Review

Systemic sclerosis: a critical digest of the recent literature

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ABSTRACT

Systemic sclerosis is a complex disease characterised by chronic multisystem involvement of internal organs; every year many studies are published on the diagnosis, pathogenesis and treatment of the disease. In this article, we provide a critical analysis of the recent literature on systemic sclerosis, with particular focus on the most relevant studies published over the last two years.

Introduction

Systemic sclerosis (SSc) is a chronic disease with autoimmune pathogenesis that mainly affects connective tissue, microvessels and small arteries, and is characterised by fibrosis and vascular obliteration in the skin and internal organs, particularly lungs, heart and digestive tract (1, 2).

Every year many studies are conducted in order to understand the pathophysiology of this disorder, and new breakthroughs are achieved in the field of diagnosis and treatment, with consequent improvements in the early diagnosis and management of the disease. In this manuscript we will provide an 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 2013 and July 2014.

Recent insights into the classification of systemic sclerosis

In 2013 the new American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for SSc were published (Table I) (3). The goal for the new criteria was the improvement of sensitivity for the definition of the disease since the 1980 criteria failed to correctly include a large proportion of SSc patients. This was particularly true in subjects either with early or long-lasting disease and very limited or no skin involvement (4).

The new classification criteria were more sensitive in all categories of SSc patients as well as in early disease subset (<3 years of disease). However, subjects with a clinical picture limited to Raynaud's phenomenon, abnormal capillaroscopy and autoantibodies, could not be classified as definite SSc and might develop the disease in subsequent years. To detect patients with very early disease, the EULAR Scleroderma Trials and Research group (EUSTAR) Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria remain a good benchmark in the clinical settings (5, 6).

Recent insights into the pathogenesis of systemic sclerosis

The pathogenesis of SSc is extremely complex, and despite many advances made in its identification in the last decades, the exact mechanisms involved are still not completely clarified.

The most ambitious goal still remains to identify the key elements, in particular in the earliest phases, to develop targeted therapies which can stop disease progression and prevent internal organ complication. In general, the pathophysiology of SSc can be summarised as a combination of microvascular damage, skin and internal organ fibrosis, and an autoaggressive immune system.

It has not yet been established which of these processes is of primary importance, or how they are temporally related during the development and progression of the disease.

Several studies have suggested that vascular injury is the primary mechanism driving pathogenesis in patients

Table I. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of SSc – from (3).

Item	Sub Item(s)	Weight (score)*
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or intersitital lung disease *(maximum score is 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3

*The total score is determined by adding the maximum weight in each category. Patients with a total score of ≥9 are classified as having definite SSc.

with SSc (7-10), including a spectrum of changes, predominantly regarding the microcirculation, that range from endothelial cells (ECs) activation with enhancement of inflammatory properties, their apoptosis with capillary destruction and devascularisation of the tissues leading to defective angiogenesis and vasculogenesis.

With regard to the angiogenesis, Manetti *et al*. investigated the possible involvement of the recently identified angiogenic signalling molecule Epidermal growth factor-like domain 7 (EGFL7) in the pathogenesis of SSc. EGFL7, also known as vascular endothelial statin, is a proangiogenic molecule which is predominantly expressed and secreted by ECs and their mesodermal progenitors that control vascular development and integrity during both physiological and pathological vasculogenesis and angiogenesis. Increasing evidence suggests that EGFL7 regulates blood vessel development by creating a permissive environment for angiogenesis (11). The principal mechanism by which this occurs is by promoting ECs proliferation, migration, sprouting and invasion (11-14). They showed that serum levels and dermal expression of EGFL7 are significantly decreased in SSc patients and correlated with the severity of nailfold capillary abnormalities. These results indicate that the loss of EGFL7 expression in ECs and their progenitors play a role in the development and progression of peripheral microvascular damage and the defective vascular repair process characteristic of SSc (15).

There are various hypotheses on how vascular alterations may lead to fibrosis; several studies have suggested that aberrant expression of adhesion molecules on leukocytes and ECs may result in the accumulation of specific subsets of activated leukocytes in the tissues of SSc patients, which may trigger the fibrotic process releasing different cytokines, chemokines, and growth factors that stimulate the synthesis of ECM (16–20).

