ENRICHMENT STRATEGIES FOR CLINICAL TRIALS TARGETING SKIN FIBROSIS AND INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS

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ABSTRACT

Purpose of review: This review gives an update on enrichment strategies for clinical trials in patients with systemic sclerosis (SSc) in two contexts - skin fibrosis in early diffuse cutaneous disease, and SSc-related interstitial lung disease (ILD) - focusing on reports from the last 18 months. Lessons have been learnt from recent studies, making this review timely.

Recent findings: Recent trials have highlighted how patients included into trials must be carefully selected to include 'progressors' i.e. those most likely to benefit from treatment, and how drug mechanism action of action will influence trial design. For skin fibrosis, current enrichment strategies are mainly on clinical grounds (including disease duration, extent of skin thickening, tendon friction rubs and anti-RNA polymerase III positivity). Gene expression signatures may play a role in the future. For ILD, current enrichment strategies (degree of lung involvement as assessed by pulmonary function and HRCT) may help to recruit the most informative patients, but should avoid being too stringent to be feasible or for findings to be generalisable.

Summary: Both skin fibrosis and ILD trials are challenging in SSc. Ongoing work on enrichment strategies should help to differentiate effective new treatments from placebo with smaller sample sizes than have been included in recent studies.

KEY WORDS: Systemic sclerosis, skin fibrosis, interstitial lung disease, enrichment strategies, clinical trials

INTRODUCTION

The last 10 years have seen significant advances in the treatment of systemic sclerosis (SSc). Most recent clinical trials have focussed on early diffuse cutaneous SSc (dcSSc) and on SSc-related interstitial lung disease (ILD). Advances in treatment for early dcSSc include autologous haematopoietic stem cell transplantation (in highly selected patients)[1], and for ILD the licencing of nintedanib (and in the US of tocilizumab)[2-5], with a recent study showing that rituximab also confers benefit[6**]. Although progress is being made, skin involvement in patients with dcSSc[7*] and SSc-related ILD both continue to be areas of unmet clinical need. Early dcSSc carries a high mortality, and although this mortality is due to internal organ involvement rather than to skin disease, extensive skin disease is painful and disabling, with a major impact on quality of life[8]. ILD, when severe, is a frequent cause of SSc-related death[9,10].

Therefore better treatments are required for both the skin fibrosis of early dcSSc and for ILD. However, SSc is a rare disease and even rarer are its diffuse cutaneous subtype and progressive SSc-related ILD (approximately 30% of patients have clinically significant ILD)[11]. This rarity is one reason why clinical trials are difficult to mount. Another reason is the heterogeneity of the SSc disease process: some patients progress whereas other do not, and this applies to both early dcSSc and SSc-related ILD. In an era of personalised medicine, a key aim should be to ensure that treatments, many of which are potentially toxic, are reserved for those patients most likely to benefit i.e. 'progressors'. Therefore ideally, inclusion and exclusion criteria should ensure that trials focus on those patients most likely to benefit. This is achievable through enrichment strategies, which are being informed by our increased understanding of predictors of disease progression.

The aim of this review is to discuss these enrichment strategies, with a focus on new work over the last 18 months. Skin fibrosis in early dcSSc and ILD will discussed in turn. For each we shall discuss predictors of disease progression, what we have learnt from recent clinical trials, and what are likely to be the best enrichment strategies for future studies.

SKIN INVOLVEMENT IN EARLY DCSS

Background. In patients with dcSSc, skin disease commences distally in the fingers and feet, and then progresses (often rapidly) to involve proximal limb and/or trunk. The skin involvement generally 'peaks' within the first 3-5 years then softens: this natural history is a major contributor to the placebo response frequently observed in clinical trials. The extent of skin involvement is generally measured using the modified Rodnan skin score (mRSS), which measures skin involvement on a 0-3 scale at 17 sites (maximum score 51). The higher the skin score, the greater the mortality, and the greater the patient's pain (skin involvement is painful) and disability, especially hand disability[8]. Hence the need for treatments specifically of skin disease.

Predictors of disease progression. 'Skin progressors' in the context of early dcSSc, are often defined as patients with a 5-unit and 25% increase in mRSS over 12 months[12-14]. Well-recognised predictors of skin progression are reviewed elsewhere[7*] but in summary, patients most likely to progress are those with tendon friction rubs[15,16], anti-RNA polymerase III positivity[13], a low mRSS, short disease duration, synovitis[12] and (potentially) those with certain gene expression profiles (e.g. 'inflammatory') on skin biopsy.

