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Personal View

"pre-scleroderma"

Beyond very early Systemic sclerosis: deciphering pre-scleroderma and its trajectories to open new avenues for preventive medicine

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Summary (142/150 words)

The identification of systemic sclerosis (SSc) patients in an oligosymptomatic phase preceding the very early manifestations of the diseases represents today a challenge in the search for a new window of opportunity in SSc. This may be identified in a clinical scenario addressed as the "pre-scleroderma" phase, where the disease would be still far away from SSc-related fibrotic or irreversible manifestations in skin and/or organs. In this perspective, this *personal view* highlights and discusses parameters and candidate definitions for a conceptual framework of "pre-scleroderma", from the identification of at risk populations to the discussion on autoantibodies and their potential functional activities. This personal view discusses how this new paradigm of "pre-scleroderma" may represent an overall game-changing approach in the management of SSc allowing the treatment of selected patients at high risk of organ involvement or skin fibrosis before such events occur.

Search strategy and selection criteria

References for this *personal view* were identified through searches of PubMed with the search terms "Systemic sclerosis", "scleroderma", "pre-scleroderma", "classification", "VEDOSS" and "very early diagnosis of systemic sclerosis" from inception of the database until January 2023. Articles were also identified through searches of the authors' own files after lively discussions on the topic. The final reference list was generated on the basis of its relevance to the discussion of a conceptual framework for "pre-scleroderma".

Introduction

Systemic sclerosis (SSc), is a rare autoimmune disease characterized by autoimmune dysfunction, microvascular involvement and abnormal deposition of collagen in the tissues [1]. The disease is burdened by a very high mortality[2]due to fibrotic interstitial lung disease (ILD), myocardial fibrosis, severe renal and GI impairment[3]. Today, SSc is still considered an orphan disease, with no validated DMARDs strategy for all patients, although unprecedented advances have been achieved in the past 10 years with recent approvals of new drugs, including targeted therapies[4,5]. The classical clinical scenario spans from an early inflammatory and vascular involvement to a progression toward irreversible fibrosis. Therefore, a very early diagnosis and timely treatments are the cornerstones to control the disease evolution. Overall SSc total annual cost ranges from USD $14 959 to $23 268 in USA and annual cost for SSc-associated ILD is USD $31 285-55 446. Similar data are also found in Europe, highlighting that the economic cost of SSc is higher when organ involvement occurs[6,7], strengthening the need for very early diagnosis and management before the onset of visceral involvement. The 2011 criteria for a Very Early Diagnosis of Systemic Sclerosis (the VEDOSS criteria) and their validation in 2021, offer today the opportunity of an earlier diagnosis[8,9] which may be achieved even earlier than with the 2013 ACR/EULAR classification criteria and the 2001 early diagnostic criteria of LeRoy and Medsger[10,11]. The VEDOSS criteria define 3 hallmark features as the first step (level-1 criteria for SSc suspicion) with the positivity for antinuclear antibodies, Raynaud's phenomenon (RP) and puffy fingers[9]: this phase is followed by a second step (level 2 criteria- very early SSc diagnosis) with the positivity of specific antibodies or capillaroscopy. In these patients, RP suggests the presence of an ongoing endothelial dysfunction with initial capillary sufferance and leaking leading to puffy fingers[12,13]. This phase may precede the evolution to sclerodactyly and the diffuse spreading of the skin involvement to limbs and trunk[14]. Therefore, these very early clinical manifestations already mirror a disease advancement which may potentially become soon irreversible. Today, the knowledge of an earlier natural history of the disease allows the identification of a window of opportunity which may be even narrower, indicating that the disease may start much earlier than expected. For this reason, the prompt therapeutic intervention before the onset of internal involvement, sclerodactyly or proximal skin fibrosis is crucial.

The identification of SSc patients in an even oligosymptomatic phase preceding the VEDOSS phase represents today a challenge in the search for a new window of opportunity. This may be identified in a clinical scenario addressed as the "pre-scleroderma" phase [15], where the disease would obviously be still far away from SSc-related fibrotic or irreversible manifestations in

skin and/or organs. In Rheumatoid Arthritis (RA), the possibility to intercept patients when mild arthralgias are present with ACPA positivity is a clear example where very early therapy has already paved the way for a therapy preventing the evolution of the disease to an overt phase, although further efforts are still needed[16]. In the next future, we hope such approach to be implemented for SSc, by developing our skills for the identification of pre-scleroderma patients and prompt introduction of an appropriate treatment. [17]

In this perspective, this *personal view* highlights and discusses parameters and candidate definitions for a conceptual framework of "pre-scleroderma", from the identification of at risk populations to the discussion on autoantibodies and their potential functional activities. A research agenda is also provided suggesting how such parameters should be explored in the future to sketch the definition of "pre-scleroderma" which would more realistically reflect the clinical profile of SSc patients in this phase of the disease.

The border between "pre-scleroderma" and VEDOSS: the challenge of defining SSc onset.

The effort to clinically define "pre-scleroderma" is fostered the necessity of approaching as much as possible the chronological area of the biological onset of SSc. Clinical trials mainly designed for patients with diffuse cutaneous systemic sclerosis (dcSSc) have defined SSc onset as the occurrence of the first non-RP symptom but recent data from the Pittsburgh registry suggest that the first SSc-related symptom, either RP or non-RP, could be used to define SSc onset in dcSSc[18]. This controversy surrounding a clear definition of SSc onset, and the consequent disease duration, mainly relies on the heterogeneous natural history of SSc which may evolve in the two main subsets, i.e. the limited (lcSSc) or diffuse (dcSSc) cutaneous subsets[19] (**Table 1**). In almost all lcSSc patients, the first symptom is RP, supposed to precede other SSc-symptoms from 2 to 5 years[18]. In these patients, a "pre-scleroderma" clinical phase would be defined before the first non-RP symptom, and would notably include patients with RP but without any other clinical manifestations[15]. On the contrary, data from observational studies on dcSSc, such as the PRESS registry, showed that in more than 50% of dcSSc patients or being at risk of developing this subset (i.e. without lcSSc-associated antibodies), the first SSc-related symptom is puffy fingers (PF), preceding RP[14]. Therefore, a definition of "pre-scleroderma" solely based on RP would neglect these patients. To overcome this issue, the 2011 VEDOSS criteria have included both RP and puffy fingers as entry/level-1 criteria in the diagnostic strategy, in addition to the positivity of anti-nuclear antibodies (ANA)[8,9,20] (**Figure 1**). This issue is of paramount importance for patients and physician, as the disease is mainly non-reversible and there is still too few therapies approved by

regulatory agencies in many countries. The burden of the disease affects patients' daily and social life, therefore very early intervention preventing organ involvement and scleroderma-related manifestations could play a key role in the management of SSc.

