Review

Clinical trial design in scleroderma: where are we and where do we go next?

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ABSTRACT

Drug development for SSc has been hindered by the relative paucity of validated outcome measures and biomarkers for use in clinical trials. The Scleroderma Clinical Trials Consortium (SCTC) conducted an interactive session at the Scleroderma International Workshop in Cambridge, UK in July 2011 to discuss clinical trial design in SSc. The following issues were discussed: 1) primary outcome for trials of SSc – skin vs. lung vs. composite; 2) ischaemic digital ulcers in SSc – healing vs. repair vs. composite; 3) pulmonary arterial hypertension in SSc; and 4) neglected aspects of SSc – opportunities for study or of lower priority and feasibility. Randomised controlled trials with collection of biospecimens are necessary to assess efficacy of therapeutic agents, validate novel outcome measures, and discover and validate potential biomarkers for each of these areas. Although SSc is a rare, heterogeneous disease, collaborative efforts led by the SCTC and other international networks will ultimately improve the design of clinical trials of promising therapies for SSc.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by vascular damage and fibrosis that can affect multiple organ systems. Disease presentation and progression is heterogeneous, with differences in organ system involvement and severity of disease (1). Genetic background and autoantibody specificity are helpful in predicting organ system involvement, but better biomarkers are necessary to monitor and predict disease activity and severity (2, 3). Clinical trials investigating therapeutic agents for the treatment of SSc have been complicated by several design challenges including varying rates and patterns of specific disease manifestations, the relative rarity of the disease, and the lack of validated or highly responsive outcome measures for some aspects of disease.

The Scleroderma Clinical Trials Consortium (SCTC) conducted an interactive session at the Scleroderma International Workshop in Cambridge, UK in July 2011 to discuss clinical trial design in SSc. The chairman of the session first provided an overview of the major issues regarding the design of clinical trials in SSc which depends upon several variables: 1) the mechanism of action of the therapy or intervention being tested; 2) whether efficacy is measured by prevention, reversal, or palliation of symptoms; and 3) what stage of disease is targeted (new-onset *vs.* early *vs.* late). The format of the session included a brief presentation by one of the co-authors on four different topics (see below) followed by an interactive discussion. The goal was to conduct an open discussion with members of the scleroderma research community, including clinicians, investigators, industry partners, and government scientific agency representatives, of feasible study designs to advance clinical trials of promising therapies for the treatment of SSc.

The following issues were discussed:

1: Primary outcome for trials of SSc – skin *vs.* lung *vs.* composite
2: Digital ulcers in SSc – healing *vs.* repair *vs.* composite
3: Pulmonary arterial hypertension in SSc
4: Neglected aspects of SSc – opportunities for study or of lower priority and feasibility

The discussions for each issue focused on the following questions:

1: What has worked and what has not worked for clinical trials in SSc?
   a. Are open-label studies of value?
   b. Do validated outcomes exist?
   c. What is good about the designs and what is lacking?
2: What is the current environment for clinical studies of SSc?
   a. What do regulatory agencies think?
   b. What do industry partners think?
   c. What is the overall feasibility?

The objective of this report is to briefly summarise the conclusions arrived at during the Workshop and help frame ongoing discussions of these important matters.

Primary outcome for SSc trials: skin *vs.* lung *vs.* composite

The majority of clinical trials in SSc have focused either on skin or lung fibrosis as the primary outcome, with the other organ systems evaluated as a secondary outcome. Composite indices are being developed (4, 5) for controlled trials.

What has worked and what has not worked for clinical trials in SSc for skin and lung disease?

– Are open-label studies of value?

In the past, proof-of-concept trials in SSc have often been designed as uncontrolled trials, which were of limited usefulness to assess and predict the efficacy and safety of therapeutic agents. Regardless of what is used as the primary outcome, open-label studies can still be considered for initial in-disease safety evaluation of therapeutic agents. However, given the wide variation in the natural history of scleroderma and the tendency for spontaneous improvement and regression to the mean for major outcomes in clinical trials (6, 7), proof-of-concept studies will need control/comparatory groups. This situation may change if reliable and valid biomarkers are developed that allow early-phase open-label studies to provide information about drug effects. For the foreseeable future, and especially for late-phase studies, randomised, placebo or active comparator-controlled trials are necessary to assess efficacy of therapies for scleroderma.

