

# Trial design: how must we move ahead?

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Scleroderma is clinically heterogeneous and a variety of plausible mechanisms of disease have been hypothesized. Recent years have witnessed a significant improvement in overall survival although all of the gains in management have been therapies for specific organ involvement, e.g. renal crisis and pulmonary arterial hypertension. Future studies will rely on improved clinical science, which involves structured validation of proposed measures of outcome; development of a combined response index; and further refinement of specific subsets of disease expression. Immunoablation with stem cell reconstitution is an example of aggressive therapy chosen as appropriate for a particularly severe disease subset and in whom the pilot data are encouraging. Good science and clinical ethics force continued consideration of equipoise between risk and benefit.

**KEY WORDS:** Scleroderma, Systemic sclerosis, Outcome measures, Trial design, Disease modification.

Systemic sclerosis (SSc, scleroderma) remains without a clearly defined pathogenesis and thus without an effective overarching approach to therapy. Increasingly sophisticated scientific studies have defined several candidate approaches of great promise including specific molecular targets for anti-fibrotic therapy as well as new approaches to modification of both vascular and immunological features of disease. Many of these concepts are addressed in this monograph. Recent advances suggest that SSc is in fact a family of closely related illnesses wherein clinical and serological phenotypes and specific genotype are closely inter-related. The search for a unifying mechanism for all forms of the syndrome, while elusive, seems within reach.

To the clinical student of scleroderma, the basic question remains: if there were a truly effective drug for scleroderma, how might we recognize that it worked and what standards of response would be considered meaningful and cost effective? Is it indeed possible that we have effective therapies in hand, yet our methods of assessing the same have led to underestimations of their effects?

The cluster of clinical entities incorporated under the label of SSc is of intimidating heterogeneity. There are clear differences in the extent and severity of skin involvement between individuals with dcSSc vs lcSSc. This would apply if skin were considered as the primary disease outcome under study, or if skin served merely as a clinical surrogate for risk of accrual of visceral involvement. Imagine a therapy that reversed skin whilst having no effect on lung or an effective agent for interstitial lung disease that had no discernable effect on skin. Just what sort of therapeutic response do we expect?

Scleroderma therapeutics is advancing. Survival from scleroderma is improving through development of specific organ-based strategies such as angiotensin-converting enzyme inhibitors for scleroderma renal crisis and perhaps from modern therapies for pulmonary vascular complications [1]. Two recent prospective randomized controlled trials suggested that either oral or intravenous cyclophosphamide may slow loss of pulmonary function in patients with scleroderma interstitial lung disease [2, 3]. These studies illustrate a new era of sophistication in scleroderma clinical research and in many ways raise more questions than answers.

The treatment effects for forced vital capacity (FVC) and for skin involvement were within the laboratory range of intra-patient variability for both measures, although secondary measures also supported the modest efficacy of the drug. A 'minimally important difference' of change in FVC, i.e. a change that paralleled improvement in some other outcome such as survival or quality of life has not been defined. The beneficial effect of cyclophosphamide was not durable beyond about 6 months after stopping cyclophosphamide, with most differences between drug and placebo essentially absent at 24 months of follow-up [4]. In balancing risk vs benefit, our increasing ability to define cohorts enriched for risk of lung progression suggests that results of future lung studies might be more easily understood. At present, cyclophosphamide must be pronounced as effective and to be judged as true evidence-based medicine for our clinical practices. The issue remains the inability to state this as generalized for all patients.

Immunoablation with stem cell reconstitution ('stem cell transplant') offers another glimpse at the future. This therapy has a moderately high treatment-related morbidity and even mortality, yet the magnitude of response from pilot study is singularly impressive. Major improvements in skin and disability and associated stabilization of visceral disease have been reported in up to 4 yrs of follow-up [5]. Controlled follow-up trials are in progress in both the European Union and North America. Harmonization of inclusion and exclusion criteria as well as in consideration of the equipoise of disease severity vs treatment-related morbidity has been the hallmark of this endeavour. Is it possible that treatment breakthrough in scleroderma will be a 'trickle down' phenomenon wherein therapy for our sickest patients comes first followed by extrapolation to less severely afflicted patient groups?

Much of this symposium focused on the critical science of outcome measures. If we know what a new therapy should look like, should not we also have confidence in our ability to measure its effects? Collaborative exercises have led to a potential combined response index that is currently being validated. When multiple domains of disease are studied simultaneously, sensitivity to change and our ability to interpret small levels of change will be more robust [6].

New trials are actually easy to predict. We will increasingly employ agents of highly specific effects and with strong scientific rationale. Studies will employ consensus definitions of homogeneous subsets and will require multicentre collaboration for successful and timely recruitment. Standardization of outcomes will permit cross-study comparisons and will enhance the reservoir of true evidence-based medicine. Regulatory agencies will benefit from the breadth and depth of disease-specific information. Our patients deserve nothing less than the highest standards of efficient, ethical and rational research.

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### Rheumatology key messages

- Scleroderma is pathobiologically complex and clinically heterogeneous.
- In the absence of a disease-specific overarching mechanism, plausible therapeutic targets are numerous.
- Development of a Combined Response Index for Systemic Sclerosis (CRISS) may offer broad applicability as well as enhanced sensitivity to change.
- Homogeneous subsets with common problems may be studied although refinement of measures of outcome is needed.

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