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Treatment of systemic sclerosis: is there any hope for the future?

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Systemic sclerosis (SSc) is an orphan connective tissue disease characterised by skin and multiorgan involvement. The following original pathological processes distinguish SSc from other connective tissue diseases: (1) microvascular modifications, initially functional and partly reversible, (2) perivascular inflammation which appears to be moderate and perhaps transitory, (3) autoimmune activation, leading to the production of specific and persistent autoantibodies and (4) fibroblast activation, producing an excess of extracellular matrix leading to fibrosis.[1] Therefore, SSc is a complex disease with the implication of multiple players in its pathogenesis.

SSc is a major medical challenge with high mortality and morbidity. In a meta-analysis, the pooled standardised mortality ratio (SMR) was measured as 3.53 (95% CI 3.03 to 4.11) and adjusted metaregression did not show significant changes in SMR over time.[2] Nevertheless, some reports did suggest an improved survival in recent years. In an Italian study, the 10-year survival showed a clear-cut increase (81%) compared with older series (69%) from the same centre.[3] However, the discrepancy may not only come from improved therapeutic management, but might be due to some changes in the natural history, to an earlier referral of the patients and, even more likely, to the better recognition of patients with milder disease. Accordingly, in the recent Italian series, there were more patients with the limited cutaneous SSc (LcSSc) than in the older study (87.5% vs 72%).[3] In terms of organ involvement and progression of the disease, the outcomes in LcSSc and diffuse cutaneous SSc (DcSSc) are different. The new classification criteria will more easily identify patients with LcSSc.[4] Therefore, it will become core to require the cutaneous subsetting for any scientific work on SSc and, beyond skin, subclassification or clustering is awaited to improve SSc patient risk stratification. Regarding morbidity, accumulating evidence has shown the huge impact of SSc on quality of life (QOL). With the support of patients associations and international medical societies, we have performed a large survey (1902 patients with SSc from 60 countries). The results confirmed the impaired QOL in SSc as measured by the short-form 36 (SF-36) questionnaire; it was particularly marked for physical health (mean±SD 43.4 ±23.4; 100=best health), but mental health was also impaired (mean±SD 52.3±23.1).[5] Patients with DcSSc had poorer QOL scores than patients with LcSSc, for the physical (mean±SD 39.8±22.3 vs 46.6±23.7; p<0.0001) and mental (mean±SD 50.3±23.2 vs 53.8 ±23.0; p=0.003) components.[5] The dimension of QOL and patient-reported outcomes is moving in SSc, and it should provide meaningful information on future drugs.

The majority of ongoing or upcoming trials target skin fibrosis and the early DcSSc subset. Indeed, no drug has been so far labelled according to the properties to reduce skin fibrosis or organ involvements. Many trials failed in the past and one might question whether the failure is mostly driven by the wrong choice of the drug, the use of imprecise outcome measures or imperfect selection of the included patients. Regarding the drug to be investigated, we will comment later on the new trials, but it is obvious that SSc is far more than a 'simple' inflammatory or autoimmune disease. The relationships between vasculopathy, immune disturbances and fibroblast activation are complex and may challenge the identification of the efficacy of a single therapeutic agent. Regarding outcome measures, although not perfect, several lines of evidence have shown that skin sclerosis measured by the modified Rodnan skin score (mRSS) is a robust surrogate marker for SSc. The last point about the targeted population has been addressed by several recent studies.[6] One of the methodological issues in past trials has been the observation that the control arm experienced a decrease in mRSS. Therefore, the drug under investigation had to show further acceleration of the decrease in skin fibrosis