Biomarker-driven proof-of-concept studies with a control group are an attractive trial design because such trials can have shorter durations than studies with clinical endpoints. If skin is the primary endpoint, collection of tissue samples are recommended and such collection is quite feasible. The specific biomarkers which should be used are not yet agreed upon and specific biomarkers have not been validated in this context. Additionally, autoantibody assessment should be done to assess if subsets of patients are responsive to particular therapies. The collection and storage of serum, plasma, and possibly DNA, RNA, and peripheral blood mononuclear cells, in clinical trials in scleroderma, is strongly encouraged to provide material to assess the utility and validity of biomarkers.

It is important to emphasise that proof-of-concept trials can at best collect evidence for possible efficacy. Firm conclusions on efficacy and safety are best drawn from randomised, double-blind, placebo or active comparator-controlled trials.

– Do validated outcomes exist?

The modified Rodnan skin score (MRSS) is a validated measure of skin thickening (8, 9) that has been shown to correlate with internal organ involvement and survival in patients with diffuse cutaneous SSc (10, 11). The advantages of using the MRSS as a primary outcome measure include the correlation with histopathologic changes on skin biopsy (9), acceptance by regulatory agencies, feasibility, and the fact that it has been partially validated as a surrogate for overall disease severity. The disadvantages include the heterogeneity of skin severity within subsets of SSc, lack of consistent correlation between MRSS and internal organ disease, particularly in patients with limited cutaneous involvement, the variability of the measure between investigators, and the improvement in MRSS that is part of the natural history of disease of SSc.

Assessment of lung disease has primarily relied on scoring the extent of interstitial lung disease on high resolution computed tomography (HRCT) of the chest (12) and/or on changes in the forced vital capacity (FVC) (13) as measured by standard spirometry (14). The advantages of using the assessment of pulmonary disease as a primary outcome for clinical trials in SSc include the clinical importance of lung disease, acceptance by regulatory agencies, and feasibility. The disadvantages include the fact that changes are often minimal and technical issues may reduce reliability of these measurements.

– What is good about the designs and what is lacking?

Although many successful clinical trials have been performed using skin or lung as the primary outcome, the systemic and heterogeneous nature of SSc indicates that a composite response measure may be a more accurate assessment of disease activity that is more likely to be responsive to change than individual measures. Potential composite measures include survival or event-free survival, scleroderma severity score, European SSc activity index, combined response index, or organ-specific composite outcomes such as for pulmonary arterial hypertension (PAH) or pulmonary fibrosis (15, 16). Composite measures may be for single organ (*e.g.* several skin measures combined) or for global disease. Composite measures in clinical trials of SSc could potentially be more clinically meaningful and responsive than traditional measures, and provide a global assessment of disease severity. A composite measure, however, will require a flexible approach, as SSc is a heterogenous disease, and activity can be concentrated in a few organs, which may confound the ability of the composite measure to assess change. This has been a major hindrance to the use of composite measures in systemic lupus erythematosus, a disease in which a combination of composite measures was recently used successfully in clinical trials (17). Although composite measures are currently under development for SSc, such instruments will require validation in the setting of at least moderately large trials.

Given the heterogeneity of SSc, performing analyses on subsets of disease, or even limiting certain clinical trials to particular patient subsets (for example

patients with a specific autoantibody reactivity) may enhance the observed efficacy of therapeutic agents.

What is the current environment for clinical studies of skin and lung disease in SSc?

– What do regulatory agencies think?

The MRSS is an accepted outcome measure by regulatory agencies. Although cyclophosphamide has shown statistically significant improvements in FVC compared with placebo for the treatment of SSc-related interstitial lung disease (13, 18), no disease modifying therapies have been approved in the United States for the specific treatment of any aspects of SSc.

–What do industry partners think?

With the development of novel biologic agents and targeted small molecules for related autoimmune diseases, the biopharmaceutical industry has showed continued and growing interest in developing disease modifying therapies for the treatment of SSc. The main interest of industry regarding novel therapeutic agents is to get rapid, reliable predictive information about whether the agent of interest is likely to be successful in phase II/III trials. For therapies that are already approved for other indications, the goal is to design clinical trials sensitive enough to detect clinically meaningful efficacy acceptable to regulatory agencies and that lead to extension of the approved treatment indications.

– What is the overall feasibility?

Many successful multi-center, randomised controlled clinical trials have been completed using skin or lung as the primary outcome, demonstrating the feasibility of these studies. The international SSc research community works cohesively on clinical trials. Eligibility criteria for previous studies have focused on patients with early disease, in hopes of counteracting the most inflammatory and immunologically active phase of SSc, before substantial irreversible damage has occurred. There remains the promise that antifibrotic therapies will be developed that reverse seemingly established disease. The development of better outcome measures (potentially a composite index) and better biomarkers that reflect disease activity and/or response to treatment will allow for more precise targeting of subsets of patients who are most likely to respond to specific therapies.

