Editorial

What can we learn from negative clinical trials in systemic sclerosis?

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Systemic sclerosis (SSc) is a complex, multisystem connective tissue disease characterised by vascular dysfunction, including remodelling, and fibrosis of skin subcutaneous and interstitial tissues (1). SSc is a rare disease with an estimated incidence of 8-30 per million population per annum. The clinical presentation, patterns of organ involvement and disease course are highly variable, which has led to significant challenges for classification and treatment. The combination of classification challenges, low prevalence with variable clinical presentation has resulted in relatively few well-designed clinical trials. Approaches in the past have been largely empiric using drugs which previously showed some effect in other related autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosis (SLE) but with little success in SSc (2). Recent advances in biomedical research have identified more specific molecular pathways which have been considered potential therapeutic targets and have been studied in clinical trials predominantly through the collaborative group – the Scleroderma Clinical Trials Consortium. Disappointingly, a number of the more rational clinical trials have had negative or equivocal results. In this review we will examine some of the recent trials and evaluate possible reasons for the largely negative results. We offer strategies to address these in future studies.

A number of clinical trials have examined non-specific immunosuppressive drugs previously used in the treatment of RA and SLE such as penicillamine, methotrexate and cyclophosphamide (3-7). Others have focused on specific pathogenic molecular targets identified by translational research of the mechanisms of disease in SSc patients. These latter studies have identified specific molecules or pathways implicated in the biology of excessive fibrosis, collagen deposition and microvascular remodelling. These have included pleiotropic antifibrotics such as relaxin (8), putative specific drivers of fibrosis such as transforming growth factor (TGF) beta (9) and antagonists of profibrotic and vasospastic endothelin (10). In general these agents may act on a variety of inflammatory pathways and in different target organs or highly specific molecular targets which it has been assumed are involved in specific organs.

The randomised clinical trial, usually placebo-controlled remains the preferred option for testing whether or not a new drug is truly efficacious in the treatment of a particular disease manifestation (11). This tightly controlled study design is best applied to a strictly pre-defined patient population with homogeneous clinical characteristics. The efficacy of a novel drug is often being examined in a very narrow clinical scenario; an example of such in SSc is the RAPIDS-1 study showing that treatment with the nonselective endothelin receptor antagonist – bosentan, may be effective in preventing new digital ulcers in patients who are likely to develop them or already have multiple digital ulcers (12). This clinical trial approach however requires that patients must be highly selected; outcome measures must be well-validated and clearly defined from the outset. SSc patients present a number of challenges in this context as it is a rare disease and patients often have a wide variation in clinical manifestations, serology and of course, single outcome measures appear to perform poorly, perhaps due to inadequate standardisation or validation. In addition, the natural history of patients with SSc may range from a

disease with slow progression of clinical features, a spontaneous improvement, or a rapidly, progressive failure of vital organs leading to early death. It has become clear recently that the natural history of specific organ involvement in SSc patients has changed over the past 20 years (13). The reasons for this change have been contentious. An example of such a change is that the primary cause of death is no longer renal crisis but is lung disease and/or pulmonary hypertension.

In recent studies investigators have attempted to focus on patients with 'early' disease, although it has been difficult to achieve international consensus as to the definition of 'early'. The European group EUSTAR has moved some way towards this by defining very early diagnostic criteria (unpublished); however this still relies on a combination of various clinical symptoms and signs or serological findings, so the overall cohort will represent a cross-section of patients with variable anatomical involvement. While patients with earlier disease may share clinical features or risk of certain complications, this does not guarantee homogeneity of either severity or activity at trial outset. Two studies of conventional immunosuppressive therapy – the Canadian/US methotrexate study recruited a cohort with a mean disease duration of 7.5 months, using an entry criterion of <3years as early (5); while in the D-penicillamine study, the mean duration of disease was 10 months (3). The former was a randomised, double-blind placebo-controlled trial of methotrexate titrated up to 15 mg/week for 12 months, in which 71 patients were recruited, although only 54 completed. The primary analysis was modified Rodnan skin score and did not show a statistically significant difference in the methotrexate treated group compared to placebo at 12 months, an improvement was recorded at 3 months but not sustained. A number of observations in regard to this study may be important: there was a small study cohort (n=71, 35 *vs*. 36 in each group); the number of completers was very low (n=54), although this may be a consequence of any placebo-controlled trial; the study period may have been too short. However, certain secondary analyses including physician global assessment, and change for both modified Rodnan skin score and the UCLA skin score were significantly improved. In a previous smaller (n=29) randomised placebo-controlled study of methotrexate in SSc patients (4) with a mean disease duration of 3 years, van den Hoogen and colleagues reported a benefit based on the number of responders (defined as a composite score: an improvement of total skin score (TSS) by > 30%, of single breath diffusion capacity (DLco) by >15%, or of the score on a visual analogue scale of general well-being (VAS) by >30%, provided that such improvements were not accompanied by persistent digital ulcerations or worsening of DLco >15%) in the active treatment group compared to the placebo treated group. This small study was controlled for 24 weeks but extended in an open fashion for 48 weeks, over which time improvements in secondary analyses such as grip strength were also observed. The D-penicillamine study was a 2 year comparative trial of low-dose versus high-dose drug, which recruited 134 patients with short disease duration as above, and a moderately severe mean skin score at baseline of 20. There was no significant difference in skin scores (the primary measure of outcome) between the two groups, however again a very low completion rate occurred, in this case only 68 patients or 50% completed the 2 year study. The desire to study new therapies in early disease has been adopted from the RA clinical trials arena, in which it is now widely accepted that studies of early disease may prove more effective as less damage has occurred. This may not be directly translated into SSc clinical trial design, as skin score has been noted to improve in many patients without any drug intervention, leading to the idea that scleroderma may soften as part of the natural history of the disease. Therefore, studying 'early' patients may in fact confound studies in which the primary outcome is skin score. Other data derived from the experiences of the SCTC suggest a confounding component of regression towards the mean. Patients enrolled in trials who are mild tend to worsen whereas those who are more severe tend to improve with time with possibly no relation to therapy assignment.

