Review

Systemic sclerosis: a critical digest of the recent literature

S. Barsotti, C. Stagnaro, A. Della Rossa

Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy.

Simone Barsotti, MD
Chiara Stagnaro, MD
Alessandra Della Rossa, MD

Please address correspondence to:
Dr Simone Barsotti,
Rheumatology Unit,
University of Pisa,
Via Roma, 67,
56126 Pisa, Italy.
E-mail: simone.barsotti.pisa@gmail.com

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ABSTRACT

Systemic sclerosis is a complex chronic disease characterised by chronic multisystem involvement of skin and internal organs. We reviewed all the articles published during the last 12 months on systemic sclerosis and in this article we provide a critical analysis of the most relevant studies regarding the pathogenesis, classification and management of the disease.

Introduction

Systemic sclerosis (SSc) is a chronic disabling disorder characterised by three pivotal aspects, obliterative and proliferative microvascular involvement, activation of the immune system and increase of extracellular matrix deposition in the skin and internal organs. In the past few years, many advances have been made in the knowledge of the disease, with an increasing awareness of the unmet needs for this disorder, which have progressively driven forward our ultimate goal, the disease control and the accomplishment of an adequate quality of life (1).

In this manuscript, we will provide our annual overview of the recent advances in the pathogenesis, diagnosis and classification and treatment of systemic sclerosis. A systemic 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 January 2014 and July 2015.

Recent insights into the classification of SSc

As previously reported (2), the 2013 American College of Rheumatology/ European League against rheumatism classification criteria have been recently developed and published (3). These criteria are more sensitive and thus able to classify consistently more patients than the older 1980 criteria, as was demonstrated in a two independent series of SSc patients. The acquisition of sensitivity was particularly evident for limited subset and for subjects without patent skin involvement, including early disease. However, the removal of sclerodactyly and puffy fingers, reduced consistently the sensitivity of the new criteria (4, 5). To overcome the issue of properly classifying subjects with sub-clinical disease, Very Early Disease Onset Systemic Sclerosis (VEDOSS) criteria have been proposed (6). In addition to well-characterised predictive factors, puffy fingers have been suggested as an important sign raising suspicion for underlying very early SSc in patients with Raynaud Phenomenon (RP) (7).

Recent data suggest that, among subjects not satisfying the 2013 ACR criteria, different subsets might be identified at different risk of SSc evolution, with faster progression of SSc in autoantibody-positive patients, particularly in those with preclinical internal organ involvement at baseline, irrespective of capillaroscopic pattern, than in autoantibody-negative patients (8, 9).

Recent insights into the pathogenesis of SSc

Although systemic sclerosis is not an inherited disease, genetic influences have long been suspected to impact the disease. Several studies reported that major histocompatibility complex (MHC) class II is the most significant in the development of the disease; however some studies reported also other non-HLA genes that are associated with SSc susceptibility (10). Particularly, a new study using microarray technique reported for the first time an association with mutation in DNASE1L3 and VCAM1 loci. DNASE1L3 was also reported to be associated with anti-centromere antibody (ACA) positivity (11). Another study recently reported for the first time an association with interleu-

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kin-12 pathway and SSc, describing β1 subunit of interleukin (IL) 12 receptor (IL12RB1) association with the development of SSc (12).

In addition to a predisposing genetic background, an early trigger is likely required to initiate the disease process in SSc. Viral infection have been reported to be associated with the disease; in particular a crucial role has been hypothesised for human cytomegalovirus and parvovirus B19 in the development of the disease (13). Other than infections, also environmental factor can be responsible of development of SSc, and a recent study investigated the effects of diesel exhaust nanoparticles on scleroderma skin cells (14). The authors reported that environmental factors due to traffic-derived pollution might play a key role in triggering an inflammatory-fibrogenic response in genetically predisposed individuals; particularly nanoparticles may induce IL-1a e IL-9 expression and up-regulated metalloproteases (MMP) type 2 and 9. Moreover, abnormalities of selenium homeostasis can be involved in the development of SSc (15).

The mechanisms underlying visceral involvement in scleroderma are unclear, mostly because relevant data on pathogenic mechanisms are limited and there are no satisfactory animal models of scleroderma (16). Manetti *et al*. proposed a new animal model mimicking the histopathological features of SSc, characterised by inactivation of urokinase-type plasminogen activator receptor (uPAR) gene. The uPAR-deficient mice present greater skin thickness, collagen content and myofibroblast count that wild type mice (17).

Clinical symptoms and histological data of early disease stages suggested that vascular injury is an important feature in the early phase of the disease. Shirai *et al*. have investigated the possible role of pentraxin3 (PTX3) and fibroblast growth factor 2 (FGF-2) in SSc-related vasculopathy (18). The authors described a strict association between PTX3 levels and suppression of endothelial progenitor cells-mediated vasculogenesis; moreover, PTX3 elevation is associated with the development of DUs and pulmonary arterial hypertension (PAH); FGF-2 was suppressed by PTX3 and was reported to be reduced in SSc patients with PAH.

There are various hypotheses on how vascular alterations may lead to fibrosis; a recent study by Maurer *et al*. (19) reported, in experimental model of bleomycin induced SSc, a strict association between vascular endothelial grow factor (VEGF) expression and the development of skin fibrosis. VEGF transgenic mice spontaneously developed skin fibrosis and the profibrotic effect become more pronounced in bleomycin model. The authors concluded that their data provide the first evidence for VEGF as a novel molecular link between fibrosis and vasculopathy in pathogenesis of SSc. Moreover, a recent article reported that upregulation of the VEGF signaling in perivascular cells which are shifted to a profibrotic phenotype may be induced by low levels of Caveolin-1 (20).