Ischaemic digital ulcers in SSc – healing *vs.* repair *vs.* composite

The definition of a digital ulcer (DU) is a denuded area with a defined border and loss of epithelialisation, loss of epidermis, and loss of dermis. Fissures, paronychia, extrusion of calcium, or ulcers over the metacarpo-phalangeal joints or elbows are excluded. For inclusion into the majority of previous clinical trials, ischaemic DU must be distal to the proximal interphalangeal (PIP) joints and on the volar surface and tips of digits (19, 20).

What has worked and what has not worked for clinical trials of ischaemic digital ulcers in SSc?

– Are open-label studies of value?

The potential advantages of open-label studies for treatment of DUs in SSc include the fact that they are easy to recruit for and complete quickly, they can provide preliminary data suggesting tolerability and efficacy of agents, and the same investigator can usually do all assessments so inter-rater variability is not a problem. The disadvantages of open-label studies include the small sample size, the need to have a long enough run-in period to assess the development of new DUs, and most notably, the fact that DUs usually heal spontaneously over time. Given these factors, controlled trials are strongly advised to evaluate new therapies for DUs, including in Phase II of drug development.

– Do validated outcomes exist?

Several validated outcome measures are currently used for studying DU in SSc including the number of active tip DU on the volar aspect, the Scleroderma Health Assessment Questionnaire (SHAQ) DU visual analogue scale (VAS), the HAQ pain VAS, HAQ-disability index, the Raynaud Condition Score, SF-36, and the Cochin Hand Function Scale (4, 21, 22). Several of these measures have only been validated for studies on Raynaud's phenomenon. In addition, unvalidated outcome measures that are often used as the primary outcome in clinical trials include the number of new DU, healing of baseline DU, and time to healing of the cardinal or largest DU. Complicating the conduct of studies of DUs is the substantial variation between investigators in which lesions are identified as DUs (vs. abrasions or other lesions) and assessment of the stage of a DU (active, healed, indeterminate) (23).

A major question regarding DU trial design is whether to focus on prevention, healing, or impact on function. The number of new DUs is the most frequently used outcome and has performed well in large multi-center clinical trials. For example, the RAPIDS 1 and 2 studies demonstrated the effectiveness of bosentan compared with placebo in the prevention of new DUs, resulting in regulatory approval of bosentan for this indication in the EU (19, 20). The US Food and Drug administration has been using healing of DUs as a major efficacy outcome. However, assessment of healing of DUs is complicated by several factors: 1) the precise time of healing may not be captured between visits; 2) a scar or eschar overlying DU may make it difficult to assess healing; and 3) it is difficult to account for the effect of trauma on DUs. The assessment of DU impact on hand function has typically been used as a secondary outcome measure and there is ongoing effort to develop a patient-reported outcome measure in SSc-associated DU (24).

– What is good about the designs and what is lacking?

Current trial designs for the study of DUs in SSc use validated and unvalidated outcome measures. A major issue with clinical trials of DUs is the poor inter-rater reliability for defining active vs. inactive DU (23). The definition of "active" DUs needs to be agreed upon, and tools to measure activity of DUs need to be developed. During the discussion, it was concluded that active distal dorsal ulcers should be included and assessed in clinical trials, even if

they are not the primary outcome. Although ulcers overlying the joints (ie. PIPs, MCPs, elbows) are likely in part related to trauma, these ulcers should be assessed in clinical trials as exploratory endpoints to assess healing in response to therapies as there may be an ischaemic component. Investigator training sessions are essential prior to multi-center clinical trials for the treatment of DUs. There is also a need to identify novel biomarkers that accurately reflect DU disease activity.

What is the current environment for clinical studies of ischaemic digital ulcers in SSc?

– What do regulatory agencies think?

Regulatory agencies in different countries may view the clinical outcomes of DUs in SSc differently. For example, the results of two clinical trials (19, 20) led to the approval of bosentan for DUs in SSc in the EU but the same data did not lead to approval of this drug for DUs in SSc by the US Food and Drug Administration.

– What do industry partners think?

