affects everyday life and
participation in work. Interestingly, al-
though age is the main risk factor for
sarcopenia in the general population, it
did not differ between sarcopenic and
non-sarcopenic SSc patients. Instead,
the number of immunosuppressive
drugs was significantly higher among
the sarcopenic subgroup. However, it
is no clear to what extent this finding
might be related to the severity of the
disease or be ascribed to the treatments
(112).

Other organ involvements
The urinary tract has been poorly inves-
tigated in SSc, but a multicentre study
involving 334 SSc subjects revealed
that lower urinary tract symptoms
(LUTS), ranging from storage to void-
ing and post-micturition symptoms, are
recorded in over 95% of the cases, usu-
ally in association with digestive com-
plaints, with strong impact on quality of
life (113). Urinary incontinence is an
other frequent symptom and is signifi-
cantly associated with limited subset
and anticientromere antibodies (ACA)
(114). Another frequent but overlooked
finding in SSc patients is small fiber in-
volvement of the skin, with neuropathic
pain; whose entity seem to be strictly
correlated with skin involvement (115).
Another aspect of small nerve fiber
involvement seem to be inner ear in-
volvement and earing loss. In a small
SSc series it was found that hearing loss
may be present in over 2/3 of the pa-
tient, in clinical practice this aspect is
however frequently missed since mild,
with prevalent sensory neural hearing
loss, abnormal pure tone audiometry and
abnormal speech reception threshold
as compared to controls (116). Ana-
lysing bone mineral density (BMD) of
the lumbar spine and deriving spine
bone quality using the trabecular bone
score (TBS), it was demonstrated that
SSc patients show significantly lower
BMD and TVS values than healthy
controls. This account for a greater risk
of osteoporosis and a lower bone qual-
ity. TBS values were found to be lower
in SSc patients with a late NVC pattern,
as compared to active and early ones.
Despite there was no statistically sig-
nificant correlation between TBS val-
ues and 25-hydroxyvitamin D levels, it
is interesting to notice that these values
were progressively lower as NVC pat-
tern progressed (117).

Patient-reported outcome (PRO)
In SSc the failure to find a true
dMARD drug and the relative small
effect of immunosuppressant or anti-
fibrotic medications on several distinct
clinical outcomes in RCT with end-
points on various organ manifestations
have always been further hampered by
the lack of a patient reported outcome
reliably defining the impact on the per-
sonal, psychological and social aspects
of the disease (92). There are several
general patient-reported outcome
(PRO) instruments (Health Assessment
Questionnaire Disability Index (HAQ-
DI), Short Form Health Survey-36
(SF-36)) and SSc-specific PROs, some
organ specific [University of Califor-
nia, Los Angeles, Scleroderma Clini-
cal Trials Consortium Gastrointestinal
Tract Scale 2.0 (UCLA SCTC GIT
2.0)], and the Mouth Handicap Scale
in SSc, Cochin Hand Function Scale
(CHFS)], and some generalised [the
Symptom Burden Index, the UK SSc
Functional Score and the scleroderma
HAQ (SHAQ)] (118). Most of the PRO
used in RCT and/or clinical practice
have not always involved the target
patient population in the development
and therefore are not always adequate
measures that can capture involvement
in a clinical/symptomatic aspect of the
disease nor the patient quality of life
(119). This is an aspect that must be
taken into account when developing
new and targeted PROs for SSc, whose
heterogeneity in clinical and sympto-
matic manifestation is raising the gap
between clinicians’ and patients’ per-
spectives.

For measures of pain and disability a
recent study by Daste et al. (120) pro-
vided the Patient Acceptable Symptom
State (PASS) and the Minimally Clini-
cally important Difference (MCID) for
5 PROs commonly in use in the prac-
tice and in RCT: joint pain intensity
assessed by a 100-mm visual analog
scale (VAS pain), global activity limi-
tation assessed by the HAQ, systemic
sclerosis-specific global activity limita-
tion assessed by the scleroderma HAQ
(SHAQ), patient-perceived activity
limitation assessed by the McMaster-
Toronto Arthritis Patient Preference
Disability Questionnaire (MACTAR),
hand-specific activity limitation as-
sessed by the Cochin Hand Function
Scale (0, no limitation, to 90, maximal
limitation); and health-related quality
of life assessed by the Medical Out-
comes Study 36-Item Short Form (SF-
36) (See Table I) (120).