Adhesion molecules as CD31, VCAM-1, ICAM-1, CD99, and members of the Junctional adhesion molecules family (JAMs), such as JAM-A and JAM-C are highly expressed at junctions between adjacent ECs and for this reason they are ideally suited to facilitate or direct the passage of leukocytes across the EC barrier. The expression of JAMs, such as JAM-A (JAM-1/F11 receptor) and JAM-C (JAM-3), has been investigated in skin and dermal microvascular ECs (MVECs), as well as in circulating levels of soluble JAM-A (sJAM-A) and sJAM-C, in samples from SSc patients. Results demonstrated that JAM-A and JAM-C are differentially expressed in the skin of patients in early-stage as compared with those in late-stage SSc and suggest that during the course of the disease JAMs may participate in EC activation and perivascular inflammatory processes at an early stage, and in defective angiogenesis and loss of microvessels at a later stage (21).

In the early phase of SSc the recruitment of immune cells to peripheral tissues largely depends on chemokine gradients. Many of the chemokines involved have redundant roles and a synergistic effect. For example, CXCL9 recruits T cells and CCL2 recruits macrophages, while CCL19 and CCL5 are chemotactic for both, in addition to dendritic cells. An increased expression of CXCL9, CXCL13, CCL2, CCL5, CCL18 and CCL19 suggests a complex mechanism by which immune cells are in SSc skin disease. Interesting data have been reported on CCL19 as a sensitive marker for the perivascular inflammation and immune cell recruitment seen in diffuse SSc skin disease (22).

Immunological activity, especially of T cells, is considered to be a key stimulus in promoting the vascular abnormalities and fibrosis observed in SSc (23). T cells, in particular helper T cells, do not represent a homogeneous population, while they contain subpopulations of Th1, Th2, Th9, Th17, and regulatory T (Treg) cells (24). In recent years, particular attention has been paid to the role for T helper 17(Th17) cells in the pathogenesis of SSc, consistent with the role of Th17 cells in other autoimmune diseases (25), and highlighting that interleukin-17A (IL-17A), one of the main cytokines produced, plays a crucial role in the pathogenesis of SSc in particular for endothelial inflammation. IL-17 positive T cells infiltrate around the vessels in the dermal and subcutaneous layers of SSc patients and might be involved in vascular injury. IL-17A is over-produced in the peripheral blood and involved skin of SSc patients and its levels are higher than in healthy individual.

It has also been recently reported that the sera from SSc patients induced the expression of adhesion molecules ICAM-1 and VCAM-1 and chemokines CCL-20 and CXCR-4 in endothelial cells and that this process is suppressed by IL-17A-neutralising antibody treatment. IL-17A similarly induces the expression of adhesion molecules and chemokines in an Extracellular signal-regulated kinase (ERK)-dependent manner (26). The link between the immune system and endothelial cells in vascular inflammatory injury seems to be getting closer to being clarified and IL-1/A could be a potential target for new biologic therapies of SSc.

The relationship between regulatory T cells (Treg) and SSc is another research focus, and it is generally thought that the immune suppression by Treg is abnormal in SSc due not only to a change in the frequency of Treg (the data in the literature are conflicting) (27–29), but also to their dysfunction.

Interestingly, it seems that both Treg and Th17 levels are elevated in SSc patient. The opposing role of Th17 and Treg cells is evident not only in their immune modulatory functions, but also in their differentiation (30).

Immune imbalance between Th17 and Treg cells in SSc could be explained by the functional heterogeneity among different subsets of Treg: resting (FrI), activated (FrII) and without immunosuppressive function (FrIII) based on the expression of FoxP3 and CD45RA. It has been recently confirmed that the increase in Treg cells is mainly due to elevated $CD4^{+}CD25^{+}$ FoxP3low-CD45RA2 (FrIII) cell (31) that produce IL17 and hence have Th17 potential, while a decreased Treg levels, along with functional deficiency, has been reported (32).

Although the focus has been on adaptive immunity in the form of T cells, recent evidence suggests that innate immunity is also critically important, in particular Toll-like receptors (TLRs).

Vascular injury, as previously indicated, is common and early in SSc, and results in the release of endogenous TLR ligands during inflammation and local tissue damage. These locally released TLR ligands bind TLRs complexed to autoantibodies, and initiate intracellular signalling pathways and may be one of the mechanisms that initiate and drive autoimmunity and subsequent fibrosis. TLRs may represent the link between immune activation and tissue fibrosis in SSc and targeting TLRs, in particular TLR8, with specifically designed antagonists appear a real therapeutic possibility (33).