Beyond the issue of the earliest parameter to be considered as SSc-related and to be included in a candidate definition of "pre-scleroderma", the identification of RP onset based on the patients' perspective remains elusive and still challenging[21], in particular because the identification of very early and mild signs/symptoms is difficult as they are unspecific and neglected by patients and some physicians, who show difficulties in precisely identifying the period of RP onset. Early SSc signs/symptoms are linked to endothelial dysfunction and related manifestations, including PF due to vascular linkage, are key parameters to be included in a candidate definition of "pre-scleroderma". Since vascular hyperreactivity is also present in primary RP and other connective tissue diseases (CTDs), vascular involvement may not be specific to "pre-scleroderma", and the severity of endothelial dysfunction as assessed by capillaroscopy or serum biomarkers (such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) or E-selectin[22]) should also be considered as a parameter differentiating "pre-scleroderma" from other early conditions. On the contrary, some authors suggest that PF and skin involvement, are also key early SSc-related parameter resulting from an early dermal/hypodermal infiltration by inflammatory cells, which precedes skin fibrosis, suggesting a continuum between PF and SSc-specific sclerodactyly[23,24]. In this scenario, very early inflammatory events may parallel endothelial dysfunction. Thus, PF as first symptom may precede two potential clinical profiles (**Table 2**): in the majority of cases, a vascular profile leading to lcSSc or, in a minority of cases, an early inflammatory profile leading to aggressive dcSSc, as illustrated in the PRESS cohort.

Beyond endothelial dysfunction, circulating autoantibodies also deserve to be considered as the other face of the coin of SSc pathogenesis. Autoantibodies were included either as ANA (step-1) or as specific antibodies (step-2) among main criteria of the VEDOSS strategy. The combination of RP, PF, ANA and SSc-specific antibodies (94%) was highly predictive for the onset of SSc according to the ACR/EULAR 2013 classification criteria, during the 5 years of follow-up in the VEDOSS publication[8]. This result confirms the relevant role of autoantibodies in the very early diagnosis of SSc, with ANA positivity always triggering the search for SSc specific antibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III antibodies). Obviously, whether patients remaining with RP, PF and ANA criteria without specific antibodies should be considered only as "pre-scleroderma" is today a matter of debate [25]. The classification of patients with isolated RP and SSc-specific auto-antibodies leads to the question of how such patients should be classified? Already as VEDOSS, considering their risk of progression, although they do not fulfill all level-1

VEDOSS criteria? or UCTD? or "pre-scleroderma"? and should we not now leave behind the definition of UCTD and really think about a new way of looking at the whole clinical picture, by including the earliest detectable phase? Likely, this may avoid leaving patients in the UCTD area of uncertainty where the therapy is not defined and hectic. Moreover, UCTD is not considered a rare disease in some countries due to its prevalence; which implies potential loss of health-related rights for patients. By only selecting 5 criteria, the 2011 VEDOSS strategy was both practical and feasible. Recent insights in the understanding of the most precocious events of SSc suggest that, beyond the 5 VEDOSS criteria, other leading parameters should be considered in the candidate definition of "pre-scleroderma". These parameters could include SSc-specific pathogenic antibodies, potential genetic factors, or the re-discovery of potentially neglected environmental triggers of SSc, thus identifying upfront patients exposed to the risk of developing the disease. For this reason, defining pre-scleroderma may widen the parameters to be considered as very early events of SSc to think outside the –VEDOSS– box (**Figure 2**).

Etiologies of SSc as a starting point to define "pre-Scleroderma" populations

Recently-proposed or well-known risk-factors for SSc onset may allow the selection of specific populations with high risk of developing SSc. In such high-risk populations, performing early screening for SSc-specific autoantibodies may help framing those who may be identified as "pre-scleroderma".

Genetics may help select at risk populations. SSc occurs more frequently in families with SSc or autoimmune diseases affected member compared to the general population. Clinical concordance between monozygotic twins is poor[26], but concordance rates are higher mainly for autoantibodies and fibrotic transcript profile. However, inheritance is not sufficient to have clinical manifestations of SSc suggesting that the combination of environmental factors on individuals with a specific genetic background contributes to SSc development. To unravel genetic complexity of SSc, GWAS and ImmunoChip studies were performed based on international collaborations[27]. The best-fitting SSc genomic risk score included 33 single nucleotide polymorphisms (SNPs) and discriminated between patients with SSc and controls (area under the receiver operating characteristic (ROC) curve (AUC)=0.673)[28]. Therefore, the effect size is not strong enough to make predictions at an individual level and a definition of "pre-scleroderma" based on genetic consideration may need stronger prediction models. The majority of the risk loci identified and replicated thus far are involved in autoimmune regulation. This finding provides further support for the hypothesis that the inciting immune dysregulations trigger and maintain the fibrotic manifestations of SSc. More recently, few genes involved in autophagy and apoptosis have been

identified as other risk loci. It is of note that many of the susceptibility SNPs are located in non-coding regions (introns). Mechanistic basis for variation in gene regulatory phenotypes remains to be investigated but these loci could act by being in linkage disequilibrium with SNPs in coding regions. However, they could also act by influencing the transcription of regulatory RNAs such as microRNAs or long-non-coding RNAs[29]. It could be also suggested that these genetic loci have a multiplicative effect on disease susceptibility by gene-gene or gene-environment interactions. Thus, although these variants by themselves or through risk score cannot provide stratification at the patient level so far, they provide directions regarding players of the disease and are instrumental to help framing candidate definitions of SSc.