A targeted therapeutic approach has also been employed in SSc clinical trials (8, 9) recently in which investigators have focussed on molecular candidates identified through basic scientific research. The relaxin study examined the effect of this naturally occurring protein, related to insulin-like growth factor (IGF-1), which has anti-fibrotic properties by virtue of an effect of down regulation of collagen production and an increase in collagen degradation, in 231 SSc patients. Phase I and II studies suggested a possible therapeutic effect on skin disease and functional disability. The Phase III randomised double-blind, placebo-controlled clinical trial was undertaken in patients with disease duration of ≤5 years failed to show any improvement in the primary end point (skin score) or the secondary analyses (pulmonary function or HAQ-DI), over placebo. In addition, the trial highlighted an increased adverse event profile in respect of hypertension and renal function in patients in whom relaxin infusions were abruptly interrupted or discontinued. In an international, multicentre placebo-controlled early phase I study a recombinant human antibody CAT-192, that neutralises TGFβ1, was evaluated in the treatment of early-stage diffuse cutaneous systemic sclerosis. The primary objective was to study safety and tolerability along with pharmacokinetics, however, secondary analyses included modified Rodnan skin score, Scleroderma (S) HAQ and a number of novel biomarkers such as serum amino-terminal propeptides of type III collagen (PIIINP) and of type I collagen (PINP), which were measured by commercial radioimmunoassay (Behringwerke, Marburg, Germany, and Orion Diagnostica, Helsinki, Finland, respectively). Forty-five patients were enrolled. There were more adverse events and serious adverse events, including deaths in the group receiving active drug and the mRSS improved in both the placebo and the active treatment groups, however, no treatment effect was seen

with CAT-192. It should be noted that this trial was designed to capture very active and early patients – anticipating worsening and thus heightening ability to recognise therapeutic signal, so these patients had severe and progressive disease as evidenced by high SHAQ and internal organ involvement, which may have created a selection bias for poor outcome. Interestingly, the PINP serum biomarker of type I collagen turnover did correlate with skin scores providing some validation to it as a biomarker of skin disease. Interestingly, the monoclonal antibody CAT-192 was shown in a post hoc analysis to have almost no biologic activity and in fact not even binding to TGFβ1 – hence the therapeutic concept, in effect, has not yet been tested.