With regard to fibrosis, most of the studies have so far been focusing on the role of fibroblasts in the pathogenesis of SSc. A distinct population of stromal (interstitial) cells, the telocytes, has been recently studied in the skin of SSc patients. Telocytes, formerly called interstitial Cajal-like cells, are CD34-positive and CD31/a-SMA/CD11c/CD90/c-kit-negative cells and have been also identified in a wide variety of human and mammalian tissues and organs (34, 35). It has been highlighted that telocytes are selectively damaged in SSc with severe ultrastructural alteration (swollen mitochondria, cytoplasmic vacuolisation, lipofuscinic bodies) suggestive of ischaemia-induced cell degeneration and are progressively lost from the clinically affected skin of SSc patients. This could be a prototypic fibrotic disorder; in fact the progressive reduction and loss of this type of cell might contribute to the organisation of the extracellular matrix, to the reduction of control of fibroblast, myofibroblast and mast cell activity, and to impairment of skin regeneration and/or reparation. However, the pathogenetic mechanisms underlying the loss of dermal telocytes and their functional consequences in SSc need to be further investigated and we must also better understand if their damage and disappearance is restricted to the skin or if it may also occur in internal organs (36).

Autoantibodies

Autoantibody positivity is a recognised feature of systemic sclerosis, although in most laboratories only anti-centromere (ACA) and anti-topoisomerase-I (ATA) autoantibodies are routinely detected. The new ACR/EULAR include, besides the classical autoantibodies, also anti-RNA polymerase III autoantibodies (ARA) (3). Recent analysis of ARA positivity in a French cohort and a meta-analysis of medical literature conducted by Sobanski *et al*. reported a high variability of positivity (range 0–41%) with a pooled prevalence of 11%. The authors reported a highly heterogeneity of the results probably related to geographic factors, that probably indicated the role of genetic background and environmental factors (37).

As a consequence of inclusion of ARA in the classification criteria, these autoantibodies will be increasingly incorporated in the routine diagnostic laboratory algorithm for SSc. However, Bonroy *et al*. reported that routine laboratory analysis for additional SSc autoantibodies should be restricted, based on the result of prior ANA/anti-ENA tests, to reach a cost-effective strategy for optimisation of laboratory resources with minimal loss in diagnostic capacity (38).

Contemporary positivity for ACA and ATA has been considered very rare in SSc. A recent cohort analysis of SSc patients performed by EUSTAR, reported that among 4687 patients included in the EUSTAR database, 29 (0.6%) had been documented double-

positive for both ATA and ACA. Clinical features of this rare subgroup of patients are similar to those with only ARA positivity (39).
Autoantibodies could have a role in the prognostic stratification of SSc patients and influence clinical phenotype and complications of the disease: recently, a subgroup of ACA positive patients with SSc-Sjögren overlap syndrome was reported, presenting with an increased risk of non Hodgkin's lymphoma (40).

Recent insights into the organ involvement of systemic sclerosis

Skin involvement

Skin involvement is another frequent feature of SSc, and the degree of skin involvement seems to correlate with disease severity, particularly with the severity of restrictive lung disorder; however, the current classification subdividing SSc into limited and diffuse cutaneous subtypes, could misclassify an intermediate group of patients with peculiar characteristics (41).
Even if the modified Rodnan skin score is a widely accepted tool to assess skin involvement in SSc, in recent years ultrasonography has been tested for the assessment of skin thickness and texture in SSc patients. Although the study published by Ch'ng *et al*. reported a great heterogeneity of subjects, definitions used and sites examined, the use of ultrasonography in SSc patients showed excellent reproducibility and can be used as a potential tool for outcome measures in systemic sclerosis (42).
Another common feature of SSc patients is the presence of digital ulcers (DU); DU cause a severe reduction in quality of life of the patients, as reported also in a recent report of the multicentre retrospective DUO registry group, where the authors stated that patients with DU presented severe impairment in work and daily activities and required more support as compared to patient without DU (43). Extensor surface ulcers seem to have the same prevalence as digital-tip ulcers in patients with SSc, and are equally disabling (44). Some authors proposed a prediction risk chart for scleroderma DU, taking into account capillaroscopic, demographic, and clinical/serological parameters. Utilising this risk chart, SSc patients could be classified into 4-risk class according to the probability of development of DU (45).
The treatment with bosentan, even if prescribed for pulmonary arterial hypertension, seems to be associated with a reduced incidence of DU compared to untreated group (46).