Although identifying triggers for SSc onset remains challenging, more than one century ago Bramwell described SSc as an occupational disease in stone masons while Erasmus hypothesized that inhaled crystalline silica in gold-miners could explain the high prevalence of SSc in this population, making SSc a disease driven by an environmental trigger [30,31]. Since then, several meta-analyses have confirmed the association between silica exposure and the onset of SSc, with or without silicosis, especially in men[32–36]. More than 10% of Japanese patients with silicosis are positive for anti-topoisomerase I antibodies and such a positivity was associated with HLA-DQB1* 0402 in this population[37,38]. Recent nationwide studies in Denmark and France have also confirmed the association between silica exposure and SSc[35,39]. Based on these considerations, several teams have suggested that silica-exposed workers positive for SSc-specific antibodies could represent a population of "pre-scleroderma" patients, even in the absence of SSc-related clinical features[40]. In the past decade, an outbreak of CTDs, including SSc, has been described in workers exposed to artificial-stone dust in Australia, Israel or Spain[41–45]. These observations confirm that silica hazards are still topical in the current era. In this population of patients exposed to dust with high silica content, a careful monitoring of the onset of SSc autoantibody positivity or of very early SSc features such as RP or PF, would enhance the current knowledge on the natural history of SSc very early stage and would help define "pre-scleroderma". Beyond silica, exploring other all-life exposure and co-exposure, i.e., approaching SSc through the exposome lens, may help to further explore SSc determinants.

Autoantibodies in pre-SSc: what can we learn from other rheumatic diseases to implement preventive medicine in SSc?

The pathogenic role of autoantibodies is well established in other connective tissue diseases such as RA or Systemic Lupus erythematosus (SLE), both characterized by a lower heterogeneity of associated autoantibodies as compared to SSc, RA being mainly associated with ACPA,

carbamylated antibodies and/or rheumatoid factor and SLE with ANA, including anti-double-stranded DNA (ds-DNA) antibodies, anti-SSA or SSB, anti-Sm or anti-Histone antibodies.

Using the Department of Defense serum repository (DoDSR), Arbuckle and colleagues demonstrated in 2003 that at least one of the considered SLE autoantibody was detected before SLE diagnosis in 88% of SLE patients included in the repository[46]. The mean interval between the autoantibody detection and diagnosis was 3.3 year. In most of the antibody-positive patients, antibodies were found before the onset of the first clinical manifestation and the appearance of new types of antibodies gradually increased up to the diagnosis of SLE. Defective efferocytosis, i.e. the ability of macrophages to phagocyte apoptotic cells and bodies, is supposed to play an important role in the onset of systemic autoimmunity in SLE[47,48]. Efferocytosis participates in immune silencing and the impairment of efferocytosis induces the persistence of apoptotic cells, expressing key nuclear autoantigens at their surface such as RhoA[49]. Persisting apoptotic bodies can also subsequently release their intra-cellular content through secondary necrosis, with release of free DNA and DNA-associated proteins in the extra-cellular medium that may trigger the production of autoantibodies, including ANA and anti-ds-DNA antibodies[47]. Interestingly, monocyte-derived macrophages from patients with SSc also showed defective efferocytosis, that may explain the production of ANA in SSc as well[50]. Whether the impairment of efferocytosis precede ANA-production is still to be demonstrated in SSc. Moreover, contrarily to what is observed in SLE, SSc patients usually develop autoantibodies with only one specificity, SSc-specific antibodies being largely mutually exclusive. The difference between epitope spreading with appearance of new autoantibody in SLE and restricted specificity against one nuclear autoantigen in SSc is still to be explored. These results suggest that "pre-scleroderma" and "pre-SLE" may have distinct underlying autoimmune processes.

In RA, several reports, using regional and national blood banks in addition with regional network of outpatient clinics, have described the presence of autoantibodies in the blood of apparently healthy subjects many years before the onset of definite RA according to the ACR/EULAR criteria. A regionwide study in Netherland demonstrated that among RA patients who had been blood donors before the diagnosis of definite RA, 49% were positive for IgM-Rheumatoid factors and/or ACPA on at least one occasion before the development of RA symptoms, with a median of 4.5 years before disease onset[51]. In patients with clinically suspect arthralgia (CSA) according to the physician judgment, subclinical inflammation on MRI in addition with ACPA and some biological or clinical markers such as CRP value and large joint involvement were independently predictive of RA onset after a follow-up of more than 6 months[52]. Based on such predictive markers recent interventional studies were conducted to limit RA onset in such

populations of pre-RA. In the TREAT EARLIER double-blind, placebo-controlled proof-of-concept trial, patients with arthralgia and subclinical joint inflammation on MRI were randomly assigned to receive a 1-year course of oral methotrexate plus a single glucocorticoid injection or placebo. Although in this study the primary objective was not met, i.e. reducing the onset of definite RA, patients in the treatment arm significantly improved in physical functioning assessed by the HAQ-DI and arthralgia, suggesting that treating early inflammatory features may improve patients' QoL[53], paving the way for further preventive approaches in RA. The population of patients included in the TREAT EARLIER trial was not enriched with patients at high risk of developing RA based on serologic markers, such as positivity of ACPA, which may explain why the primary objective was not met[17]. Considering the heterogeneity of SSc, the careful selection of patients at high risk of progression would be crucial to implement preventive medicine and apply the TREAT EARLIER approach in "pre-scleroderma" patients.