The biopharmaceutical industry continues to support multi-center clinical trials for new agents to treat DUs. There are currently large, multi-center, international clinical trials being initiated for evaluating endothelin receptor antagonists and phosphodiesterase-5 inhibitors for the treatment of DUs. Although consideration must be given to the cost of therapies for a complication that may improve spontaneously, the substantial morbidity associated with DUs has resulted in continued interest and support to develop effective therapies for this complication of SSc.

– What is the overall feasibility?

Clinical trials on DUs are feasible but require multi-center collaborations to recruit a large enough number of patients. Although DUs heal spontaneously, the lesions are a source of substantial morbidity for patients with SSc and there needs to be an increased awareness and understanding of the clinical impact of DUs on patients with SSc. In order to improve the validity of results from trials of DUs in SSc, appropriate training of investigators is paramount to improve inter-rater reliability.

Pulmonary arterial hypertension in SSc

Although some drugs have been approved for the treatment of pulmonary arterial hypertension (PAH), including SSc-related PAH, therapeutic responses for these patients appear to be lower than for non-SSc-related PAH. In addition, outcomes in SSc-PAH are poorer than for patients with idiopathic disease and other connective tissue disease (CTD)-associated PAH (25). Potential explanations for more aggressive disease in SSc-PAH are related to differences in pathophysiology and pathology, with a higher prevalence of pulmonary veno-occlusive disease (26, 27). In addition, patients with SSc have other comorbidities such as interstitial lung disease (ILD), right and left heart disease, and renal insufficiency that may influence response to therapies and survival.

What has worked and what has not worked for clinical trials in SSc-PAH?

– Are open-label studies of value?

Therapies currently available for the treatment of SSc-PAH have received regulatory approval as part of large randomised controlled trials for all WHO Group I PAH subgroups. Given the role of autoimmunity in SSc-related PAH, clinical trials of immunomodulatory or targeted molecular therapies will be important in the development of specific or adjuvant therapies for SSc-related PAH. Open-label studies of such agents in the SSc-PAH subgroup may be useful to gain information on proof-of-concept, potential biomarkers, and safety; open-label studies that include data from right-heart catheterisation (RHC) may be of particularly high value. However, as with studies for skin and ILD, double-blind, placebo or active comparator-controlled studies are necessary to properly assess the safety and efficacy of therapies in SSc-PAH as well.

– Do validated outcomes exist?

Improvement in exercise capacity as measured by the 6 minute walk test (6MWT) has traditionally been accepted by regulatory agencies for the approval of PAH-specific therapies. However, the validity of the 6MWT in patients with SSc is questionable given the presence of comorbidities that can affect the results including anemia, musculoskeletal disease (contractures, myositis, arthritis), and ILD (28). Hemodynamic and echocardiographic indices as well as dyspnea scales have been used as secondary outcome measures.

What is good about the designs and what is lacking?

The regulatory approval in the past 15 years of several PAH-specific therapies for patients with SSc-PAH indicates that the current clinical trial design (including the SSc-PAH subgroup in larger trials) has been effective. However, given the unique phenotype observed in SSc-PAH, several issues need to be addressed in order to improve clinical trial design in this subgroup of patients with PAH:

- A better understanding of the pathophysiology is needed, including development of preclinical models.
- Improved definitions and measurements of important and relevant comorbidities are needed.
- Better outcome measures, and potentially a composite response index (5), need to be developed and validated.
- Because of the high mortality associated with SSc-related PAH, studies evaluating prevention and early intervention (such as targeting borderline mean pulmonary arterial pressures on RHC) are necessary.
- Regulatory agencies, the biopharmaceutical industry, and cardiologists/pulmonologists need to recognise the importance of developing novel treatments specifically targeting SSc-related PAH.

What is the current environment for clinical studies of SSc-PAH?

– What do regulatory agencies think?

Regulatory agencies recognise the need for PAH-specific therapies given the high morbidity and mortality associated with this disease. However, the scleroderma community needs to convince agencies of the importance of developing novel treatments specifically

targeting SSc-related PAH (*i.e.* the subgroup of patients with PAH and SSc).

– What do industry partners think?
Industry-sponsored clinical trials will likely continue to include patients with connective tissue disease-PAH for licensing purposes. Biopharmaceutical companies, particularly those developing immunomodulatory agents, are beginning to recognise the importance and feasibility of performing clinical trials in the SSc-PAH subgroup.

– What is the overall feasibility?
Clinical trials for novel agents specifically targeting SSc-related PAH are feasible, but require multi-centre, interdisciplinary collaborative efforts.