Gastrointestinal involvement

Although frequently overlooked, GI involvement is the most common internal complication in SSc patients (47). GI manifestation can also influence the nutritional status of patients; in a recent study conducted in Utah, two different questionnaires (malnutrition universal screening tool and Subjective Global Assessment) were distributed to 24 SSc patients, and it resulted that about half of them have moderate or severe malnutrition (48).
The new frontier of evaluation of GI involvement in patients with SSc was represented by *ad hoc* designed questionnaires. One of the most useful questionnaires proposed was GIT 2.0. Bae *et al*. compared the results obtained with GIT 2.0 in the upper GI symptoms scale with objective examination and laboratory tests; they reported high sensitivity but low specificity of GIT for upper GI involvement and proposed the questionnaire only as a complement to objective tests for assessment of SSc patients (49).
Gastric antral vascular ectasia (GAVE) or *watermelon stomach* is a condition associated with dilated small blood vessels in the antrum, or the last part of the stomach. Two main studies were published on GAVE in SSc patients. In the first one, reporting the results obtained in the SCOT trial, Hung *et al*. analysed a cohort of 103 patients with early diffuse SSc and reported GAVE in 23 of them (22.3%) detected by endoscopy. ATA and anti U1RNP showed a trend to a negative association with GAVE; authors also reported that patients with GAVE tended to have a higher frequency of other gastric vascular ectasias outside the antrum, suggesting that GAVE could represent part of the spectrum of the vasculopathy in SSc (50). In a EUSTAR case-control study, the authors reported a prevalence of GAVE in the order of 1% in patients with SSc; authors reported a positive correlation with ARA antibodies and lowered DLCO values despite less frequent pulmonary fibrosis. SSc-GAVE was associated with anaemia. During the follow-up SSc-GAVE patients had a similar survival rate compared to controls, but a higher number of scleroderma renal crises occurred (51).
In SSc patients, the reduction of orocecal transit time is frequent. Gemignani *et al*. examined a group of 50 SSc patients and 60 healthy volunteers with glucose, lactulose-hydrogen, octanoic acid breath tests and manometry. The study reported a higher prevalence of ineffective esophageal motility compared with healthy subjects (63% vs 5%), but also a delayed gastric emptying and a reduction in small intestine motility (52).

Muscoloskeletal involvement

Joint involvement, although often underrated, is another frequent feature of SSc and compromises patients quality of life. In the last years a growing interest has raised on ultrasound as a non-invasive screening instrument for joint and tendon involvement in SSc patients. US was reported to be useful to assess all features of joint involvement in SSc, including synovitis, tenosynovitis, calcinosis, acroosteolysis, and distal vascularisation and is sensitive for calcinosis and acro-osteolysis detection (53). Iagnocco *et al*. reported a varied and complex involvement both at joint and periarticular tissues level; in their work they demonstrated that the most frequent sites of inflammatory findings were wrists as compared to hands (54).
Palpable tendon friction rubs (TFRs) are a common feature in patients with SSc. In a case-control study Doré *et al*. retrospective analysed a large cohort of SSc patients and reported that patients with early diffuse SSc are at an increased risk of developing renal, cardiac, and GI involvement and have a reduced survival rate (55). A recent study using magnetic resonance and ultrasound hypothesised that morphological substrate of TFRs is represented by deep connective tissue infiltrates surrounding tendons (56).

Myositis also represents a poor prognostic factor in SSc; Jung *et al*. identified risk factors for muscular involvement in SSc: male sex, younger age, diffuse cutaneous SSc, TFRs and forced vital capacity <70%. Patients with myositis presented a higher incidence of antiRNP and ATA positivity and a poor prognosis, with higher modified Rodnan skin score, higher Health Assessment Questionnaire and a reduced survival rate (57).

Vascular involvement

Many data support the finding that in SSc the most significant component of the disease is represented by the vascular system and that blood vessels are likely the initial target of the disease process. The vasculopathy induces a tissue injury via an ischaemia-reperfusion mechanism, and triggers progressive tissue fibrosis. Eventually the fibrotic vascular process reduces the vessel's lumen and results in the hypoxic effect in the involved tissue (skin, lung, kidney, heart) (10).

One of the techniques often used in the study of SSc is represented by nailfold videocapillaroscopy (NVC) and its utility has been confirmed in recent studies with the correlation between capillaroscopic patterns and extent of organ involvement (58). In particular, the severity of NVC pattern (number of giant capillary loop, avascular areas) was reported to correlate with the risk of developing pulmonary arterial hypertension (59) and a more severe disease, representing an independent predictor of death in SSc (60). Recent studies confirmed that a worse NVC pattern directly correlate with the risk of development of digital ulcers (61), and a reduction in dermal thickness and fingertip blood perfusion (62). Capillaroscopic skin ulcer risk index (CSURI) has been validated as a useful tool in predicting the appearance of new scleroderma ulcers and/or persistence of non-healing lesions (63) and the reliability of this score has recently been confirmed with the use of different capillaroscopic devices (64).