These thresholds are essential in evalu-
ating the practical effect of an interven-
tion (pharmacological or non-pharma-
cological) from the patient perspective,
which is unique and complementary to
the physician assessment and whose
statistical significance is not always
a life-changing difference.
PASS itself has been evaluated as an
outcome measure alone in a secondary
analysis of the Safety and Efficacy of
Subcutaneous Tocilizumab in Adults
with Systemic Sclerosis (faSScinate)
trial (121). Authors have evaluated 3
different ways to evaluate patients’
perception of their symptom state; by
asking to answer on a 7-point Likert
scale with scores from -3 (highly unac-
cetable) to 3 (highly acceptable) to the
question ‘Considering all of the ways
your scleroderma has affected you over
the last week, how acceptable would
you rate your level of symptoms?’ (PASS
1) or using a dichotomous out-

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is composed of four items for each of seven domains (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference), scored on a 5-point scale, plus a single pain intensity item, measured on an 11-point rating scale. Kwakkenbos et al. (122), applied PROMIS-29 to a total of 696 patients, 87% females and with a long disease duration (9.7±8 years). With respect to the standard (the US population), the mean PROMIS-29v2 domain scores were reported to be 0.7 S.D. lower (worse) for physical function, 0.6 S.D. higher (worse) for pain intensity and fatigue, 0.3 S.D. lower (worse) for social roles, 0.3 S.D. higher (worse) for sleep problems and similar for symptoms of depression (0.1 S.D. higher) and anxiety (0.2 S.D. higher).

Construct validity of PROMIS-29 was demonstrated by showing significant correlation with legacy score such as the HAQ-DI or the CHFS. It also demonstrated a correlation, significant albeit weak, between older SSc patients and depression or lower scores of anxiety and fatigue. Disease features that were reflected in lower performance score were high mRSS, gastrointestinal (GI) involvement and the presence of joint contractures. Further research should concentrate on finding the minimally important difference (MID) and the sensitivity to change of PROMIS, both key information for the applicability of this PRO in RCT or clinical practice. On the SPIN cohort another patient-centered study was conducted to analyse patient exercise habits by a simple questionnaire (123). Patients responded to a single item related to exercise, “Do you exercise at present?” with yes/no responses on a 5-point Likert scale (from -2 (much worse) to 2 (much better)). At the end of the trial the vast majority of patients had achieved PASS by all the 3 methods (69, 71 and 78% for PASS 1, 2 and 3, respectively), with increasing figures during the trial and with a statistically significant capacity for PASS 1 to discriminate placebo from the active drug. PASS had a moderate correlation to clinical outcomes and PROs of the Fasscinate study such as mRSS, physician global assessment [physician global visual analogue scale (VAS)], patient global assessment (patient global VAS) and HAQ-DI, thus proving its complementarity in patients’ assessment and the possibility to be evaluated in future clinical trials of SSc (121). The Scleroderma Patient-centered Intervention Network Cohort Study (SPIN) investigators, an initiative collecting data from English speaking SSc cohorts in Canada, US and UK, reported the application of the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) v29 in their patients (122). PROMIS-29 is part of an initiative of the NIH to collect item banks for measuring patient-reported outcomes across various medical conditions which are standardised to the general US population. PROMIS-29 PASS MCID Responsiveness

### Table 1. Patient acceptable symptom state and minimal clinically important difference of 5 PROs commonly used in clinical practice and randomised controlled trials.

<table>
<thead>
<tr>
<th>PRO</th>
<th>PASS Mean (95%CI)</th>
<th>MCID</th>
<th>Responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint-pain visual analog scale (0-100)</td>
<td>53.75, (95%CI)34-68</td>
<td>6.74 ± 32.02</td>
<td>-5.08 ± 31.67</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>1.41, 1.13-1.63</td>
<td>-0.21 ± 0.48</td>
<td>0.04 ± 0.40</td>
</tr>
<tr>
<td>shHAQ (0-3)</td>
<td>1.27, 1.07-1.62</td>
<td>-0.13 ± 0.45</td>
<td>0.14 ± 0.41</td>
</tr>
<tr>
<td>Cochin Hand Function Scale (0-90)</td>
<td>26, 17-37</td>
<td>-3.38 ± 9.87</td>
<td>1.43 ± 13.11</td>
</tr>
<tr>
<td>MACTAR (0-30)</td>
<td>19.4, 17.2-21.9</td>
<td>-5.69 ± 6.79</td>
<td>-2.63 ± 4.84</td>
</tr>
</tbody>
</table>

