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REVIEW ARTICLE

Early systemic sclerosis—opportunities for treatment

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Abstract Systemic sclerosis (SSc) is characterized by microvasculopathy (Raynaud's phenomenon and fibrointimal proliferation), presence of autoantibodies and collagen deposition in skin (scleroderma) and internal organs. Microvasculopathy, detected by nailfold capillaroscopy, and disease-specific autoantibodies (anti-topoisomerase I, anti-centromere, anti-RNA polymerase III antibodies) usually appear earlier, even years before scleroderma. At that stage of the disease, immune activation with T cells and B cells promote fibrosis. Diagnosis of SSc has been relied on scleroderma, and by this time, internal organs may have developed fibrosis, a lethal feature with no available treatment. The new EULAR/ACR 2013 criteria for the classification of SSc will help identify SSc patients before fibrosis of internal organs. The early diagnosis of SSc, before the development of fibrosis in internal organs, will allow the introduction of immunosuppressive medications in these patients in a controlled setting (randomized trials). It is anticipated that this approach will change the hitherto grim prognosis of SSc for the better.

Keywords Classification · Criteria · Early systemic sclerosis · Immunosuppression · Treatment

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Systemic sclerosis (SSc) is a multisystem autoimmune disease of unknown aetiology. It is characterized by microvascular changes, exemplified by Raynaud's phenomenon, and fibrointimal proliferation, activation of the immune system, exemplified by the presence of autoantibodies (autoAbs), and eventual excessive and widespread collagen deposition. The disease affects the skin with thickening, which defines the two subsets of SSc, diffuse cutaneous and limited cutaneous SSc (dcSSc and lcSSc, respectively), digital ulcers and scars, which reflect microvascular abnormalities. It also affects joints, muscles, the gastrointestinal tract, lungs, heart and kidneys [1]. All manifestations may severely affect the quality of life [2, 3]. In particular, pulmonary (interstitial lung disease, pulmonary arterial hypertension), cardiac and renal (scleroderma renal crisis) manifestations carry a very poor prognosis [4–8]. Autoantibodies associated with SSc include anti-topoisomerase I abs, which are associated with dcSSc, anti-centromere abs which are associated with lcSSc and anti-RNA polymerase III abs which are associated with scleroderma renal crisis.

Treatment of SSc is unsatisfactory

The treatment of SSc has been disappointing. Up to few years back, there were no treatments that could have a meaningful beneficial impact on patients' life. In fact, as practicing physicians, we were embarrassed when we had to see a SSc

patient because there was nothing to offer them, apart from sympathy. In recent years, there has been some progress on particular aspects of the disease. Cyclophosphamide [9, 10] and mycophenolate mofetil (MMF) [11–14] were used for the treatment of SSc-ILD off-label mostly in small case series and resulted in stabilization of lung function. Endothelin receptor antagonists and phosphodiesterase-5 inhibitor showed some efficacy in SSc-PAH [15]. More recently, it has been reported that treatment with rituximab, an anti-CD20 monoclonal antibody which deletes B cells, may stabilize lung function and improve skin fibrosis in small case series [16–18]. Despite these therapeutic advances, the treatment of SSc remains unsatisfactory and leaves much to be desired.

The question arises as to why the treatment of SSc remains so disappointing to date. This has been in part due to our lack of the full understanding of the exact cellular and molecular pathophysiologic mechanisms involved in the disease and need to identify the therapeutic opportunity window(s). So far, treatment of SSc has been applied to patients fulfilling the 1980 ACR classification criteria for SSc [19], which by and large are based on clinical features that are the sequel of the disease. These criteria include one major criterion (scleroderma proximal to MCP and/or MTP joints) and three minor criteria (sclerodactyly, digital ulcers, bibasilar pulmonary fibrosis), and a patient had to satisfy the major criterion or two minor criteria. However, by that time, a patient has excess collagen and other extracellular matrix deposition in the skin and internal organs, and associated lethal manifestations [20]. At this stage of the disease, treatment should be logically directed towards removing the deposited extracellular matrix from the affected sites, which arguably is a very difficult task.