Even if some studies have reported that foot nailfold capillaroscopy is not useful to detect typical scleroderma pattern in SSc patients (65), recent data reported that in selected patients the NVC of the toes could find SSc characteristic patterns. Toes NVC should be performed especially in patients with severe finger contracture that may impede the capillaroscopic examination of the hands (66).

The NVC pattern tend to change with therapy and Cutolo *et al*. in a recent work reported an improvement of the capillary number and a reduction of giant capillaries using a combination treatment with endothelin-1 receptor antagonist and iloprost (67).

A number of new techniques have also been proposed for the study of vascularisation in SSc: in a pilot study Pfeil *et al*. (68), reported the results obtained with the use of fluorescence optical imaging (FOI), identifying enhancement due to inflammation in SSc patients, while no enhancement was retrieved in healthy people with primary Raynaud's phenomenon. Authors also reported a reduction of digital inflammation during treatment with iloprost.

The use of laser speckle imaging has also demonstrated to be useful in the assessment of blood perfusion and in a recent study the negative relationship between skin perfusion of fingers and capillaroscopic damage was reported, finding a correlation between structural and functional aspects of SSc microvasculature (69). Using a new technique, the laser speckle contrast analysis (LASCA), Ruaro *et al*. reported a reduction of peripheral blood perfusion in SSc patients and a correlation with the progression of NVC of microangiopathy (70).

Cardiac involvement

Cardiopulmonary involvement is the leading cause of death in SSc. In particular, primary myocardial involvement is very common in systemic sclerosis and patients with SSc have an increased risk of development of atherosclerosis, myocardial infarction and strokes (71). Chu *et al*. (72) conducted a 10-year follow-up study on 1,344 patients with systemic sclerosis and 13,440 controls (mean age at baseline: 50.6 years) and monitored acute myocardial infarction incidence. Acute myocardial infarction was diagnosed in 31 SSc patients and in 203 controls during follow-up; the authors have thus determined that systemic sclerosis was an independent risk factor for acute myocardial infarction incidence; immunosuppressive therapy could not suppress the risk of acute myocardial infarction.

SSc patients are often asymptomatic for CV disease, but a large majority of them could present subclinical atherosclerosis (73); the identification of serological biomarkers for subclinical atherosclerosis could reduce the time for diagnosing atherosclerosis in SSc patients and could help to identify patients in an early phase of the disease. A recent study reported a significant association between carotid plaque, intima media thickness and serum biomarkers (74). ECG could also be used to identify alterations suggestive of ischaemia and could help in the identification of those patients at higher risk for further investigation; however, the execution of a Holter ECG could improve the sensibility of the assessment (75). Cardiac ultrasounds could help in the identification of patients with high risks of cardiac complications; however, in addition to standard echocardiography the use of 2D strain could allow an earlier detection of LV abnormalities (76). Although not widely available, cardiac MRI could help to uncover subclinical heart involvement in SSc patients. Up to 43% of asymptomatic patients could present myocardial fibrosis, leading to cardiac remodelling with possible development of heart failure (77); MRI could also be effective to identify left ventricle dysfunction in an early stage of the disease (78). MRI could also be repeated during the follow-up of patients to monitor the response to treatment, *e.g*. soft tissue oedema (79).

Pulmonary involvement

Actually high resolution computerised tomography (HRCT) represents the gold standard for the assessment of the extension and severity of interstitial lung disease (ILD), although the evaluation with quantitative analysis seems to better correlate with therapeutic response than the qualitative analysis (80). The presence of extensive lung in-

volvement (>20%) at a baseline HRCT is associated with an increased risk (three-fold) of deterioration of the respiratory conditions of the patients (need for home oxygen or lung transplantation), or death. The reduction of diffusion capacity of the lung for carbon monoxide (DLCO) by alveolar volume (VA) ratio (ml/min/mmHg/l) and forced vital capacity were also strongly predictive of a worse outcome (81).

There is an increasing interest also in the identification of new biomarkers for the prediction of the progression of SSc-ILD and for monitoring treatment response: a recent study reported promising results for biomarkers of the serum KL-6, surfactant protein-D (SP-D) and CC-chemokine ligand 18 (CCL18) (82). Unfortunately, in a recent review, the author reported contrasting data on the utility of SP-D and CCL18 and the effective utility of these biomarkers is still doubtful; however, simply the titre of C-reactive protein (CRP) could help to predict patient's prognosis: elevation of CRP at baseline has been reported to correlate with shorter survival rate and long-term decline in forced vital capacity (FVC) (83).