SRM: standardised response means; PASS: patient acceptable symptom state; MCID: minimally clinically important difference. Adapted from reference 3.
RCS, but encompassed feelings as “tingling”, “numbness”, “hypersensitivity”. Neither the other themes emerged in the FG were fully captured by current PROs (e.g. impact on daily life, trigger factors, constant vigilance, adaptation, emotional impact) indicating the need of a new measure, which should include patient participation in its development (125). Patients contribution to research in SSc is a key factor for RP and its categorisation for the aim of clinical research. A study by Pauling et al. has recently demonstrated that the experience of RP is better described in SSc patients by 4 different patterns of evolution in time. The pattern described by the majority of the patients in the study is that of intermittent longer-lasting attacks (with the circulation in fingers not always returning to normal between attacks). Patterns may evolve in time and correlate well with other PROs as SHAQ, and in particular the V AS GI SHAQ, indicating a relationship between different patients’ experience. Further longitudinal studies should clarify whether this is a pathogenetic link or a connection between different pain experiences (126).

Recently, a new skin-related quality of life PRO in patients with SSc has been developed by Man et al. the Scleroderma Skin PRO (SSPRO) (127). This includes, in its final version, 18 items obtained by a process consisting on patient focus groups, revisions of expert panels composed by rheumatologists but also dermatologists, psychometrists and biostatisticians and cognitive interviews. SSPRO has been tested in patients with SSc included in a study at the Boston University Medical Center (BUMC). The constructs around which SSPRO is built are physical limitations (PL) related to skin tightness, physical effects (PE), emotional effects (EE) and social effects (SE). Skin severity levels from 1 to 6 were collapsed to three categories: mild, moderate and severe. SSPRO scores were different in limited cutaneous(lc)-SSc and diffuse-cutaneous(dc)-SSc. They also correlated well with the patient-reported skin severity of the SHAQ visual analogue scale (VAS) (construct validity) but interestingly correlation was weak when SSPRO was associated to physician-reported outcomes including physicians’ assessment of overall skin disease, global assessment of disease and most importantly, the mRSS. SSPRO showed also internal consistency and moderate-to-high test–retest reliability. The great advantage of SSPRO is the direct SSc patient’s participation in its development which helps capturing unique features of the disease with an impact on relevant physical, psychological and social domains (127). It is a new instrument, complementary to other solid and well validated measures, to assess the skin in SSc and that needs further attention (e.g. research of the MID) for its promising added value in clinical trials of organ-targeted treatments.

Another sphere of symptoms that are very important to the daily impact of the disease on the patient’s quality of life but evaluated with difficulty by objective clinical measures concerns the upper GI tract. In particular, swallowing difficulties (SD) can interfere with one basic life activity and pleasure, eating, but also with oral medication intake and hence patients’ adherence to therapy. One recent study by Messerli et al. (128) has evaluated the prevalence and pattern of SD in medication intake through a self-reported questionnaire. Authors conducted a systematic literature review (SLR) about SD evaluated in a systematic and structured form as an outcome measure. Items identified by the SLR were included in a questionnaire (named SWAME- CO for SWAllowing difficulties with MDication intake and COPing strategies), composed of 30 items covering themes as complaints, intensity of the problem, localisation (mouth, throat, pharynx, oesophagus), coping strategies, adherence. Preliminary, face and content validity was evaluated in small groups composed of patients and health care professionals, secondly it was proposed to a small cohort of patients (n=46). The final analysis on patients revealed that approximate half of them have SD with medication intake, mostly located at the pharynx (43%) or oesophagus (34%) level. As a result, 10% of patients stopped the medication and 40% modified the form of the medication by splitting tablets, crushing pills, opening the capsule etc. This problem was affecting the take of drugs central to SSc therapy such as calcium antagonists or PDE5 inhibitors. The use of PRO is the easiest and more reliable way to quantify this essential symptom and try to adopt medically valid coping methods without altering the drug and potentially increasing toxicity and/or side effects.

**Treatment**

SSc is associated to a very high social and economic cost, especially in the presence of some clinical manifestations such as lung and GI involvement (128-130). In 2017, a European task force updated the 2009 recommendations for the treatment of SSc; the approaches are divided in 6 major subgroups that include the treatment of RP, DUs, PAH, skin, ILD, renal disease and GI involvement. Despite these new recommendations, the treatment for SSc patients continues to be complex, mainly because the disease is heterogeneous, and it is difficult to target all the three mechanisms that are involved in SSc pathogenesis: the immune system activation, vascular abnormalities and tissue fibrosis (130). Although substantial progresses for the first two mechanisms have been made in last years, there still lack of an effective antifibrotic treatment, even if novel therapies are under investigation.