Lessons from recent clinical trials. Because 'progressors' tend to have early disease with low skin scores, most recent clinical trials in early dcSSc have mandated that patients are only included with disease duration less than 5 years (sometimes less than 18 months) and with skin scores within designated boundaries (Table 1)[3,17-21]. Despite this approach, several recent studies have failed to meet their primary endpoint. This could of course be because the treatment was ineffective, but another explanation might be that certain subsets of patients did benefit, but that the studies were neither designed nor adequately powered to draw firm conclusions about these subsets, although sometimes inferences can be made from post hoc analyses, as discussed below. For example, in the randomised controlled trial (RCT) comparing abatacept to placebo (ASSET trial)[18], overall there was

no statistically significant treatment effect in terms of mRSS, but those patients with the inflammatory or normal-like expression profiles did respond.

Enrichment strategies. These must be feasible, recognising that if inclusion and exclusion criteria are too strict, very few patients will be recruited. When deciding upon inclusion and exclusion criteria a sensible approach might be to allow a degree of flexibility, but to factor in certain pre-specified subgroup analyses. It is generally agreed that at present, selecting patients with short disease duration and low skin scores will continue to be the main enrichment strategy, although there are different opinions as to upper cut-offs for disease duration and mRSS[14,22-23]. However, rather than setting a fixed upper limit for the mRSS (e.g. 22, although noting that many investigators consider this too strict a cut-off [Table 1]), a 'trade-off' between disease duration and mRSS could be allowed[13], increasing the numbers of patients eligible for recruitment. Using the example of an mRSS of 22, patients with higher skin scores have been shown to progress if their disease duration is less than 10 months and such patients could therefore justifiably be included into clinical trials[13]. In a recent analysis of the Pittsburgh cohort[24**], anti-RNA polymerase III positivity and the presence of friction rubs predicted progression over 5 years, and when the data from the ASSET trial[18] were stratified for the presence of both these predictors, each predictor mitigated the placebo response thus helping to differentiate between treatment groups. These findings support the prediction models derived from the European Scleroderma Observational Study, the second of which included anti-RNA polymerase III positivity[13].

Gene expression signatures in skin or blood samples may predict early dcSSc disease trajectory and treatment response, although results have been conflicting. As mentioned above, an inflammatory or normal-like expression profile (as opposed to a fibrotic profile) was associated with response to abatacept[18]. In the ASSET trial of abatacept [18], background immunosuppressive treatment was not permitted, and a stratification based on anti-RNA polymerase III positivity was not performed. Future studies are needed to determine whether skin gene expression profiling can provide

predictive information beyond stratification based on antibody profile in the setting of background immunosuppressive treatment. In the phase 2 trial of tocilizumab, expression of certain fibrotic and inflammatory genes from forearm skin biopsies was associated with progression in mRSS[25]. This contrasts with findings from the Prospective Registry for Early Systemic Sclerosis, which suggested that gene expression profiles did not predict future progression, although they were associated with prior progression[26]. This is an area of active research [27**]. Different approaches under investigation include weighted gene co-expression network analysis (WGCNA) and machine learning methods [28,29**]. In early-stage disease, differences between molecular pathways that are activated may underpin the contrasting natural history, clinical and candidate biomarker responses to new or current treatment approaches[30].

Other approaches to enrichment have also been proposed, with several developments/suggestions in the last 18 months relating to identification of candidate biomarkers for stratifying patients. These may depend on the drug being tested. For example, further analysis of data from the abatacept trial[31*] has shown that expression of the Costimulation of the CD28 Family Reactome Pathway was increased in patients in the 'inflammatory' subset and that expression decreased with abatacept, suggesting that high baseline expression might predict treatment response. A post-hoc analysis of the DesiReS trial[32*] comparing rituximab to placebo (noting that this was not a study specifically of early dcSSc[33]), concluded that high CD19-positive cell counts were associated with improvement in mRSS with rituximab. In those patients with high CD19-positive cell counts but mRSS < 17, serum surfactant level protein D was also associated with improvement in mRSS[32*]. A recent study reported that transcriptional signatures of monocytes (from peripheral blood)[34] associate with disease outcome, suggesting that these profiles might in the future also be helpful in stratifying patients for enrolment into clinical trials.

In conclusion, up until now cohort enrichment has been dependent upon clinical variables, mainly disease duration and mRSS, with recent studies informing appropriate 'boundaries' for these.

Including anti-RNA polymerase III improves accuracy in predicting progressors, but may prove too restrictive for most clinical trials. Pre-specified subgroup analysis for anti-RNA polymerase III and presence of tendon friction rubs is an attractive option, and consideration should be given to stratifying future skin trials by anti-RNA polymerase III positivity. Although progress is being made in elucidating the significance of gene expression profiling and different biomarkers, at present it remains unknown as to whether these will prove to be successful enrichment strategies.