More recent studies have aimed at therapeutic intervention in a specific disease manifestation, in particular interstitial lung disease and pulmonary arterial hypertension (PAH). The latter is beyond the scope of this review as there is a substantial literature in this area alone. There are, however, three studies which have focussed on the objective of preventing progression or reversal of interstitial lung disease associated with SSc (6, 7, 14). Two of these studies essentially examined the effect of cylcophosphamide, either by oral or intravenous administration in ILD-SSc, using different methodological approaches and outcomes The oral Scleroderma Lung Study showed some modest but significant effect on lung function and skin score, while the study of intravenous cyclophosphamide showed a trend toward a difference between the active treatment group and placebo. The most recent randomised, prospective, placebo-controlled trial examined the effect of bosentan in ILD secondary to SSc, based on the rationale that endothelin has many biologic properties relevant to the pathogenesis of SSc, and may also play an important role in the pathogenesis of ILD. This was a prospective, double-blind, randomised, placebo-controlled, parallel group study for 12 months: the active treatment group receiving 62.5 mg bid escalating to 125mg bid after 4 weeks. The design aimed to recruit patients with ILD, but without significant PAH, a complicated inclusion criteria algorithm was employed – a diffusing capacity for carbon monoxide (DL_{CO}) <80% predicted; 6-minute walk distance (6MWD) of between 150 and 500 m or ≥500 m with decrease in oxygen saturation (SpO_2) of ≥4%; SSc <3 years duration with dyspnea on exertion or SSc ≥3 years with signs of active ILD, i.e. two out of 4 of the following in the previous 12 months: 1) worsening dyspnea, 2) worsening pulmonary function tests (PFTs; worsening FVC ≥7% and/or worsening DL_{CO} ≥10%), 3) new ground glass or reticular abnormalities on HRCT scan in at least 5% of overall lung parenchyma (or 15% of a lobe) and extending to the level of the pulmonary venous confluence or higher, or 4) neutrophilia and/or eosinophilia on bronchoalveolar lavage (neutrophil differential count ≥5%; eosinophil differential count ≥4%) in the absence of infection. The primary analysis was change in 6-minute walk distance (6MWD) followed by a variety of secondary endpoints including time to death (all causes) or worsening PFTs, decrease from baseline ≥10% FVC; ≥15% DL_{CO} with ≥6% decrease in FVC. In conclusion, this study failed to show any significant changes in either the primary or the various secondary endpoints in this group of patients.

Clinical trials in SSc pose significant problems for investigators. Since SSc is a rare 'orphan' disease, recruitment of subjects to clinical trials will always present a challenge. This challenge is further increased because heterogeneous clinical and serological features create a diverse mixture of disease subgroups, frequently reflected in the clinical trials above as many small or multiple subgroups. Furthermore, as discussed the natural history of patients – even those with similar patterns of symptoms and signs – may lead to different natural outcomes. It is clear from many of the clinical trials to date that inclusion of placebo control, while desirable from a study design perspective, causes serious problems in terms of completer numbers which are often 50% or lower, creating problems for data analysis and interpretation. Many investigators embarking on clinical trial design attempt to reduce the effect of these issues by better defining the patient population according to 'early' disease, specific molecular targets or a combination of molecular drug target in well-defined patient populations. This approach, however, as evidenced above is not always successful. This may result from a mismatch of molecular target and its role in disease pathogenesis, or the lack of sensitive outcome measures, which even when well-defined, validated and standardised may not differentiate small changes over long time points. Several investigators in the studies above have identified the slow progression of disease as an important issue making measurements of change in outcome difficult. This has often lead to the development of multiple endpoints or combination outcome measures; however studies employing such instruments have not been very successful. More recently, there has been a focus on the use of longitudinal observational studies, databases and registries; their use is increasingly recognised, and proposed, as an alternative to the randomised, controlled clinical trial, by the chairman of NICE in the 2008 Harveian Oration (11). It should be recognised that the assessment of drug effectiveness in such open database studies may be confounded if the cohort is too small, especially in rare diseases such as SSc. Indeed, a recent longitudinal observational study published by a UK group demonstrated this phenomenon very clearly (15).

What can we learn from the clinical trials in SSc so far?

In comparison to 20 years ago, we can now confidently say that clinical trials are possible in SSc patients, which is a significant advance. Negative clinical trials may result from a number of design faults – small numbers of patients, heterogeneous patient populations, those with poorly defined or indeed over-complicated inclusion criteria, studies in which the outcome measures are insensitive or may not match the expected clinical change. These may appear obvious however the reality is that many outcome measures are neither linear nor specific to disease activity, in contrast to disease severity or dam-

age. The worldwide SSc community and the SCTC, in particular, are faced with an unprecedented opportunity in a global research setting. We are now, for the first time, in a position to recruit well-defined patient populations from academic centres in over 30 countries on almost all continents. The clinical research networks in Europe, North/South America and Australia have improved significantly, and in parallel, communication has become more advanced and simplified. We have made significant strides in standardisation of classification and diagnosis in SSc, and further work is ongoing to facilitate this integration. This will allow the development of protocols for clinical trials in large numbers of homogenous patient populations (appropriately powered), defined by narrow clinical and/or serological features, disease duration or rate of progression. Positive trials are possible when endpoints are well defined – witness the cyclophosphamide studies of ILD, the multiple drugs for PAH and even the bosentan digital ulcer studies (RAPIDS-1 and RAPIDS-2). It should also allow targeted therapeutic interventions for specific disease manifestations, in highly selected patient populations more likely to provide positive results. Some may argue that these patients are not representative of real-life patients, but it is only by this approach, I believe we will improve our knowledge and expertise in treating specific manifestations of SSc, which is undoubtedly a complex and rare disease with multiple, diverse but interrelated pathogenic mechanisms.

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