Several factors are involved in in the development of skin fibrosis in SSc patients. A recent study report a crucial involvement of IL-17, particularly IL-17A and related family (21); the authors analysed the expression of positive cells for IL-17 in the skin of patients reporting differences between SSc related skin fibrosis (increased IL-17A) and morphea (increased IL-17F). Moreover, the authors reported in both the diseases, a specific IL-17C/IL-17E combination (low the first, high the second) that may play a role in the development of fibrosis. In another study, Kudo *et al*. (22) reported that in SSc patients skin the reduction of IL-20 can contribute to cutaneous fibrosis, reducing keratinocyte proliferation; the authors also reported that IL-20 administration was able to inhibit bleomycin-induced fibrosis in a mouse model.

A novel animal model hypothesised the key role of IL-17 in the development of antinuclear antibodies in SSc patients; in a recent article, authors reported that intestinal microbiota, and particularly segmented filamentous bacteria that may be present in experimental condition, might induce an IL17 mediated Th17 response capable to induce spontaneously antinuclear antibodies in adult life (23).

Several published articles suggest a central role of transforming growth factor β (TGF-β) in fibroblast activation and tissue fibrosis in SSc. A recent study by Tomcik *et al*. reported promising result of reduction of TGF-β activity on fibroblast by inhibition of heat shock protein 90 (Hsp90); particularly inhibition of Hsp90 abrogates the stimulatory effect of TGF-β on fibroblasts and reduced the fibrosis deposition in an experimental model (24). Another recent study describes the effect of constitutive androstane receptor (CAR) on fibroblast activation: CAR is up-regulated in the skin and dermal fibroblast of SSc patients and its activation increases the profibrotic effect of TGF-β. Thus, CAR may be involved in targeting aberrant TGFβ signaling in SSc (25).

Histologically, endothelial cell damage is accompanied by the presence of perivascular leukocytes infiltrates. Also in experimental model of systemic sclerosis the development of skin fibrosis was strictly associated with increasing of skin infiltrate of leukocytes including macrophages, neutrophils and T lymphocytes (26). In a recent review, the authors hypothesised a role in the pathogenesis of inflammation in SSc for several member of IL-1 family: abnormal expression of IL-1 have been probed but a possible role in the pathogenesis of SSc has been suspected also for IL-36, IL-37, and IL-38 (27).

IL-1β was found increased in skin of SSc patients, that presented also elevation of NLRP3 (nucleotide-binding domain, leucine-rich-repeat-containing family, pyrin domain-containing 3), IL-18, caspase-1 and endothelin-1 (28). Skin fibrosis evaluated by modified Rodnan skin score had significant correlation with IL-1β and NLRP3.

IL-6 might also be involved in the development of systemic sclerosis. A recent study by Desallais *et al*. reported that serum and skin levels of IL-6 were significantly increased in patients with early SSc and that a monoclonal anti-IL-6R antibody prevent the development of bleomycin induced dermal fibrosis in mice (29).

The analysis for chemokine expression in the skin of SSc patients reported that CCL18, CCL19 and CXCL13, were up-regulated in diffuse cutaneous SSc skin, and CCL18 in limited cutaneous SSc skin. Expression of CCL19 corre-

lated with markers of vascular inflammation and macrophage recruitment; CCL19 have a role in the recruitment of immune cells to the peripheral tissue and may be a sensitive marker for the perivascular inflammation and immune cell recruitment in diffuse cutaneous SSc skin disease (28).

Agonistic autoantibodies against the angiotensin II receptor type 1 (AR1R) and the endothelin receptor type A (ETAR) have been identified in SSc patients and can be involved in the pathogenesis of the disease. These agonistic autoantibodies may stimulate blood mononuclear cells to produce more IL-18 and CCL18. It suggest that AT1R and ETAR activation may be co-responsible of the pathogenesis or the onset of the SSc (30).

The excessive deposition of extracellular matrix, including type I collagen, represent a key characteristic of SSc. A recent study aimed to investigate the mechanisms under collagen hyperproduction reported the possible key-role of JunB, a member of the activator protein 1 family of transcription factor, in the aberrant over-expression of type I collagen (31). A possible role in the development of SSc-related fibrosis has also been reported for myocardin related transcription factor A (MRTF-A). MRTF-A is elevated in SSc patients and may act as a central regulator linked to remodeling of the extracellular matrix and synthesis of type I collagen (32).

In SSc patients an increased Wnt activity has been reported; moreover, the gene encoding Wnt inhibition factor 1 (WIF-1) was decreased in skin fibroblast and correlate with increased production of collagen. Novel data show that inhibition of morphogen pathways (including Wnt but also Hedgehog and Notch pathways) can be effective and safe for the treatment of fibrosis, particularly when treated with combination therapies (33).

Several factors can contribute to the increasing of Wnt signaling. In particular, a novel study reported that hyper methylation of DKK1 e SFRP1 resulted in impaired transcription and decreased expression of these promoters in SSc patients and may induce increased Wnt signaling leading to aberrant collagen deposition (34). Moreover, a recent study by Svegliati *et al*. reported as oxidative DNA damage induced by SSc patients autoantibodies as well ultraviolet light, hydrogen peroxide or bleomycine can enable Wnt activation that contributes to fibrosis (35).