Neglected aspects of SSc – opportunities for study or of lower priority and feasibility?
Manifestations of SSc affecting several different organ systems have largely been neglected in therapeutic clinical trials, including gastrointestinal (GI) disease, renal disease, myopathy, calcinosis, joint disease, and cardiac disease.

What has worked and what has not worked for clinical trials in neglected aspects of SSc?
– Are open-label studies of value?
For rarer manifestations of SSc, open-label trials may be necessary to assess proof-of-concept. However, controlled studies will be necessary to confirm results of smaller, earlier-phase studies. Assessment of disease activity in these neglected areas should be included as secondary endpoints in large randomised controlled trials in order to gain a better understanding of the natural history of disease and potential for therapeutic response in these areas.

– Do validated outcomes exist?
Validated outcome measures are lacking for most of these manifestations, with the exception of the UCLA SCTC GIT 2.0 instrument (29, 30) for GI disease and glomerular filtration rate and blood pressure for renal disease. The SCTC is currently initiating efforts to study these rare manifestations to define the natural course, classify clinical subsets, and develop validated outcome measures for use in clinical trials.

– What is good about the designs and what is lacking?
In order to perform clinical studies in these areas, appropriate patient selection and development of validated outcome measures are needed. Outcome measures that have been validated for other diseases (*i.e.* DAS28 for rheumatoid arthritis), but not fully validated for SSc, could be used to assess disease activity in these neglected organ systems.

What is the current environment for studies regarding neglected aspects of SSc?
– What do regulatory agencies think?
Regulatory agencies have not been asked to address issues related to these less commonly-studied manifestations of SSc. Given the substantial morbidity/disability (GI, calcinosis, joint, and muscle disease) and mortality (renal and cardiac disease) associated with these understudied manifestations, it is important that the scleroderma clinical research community work with government regulators to help develop feasible pathways to drug approval for these aspects of SSc.

– What do industry partners think?
Just as academic researchers have not concentrated efforts on studying these aspects of SSc, the biopharmaceutical industry has not made these problems a focus of their interests. However, with the development of validated outcome measures and an increased research focus on these problems, industry could become more engaged in seeking therapeutic solutions.

– What is the overall feasibility?
The importance of these rarer manifestations in SSc is currently recognised by the SSc research community and efforts to accelerate the development of outcome measures for these areas are underway. Collaborative efforts have been initiated by the SCTC to develop and assess tools in SSc patient cohorts enriched for these manifestations. Feasibility of clinical trials in these areas will be increased with the assistance of experts from other disciplines (*i.e.* gastroenterology, nephrology, myopathy/neurology, dermatology, and cardiology).

Summary and conclusions
Drug development for SSc has been hindered by the relative paucity of validated outcome measures and biomarkers for use in clinical trials. Randomised controlled trials with collection of biospecimens are necessary to assess efficacy of therapeutic agents, validate novel outcome measures, and discover and validate potential biomarkers. Clinical trial design and conduct for rare diseases, such as SSc, present some unique challenges (31). Recruitment of adequate numbers of study subjects is often difficult with rare diseases necessitating either extended recruitment periods and/or a large number of study sites, each often enrolling a small number of subjects. These factors can result in higher costs per study subject than for trials of more common diseases. There is increasing use of trial designs that are aimed specifically at conducting studies with small numbers of subjects with rare diseases. Additionally, the US Food and Drug Administration, in response to the passage of the Orphan Drug Act in 1983, has special programs and pathways to help facilitate the development of new drugs to treat rare diseases. Although SSc is a rare, heterogeneous disease, collaborative efforts led by the SCTC and other international networks will ultimately improve the design of clinical trials of promising therapies for SSc.

Competing interests
L. Chung has served on the Advisory Board for Gilead, received honoraria from Gilead and Actelion, and received research support from United Therapeutics, Pfizer, Gilead and Actelion;
C.P. Dentonhas been a consultant to Actelion, Pfizer, CSK, Medimmune and Roche Pharmaceuticals;
O. Distler had consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergoves, BMS, Sanofi-Aventis, United Biosource, Medac, Biovitrum, Novartis, 4D Science, Active Biotech, Bayer and Boehringer in the area of potential treatments of sclerderma and its complications;

D. Khanna reports consultancies, received grants from and/or speakers' bureau for Actelion, Gilead, DIGNA, Sanofi-Aventis, United Therapeutics, and National Institutes of Health;
P.A. Merkel is a paid consultant to Actelion Pharmaceuticals Inc., and has received research support from Actelion Pharmaceuticals, Celgene, and Genzyme.

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