Novel insights are also published on other test routinely performed in the assessment of SSc-ILD. Analysing the results of DLCO in a large group of SSc Canadian patients subdivided in two groups, one with ILD and the other with pulmonary hypertension (PH), the authors reported that subjects with ILD had significantly lower DLCO single breathing (sb) but not DLCOsb/VAsb, whereas those with PH had both DLCOsb and DLCOsb/Vasb significantly lower (84). Low DLCOsb seems to be the most sensitive measure to detect abnormalities in gas exchange, but it reflects both ILD and pulmonary vascular disease. Bronchoalveolar lavage (BAL) fluid could help to better characterise SSc-ILD patients, and biomarkers such as KL-6, CXCL5 and CXCL8 in BAL fluids are reported to correlate with the severity of fibrosis depicted on HRCT (85).

Pulmonary arterial hypertension (PAH) is a frequent and life-shortening complication of SSc. The gold standard for the detection of PAH is right heart catheterisation (RHC), and patients with borderline mean PAP may be at increased risk of progression to PH (86) especially if it is associated with elevated trans pulmonary gradient (≥11 mmHg) at baseline.

A recent meta-analysis (87) studied the results of all works published on survival and prognostic factors for SSc-PH; the authors included 22 studies for a total of more than two-thousand patients. They reported that the severity of PH was associated with age, male sex, lower DLCO, pericardial effusion and confirmed an association with the parameters classically associated with the severity of idiopathic PH, including the 6-minute walk distance, mean pulmonary artery pressure, cardiac index, and right atrial pressure. The survival rate reported at 1, 2 and 3 years respectively of 81%, 64% and 52% with no significant change in survival over time. The same results were reported in a recent publication (88) in which the authors underlined that, despite an improvement in the clinical status, and unlike in idiopathic PH, mortality in SSc has not improved since the introduction of novel pharmacologic treatment. However, in a recent study, Chung *et al*. (89) reported better results with recent treatment, with 1-, 2-, and 3-year cumulative survival rates of 93%, 88%, and 75%, respectively.

Iudici *et al*., in a multicentric Italian population analysis, identified an increased risk of developing PH in patients with reduced DLCO (<55%) and an elevation of estimated echocardiographic systolic pulmonary arterial pressure (sPAP) > 40 mmHg, and suggested careful monitoring in these subgroups of patients (90). An analysis of two large cohorts reported that screening with trans-thoracic echocardiography (TTE) and pulmonary function test (PFT) are able to identify the majority of patients with pulmonary artery hypertension (PAH), underlining that both TTE and PFT together are useful for the diagnosis of PAH (91).

Strong correlation was also found between mean pulmonary artery pressure (mPAP) measured by right heart catheterisation and main pulmonary artery diameter (>30 mm) measured by HRCT (92).

Exercise-induced pulmonary arterial hypertension is a frequent finding in SSc patients and recent papers have emphasised the role of exercise Doppler echocardiography in the workout of SSc-patients, reporting in a large cohort with normal resting sPAP a significant exercise-induced PAH in 42% of SSc-patients (93).

Currently there have been many disputes on the role of exercise-induced PH in SSc patients: some authors suggest the heterogeneity of the mechanisms underlying exercise-induced pulmonary hypertension in SSc (93), while other groups suggest that exercise-induced PH seems to be related to a reduced pulmonary vascular reserve, and not to an increase in pulmonary capillary wedge pressure (PCWP) (94). Recent reports have identified that the inappropriate response to exercise, independently from other clinical associations, can predict the development of PH or PAH during the follow-up (95). These results, however, are still not free from criticism (96).

The use of RHC is the gold standard for the diagnosis of PAH in SSC patients. Some authors have recently proposed useful tools for the screening of the patients eligible for RHC. One of the most interesting studies published has been represented by the DETECT study (97): analysing the results in 62 experienced centres, the authors proposed an evidence-based screening algorithm with the goal of minimising the number of missed PAH diagnoses, thus optimising the use of diagnostic RHC. The authors proposed a tool composed by 8 variables, which form the basis of a 2-step algorithm: the first step assesses the need for a patient to be referred for echocardiographic evaluation; the second step assesses the need for a patient to be referred for RHC. On the contrary, other authors have proposed, based on a systematic review of the literature and expert opinion, a core set of measures composed by clinical evaluation, echocardiography and PFT (98).

Psychiatric involvement

Patients with SSc, compared with general population but also with arthritis, tend to present a higher prevalence of major

depressive disorders, that seem to correlate with GI tract involvement in particular (99). Golemati *et al*. have reported an increase in depression and anxiety, with a reduction in positive reappraisal, problem solving, seeking of support and assertiveness; they were found to look more often for divine help, and they expressed wishing and denial; they also reported that GI, lung dysfunction and skin involvement correlated with psychological features (100).