Whether ANA positivity precedes the first clinical manifestations of SSc is still controversial. Based on a similar approach as for SLE, a recent study, using the DODSR, identified autoantibodies years before SSc onset, in particular in SSc patients with scleroderma renal crisis (SRC). In fact, 75% of SRC patients (12/16 patients) were positive for at least one autoantibody before SSc diagnosis[54]. The earliest detection of autoantibody in one SSc patient with SRC was 27.1 years prior to clinical diagnosis of SSc and remained positive up to diagnosis. In this study, the onset of SRC was preceded in some patients by an increase of autoantibody levels against RNA polymerase III, strengthening the predictive value of these autoantibodies and suggesting a more specific immune response in SSc as compared to the epitope spreading observed in SLE. Another work using The Dallas Heart Study (DHS), a multiethnic population-based probability sample of Dallas County residents in the USA, demonstrated that ANA positivity in the general population was associated with markers of endothelial dysfunction (such as soluble ICAM-1 and VCAM-1), suggesting that early systemic autoimmunity is linked to vasculopathy[55]. The recent VEDOSS publication also demonstrated that ANA positivity is a crucial parameter in this patient group as 89.2% of ANA-negative patients did not progress to SSc as defined by the ACR/EULAR criteria within 5 years. This result strengthened the hypothesis that autoimmunity was an early necessary event in the pathogenesis of the disease[8]. Subsequently, when each VEDOSS criterion was considered separately (in addition to RP) the positivity for SSc-specific antibodies included in the ACR/EULAR criteria (i.e. anticentromere, anti-topoisomerase I/Scl-70 or anti-RNA polymerase III antibodies) was the best isolated predictor of progression to SSc fulfilling the ACR/EULAR classification criteria. The VEDOSS approach further demonstrates the central role of selected SSc-antibodies to decipher the earliest events of the disease[20]. In the VEDOSS publication, RP was

a mandatory inclusion criterion, precluding any conclusion regarding patients with isolated positivity of specific SSc-related antibodies without RP. Patients with isolated PF without RP were not included either. In such patients, the early natural history of the disease remains a grey area to be further explored. The predictive role of other SSc-related antibodies (such as anti-Th/To or anti-U3RNP antibodies) than those included in the ACR/EULAR classification, remains to be also determined in the VEDOSS population[56].

In SSc, specific antibodies have become an important parameter of baseline assessment as they may predict clinical trajectory, organ involvement and SSc severity in very early phases of the disease. In the GENISOS cohort, which aimed to identify early predictors of visceral involvement in SSc patients, among clinical and biological candidate baseline parameters only the presence of anti-topoisomerase I antibodies was associated with lower FVC levels as well as accelerated decline rate in FVC within the first 3 years of follow-up in definite SSc patients[57]. Similar results were obtained from the Royal Free hospital cohort, where anti-topoisomerase I antibodies could better predict the onset of pulmonary fibrosis regardless of the cutaneous subtypes[56]. In the EUSTAR cohort, autoantibodies also outperformed the skin-based classification (diffuse, lcSSc and sine scleroderma) in the prediction of overall survival. In patients with SSc sine scleroderma, anti-topoisomerase I antibody was also the only independent predictor of progression to SSc with cutaneous fibrosis (i.e. lcSSc or dcSSc)[58].

Based on this predictive value of autoantibodies on disease trajectories, enrichment strategies based on antibody profile or early symptoms with high risk of progression, such as positivity for anti-topoisomerase I or anti-RNA polymerase III antibodies and PF as first-SSc-related sign, may allow a successful implementation of preventive strategy to control the disease and limit visceral involvement in SSc. Interestingly, in addition to clinical trajectories, data from the UK BIOPSY (BIOlogical Phenotyping of diffuse SYstemic sclerosis) cohort also demonstrated that anti-topoisomerase I and anti-RNA polymerase III antibodies were associated with longitudinal changes in serum protein markers of fibrosis and divergent gene expression profiles on skin biopsies and blood samples from SSc patients[59]. Such specific and divergent associations of autoantibody subtypes with markers of the pathobiology of SSc suggest that these mutually exclusive antibodies may also play direct but distinct roles in the pathogenesis and progression of the disease.

Pathogenic role of autoantibodies: evidence for a pre-SSc phase based on pathogenesis and new antibodies identified as candidate parameters for a definition of "pre-scleroderma"

One major evidence for the pathogenic role of autoantibodies in SSc is the decrease of anti-topoisomerase I titers after stem cell transplantation in responders as compared to sustained or increasing titers in non-responder or relapsing patients[60]. Several translational studies also suggest a pathogenic role of SSc-related antibodies, mainly focusing on anti-topoisomerase I antibodies[61]. Some mouse models of SSc are also based on anti-topoisomerase I antibody production[62]. In humans, topoisomerase I from apoptotic cells bound to the membrane of fibroblasts which can be recognized by anti-topoisomerase I antibodies[63]. This result strengthens the hypothesis supporting that cell death and impaired apoptotic cell clearance play a role in SSc pathogenesis. Interestingly crystalline silica also induced macrophage or epithelial cell death, production of autoantibodies in mouse models and impaired efferocytosis capacities of human and mouse macrophages, further linking a well-established environmental risk factor of SSc with the early autoimmune events of the disease[64,65]. Immune complexes composed by autoantibodies and autoantigens can activate endothelial cells and fibroblasts[66,67]. All these studies support the role of SSc-associated antibodies as important players in the early pathogenic events of SSc, strengthening the relevance of including these antibodies in candidate definitions of "pre-scleroderma". Despite their high prevalence in SSc, the pathogenic role of anticentromere antibodies must be further explored.

