Disease modification in systemic sclerosis: the search for the Holy Grail

"...agents that have been previously found to be 'ineffective' should be looked at again in clinical trials with more specific criteria for recruitment and more composite primary end points."

KEYWORDS: scleroderma ■ systemic sclerosis ■ treatment

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Descriptions of a systemic sclerosis (SSc)-like illness can be found in the writings of Hippocrates (460– 370 BC), however the first well-documented case was reported by Carlo Cursio in 1755. He described a 17-year-old female patient from Naples (Italy) who presented with "an excessive tension and hardness of her skin all over her body, by which she found herself so bound and straiten'd, that she could hardly move her limbs." She was treated with warm milk, vapor baths, "bleeding from her foot" and quicksilver, and reportedly her skin became soft and flexible after a period of 11 months [1]. Not all patients with SSc are as fortunate. More than 250 years have since passed and there is no treatment for SSc.

The etiology of SSc is unknown and the complex pathogenesis is not clearly understood. The initial stage of the disease is characterized by an early inflammatory infiltrate, microvascular dysfunction and dysregulated immunity, which is superseded by overwhelming fibrosis [2].

Treatment studies for SSc are few and difficult to conduct owing to a low disease prevalence, a complicated pathogenesis unique to individual patients (even with a similar disease phenotype) and suboptimal primary outcome measures, such as the modified Rodnan skin score (mRSS), which may not correlate well with disease activity and severity in all patients.

Trials with agents such as imatinib, IFN-γ, IFN-α, D-penicillamine, relaxin and minocycline, which target only the fibrotic component of the disease, have shown improvement in open-label studies for the treatment of SSc. However, when randomized studies were carried out, a similar benefit was not observed. Agents that potentially target other pathogenic mechanisms of the disease (i.e., vascular damage, autoimmunity and fibrosis), such as cyclophosphamide, methotrexate, mycophenolate and cyclosporine, have also shown improvement in skin scores in open-label studies, but not in most randomized controlled trials [3–6].

An exception is cyclophosphamide in the scleroderma lung study. The primary end point of the study was forced vital capacity (FVC) and it was noted that the improvement in FVC was higher in patients who had more severe fibrosis. This may indicate that there are some phenotypic subsets of patients who may have a more favorable response to immunomodulation than others. Improvement in skin scores was also seen initially, but ceased once the study drug was withdrawn, implying that the mRSS may not be the best measure for disease activity [7]. One can conclude that it is quite possible that lack of efficacy seen with the above agents is because of lack of proper recruitment and suboptimal primary outcome measures.

The pathogenesis of the disease is complicated and involves multiple pathways. Multiple genetic defects are also postulated to play a role in some of the underlying pathogenic mechanisms. However, the classification of SSc is solely based on phenotypic presentation and patients are recruited for trials based on this factor. It is therefore reasonable to assume that patients with the same phenotype may have significant differences in the underlying pathogenic mechanism. Adding to the complexity of trial design for SSc is the variable disease course, where some patients with initial severe disease improve without treatment (as is the example of Cursio's case above) and others with milder disease manifestations may suddenly develop life-threatening organ system complications.

Future Medicine part of fsg

It is also still unclear what subset of patients improve spontaneously and what subset get progressively worse; this also acts as a confounding factor in treatment trials. Further study, possibly focusing on individual genetic and pathogenic processes, is thus required to help define study patients better.

It is also very important to take into account the phase of the disease at the time of recruitment. Patients in the early inflammatory phase should theoretically benefit most from immunomodulation, thus it may be beneficial to conduct treatment studies with patients who are in the early inflammatory phase, although due to the rarity of the disease and the pressures of study recruitment this may not always be feasible. Use of validated disease severity and activity scores for each organ system would also be useful to better characterize patients in a clinical trial. This is because involvement of different organs may indicate not only a different phenotype of the disease, but also a different pathogenic mechanism. Organ involvement and how it relates to other parts of the body should also be taken into consideration when studying treatments in SSc. For example, presence of severe gastroesophageal reflux disease may have an effect on study results in immunomodulatory studies for lung disease.

Based on an initial observation that the overall disease activity in diffuse SSc correlated with the degree of skin involvement, most studies used the mRSS as a primary outcome measure [8]. However, recent evidence suggests that skin scores may not have a linear correlation with overall disease activity [9], thus there is a need for designing either more representative primary outcomes or including more than one primary outcome measure.

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Another disease assessment tool, the Medsger severity scale, was published by Medsger *et al.* in 1999 and later modified in 2003 [10,11]. Unlike the mRSS, this scale is a composite of disease activity measures in nine different organ systems. It is easy to administer and has been widely accepted as a good measure of disease activity in SSc; however, it has rarely been used as a primary outcome measure in major trials. We believe this scale would be a good place to start in designing future trials for SSc [11].

The Scleroderma Clinical Trials Consortium suggested response measures for disease activity in SSc (2007). These included selected items in 11 different domains for disease assessment. The domains included skin, musculoskeletal, cardiac, pulmonary, renal, gastrointestinal, health-related quality of life and function, global health, Raynauds phenomenon, digital ulcers and biomarkers (erythrocyte sedimentation rate and C-reactive protein). In all, a total of 31 core set measures were selected for these 11 domains. This consortium recommended that these observations be applied to future observational and clinical trials in SSc [12]. Other important aspects of trial design for patients with SSc were addressed by the Scleroderma Clinical Trials Consortium at the Scleroderma International Workshop in July 2011. This workshop recommended using composite end points for future studies, rather than just skin scores. The workshop concluded that currently there is a paucity of validated outcome measures and also recommended the possible use of biospecimens to better assess efficacy of therapeutic trial agents [13].

Thus, in light of the above arguments, agents that have been previously found to be 'ineffective' should be looked at again in clinical trials with more specific criteria for recruitment and more composite primary end points.

> *"...the search for therapies for systemic sclerosis, although inconclusive, is far from over."*

The evidence that all immunosuppressive and antifibrotic therapies have failed patients suffering from this chronic illness is still inconclusive. Clinical experience and many open-label trials have shown improvement in patients. Biomarkers that reliably approximate disease activity, a better understanding of the pathogenesis, a better defined patient selection criteria and studies with multiple primary end points are needed to better evaluate available treatments. Therefore, the search for therapies for SSc, although inconclusive, is far from over.

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