**Immunosuppressive treatment**

A better knowledge of the use of existing therapies would be desirable with regard to the immunosuppressive treatment. For example, for corticosteroids too, that are still widely used in SSc mainly for arthritis, myositis and ILD, there are many unknown aspects that should be investigated (131).

Available evidences demonstrated that cyclophosphamide (CTX) remains one of the most prescribed and effective treatments for SSc-ILD (132-133), but it is associated to severe adverse events, including severe immunosuppression, hepatic toxicity and hypogonadism (134), that has been confirmed also in males patients who may have lower lev-
els of testosterone (135). A recent article, published by a Saigusa et al. (136), proposes the possibility of identifying the patients responsive to CTX using plasmin-a2-plasmin inhibitor complex (PIC) as a test for quantifying plasmin levels, as in patients responsive to CTX the PIC levels are higher compared to non-responders and decrease significantly after the treatment (136).

Interestingly, recently evidences about the use of mycophenolate mofetil (MMF) in the treatment of SSc-ILD have been published (137). Reporting results derived from patients enrolled in the scleroderma lung study (SLS) II (138), compared to the placebo arm of the SLS I (139), an improvement in pulmonary function tests (PFTs) and in skin involvement have been reported. Despite the evident biases that can be produced by the use of patients and controls enrolled in different studies, Volkman and et al. reported a significant improvement in dyspnea and PFTs (including FVC and diffusion lung capacity of CO) (140). In addition to the improvement in the PFTs, a recent study reported an improvement also in the percentage of ILD involvement assessed by a novel computerised automated system analysis for high resolution computed tomography (CALIPER)(141). MMF has been reported to be effective also in the treatment of skin involvement in SSc patients, with an improvement of mRSS and tadalafil could be associated to a better outcome on the left and right ventricular function (146), and the best results for this treatment have been reported in patients treated with the combination as the first therapeutic approach (147-148). The rate of side effects reported with the combination therapy in SSc patients is very high but SAEs are rare and limited (148). The efficacy of tadalafil seems to be associated to changes in gene expression profiles especially for genes regarding the Stat4-dependent, NO-dependent IL-12 pathways and in genes encoding for ECM components; moreover, the gene expression pattern may help to identify patients at higher possibility to respond to the treatment (149). Promising results about for the reduction of morbidity and mortality for selexipag, a selective prostacyclin receptor agonist, in the treatment of patients with PAH have been reported (150). Recently, a subgroup analysis about patients with CTD has been described; despite patients with SSc were more severe compared to other CTD-PAH patients at the baseline evaluation, selexipag allowed to delay the progression of PAH also in this subgroup of patients (151).

Riociguat, a soluble guanylate cyclase stimulator, was reported to improve cardiac and respiratory functional in SSc patients with efficacy and safety similar to the non-CTD population (152). Additionally, riociguat was effective in the treatment of skin involvement in animal models of SSc and a multinational randomised trial started to check the efficacy of riociguat in skin involvement of SSc patients (153). Despite these promising results, it should be considered that SSc-PAH patients continue to have a worst prognosis compared to patients with idiopathic PAH, as the right ventricle function may not improve even after the institution of a vasodilator therapy (154). Results about vasoactive therapy for the treatment of RP secondary to SSc confirmed that sildenafil is able to increase the finger blood flow assessed by laser doppler imaging and improve RP severity and duration (155). Iloprost remains one of the most effective therapy for long-term treatment of RP and DUs in SSc patients (156), and recently the possibility of a home-based treatment with automated pumps has been tested in a small population with promising results (157). However, as reported in PAH treatment, also in the treatment of RP the association between two drugs, as bosentan and iloprost may be more effective compared to iloprost alone on nailfold capillary architecture (158). The promising results achieved by the treatment with selexipag in SSc-PAH have not been confirmed for the treatment of RP secondary to SSc (159), even if this the results of this study may have been influenced by the relatively short exposure to the drug.

In addition to the systemic approach, there may still be the room for topical treatment in SSc-ILD: as reported by Hughes et al., the application of topical glycerine trinitrate may improve the blood flow in SSc-DUs (160). A study about local injections of botulin toxin A for secondary RP failed to confirm an improvement of local blood flow in SSc fingers (161), while the results with botulin toxin B are more promising (162).