Hypoxia may play an important role in the pathogenesis of systemic sclerosis; particularly in SSc patients may exist an abnormal response to hypoxia. Carbonic anhydrase IX is one of the hypoxia markers and may be released into the serum in response to hypoxic stimuli in SSc. A recent study by Makino *et al*. reported that patients diagnosed as scleroderma spectrum disorder presented lower carbonic anhydrase levels compared to healthy subjects in spite of the presence of hypoxia. The authors concluded that these findings may suggest an abnormal response to hypoxia in SSc patients and scleroderma spectrum disorders that may be involved in the pathogenesis of the disease (36).

Vitamin D insufficiency or deficiency has been implicated in triggering and enhancing several different autoimmune diseases. Several articles reported as the levels of vitamin D3 are decreased in patients with systemic sclerosis (SSc) and 25(OH)D3 levels have been reported to negatively correlate with several laboratory and clinical parameters in systemic sclerosis patients (37, 38). Effects of 1,25(OH)2D3 on immune cells include ability to decrease autoimmunity and, conversely, vitamin D deficiency contributes to increased autoimmunity (39). In a recent study, the authors reported that suppression of vitamin D receptors (VDR) enhanced the sensitivity of fibroblasts towards TGFb; conversely, activation of VDR reduced the effect of TGFb on fibroblasts, inhibited collagen release and myofibroblast differentiation (40). Topical vitamin D analogues seem to be effective in reducing skin fibrosis in experimental model of beomycin-induced fibrosis and enhances thymic stromal lymphopoietin (TSLP)-dependent Th2 cytokine and IL-13 expression (41).

PAH is a common complication of SSc. PAH carries a very severe prognosis, representing one of the leading causes of death in patients. In the last year, great interest was directed in the study of the mechanisms responsible of PAH in SSc patients.

Great interest has been given to the effects of endothelin (ET) 1 and angiotensin (Ang) II toward their receptors ET receptor type A and Ang receptor type-1 on the PAH pathogenesis. In particular stimulating autoantibodies targeting and activating Ang and ET receptors were detected in patients with SSc-PAH and predicted PAH related mortality. Transfer of SSc sera containing autoantibodies in healthy mice led to increased muscle actin expressions and inflammatory pulmonary vasculopathy (42). However, some authors assert that, even if Anti Ang type 1 and anti ET-1 may have a pathogenic role in vascular disease, their role in the in the development of SSc-PAH is not certain (43).

In the pathogenesis of SSc-PAH also other mechanisms, such as oxidative stress can be involved. A recent study reported the increase of NADPH-derived reactive oxygen species production in SSc-PAH patients and their correlation with the activation of collagen synthesis in vascular smooth muscle cells. The authors concluded that this mechanism can cause and/or maintain PAH in SSc patients (44).

Novel data have hypothesised the involvement of bone morphogenetic protein receptor (BMPR) II in the development of SSc-PAH. The reduced expression of BMPR II is associated with heritable PAH and idiopathic PAH; recent studies reported a reduced BMPR II protein also in the lung tissue of patients with SSc related PAH, proposing an unifying mechanism across different forms of PAH (45).

Recent insights into clinical manifestations of SSc

Autoantibodies

The importance of SSc antibodies for diagnosis has become increasingly recognised, as evidenced by incorporation into the 2013 American College of Rheumatology/the European League Against Rheumatism clinical classification criteria for SSc. With the availability of new laboratory techniques and the diffusion of large cohorts of pooled patients, new clinical associations have been described.

Anti RNA polymerase III (RNAP) antibodies, which are positive in 10–25% of the subjects, have been linked with gastral antral ectasia and with rapid onset and evolution of the disease (46). Moreover, this autoantibody has been associated with the occurrence of malignancy in two independent cohorts of SSc subjects (47, 48), one of which the largest ever studied (48). The association with cancer and RNAP antibodies is in close temporal relationship to onset of SSc, which supports the paraneoplastic phenomenon in this subset of SSc cases. An index of cautious suspicion should be maintained in these cases, and investigations for underlying malignancy should be considered when clinically appropriate.

Anti SSA/Ro52 have been linked with certain clinical manifestations in SSc, such as the higher frequency of interstitial lung disease (ILD) and overlap features in a Canadian series (49), although this association has not been confirmed in a cross-sectional and observational study from Spain (50). Although QTc prolongation is a common feature in SSc patients (25%) in a univariate analysis, Ro antibodies were not associated with prolongation of the QTc interval, as is the case in systemic lupus erythematosus. The reasons for this difference, as well as the cause of abnormalities in cardiac repolarisation in SSc, will require further study (51).

Autoantibody-negative SSc is a rare entity (<2%) and seems to be associated with a favourable outcome (52). In this regard, autoantibodies to the Th/To autoantigen are important in patients with SSc who have been considered negative for SSc-specific or SSc-associated antibodies by widely available commercial assays. Rpp25 can be considered a major target of anti-Th/To antibodies, the detection of these specificities could be a useful aid in the clinical assessment of SSc patients (53). Anti PM-Scl is another rare specificity in SSc which have been associated with myositis and overlap features. PM-1α is a major epitope of the PM/Scl complex. Anti-PM-1α antibodies are relatively common in SSc and are associated with a distinct clinical phenotype, consistent with that described in association with other anti-PM/Scl autoantibodies. Anti-PM-1α can be present in the absence of other specific SSc antibody. Thus, anti-PM-1α antibodies may have considerable diagnostic and prognostic relevance in SSc (54).