Beyond ANA, other autoantibodies may also play a direct pathogenic role in SSc. Several autoantibodies targeting antigens, notably expressed on endothelial cells were identified, directly linking endothelial dysfunction and autoimmunity in SSc pathogenesis[68]. Increased titers of autoantibodies against Endothelin receptor type-A (ETAR) and angiotensin receptor type-1 (AT1R) have been detected in SSc patients[69,70]. By regulating vascular tone and by participating in the regulation of fibrosis and inflammation, these receptors and associated-autoantibodies could trigger SSc onset. The transfer of anti-AT1R antibodies with activating and agonistic properties induced skin and lung inflammation in mice, supporting a pathogenic role of these autoantibodies[71]. CXCL4 has recently been identified as a potential auto-antigen is SSc[72]. CXCL4 antibodies production in SSc patients could be triggered by CXCL4-DNA complexes, both increasing the production of type-I interferon by plasmacytoid dendritic cells[73]. Interestingly, interferon type I signature has also been identified in blood monocytes from early SSc patients before the onset of fibrotic manifestations, although the links between such IFN type I signature and CXCL4 autoantibody remain hypothetical[74,75]. Functional autoantibodies may also directly favor fibroblast activation. IgG with agonistic properties for PDGF receptor identified in the serum of SSc patients can induce type I collagen–gene expression and myofibroblast conversion in human primary fibroblasts from healthy donors, suggesting a direct link between autoimmunity and fibrosis.

In SSc patients, autoantibodies against the muscarinic-3 receptor (M3-R) have been identified and could inhibit the contraction of smooth muscle cells and could block indirect muscle response induced by electric field neural stimulation, linking peripheral neural system dysregulation and SSc-pathogenesis[76,77]. Anti-M3-R autoantibodies can block cholinergic signaling through M3-R inactivation at neural and muscular levels. These pathogenic properties of anti-M3-R antibodies have been associated with SSc-related gastro-intestinal dysmotility. Whether M3-R-antibodies are detected in patients with VEDOSS or earlier SSc stages or not is still to be determined. Since peripheral neural system dysregulation is closely linked to vascular tone, a better understanding of the neuroendothelial system may also shed some light on the pathogenesis of pre-scleroderma, beyond the neural effects of autoantibodies in SSc[78].

The predictive value of these functional autoantibodies for the onset of SSc in population of pre-scleroderma patients or in the general population is still to be determined. Moreover, these considerations on ANA and functional antibodies in SSc patients highlight that autoantibody heterogeneity may suggest that distinct processes may lead to different phenotypes. In fact, several times in the last decades the community was questioning whether we are facing one single heterogeneous disease or several diseases sharing common features. Therefore, such a clinical heterogeneity may suggest that several candidate definitions or a composite definition may be needed upfront to define "pre-scleroderma" and accurately predict disease trajectory[19]. The various causes of the disease, linked to distinct antibody subtypes (e.g. cancer with anti-RNA polymerase III, silica-induced SSc with anti-topoisomerase I antibodies) with distinct molecular signatures, as demonstrated in the SSc BIOPSY cohort, also support the existence of distinct nosological entities under the "systemic sclerosis" banner[59].

Preventive medicine in systemic sclerosis: should we treat patients earlier?

Among rheumatic diseases, SSc still holds the highest mortality burden. Therefore, the main question among patients and clinicians, is whether a very early *preventive* treatment should be implemented when physicians intercept patients in very early and pre-clinical stages. Regarding organ involvement, the results from the tocilizumab studies have demonstrated that selecting a population at high risk of progressive ILD allowed lung function preservation[79,80]. Based on these results, some experts have suggested that SSc patients with limited ILD but at high risk of progression may benefit from early treatment, before the establishment of irreversible fibrotic changes in the lung parenchyma. This strongly suggests that treatment should be proposed in prevention of progression and not only restricted to the treatment of "progressive fibrotic interstitial lung disease"[4,81]. This topic is highly important for the SSc community, as preserving

health status, rather than curing advanced disease is among the main priorities reported by patients' representatives. Such an approach would be obviously a "*turn of the tide*" in SSc-ILD management suggesting that prevention may prevail on treatment of progressing disease (**Figure 3**). Beyond single organ involvement, it remains to be determined whether a very early therapeutic approach (i.e., VEDOSS patients) should be implemented even earlier with the preventive treatment of "pre-scleroderma" patients to preempt the further evolution into VEDOSS and SSc-related organ involvement. Beyond approaches based on a priori, i.e. identified symptoms or biological markers such as autoantibodies, other techniques without a priori, including transcriptomic or proteomic approaches may help selecting at risk populations, although these techniques are not yet ready to be used in clinical practice[75,82].

As discussed in this *personal view*, we should prepare the community to the careful selection of targeted populations in the next future to implement strategies that might prevent disease evolution in a much earlier phase. Such an approach would improve or maintain the quality of life of SSc patients and enormously reduce the disease direct and indirect costs. The stratification and selection of these targeted populations might start from antibody subtypes (e.g. anti-RNA pol III versus anti-topoisomerase I versus anticentromere), clinical presentations (e.g. RP versus PF), molecular signatures in blood or Skin (e.g. high IFN-type I signature) and new considerations to be put on the research agenda (e.g. genetic risk factors or silica-exposure as a risk factor of severity) (**Figure 4 and Table 2**)**.** Without a consensus definition of "pre-scleroderma" and an evaluation of its prevalence, major therapeutic issues will remain unanswered (**Table 2**). By highlighting the importance of autoantibodies and very early clinical signs and symptoms in the definition of clinical trajectories, this *personal view* may provide some leads to propose a framework for "pre-scleroderma" and offers a preventive medicine perspective which may open new avenues for this devastating fibrotic disorder. This new paradigm of "pre-scleroderma" may thus represent an overall game-changing approach in the management of SSc allowing the treatment of selected patients at high risk of organ involvement or skin fibrosis before such events occur.

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Personal View
"pre-scleroderma"

Beyond very early Systemic sclerosis:

deciphering pre-scleroderma and its trajectories to open new avenues for preventive medicine ?