that was already 'naturally' ongoing. Despite the pathogenesis of scleroderma starts to be better known, this very SSc-specific natural regression of skin fibrosis after few years of extracellular matrix accumulation still remains poorly understood. One recent study has shed new lights that may translate in future trials; it highlights a regulatory role of the nuclear receptor NR4A1 in transforming growth factor β (TGF-β) signalling and fibrosis, providing the first proof of concept for targeting NR4A1 in fibrotic diseases.[7] If accelerating the spontaneous decrease is very challenging, one might question how we could target patients earlier at the time when matrix deposition starts or is active. This has been the matter of European Scleroderma Trials and Research group (EUSTAR) project that aimed at identifying the parameters predicting skin progression in patients with DcSSc. A total of >800 patients with mRSS≥7 at baseline visit, valid data for mRSS at second visit, and available follow-up of 12±2 months were studied. Worsening of skin fibrosis defined as increase in mRSS>5 points and ≥25% from baseline to second visit was observed in about 10% of the patients. The univariate and multivariate analyses primarily suggested that joint synovitis, short disease duration and lower mRSS at baseline were predictive of progressive skin disease.[8] One important result was by example that 12.3% of patients with a low mRSS at baseline (≤22/51) were progressing compared with only 2.9% with an mRSS>22/51 ($p<0.001$). Regarding disease duration, the difference in the cumulative percentage between progressors and non-progressors increased within 15 months and stayed stable, emphasising that progressors must be captured early in the course of the disease.[8] It must be pointed out that the analyses were made for 12-month follow-up, which is considered by many experts as the optimal trial duration to detect meaningful changes in skin fibrosis. Additional analyses (yet unpublished) have been performed using this cohort. For example, although it could have been intuitive to believe that recent disease activity could predict further skin progression, we observed that the 'patient-reported worsening of skin fibrosis' within the past month prior to baseline, the modified skin progression rate at baseline and progression of skin fibrosis in the previous year were not associated with progression of skin fibrosis. Indeed, previous activity appears to enrich for patients that have already reached their peak skin score. We also aimed to identify patients with 'natural' regression of skin fibrosis, as these patients might benefit less from therapeutic interventions and might not be the right candidates for clinical trials. Again, baseline mRSS was an important parameter and patients with high baseline mRSS were most likely to improve, whereas presence of tendon friction rubs was inversely correlated.[9] Altogether, baseline mRSS appears as key to predict progression/regression in patients with SSc at least in the DcSSc and in the earlier years.

This observation is pivotal for clinical practice and clinical study design. In fact in early DcSSc, it strongly supports a therapeutic window of opportunity before severe skin fibrosis has occurred. Indeed, most recently performed clinical trials that failed to show any efficacy used a minimum mRSS of 16–20 as an inclusion criterion and recruited patients with an average baseline mRSS of 25/51.[10] While this is unlikely to be the only explanation for a negative study, high baseline mRSS and the resulting ceiling effect and regression to the mean effect might be an important factor contributing to the failure of clinical trials in skin fibrosis. The above EUSTAR data were mainly obtained from European patients and it must be highlighted that ethnic/geographical influences can affect SSc. For example, while anti-RNA polymerase III (RNA pol III) antibodies are rare in Europeans, its frequency can reach 20–25% of patients in the USA.[11–13] These patients reach early their peak in skin fibrosis (reflected by early high skin score), and then also decrease more promptly than negative patients. Therefore, the time of recruitment and time for end point will have to be established in RNA pol III patients. Beyond inclusion criteria, improving outcome measures is another way to improve clinimetrics in SSc trials and the development of a composite index (Combined Response Index for Systemic Sclerosis, CRISS) is an important achievement.14 The composite response index for trials of early DcSSc includes core items that assess change in two prominent manifestations of early DcSSc (skin and interstitial lung disease), functional disability (Health Assessment Questionnaire Disability Index, HAQ-DI) and patient and physician global assessments. In addition, the score captures a clinically meaningful worsening of internal organ involvement requiring treatment.[14] It is included in the majority of ongoing trials for further validation.

The current era for the treatment of SSc is probably the most exciting of the last decades. Several explanations support the major interest in SSc by investigators and pharmaceutical companies. First, huge developments have been achieved in other autoimmune diseases such as rheumatoid arthritis, but further improvements in these areas are very challenging and require major investments. Today, the SSc clinical spectrum is better known and defined, but unmet needs still remain a critical issue in this rare disease. Refocusing immunotherapies, already used by the rheumatologists in other diseases, makes sense and is in line with the genetic data that demonstrated the shared autoimmunity between several different autoimmune diseases.[15] Concomitantly, drug agencies offer special pathways for the development of drugs in the field of rare diseases that can clearly accelerate approval of specific treatments. Finally, fibrosis contributes to as much as 45% of deaths in the industrialised countries.[16] Furthermore, as pulmonary, renal, hepatic and even dermal fibrosis share common pathways, SSc is considered as a prototype entity for fibrotic diseases. Therefore, progresses made in SSc are expected to be translated into other fibrotic conditions. It is striking to see that when querying the clinicaltrial.gov website, about 300 studies are found for the term