Organ involvement

Skin

Skin involvement is a frequent feature in SSc subjects. The disease is classically divided into two subsets on the basis of the involvement of the skin distally or proximally to the metacarpophalangeal joints. This classification bears relevance for the outcome as the extension of skin involvement correlates inversely with survival (55).

Modified Rodnan Skin Score (MRSS), remains the best method for the objective assessment of skin involvement both in clinical practice and in research settings that combines feasibility, an acceptable reliability, responsiveness to change and correlation with physician global correlates of health status. Among the variables that could represent confounders in the evaluation of responsiveness to change of this outcome measure, treatment modalities and menopausal status should be taken into consideration (56, 57).

Prediction score for skin progression in diffuse disease, have been developed using EUSTAR cohort; short disease duration, low baseline MRSS and joint synovitis were pointed as independent predictors of progressive skin fibrosis within 1 year from disease onset (58).

Musculoskeletal involvement

In addition to skin involvement, the presence of synovitis and tendon friction rubs have been recently confirmed as a simple and easily detectable clinical marker for identifying poor outcome patients in a EUSTAR prospective study (59).

Musculoskeletal manifestations are a major cause of morbidity and disability, including arthralgia/arthritis, tendon friction rubs, joint contractures, digital tuft resorption, subcutaneous calcinosis, and muscle weakness. Joint contractures have been reported to occur frequently and early in SSc patients, mainly affecting the dominant hand and may be related to outcome (60).

Hand and face disability contribute significantly to global disability as assessed by Health related Quality of Life (HRQol) and therefore should be taken into account, both in clinical practice and in clinical trials (61).

Hand calcinosis is an overlooked feature the disease that can contribute to limit range of motion and to the appearance of hard to heal DUs. Recently, a novel reliable and reproducible radiographic scoring system for calcinosis have been proposed for use in clinical trials (62).

Finally, low bone mineral density (BMD) and fracture are frequently seen in SSc patients (63). Non-Caucasian ethnicity, postmenopausal status, low BMI, low body weight, ScL-70 positivity, small bowel bacterial overgrowth, lower gastrointestinal involvement, ILD, PAH, history of falls, ≥10 kg weight loss, family history of osteoporosis and kyphoscoliosis were associated to low BMD in a single centre study. SSc patients with low bone density have a higher 10-year risk of developing a major osteoporotic fracture, and have a higher 10-year risk of developing a femoral neck fracture. Whether these associations are disease specific or spurious (*i.e.* related to major organ involvement or to treatments) and the best therapeutic approach in the SSc population need to be addressed in future research (64).

Vascular involvement

Vasculopathy is a central key feature of SSc and structural abnormalities of the microvascular lining are evident in visceral organs as well as in skin in the earliest stages of the disease (65). Clinical and histologic findings suggest a central role for these alterations especially at the beginning of the disease. Both permeability and vasomotility alteration might be due to an imbalance consisting of an increase of vasocostricting factors associated to a relative decrease of vasodilator substances (66, 67). Peripheral microvascular damage in this disease is characterised by dynamic alteration of the capillaries that carries a progressive decrease in their density and compensatory increase in capillary dimension. Microvascular changes are typically observed in the nailfold bed by capillary microscopy and are in fact

utilised for the early diagnosis of SSc and prognostication of disease evolution (68). Typical microvascular alterations, called the scleroderma pattern, are detectable at nailfold capillaroscopy in a significant percentage of SSc patients, with variable prevalence across studies. Capillary microscopic alteration and evolution have been correlated with the appearance of DUs (69, 70). In SSc, DUs are an early manifestation of vasculopathy and represent a considerable burden, having a strong impact on quality of life and function (67). They result from ischemia due to vasospasm, intimal fibro-proliferation and thrombosis of the digital arteries; additional co-factors as sclerodactyly, calcinosis and local trauma may further contribute to their genesis (71).

DUs are thought to be a clinical parameter of severe vasculopathy that can be associated with or predict other vascular or systemic lesions. Treatment of DUs remains challenging and the identification of reliable predictors of this complication is of paramount importance. The measurement of capillary abnormalities can take advantage of quantitative or semi-quantitative ranking methods in order to obtain a score of prediction for single patients (72, 73). Recently it has been claimed that the detection of new DU might be also a warning sign to predict organ involvement in very early SSc (74). Telangiectasia are a simple and easily detected clinical parameter that could be useful to provide information on the severity of vascular involvement, particularly in some ethnic groups (75).

An extensive literature review according to the PRISMA statement identified the clinical and serological parameters associated most consistently with DUs. Diffuse systemic sclerosis, early onset of RP, early first non-RP symptom and a great extent of skin fibrosis (high MRSS), anti-topoisomerase I positive autoantibodies, late nailfold videocapillaroscopy (NVC) scleroderma pattern and worsening of NVC SSc patterns are strong predictors for DUs. Patients with DUs have higher endothelin-1 serum levels, on the other hand, VEGF levels are reduced in SSc patients with DUs and significantly higher serum VEGF value are found in early stages of disease in SSc patients without digital ischemic manifestations (76).

Since the prevalence and severity of peripheral vascular involvement is a reflection of the systemic nature of SSc, numerous effort have been made in order to find the earliest functional abnormalities that could help to predict the evolution of the disease. Rosato *et al*. pointed out that the detection of an increase of intrarenal stiffness may predict the occurrence of new DUs in SSc. The authors conclude that Doppler indices could be used in association with capillaroscopic and clinical findings or serologic tests for the identification of patients at higher risk of developing DUs (77).