Immune and vascular changes in early SSc promote collagen deposition

A crucial question is whether we can apply treatment earlier before collagen deposition occurs or not. It should be reminded that autoimmune disease is a condition where the induction of autoimmunity (presence of autoantibodies) is associated with tissue damage. Let's review few data on the pathogenesis of SSc [20–22] as this may give us some clues as to when the therapeutic window(s) in the disease might be. Two of the cardinal manifestations of SSc, RP and autoAbs appear years before skin fibrosis [23]. In these patients, SSc-type nailfold capillaroscopy changes (giant capillaries, disappearance of capillaries) are detected. Early on, skin biopsies of clinically normal skin exhibit endothelial cell dysfunction and perivascular oedema [24, 25], then mononuclear cell infiltrates with T cells and macrophages and later on collagen deposition [25]. Even during the skin in durative phase of the disease, there is an increase in total dermal collagen content [26]. As the disease progresses and extracellular matrix is deposited in the skin, inflammatory infiltrates gradually decrease and disappear [21]. This, we propose to be the healing phase of the disease. T cells in SSc skin lesions are oligoclonal, indicating an antigen-driven proliferation process [27]. They are of Th2 cell phenotype, which induce fibroblast activation and collagen deposition [21], and pro-inflammatory Th17 cells which may have a bidirectional effect on fibrosis in SSc [28, 29]. Some autoAbs detected in patients with SSc promote fibrosis and/or autoimmunity. Topoisomerase and anti-topoisomerase I autoAbs bind to fibroblasts and promote inflammation and fibrosis [30, 31], and anti-matrix metalloproteinase-3autoAbs promote fibrosis [32], and functional autoAbs against CD22, a major inhibitory B cell coreceptor promote autoimmunity [21, 33]. Stimulatory autoAbs against platelet-derived growth factor receptor were found to promote fibrosis [34], although this was not confirmed by others [35, 36]. In pathophysiologic perspectives, this signifies the disease evolution into the collagen deposition stage during this pre-scleroderma (pre-tight skin) stage. Whether this phase can be considered to herald the beginning of the healing phase of the disease, remains to be determined.

New classification for SSc

There have been proposals for the classification of pre-scleroderma SSc in the past. In 2001, LeRoy and Medsger proposed criteria for early SSc which included RP plus SSc-type nailfold capillary changes (mega capillaries, avascular areas) and/or SSc-associated autoantibodies (anti-Topoisomerase I, or anti-RNA polymerase III, or anti-Th/To, or anti-PMSc antibodies [37]. Seven years later, Koenig et al. published a seminal clinical paper on 586 patients with RP who were followed up for 20 years [23]. Nearly 80 % of patients with RP, SSc-related autoAbs and typical nailfold capillaroscopy changes developed SSc, relative to 35.4 % of patients with RP and SSc-related autoAbs and 26 % of patients with RP and typical nailfold capillaroscopy changes [23]. Recently, ACR and EULAR published the 2013 new classification criteria for SSc [38] (Table 1). According to these criteria, a patient with RP, SSc-related autoAbs (anti-topoisomerase I [Scl70], anti-centromere autoAb, anti-RNA polymerase III), abnormal nailfold capillaries and puffy hands would have SSc. In developing these criteria, the odds ratio (OR) of RP for SSc relative to other rheumatic diseases was found to be 24, of anti-topoisomerase antibody was 25, of anti-RNA polymerase III antibody was 75, of anti-centromere antibody was 14, and the OR of abnormal capillaroscopy was 10 [39]. However, the OR of abnormal nailfold capillaroscopy for the subsequent development of

Table 1 The ACR/EULAR classification criteria for SSc

Criterion	Score
1. Skin thickening of fingers extending proximal to MCP joints	9
2. Skin thickening of fingers only	
Puffy fingers	2
Sclerodactyly	4
3. Fingertip lesions	
Ulcers	2
Pitting scars	3
4. Telangiectasia	2
5. Abnormal nailfold capillaries	2
6. Pulmonary arterial hypertension and/or interstitial lung disease	3
7. Raynaud's phenomenon	3
8. SSc-associated autoantibodies (max score, 3)	3
Anti-centromere	
Anti-topoisomerase	
Anti-RNA polymerase III	

Definite SSc when ≥9 score. Exclusion criteria: nephrogenic fibrosis, generalized morphea, eosinophilic fasciitis, porphyria, scleredema diabeticorum, scleromyxedema, lichen sclerosus, graft-versus-host disease, diabetic cheiroarthropathy, erythromelalgia

SSc can reach 163 with positive predictive value of 52 % and negative predictive value of 99 % [40].

Early SSc may have internal organ involvement

A patient with RP, SSc-related autoAbs, fingertip pitting scars is also classified as having SSc according to 2013 classification criteria for SSc [38]. However, by the time a patient develops fingertip pitting scars and ulcers (nutritional changes), she or he apparently has microvascular pathological changes, such as fibrointimal hyperplasia, and/or recent or organizing thrombus [41]. In a cohort of patients with very early diagnosis of SSc (VEDOSS) (RP, puffy fingers, ANA plus typical capillaroscopy abnormalities and/or SSc-associated autoantibodies) and a mean duration of disease 7.1 years, pulmonary disease (fibrosis or ground glass opacities on high resolution CT scan or DLCO<80 % predicted) and/or lower oesophageal sphincter dysfunction was present in 80 % of patients [42]. Other studies also found preclinical internal organ involvement in pre-scleroderma patients. DLCO<80 % was detected in 11/32 patients with RP plus SSc-associated autoAbs plus SSc-type nailfold capillary changes, 6/16 patients with RP plus SSc-autoAbs and in 2/23 patients with RP plus SSc-type nailfold capillary changes [43]. Also, lower oesophageal sphincter dysfunction (basal pressure<15 mm Hg) was detected in 4/18 patients with RP plus SSc-type autoAbs and/or SSc-type nailfold capillary changes [44]. These patients with early SSc not meeting the ACR/EULAR 2013 criteria have elevated levels of soluble vascular cell adhesion molecule-1 and IL-13, markers of endothelial cell and Th2 cell activation, respectively [45].