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Figures (4) and Tables (2)

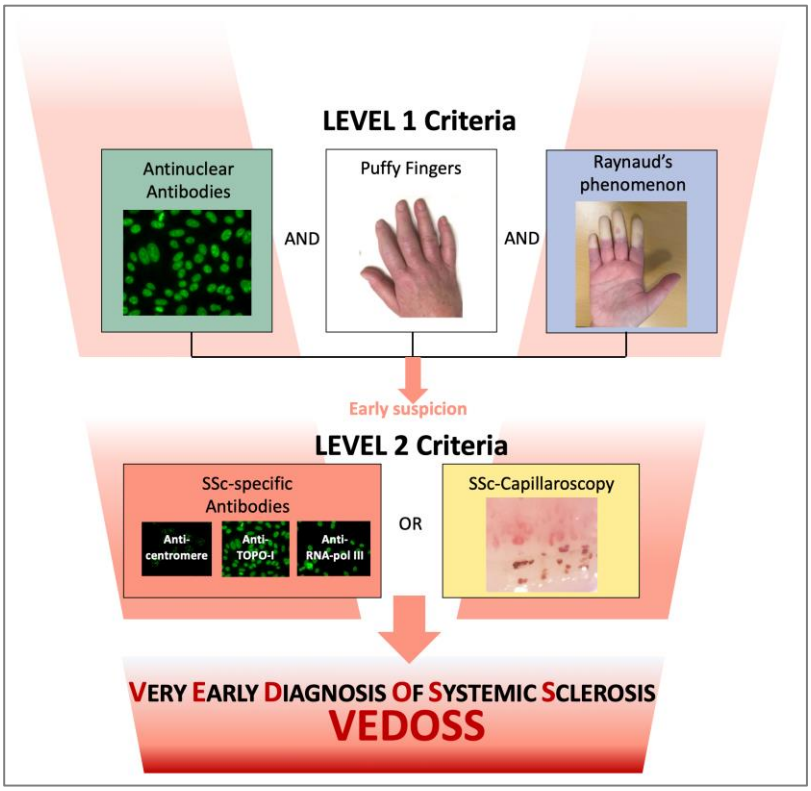

Figure 1 : parameters included in the VEDOSS strategy

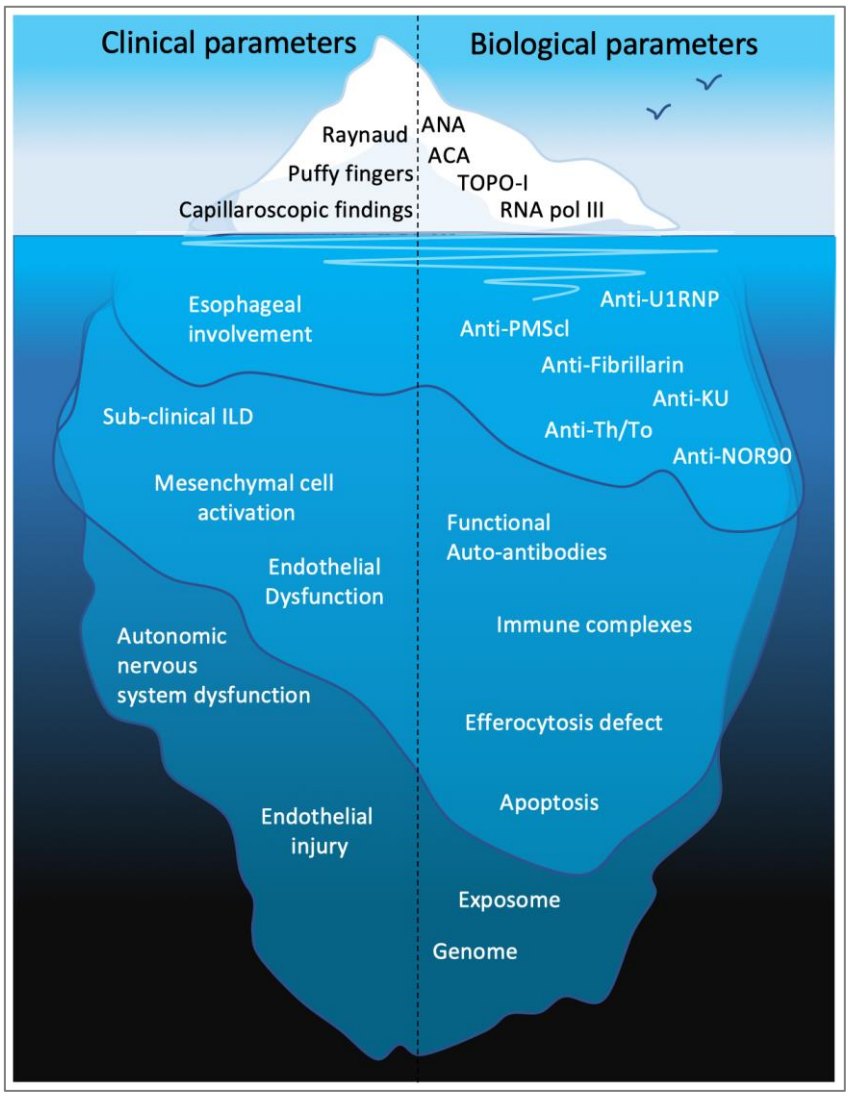

Figure 2 Candidate parameters for an updated definition of "pre-scleroderma"

Parameters outside the water are currently used in the definition of very early or early SSc, parameters under the water are not currently endorsed for the definitions of early SSc and could be considered for candidate definitions of pre-scleroderma