Table 1 Main ongoing phase II/III clinical trials on systemic sclerosis

Title	Primary outcome	Reference
Efficacy and Safety of riociguat in patients with systemic sclerosis	Change in mRSS	NCT02283762
Proof-of-concept trial of IVA337 in diffuse cutaneous systemic sclerosis (FASST)	Change in mRSS	NCT02503644
IVIG treatment in systemic sclerosis	Change in mRSS	NCT01785056
A study of the efficacy and safety of tocilizumab in participants with Systemic Sclerosis (SSc) (focuSSced)	Change in mRSS	NCT02453256
A Study of subcutaneous abatacept to treat diffuse cutaneous Systemic Sclerosis (ASSET)	Incidence of adverse events/ change in mRSS	NCT02161406
IL1-TRAP, Rilonacept, in Systemic Sclerosis	4-gene skin biomarker	NCT01538719
Cyclophosphamide systemic sclerosis-associated interstitial lung disease	Forced vital capacity	NCT01570764
Rituximab versus cyclophosphamide in connective tissue disease-ILD (RECITAL)	Absolute change in FVC	NCT01862926
A trial to compare nintedanib with placebo for patients with scleroderma related lung fibrosis	Annual rate of decline in FVC in mL	NCT02597933
Scleroderma treatment with autologous transplant (STAT) study	Event-free survival	NCT01413100
Autologous stem cell SSc immune suppression trial (DIScl2011)	Time to treatment failure	NCT01445821
Allogeneic hematopoietic cell transplantation after non-myeloablative conditioning for patients with severe Systemic Sclerosis	Event-free survival	NCT00622895
Clinical trial of probiotics in Systemic Sclerosis associated gastrointestinal disease	Gastrointestinal change score	NCT01804959
Gastroesophageal reflux treatment in scleroderma (GERD-SSc)	Change in severity of heart burn and regurgitation	NCT01878526
Rituximab for treatment of Systemic Sclerosis-Associated pulmonary arterial hypertension (SSc-PAH)	Change in pulmonary vascular resistance	NCT01086540
Early treatment of borderline pulmonary arterial hypertension associated with Systemic Sclerosis (SSc-APAH) (EDITA)	Mean pulmonary arterial pressure change from baseline	NCT02290613
Zibotentan better renal scleroderma outcome study (ZEBRA)	Biomarker (sVCAM 1)	NCT02047708
Safety, tolerability, efficacy, and pharmacokinetics of JBT-101 in systemic sclerosis *(*resunab: endocannabinoid-mimetic drug*)*	Treatment emergent adverse events and CRISS	NCT02465437
Subcutaneous injection of autologous adipose tissue-derived stromal vascular fraction into the fingers of patients with systemic sclerosis (scleradec2)	Cochin hand functional scale	NCT02558543

CRISS, Combined Response Index for Systemic Sclerosis; mRSS, modified Rodnan skin score.

'systemic sclerosis' with >200 interventional studies. A careful look at clinical trial details provides >50 phase II/III trials with about 20 trials on active recruitment. The major active studies are listed in table 1. The majority of the ongoing studies target skin fibrosis, and interleukin 6,[17] interleukin 1 and CTLA4[18] are targeted using compounds already on the market. The results of faSScinate trial evaluating tocilizumab are very encouraging to finally get one positive trial on mRSS.[17] The results of this study showed not only an improvement in skin fibrosis but there was also an encouraging signal on changes in pulmonary functional tests to be both confirmed in the ongoing large phase III focuSSced trial. It is also interesting to see that drugs with other mechanism of action that showed very promising preclinical data are developed for fibrosis. These drugs can be regarded as potential antifibrotic ones with various actions: riociguat is a stimulator of soluble guanylate cyclase,[19] whereas IVA337 is a panPPAR agonist.[20] With regard to the complex pathogenesis of SSc, one might anticipate in the near future that combination therapies will have to be investigated and accordingly first investigating immunotherapies and antifibrotic drugs separately makes sense. However, in an optimistic and ambitious vision, the very efficient treatment might be their combination. The above-cited trials all target enriched population at various levels, but riociguat and IVA337 studies include patients with early DcSSc with lower baseline mRSS, in line with the recent EUSTAR findings. Lung is another key target for SSc and the recent approval of nintedanib in idiopathic lung fibrosis together with good preclinical data has allowed the large ongoing trial on SSc.[21] Intense immunosuppression, achieved with hematopoietic stem cell transplantation, showed a significant decrease in patients reaching end organ failure, but more data are needed to further clarify the risk/benefit ratio and the criteria that may select patient for such therapy.[22] Gastrointestinal (GI) involvement is not the most severe complication of the disease, but it is very prevalent and disabling. Specific data on SSc GI system will be important for the routine management of the patients. Pulmonary arterial hypertension is probably less prevalent than it was few years ago, but it still remains a very severe complication with poor outcomes.[23]

The analysis of the literature shows that the scientific work and clinical trials in SSc are numerous. SSc complexity and severity have attracted several investigators and pushed towards the building of very active networks to share ideas and forces to improve the field.[24] A better understanding of the pathogenesis, the natural history and the identification of parameters for selecting enriched populations are already major achievements and raise hope for patients with SSc. Our community must further foster collaborations between scientists, and with companies, to translate all the efforts that are made into clinical care to improve the QOL and survival of patients with SSc.

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