New techniques for the assessment of the microcirculation have been recent introduced. Laser speckle contrast imaging (LASCA) has proven useful both for the evaluation of blood flow in different skin area, and for the dynamic evaluation of blood flow after physical stimuli (78, 79).

An alteration of the kinetics of post occlusive reactive hyperemia was noticed in SSc subjects. Whether the altered PORH response results from structural abnormalities in the digital arteries or from a specific microvascular dysfunction, remains unclear (80).

Blunted thermal hyperemia by laser Doppler flow (LDF), has been associated with the onset of DUs in SSc during 3 years of follow-up (81).

Provisional data indicate that the use of bosentan might revert the microvascular perfusion abnormalities leading to skin ulceration (82, 83), thus confirming the morphological finding of improvement of microangiopathy detected by capillaroscopy after bosentan treatment (83, 84). Moreover, in an *in vitro* assay of cell viability and chemoinvasion, the addition of bosentan at different concentration to dermal microvascular endothelial cells (MVEC) challenged with SSc sera, significantly restored cell viability (85)

Pulmonary involvement

SSc is associated with high morbidity and mortality and lung complications have represented the major causes of mortality over recent decades (86). ILD and PAH are the two sides of a spectrum which may encompass from isolated ILD to isolated PAH and various combinations of the two entities. In severe forms of ILD, secondary pulmonary hypertension (ILD-PH) may superimpose to this complex picture (87). The prevalence and severity of ILD and PAH is higher in African Americans as compared to Caucasian subjects (88, 89). Since neither access to care nor socioeconomic status can completely explain this health disparity, recently it has been claimed that a deficit of Caveolin-1 may predispose African Americans to ILD. Activation of their monocytes by strengthened TGF-beta signal, primes them for a heightened response to a variety of external insults, such as viral infections or environmental factors, thus predisposing them to a number of fibrosing disorders, including SSc and its complications (89).

Besides monocytes, another cellular player in the pathogenesis of ILD are CD161+ Vδ1+ γδ T lymphocytes, which act as a regulatory element, via IFN gamma production (90).

As far as the clinical assessment of ILD is concerned, the diagnosis at an early stage is a crucial element, since the prompt treatment of progressive cases might improve outcome. The gold standard for the diagnosis and follow-up is represented by high resolution CT scan, but regular screening has to be weighed against the risk for excessive radiation exposure. For this reason, new protocols with reduced number of slices have been proposed (91).

Computed-based methods of scoring is a useful aid for the initial staging of ILD, dichotomising the therapeutic choice and reliable follow-up of the patients (92).

An emerging method to reduce radiation risk is the regular screening of SSc subjects by non-invasive methods, such as lung ultrasound, as a tool for timely HRCT, avoiding unnecessary exposure in asymptomatic subjects (93).

Lung diffusion capacity for nitric oxide (DLNO) might be more sensitive than DLCO in detecting functional impairment in SSc patients without any radiologic or haemodynamic alterations

and may represent a useful tool for the early identification of patients to be closely monitored (94).

Fibrosis of the lung is a hallmark of idiopathic pulmonary fibrosis (IPF) as well as of SSc-related ILD. Although the two conditions share a number of clinical features, they are fairly divergent as far as epidemiology, HRCT patterns, histology, natural history of the disease and response to treatment, are concerned although showing similar survival rates after orthotropic lung transplantation (95, 96).

In a large cohort of SSc subjects followed for 15 years, clinical significant ILD occurred most commonly within the first 3 years of the disease and over 2/3 of the subjects presented clinically overt lung involvement within the first 5 years of the disease. ILD was more prevalent in diffuse disease. The variables that predicted clinically significant ILD development were dc-SSc, greater age at onset, lower forced vital capacity and DLCO, and the presence of anti-topoisomerase I antibody, while the presence of anticentromere antibody was protective. Predictably, clinical significant ILD was associated with worse survival (HR 2,4) (97).

Winstone and co-workers conducted a systematic review to identify variables that predict mortality and ILD progression in SSc-ILD. Older age, lower FVC, and lower diffusing capacity of carbon monoxide predicted mortality in more than one study. Male sex, extent of disease on high-resolution CT (HRCT) scan, presence of honeycombing, elevated KL-6 values, and increased alveolar epithelial permeability were identified as predictors of both mortality and ILD progression on unadjusted analysis. The extent of disease on HRCT scan was the only variable that independently predicted both mortality and ILD progression (98).

Incidence rates of PH in unselected SSc series are 1–2% per year. Factors associated with increased risk of PH are greater age at disease onset, increase in serum creatinine levels, lower DLCO, and the presence of anti-RNA polymerase III or anti-U3 RNP antibodies, while anti-topoisomerase I antibody positivity reduces the hazard (97, 99).

Early identification of patients with PH is pivotal in SSc, in the context of growing number of emerging therapies for this disorder. Early treatment, treat to target approach and strict follow-up have contributed to substantially improve the outcome.

Cardiopulmonary exercise test (CPET), might be useful in asymptomatic patients in disclosing early pulmonary vasculopathy (100). Furthermore, novel methods for the assessment of oxygen uptake could be another adjunct for unravelling the subjects at risk (101).

Patients with SSc-CTD-PAH have higher mortality rates than patients with non-SSc-CTD-PAH. In the REVEAL registry, outcome has been associated to older age, lower baseline systolic blood pressure and 6-minute walking distance or markedly elevated mean RAP or PVR (102).