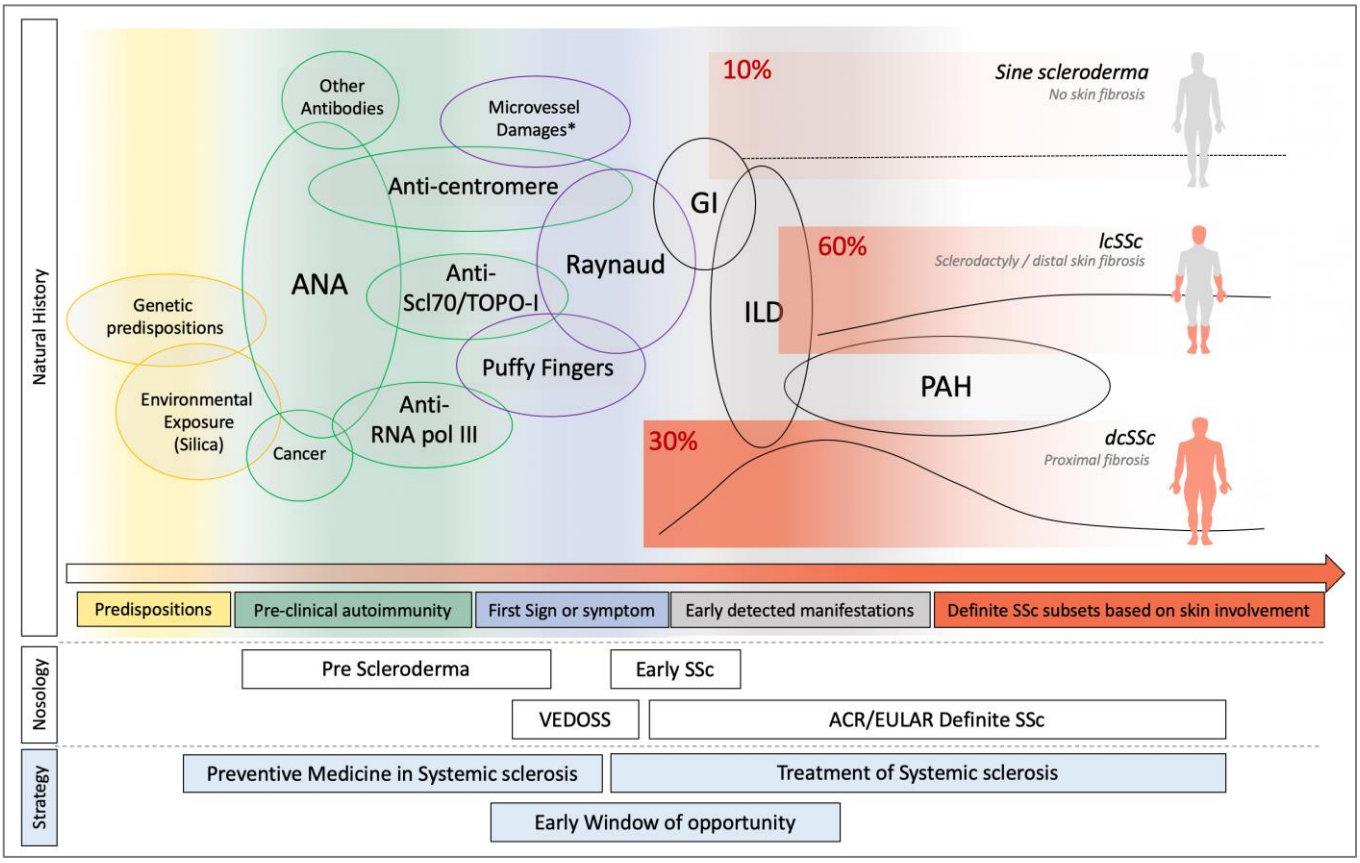

Figure 3: Natural history of Systemic sclerosis: from individual predispositions to heterogeneous definite subsets

**including microvascular damage assessed by videocapillaroscopy*

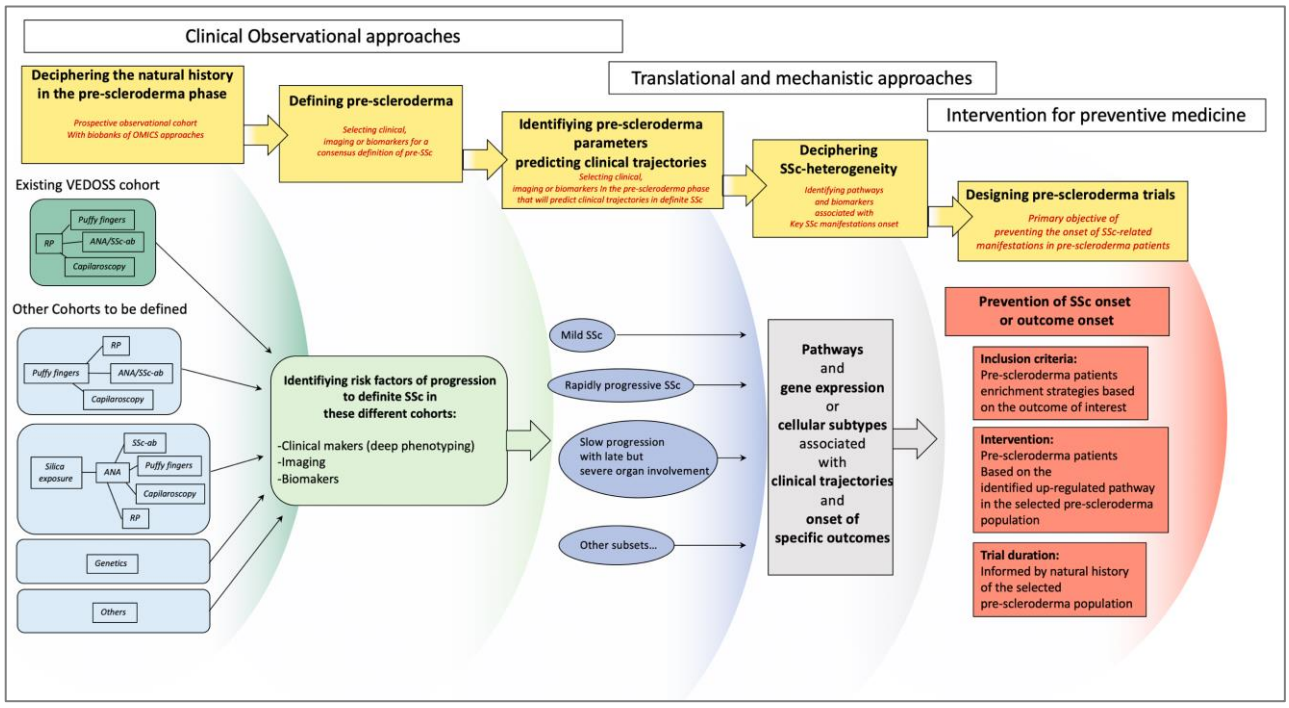

Figure 4: a Roadmap towards the implementation of preventive medicine in SSc

TABLES (2 tables):