**Antifibrotic drugs**

In an open-label trial about dasatinib, a tyrosine kinase inhibitor with potential antifibrotic effect, the drug failed to demonstrate improvement in mRSS or pulmonary function tests, while an improvement of percentage of changes on quantitative HRCT suggested a possible antifibrotic effect, almost in some patients (163). Despite preclinical evidence suggested that calcium channel blockers (CCBs) may have an anti-fibrotic effect (164), a recent retrospective study did not
confirm these observation in the skin of SSc patients (165).

Encouraging preclinical results have been published about antifibrotic treatment as nintedanib and pirfenidone in animal models (166-167), and clinical trials in SSc patients are ongoing (168).

Recently, a double-blind, randomised, placebo-controlled clinical trial has been published about the potential use of SAR100842, a potent lysophosphatidic acid 1 receptor antagonist, for the treatment of skin fibrosis in a small group of SSc patients. SAR100842 was relatively well tolerated and allowed a significant reduction of mRSS compared to placebo with a responder rate of 69.2%. These promising results should be confirmed in larger confirmatory trials (169).

Transplant and cellular treatment

Autologous stem cell transplantation (ASCT) may represent a potential therapeutic option for refractory SSc and is now included in the EULAR recommendations (133). The protocols proposed for mobilisation and conditioning regimens are heterogeneous and they could influence transplant related mortality (170) but patients’ characteristics, particularly for cardiac dysfunctions, remains the most important prognostic factor for the prognosis and mortality of patients receiving ASCT (170-171). However, despite the mortality for the ASCT procedure is still high, the prognosis in patients with severe disease seems to be favourable (172). Negative prognostic factors for ASCT transplantation response may include the pre-transplant B cell clonal expansion (173) and the presence of a specific epitope for anti-topoisomerase I (489-573) (174). A combined therapeutic approach with CTX, plasmapheresis and mesenchymal stem cells transplantation, could be feasible and beneficial for SSc patients (175). Novel data supports the possibility to candidate SSc patients to lung transplantation for the treatment of ILD or PAH, provided that patients are adequately screened for other organs involvement (176). Renal transplantation in SSc patients with end-stage renal disease may be associated to excellent results for patients and graft survival (177).

Treatment for specific organ involvements

Despite the therapeutic advances in vasoactive treatments, ischaemic DUs continue to represent a major burden for SSc patients and the control of DUs may improve the function of the hands in patients (178). Although the treatment for SSc-DUs cannot disregard the need for a systemic approach, local treatment is crucial for the healing of the wound. Debridement, essential passage for the local approach, can cause severe pain and the application of local lidocaine 4% is associated to a reduction for the pain associated to the procedure and may safely improve the local management of digital wound in SSc (179). A retrospective report confirmed the possible role of hyperbaric oxygen therapy in favourable healing in a small cohort of SSc patients with refractory skin ulcers (180).

GI in SSc if frequent and difficult to treat as the pathogenesis is still not understood (181). For the treatment of GI, prucalopride, a serotonin receptor 4 antagonist, increased the number of intestinal evacuations and improved the GI symptoms in a small randomised trial, although the safety profile is not completely exempt from adverse events (182). Domperidone and algycon may be both equally effective for the treatment of upper GI in SSc patients, and may represents a safe add-on to the standard proton pump inhibitor treatment (183).

References


44. TANIGUCHI T, ASANO Y, NAKAMURA K et al.: FoxI1 Deficiency Induces CXCL6 Expression in Dermal Fibroblasts and Endothelial Cells, Contributing to the Development of Fibrosis and Vasculopathy in Scleroderma. J Rheumatol 2017; 44: 1198-205.


46. DING Q, YEUNG M, CAMIRAD G et al.: Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice. J Clin Invest 2011; 121: 3645-56.


56. LEGÁNY N, BERTA L, KOVÁCS L, BALOG A, TOLDI G: The role of B7 family costimulatory molecules and indoleamine 2,3-dioxye-

One year in review 2018: systemic sclerosis / M. Orlandi et al.
One year in review 2018: systemic sclerosis / M. Orlandi et al.


presence of significant pulmonary fibrosis. Medicine (Baltimore) 2018; 97: e5066.
129. BAQIR M, MAKOL A, OSBORNE TG, BAR-THOMAI BJ, RYU JH: Mycophenolate mofetil for scleroderma-related interstitial


177. BRASCHI F, BARTOLI F, BRUNI C et al.: Lonidacine controls pain and allows safe wound