Analysis of the data from the ASPIRE registry of patients referred to a PH tertiary care centre, has pointed out that, in addition to clinical characteristics, a number of CT features might predict an ominous outcome, independently of the type of PH, such as the presence of pleural effusion, septal lines and dilatation of the inferior vena cava. Identifying high risk subjects would enable clinicians to timely set more aggressive treatment and monitoring (103).

The PHAROS registry is a prospective observational longitudinal cohort study that was established to determine the time to PH in a group of patients with pre-determined high-risk factors for developing PH and PAH, and the natural history of definite SSc-PAH and SSc-PH. In addition to a low DLco, a high FVC/ DLco ratio, and an entry echo sPAP of 40 mmHg, exercise-induced hypoxia is strongly associated with future PH. Frequent false elevations in echo sPAP imposes a RHC to confirm PH (104).

Heart involvement

Cardiac manifestations of SSc can affect all the structures of the heart. Primary myocardial involvement results from the underling vascular lesions and fibrosis that impairs microcirculation and myocardial function (105). This condition is often overlooked, since standard echocardiography is not sensitive in its detection, but carries an ominous prognosis. New methods, such as tissue Doppler echocardiography (TDE)-derived indexes or magnetic resonance, disclose subclinical heart involvement in a high rate of SSc subjects (106). The prevalence of myocardial fibrosis attributable to SSc on magnetic resonance imaging (MRI) is as high as 45%, is more frequent and severe in diffuse subset, is associated with lower left ventricular ejection fraction (LVEF) and affects mainly basal left ventricular walls. Microvascular damage is common and is associated with elevated ultrasensitive CRP levels. Cardiac damage due to SSc, on the other hand, is not associated with coronary artery disease (107, 108).

Microvascular damage occurs early in the course of the disease. Co-localisation of perfusion defects and delayed contrast enhancement indicative of fibrosis confirms the hypothesis that myocardial hypoxia may play a role in the pathogenesis of myocardial fibrosis (108).

Significantly higher risk of coronary heart disease in SSc patients, compared with the general population, has been found in the largest cohort studies. However, no difference in either atherosclerotic plaque occurrence or intima-media thickness was detected in SSc (109, 110) and although endothelial changes are a hallmark of the disease, they occur mostly in smaller arterioles and microvascular bed and not in medium or large vessels (111).

Cardiac arrhythmias are associated with poor outcome in this disease. Impaired LA function might contribute to the appearance of atrial fibrillation or supraventricular arrhythmias (112). Interatrial electromechanical delay might be an easy to detect parameter by TDE imaging to foresee subclinical heart involvement in SSc (113). The management of arrhythmias is particularly challenging in SSc, both for the frequent employment of medications that can affect QTc prolongation and for the clinical features of the disease, which largely impact on the tolerability of anti-arrhythmic drugs (105).

Among tissue specific markers, Nt-Pro

BNP has been claimed to be a useful prognostic marker for identifying SSc subjects at risk of future heart involvement (114).

Gastro-intestinal involvement

Gastro-intestinal (GI) involvement represents one of the most common manifestations of SSc, exceeded only by skin involvement. Oesophageal and ano-rectal involvement are the earliest GI manifestations, as shown by the frequent detection of these abnormalities in VEDOSS disease (115).

GI involvement is quite heterogeneous, varying from asymptomatic disease to significant dysmotility causing complications such as malabsorption, weight loss and severe malnutrition (116). At present, there is little published evidence available to guide clinicians on the best approach to this manifestation. A pragmatic behaviour should be based on the prevalent complaints of the patient, that address the diagnostic and therapeutic process to be followed (117).

In this regard, validated questionnaires to test GI involvement might represent useful screening tools, both in clinical practice and in research settings. GI involvement is, indeed, frequently overlooked, but can affect numerous aspect of SSc, such as quality of life, nutritional status, severity of other visceral involvements, therapeutic choice and outcome (118).

The Gastro Esophageal Reflux Disease (GERD) questionnaire is a sensitive, non invasive diagnostic screening tool for diagnosis of GERD in the general population, that has shown high sensitivity for GERD also in SSc subjects (119).

Disease specific instruments for GI involvement in SSc have been developed and validated, such as the UCLA-GIT 2.0 instrument (120, 121) and, more recently, the PROMIS scale (122).

UCLA GIT 2.0 has been translated and validated in numerous languages, including French and Dutch (123, 124).

Small intestinal bacterial overgrowth (SIBO) is a not uncommon, late onset manifestation that should be taken into account in patients with diarrhoea, weight loss, and other less well defined abdominal complaints. The treatment is based on cycles of antibiotics, although recurrence or lack of cure is not uncommon, in part for the high rate of subjects chronically treated with proton pump inhibitors, a known risk factor for recurrence (125).

Cancer

Increased frequency of few types of cancer has been reported in numerous rheumatic diseases, including systemic sclerosis. In rheumatic patients, in particular SSc, imaging of the chest (an anatomic region that includes the radiosensitive organs lung, female breast and bone marrow) is commonly performed. The available epidemiological evidence linking radiation exposure to increased cancer risk is well established for doses >10–50 mSv, which may be experienced by our patients during one admission, after one episode of care, or in some circumstances after a single examination. In a population study of people exposed to CT scan when aged 0–19 years, cancer incidence was increased by 24% compared with the incidence in unexposed people (126). Therefore, the risk of cumulative excessive radiation exposure, should be carefully balanced against the clinical benefit of submitting our patients to serial radiological assessments (127). This is particularly true for CT scans, which expose the patient to significant radiation doses.