Table 1: clinical vignettes

Real Cases	Clinical history	Teaching points
From "pre-scleroderma" to lcSSc. **Male,** **in his 50s**	This patient was initially admitted to the neurovascular unit for a transitory ischemic attack due to atrial fibrillation. Initial work-up revealed ANA positivity with anti-centromere antibodies (ACA). At that time the patient had no RP, no puffy fingers and no other signs of SSc. 6 months later, he reported RP attacks that never occurred before, the clinical examination was still normal, including normal nailfold capillaroscopy. Visceral evaluation, including CT scan and echocardiograms was normal. 5 years later the patient developed giant capillaries on capillaroscopy. 10 years later, skin telangiectasia were noticed, and more than 15 years after initial blood test revealing isolated ACA, the patient developed sclerodactyly, consistent with a diagnosis of lcSSc.	**This case illustrates that isolated ACA may precede the onset of SSc and suggests that SSc patients with ACA and RP represent a subset of pre-scleroderma patients, preceding the onset of lcSSc.**
From "pre-scleroderma" to dcSSc. **Male,** **in his 30s**	A stone-mason with massive past-occupational exposure to crystalline silica for more than 15 years reported rapidly progressive swelling of his fingers, without RP or any other sign of SSc. 3 months later he reported proximal progression of skin edema with arthralgia. 6 months later he noticed a first episode of RP attack while driving his motorcycle in the wind. 9 months later he developed diffuse skin fibrosis and a first digital ulcer. Blood test performed by his general practitioner revealed positivity for anti-TOPO-I antibodies. A diagnosis of dcSSc was made and CT-scan performed in a reference center revealed no interstitial lung disease or silicosis. MMF was initiated with low dose of steroids. The patient is still under careful monitoring for the onset of visceral involvement.	**This case illustrates that silica-workers are a population at high risk of dcSSc with anti-TOPO-I positivity, even without silicosis. This case also suggests that this specific population could be an adapted candidate population for early screening with an early window of opportunity, since the patient presented here has still no sign of ILD. These patients may thus benefit from early introduction of immunosuppressive therapy such as MMF that may improve skin involvement and prevent the onset of visceral manifestations.**
Case 3 : Scleroderma Renal crisis as first SSc-related symptom **Male in his 60s**	A male farmer was admitted to the Division of Nephrology for an abrupt acute kidney failure characterized by anuria, flash edema, tachycardia and hypertension. The patient was rescued with specific treatment and dialyis and after 6 months reported the onset of RP and swollen hands (puffy fingers). The specific labwork revealed ANA 1:2560 and anti-TOPO-I antibodies. There was no heart of lung involvement at that time but the patient reported bothersome episodes of GERD for several years. Nailfold video-capillaroscopy showed an active pattern. The patient was diagnosed with VEDOSS and a treatment with vasodilators, PPI and MMF was started. The patient recovered his activity as a farmer and is kept under a tight follow up. He still complains for GERD, the kidney function has been recovered and he never developed any other sign/symptom of SSc	**This case shows that SRC may represent the onset of the disease and that ANA and anti-TOPO-I antibodies can precede the clinical manifestations, in particular skin and lung involvement. In this case, MMF introduction before skin or lung involvement may have prevented the onset of such SSc-related manifestations.**
Case 4 : **LcSSc with anti-Scl70 and early visceral manifestations without RP** **Female in her 50s**	A female was referred because she suffered from persistent arthralgias, a swollen knee potentially due to osteoarthritis. She was treated successfully with a knee injection of steroids and systemic NSAIDs. However, a few months later she consulted again because of several skin lesions over her limbs that were diagnosed as morphea by the dermatologist. 6 months later she reported muscle weakness, attacks of tachycardia: the holter EKG identified paroxysmal tachycardia and more than 1000 VEB with bigeminal rhythm. The labwork disclosed ANA 1: 1280 and anti-TOPO-I antibodies, CK levels above normal range at 890 units and high troponin levels at 30. Cardiac MRI showed diffuse myocardial edema. She was diagnosed with lcSSc and submitted to steroid pulses of 1 gr for three consecutive days and prednisone maintenance of 12.5 mg/day and IVIG. The treatment led to complete remission with normalization of ck and troponin and disappearance of rhythm abnormalities as well as skin lesions. She is still today on IVIG while steroids were withdrawn: she never developed RP or puffy fingers nor any other SSc-related symptoms.	**In this case of lcSSc, the main reason for treatment initiation was arrhythmia secondary to myocarditis. The treatment led to complete remission which is maintained today. Again, the hypothesis is that disease progression was prevented by early treatment initiation.**

Table 2 : Main un-answered questions for the research agenda regarding therapeutic strategies in pre-scleroderma patients

Q1	Should we initiate immunosuppressant like mycophenolate mofetil in patients with pre-scleroderma and at high risk of dcSSc, such as patients with isolated puffy hands and anti-Scl70 antibodies even in the absence of RP ?
Q2	Should we prioritize B-cell targeted therapy, such as rituximab or belimumab, in inflammatory patients ?
Q3	Considering early immunomodulatory strategy, what could be the place of steroids ?
Q4	In patients with RP and anti-centromere antibodies, should we initiate anti-platelet agents despite the absence of any other SSc-related symptoms ?