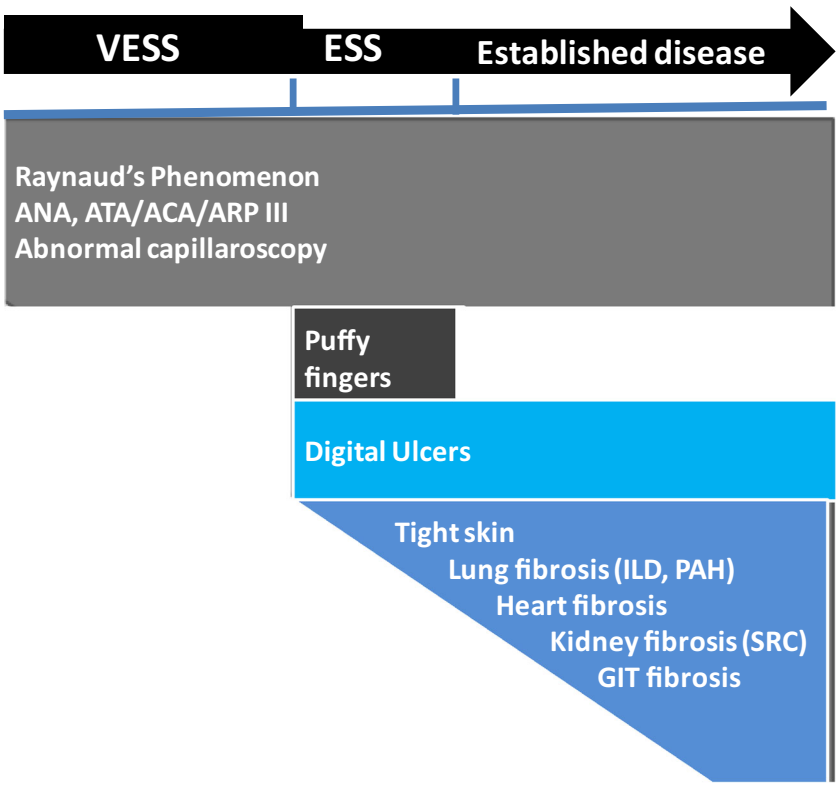

Fig. 1 The proposed three stages of SSc. Very early SSc (VESS), early SSc (ESS) and established disease. *ATA* anti-topoisomerase antibody, *ACA* anti-centromere antibody, *ARP III* anti-RNA polymerase III antibody, *ILD* interstitial lung disease, *PAH* pulmonary arterial hypertension, *SRC* scleroderma renal crisis, *GIT* gastrointestinal tract

Early treatment before collagen deposition may be the answer to SSc management

There must be a window of opportunity for effective therapy for SSc, and this appears to be confined to pre-scleroderma stage of the disease which in our view is the inflammatory phase of the disease, whilst the later phases, healing predominates with collagen matrix laying. This healing phase is dysregulated and results in the vascular obliterative and fibrotic complications of SSc. The very early and early SSc stages we propose are slightly different from that proposed by Matucci-Cerinic et al. [46] (Fig. 1). In their proposal, they include digital ulcers as a very early SSc. However, by that time, patients have significant microvascular fibrointimal proliferation that most likely is not confined only to microvessels of the digits. In patients with very early diagnosis of SSc (RP, puffy fingers, ANA positivity PLUS nailfold capillaroscopy SSc pattern and/or SSc-specific autoAbs), 22.7 % had DUs, 24.5 % had lung involvement, 27.3 % had gastrointestinal tract (GIT) involvement and 27.3 % had lung and GIT involvement. In addition, DUs were not seen in patients without internal organ involvement [42]. When applying a treatment for a disease/condition, the treatment's benefit must outweigh harm. Accordingly, in autoimmune diseases, immunosuppressants are prescribed according to disease manifestations, namely mild immunosuppressants for mild manifestations and strong immunosuppressants for life/organ threatening manifestations. If there was a biomarker with high predictive value for internal organ manifestations in SSc, then even strong immunosuppression might be justified early. However, it is time to consider and prescribe mild immunosuppression in RP patients with typical nailfold capillaroscopy changes and anti-topoisomerase I and/or anti-RNA III polymerase autoAbs in a well-monitored environment (randomized controlled trials). This could be the real window of therapeutic opportunity. There is extensive experience with mild immunosuppressants in other rheumatic diseases which indicates that these are relatively safe. Furthermore, as new pathogenic mechanisms for SSc come to light [22], other medications, apart from immunosuppressants are candidate therapeutic agents at the pre-scleroderma stage of SSc. However, those presenting with raised inflammatory markers would require more aggressive immunosuppression. In conclusion, based on this recent developments, we foresee a much brighter future for patients with SSc.

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