In their extensive review analysing the relationship between scleroderma and breast cancer, Colaci *et al*. found a significant increase in the incidence of this malignancy in patients with SSc compared to sex- and age-matched general population in a case series from northern Italy. These findings were independent of clinical and serological features of the study population, smoking habit, total x-ray exposure or therapy with cyclophosphamide, which are known risk factors for developing certain malignancies (128).

RNAP antibodies have been associated with occurrence of cancer in SSc. RNAP is critical for regulation of sustained cellular protein synthesis and is therefore a fundamental determinant of normal cellular growth. However, the biological basis for an association between specific autoantibody subtypes against RNAP and malignancy in the context of SSc is unclear. The presence of anti-RNAP antibody may initiate an anti-tumour immune response that, in the appropriate setting, may cross-react against specific host tissue, resulting in target tissue damage (129).

The long-term use of calcium channel blockers (CCBs) has been associated to a significant relationship with breast cancer (130).

CCBs may interfere with cellular regulatory mechanisms by modifying intracellular calcium levels and could potentially affect programmed cell death, promoting the following development of malignancies (131). However, since data from observational studies does not robustly demonstrate a causal relationship, and a modest increase of risk is observed only after long-term use (more than 10 years), at present it should be borne in mind that the use of CCBs appears to be of benefit in the management of RP and to be protective against potentially severe manifestations of the disease, such as primitive heart involvement (132). When these medications are to be used, particular caution should be taken in patients with multiple risk factors for breast cancer, bearing in mind a stricter follow-up, or alternative drugs after long-term use.

Therapy

The activation of the immune system is a key pathogenic mechanism in SSc; in this disease we can typically find both humoral and cellular immunity abnormalities which mainly cause production of specific autoantibodies and profibrotic cytokines. The use of immunosuppressive drugs is recommended in patients with dcSSc and the treatment should be started as early as possible to induce remission or, at least, to achieve low disease activity before damage occurs. A clear algorithm for the treatment of various SSc manifestations is still lacking and, until now, the majority of trials have investigated the possible effects of many immunosuppressants on lung and/or skin involvement. ILD is a frequent complication of SSc associated to a shortened survival; most SSc-IDL patients present a stable or

slowly progressive lung disease while some of them experience a rapidly progressive loss of lung function, usually during the first years of the disease. Only the latter should be treated with immunosuppressive drugs, however, it is often difficult to discriminate between these two categories of patients. According to a recent work by Iudici *et al*., patients with a high risk of a progressive lung function decline are all those who present, at the baseline, an extent of lung fibrosis >20% at HRTC or an indeterminate extent of disease plus an FVC <70%; moreover, present high risk of progressive lung disease and all the patients who, during follow-up, experience a significant decrease of FVC (>10%) or of DLCO (>15%) or both regardless of the extent of lung involvement (133). Cappelli *et al*. have recently reaffirmed that the first-line therapy in these patients is cyclophosphamide (CYC) which has shown to be able to stabilise and even to improve lung function. CYC pulses (0.5–2 g/m^2 for each pulse) are better tolerated than oral administration, but it is not already clear which is the correct dose (maximum dose of 30–50g) and the correct duration of CYC therapy (usually 6–18 months). It has also been observed that CYC positive effects on lung function vanish 6–12 months after the end of therapy, so patients treated with CYC need a maintenance therapy with azathioprine (2–3mg/kg/day) or with mycophenolate mofetil (MMF 2g/day). The results of observational studies suggest that MMF could be a valid alternative to CYC when this is contraindicated or in young women to preserve fertility and also that it could have positive effects on skin fibrosis. When the first-line therapy with CYC fails, a valid therapeutic option might be rituximab (RTX) (134). RTX is a chimeric monoclonal antibody directed against CD20 which is an antigen expressed on B-lymphocytes. B cell abnormalities, characterised by autoantibody production, hypergammaglobulinaemia and B cell hyperactivity, are important features of SSc. For this reason, RTX has been used in some small studies and it seems to be a promising treatment of IDL and skin disease. In a recent prospective study, 20 patients with dcSSc were treated with RTX and followed up for at least 24 months. All patients experienced a significant improvement of skin score at 12 months. Moreover, the drug demonstrated to be effective on lung disease since it prevented the development of ILD in patients without lung involvement at baseline and it stabilised pulmonary function test and HRTC in patients with baseline restrictive lung disease. Therefore, RTX seems to be an effective and safe treatment for SSc patients with or without lung involvement (135).

Platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β) are considered two key signaling molecules in the pathogenesis of excessive fibrosis, which characterised SSc. They are produced by fibroblasts as a response to signals mediated by tyrosine kinase receptors, therefore the inhibition of tyrosine kinase could be an important target for SSc treatment. Imatinib mesylate is a small molecule that is able to inhibit tyrosine kinase blocking the effects of PDGF and TGF-β; the first studies, in which the potential effectiveness of this drug in scleroderma patients was tested, gave controversial results and imatinib seemed to have poor tolerability. In two recent works, instead, it has been demonstrated that low-dose imatinib is safe and well tolerated in the long term and that imatinib is able to stabilise lung function in patients with SSc-ILD refractory to CYC while it has no effects on skin involvement (136, 137). Since TGF-β is implicated in SSc pathogenesis as is demonstrated by the over-expression of TGF-β-regulated genes in skin and lungs of scleroderma patients, in a recent study it has been evaluated whether the inhibition of this growth factor could bring benefits to SSc patients. Fifteen dcSSc patients have been treated with fresolimumab, a human IgG4 monoclonal antibody able to neutralise all 3 TGF-β isoforms; these patients underwent serial skin biopsies, performed before and after the treatment, to analyse whether there were changes in expression of TGF-β-regulated genes thrombospondin-1 (THBS-1) and cartilage oligomeric protein (COMP). In all these patients THBS-1 and COMP expressions rapidly declined after fresolimumab treatment and clinical skin disease, assessed using MRSS, significantly decreased. Moreover, the decrease in mRSS seems to be strictly correlated with the degree and speed of skin biomarkers' decline. Fresolimumab could be a useful drug for the treatment of SSc, but further studies on a larger number of patients are necessary to confirm its efficacy and to evaluate its safety (138).

Among the biologic drugs commonly used for the treatment of other autoimmune diseases, tocilizumab, a monoclonal antibody directed against IL-6 receptor, might be useful in SSc patients since it has been demonstrated that fibroblasts isolated from skin of scleroderma patients produce high levels of IL-6. Tocilizumab has shown to be effective on skin and joint involvement, but further studies are necessary to confirm these data (134). A phase III, multicentre, randomised, double-blind trial to assess the efficacy and safety of tocilizumab in patients with SSc is in progress (139).

SSc patients could also develop severe vascular manifestations such as PAH and DUs. A new drug for the treatment of PAH has recently been approved; it is an endothelin receptor antagonist (ERA) called macitentan. It prevents the binding of endothelin-1 (ET-1) to both endothelin A (ET_A) and endothelin B (ET_B) receptors, but it has a 50-fold increasing selectivity for ET_A subtype which seems to be more represented in the pulmonary arterial smooth muscle cells. Its selectivity and its high affinity for ET_A receptors make macitentan a powerful and effective drug in the treatment of PAH. It has been demonstrated that it is able to improve the survival of patients with PAH by delaying the disease progression and it is also more tolerated than other ERAs (140). Riociguat is a stimulator of soluble guanylate cyclase, which has been recently approved for the treatment of pulmonary hypertension. A randomised, double-blind, placebo-controlled phase II study is in progress to investigate the efficacy and safety of riociguat in patients with dcSSc; it could improve skin and lung fibrosis, but it could also have

positive effects on RP and DUs (141).
Furthermore, researches have recently tried to understand whether drugs with vascular effects and already used for the treatment of PAH, could be helpful also in the management of DUs. Twenty scleroderma patients with DUs were treated with the ERA ambrisentan for 24 weeks: all baseline DUs completely healed in 14 patients while a mean of 3.2 new DUs per patients developed during the study. This prospective pilot work suggests that ambrisentan, unlike bosentan, could promote the healing of existing DUs, but it cannot prevent the development of new DUs. However, these results need to be confirmed by further studies on a larger number of patients (142).
It has already been demonstrated that sildenafil, which is a phosphodiesterase-5 (PDE-5) inhibitor approved in the treatment of PAH, could improve RP and DUs. The results of a new prospective, randomised, double-blind, placebo-controlled study (SEDUCE study) conducted in 25 French centres to investigate the efficacy of sildenafil on DU healing in SSc have been recently published. Eighty-four patients were randomised and it was observed that the number of DUs was lower in the sildenafil group, suggesting a higher healing rate in patients treated with PDE-5 inhibitor. The time of healing was significantly shorter when sildenafil was administrated to patients already receiving bosentan. Therefore, we can deduce that combination therapy with bosentan and sildenafil could be more effective in the healing of DUs (143).
In scleroderma patients who are refractory to conventional treatments, autologous haematopoietic stem cell transplantation (HSTC) could represent a possible therapeutic option. This procedure has been used as a rescue therapy in several refractory autoimmune diseases with positive effects. The mechanisms underlying the benefits of HSTC in autoimmune diseases are not already fully understood, but it is supposed that it causes a re-establishment of immunological tolerance in association to a non-specific immunosuppressive effect. This procedure should be proposed to very carefully selected patients who are, in the case of SSc, patients with dcSSc, mild-moderate internal organ involvement and a maximum disease duration of 4–5 years or patients with lcSSc and progressive internal organ involvement. HSTC seems to cause an improvement of MRSS, lung function and vasculopathy. Despite its potential benefits, we must not forget that HSTC is dangerous therapeutic option with a high risk of death and a higher morbidity rate (144, 145).
In patients resistant to conventional treatments, a therapeutic option could also be represented by intravenous immunoglobulins (IVIG). They seem to have an immunoregulatory activity, but their mechanisms of action remain unclear. Experimental data collected in the last few years about the effects of IVIG on scleroderma patients show that IVIG may improve several clinical manifestations of SSc, such as skin and joint involvement, calcinosis and even ILD. They are usually administered in several pulses, each consisting of 1–2g/kg divided over 2–5 consecutive days, although optimal dosages and timing of administration are not yet defined. Even though it has been demonstrated that IVIG has positive effects on some SSc manifestations, data about their use in SSc remain relatively insufficient so further studies are necessary to confirm IVIG efficacy in SSc, to understand their mechanisms of action and to identify optimal dose and time of administration (146). At the moment, a double-blind, randomised, placebo-controlled study is in progress to assess the safety and efficacy of IVIG in scleroderma patients (147).

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