GI impairment had influences on the quality of sleep: in a recent multicentre Canadian cohort study, sleep disturbance was reported in a vast majority of SSc patients and was found to be correlated, other than GI symptoms, with pain and pruritus severity (101).

Sexuality

Sexual dysfunction is common in patients with SSc and in recent years this aspect of the psycho-social life of patients has been the subject of some interesting studies.

In both genders, sexual dysfunction seems to be associated with microcirculation and impairment of blood flow. However, in males, erectile dysfunction seems to be associated with a higher disease activity and visceral impairment but no association was retrieved with NVC alteration or specific pattern (102). On the contrary, in females the clitoral blood flow evaluated by Doppler analysis was reduced compared with healthy controls, especially in women with digital ulcers and was correlated with NVC damage progression (103).

Socio-economic impact

Systemic sclerosis can have strong repercussions on the socio-economic life of patients; although a low social level (as assessed by the level of education) does not seem to correlate with the prognosis of the disease (104), SSc patients may be more easily in financial straits. Lòpez-Bastida *et al*., analysing socio-economic costs and health-related quality of life in patients with SSc in a cross sectional study conducted in Spain, reported that SSc patients incurred considerable societal costs and experienced substantial deterioration in health-related quality of life (105).

Association between malignancies

The risk of developing cancer in patients with systemic sclerosis (SSc) has been investigated in many studies but the results are still controversial. In a recent meta-analysis of all published articles linking SSc to the risk of cancer development, Zhang JQ *et al*. reported an increased risk for lung, non-Hodgkin's lymphoma and haematopoietic cancers, but not for breast cancer among patients with SSc. However, the authors recognised that a major limit of their study was that some of the available data were outdated and that newer studies were needed (106). On the contrary, in a recent single centre study, conducted in Italy on the prevalence of breast cancer in SSc, Colaci *et al*. (107) reported that patients with SSc compared to healthy subjects of the same geographical area, presented a higher incidence of breast cancer; SSc and breast cancer were often strictly temporally associated. New data have also confirmed an increased incidence of lung cancer in SSc patients, especially in those with ATA positivity and with interstitial lung disease (108).

Prognosis

Although the prognosis in patients with systemic sclerosis is gradually improving, the results in the long-term follow-up are still far from be satisfactory. Poor prognosis was reported to be associated with muscular manifestations, presence of TFR, extensive cutaneous, heart and interstitial lung involvement as well as PAH. To help the prognostic stratification of SSc patients, Domisic *et al*. (109) proposed a prognostic models for stratifying patients into groups by risk of short-term mortality. Analysing a cohort of US Caucasian patients with early diffuse SSc, the authors identified four independent predictor variables for the prognosis of SSc patients: age at first visit, skin thickness progression rate, gastrointestinal tract severity, and anaemia.

Recent insights into the therapies of systemic sclerosis

SSc is a heterogeneous systemic disorder with tissue involvement which is characterised by alterations of the microvasculature, the immune system and a fibrotic process with massive deposition of collagen and other matrix substances in the connective tissue. The treatment strategies in SSc are targeted to these process and in 2013-2014 important steps toward new therapies have been made (110).

In the last years the researchers addressed increasing attention to targeting the inflammatory process characterising SSc.

Glucocorticoid (GC) therapy in SSc was tested for long time with unclear results and sometimes with serious adverse events; the treatment with GC was tested in the treatment of ILD, cutaneous involvement, myopathy, arthritis and cardiac involvement in different dosages and in different associations with other immunosuppressive drugs (111). The main adverse events reported were infections as well as scleroderma renal crisis, especially in patients with early diffuse disease and in association with anti-thymocyte treatment; moreover, the evidence of a beneficial role of GCs in SSc is limited (111).

Immunosuppressive drugs were the treatment of choice for ILD secondary to SSc. The first choice treatment is cyclophosphamide (CYC), the only immunosuppressive agent shown to be effective for the treatment of SSc-related ILD in a randomised, controlled trial (112). Mycophenolate represents an emerging drug proposed for the treatment of SSc, especially for severe skin involvement (113); however, in a 2-year study on the progression of ILD, the authors have reported that mycophenolate did not seem to be more effective than CYC and its administration should be reserved to those patients for whom it was contraindicated or who did not tolerate it (114). In refractory cases a treatment with rituximab, a biotechnological agent targeted against $CD20^+$ B lymphocytes, could be evaluated. In a recent report rituximab seems to be effective in reducing skin thickness and in improving lung function in severe progressive SSc patients (115).

Biotechnological drugs could be proposed in patients with SSc associated polyarthritis and myopathy; in an observational study conducted on behalf

of EUSTAR, the authors have reported promising results in a group of refractory patients treated with tocilizumab and abatacept, although the latter did not improve muscular outcome. The treatments were well tolerated even though no significant changes were reported for skin or lung fibrosis during the treatment (116).

Recent data suggest that the tyrosine kinase inhibition could be a promising therapeutic target in SSc. Imatinib mesylate (Gleevec) is a small molecule tested in preliminary clinical trials, but the benefit/risk ratio was reported to be unfavorable and the clinical results were controversial; currently, imatinib was proposed only in selected patients with severe and refractory disease (117). In a recent phase II pilot study on the use of low-dose imatinib in the treatment of SSc-ILD refractory to CYC, the authors have reported a lung function stabilisation and a beneficial outcome in a large proportion of patients, without severe adverse events (118). Although previous data reported a great number of severe adverse events (119), a recent long-term follow-up study has reported good results as far as safety and tolerability are concerned (120). Imatinib seems to be ineffective in the treatment of skin fibrosis in SSc patients with diffuse disease (121).

Vascular manifestations represent one of the most severe SSc complications. In particlular, patients could develop painful digital ulcerations and PH, one of the leading causes of death in SSc patients. The treatment of vascular manifestations has significantly evolved over the last few years with the introduction of new therapies or the optimisation of already available drugs. Endothelin receptors antagonists (ERA) demonstrated efficacy in improving dyspnoea scores, subjective and objective measures of function, haemodynamic parameters and quality of life. In recent reports bosentan has been confirmed to be effective in the prevention of digital ulcers and in the stabilisation of pulmonary arterial hypertension (122), and its use has been also proposed for the treatment of scleroderma renal crisis (123). Macitentan is a novel ERA recently approved for the treatment of PAH, even if secondary to SSc (124) and has demonstrated to delay disease progression and to reduce hospitalisations for PAH. Clinical studies are in progress for other indications, particularly for ischaemic digital ulcers secondary to systemic sclerosis (125).

For the treatment of active digital ulcers, intravenous prostanoids represents the only approved drugs, but they could induce dose-limiting side effects and require hospitalisation. A recent study evaluated the effect of iontophoresis of treprostinil in SSc, demonstrating an increase in skin blood flow in SSc patients without serious adverse events (126).

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor approved in the treatment of PAH; it was reported to be an alternative option for microvascular involvement in SSc patients. Sildenafil could improve Raynaud's phenomenon and DUs secondary to SSc (127); recent data from a prospective pilot study have confirmed these observations, reporting in treated patients no occurrence of new digital ulcers and gradual healing of the existing ulcers, aside from the improvement of PAH parameters (128).

Riociguat is a novel drug, stimulator of soluble guanylate cyclase (sGC), representing a new approach to treat pulmonary hypertension (PH); it has demonstrated an improvement in pulmonary vascular haemodynamics and has increased the exercise ability in patients with PAH. Other trials of riociguat are in progress for lung fibrosis and scleroderma (129).

Novel encouraging results were also reported on the potential of high-dose cytotoxic therapies and autologous haemopoietic stem-cell transplantation (HSCT) as an intensive immunomodulatory therapy for SSc (130). The small randomised ASSIST trial in 2011 (131) demonstrated benefit in skin and pulmonary function parameters over the two year study period, and several studies were published on the use of HSCT in refractory and severe cases, and a recent review of the literature has reported promising results especially in the treatment of pulmonary fibrosis, although it is associated with toxicity and high treatment-related mortality (132).

The ASTIS trial with 156 patients randomised to either autologous HSCT or cyclophosphamide showed an improved event free survival at two years which continued with longer follow-up. (ref: van Laar *et al*., JAMA June 2014) Many patients on the transplant arm experienced reversal of fibrosis in the skin, normalisation of microvasculature and loss of autoantibodies, giving hope that a true disease modification may be possible for SSc. However the high treatment-related mortality of 10% mandates further refinements of selection criteria and transplant protocols. A rigorous screening for pre-existing cardiac disorders, as well as for pulmonary arterial hypertension, primary cardiac or pericardial disease, seems to reduce the risk of mortality; however, the procedure is still encumbered by elevated CV mortality and the guidelines for cardiac screening should be updated (133). The use of thiothepa and a reduced dosage of cyclophosphamide seem to be a less cardio-toxic regimen for HSCT (134).

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