SSc-RELATED ILD

Background. Clinical trials of SSc-related ILD are challenging. A recent post hoc analysis of 826 patients with SSc-ILD from the European Scleroderma Trials and Research group (EUSTAR) database (these 826 were selected out of 2259 patients with ILD on the basis that serial lung function data were available)[35], most studied over a mean of 5 years, showed that 23-27% of patients experienced forced vital capacity (FVC) decline during any 12-month period, and that the pattern of FVC change/stability was often inconsistent between consecutive 12 month periods. A rapid decline in FVC was seen in only 8% of patients[35]. We need to be able to predict accurately those patients who progress, otherwise RCTs risk including patients who are not likely to deteriorate and who will therefore weaken the ability of the trial to detect differences between treatment groups.

Predictors of ILD and its progression. Features of SSc known to predict *development* of ILD include diffuse cutaneous subtype, greater age at onset, low FVC and diffusing capacity for carbon monoxide (DL_{CO}) and anti-topoisomerase antibody[36,37]. Anticentromere antibody confers protection[36,37]. *Progression* of ILD can be defined in different ways: one definition for significant progression is FVC decline $\geq$ 10%, or FVC decline 5 – 10% and DL_{CO} decline $\geq$ 15%[38,39**], and for moderate progression FVC decline of 5% to 10%. Predictors of *progression* are reviewed by Distler et al[38]: these include imaging features (specifically the extent of lung fibrosis on high-resolution computed tomography (HRCT)[40], anti-topoisomerase antibodies (particularly, it has been suggested, when detected by passive immunodiffusion against calf thymus extract[41]), pulmonary function tests (low

baseline FVC and/or DL_{CO}) different biomarkers including the pneumoprotein KL-6[42], and certain inflammatory markers. A model combining SpO_2 after a 6-minute walk test and the presence of arthritis[43] has also been proposed. Multivariable mixed-effect models from the EUSTAR cohort indicated that the strongest predictors of progression over 5 years were male sex, reflux/dysphagia symptoms and high baseline mRSS[35].

Lessons from recent clinical trials. The three major studies examining SSc-ILD in the last seven years have been Scleroderma Lung Study II (SLS II)[44], Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS)[2] and Study of the Efficacy and Safety of Tocilizumab in Participants with Systemic Sclerosis (focuSSced)[3]: although this last was not a study primarily of SSc-ILD, 136 of the 210 patients recruited (65%) had ILD at baseline. FVC was the primary outcome measure in SLS II and SENSCIS, and a secondary outcome in focuSSced. Using the FVC as an outcome measure needs to be taken in the context of an FVC decline over the first 12 month period of only -0.1% (SD 10.3%) in a cohort of 1092 patients with SSc-ILD from the EUSTAR database[39**], with a further decline of -1.3% (SD 10.1%) over a second 12 month period in 624 patients. Hoffmann-Vold et al. applied the enrichment criteria of all three RCTs to the EUSTAR ILD cohort[39**] and observed that only the strict enrichment strategy of the focuSSced trial was able to predict progression, and this was at the expense of feasibility: only 36/2259 (1.6%) patients fulfilled the focuSSced criteria (compared to 132/2259 (5.8%) the SLS II criteria, and 704/2259 (31.2%) the SENSCIS criteria), raising questions about generalisability of the results. Of note, 1529/2259 (67.7%) of patients did not fulfil the enrichment criteria of any of the three RCTs under consideration. No single enrichment criterion predicted progressive ILD, but those patients with an FVC < 70% at baseline were less likely to progress than those with a higher FVC[39**]. This finding (progression in those with higher FVC) is consistent with an analysis of data from the SENSCIS study[45*] which suggested that in the placebo group, patients with greater degrees of ILD on HRCT (and higher FVC% predicted) experienced greater declines in FVC% predicted. However, these relationships were not seen in the nintedanib group, suggesting that benefit from nintedanib occurred irrespective of the degree of lung disease on

HRCT[45*]. One possible lesson from these findings from SLSII, SENSCIS and focuSSced is that at present (pending development of more effective enrichment strategies) the advantages of inclusivity (i.e. less strict inclusion and exclusion criteria) may more than offset the disadvantages.

Enrichment strategies. As discussed above, current enrichment strategies have proved unsatisfactory. Therefore we need to identify others. Gene expression and other studies in lung tissue from patients with SSc-ILD are helping to unravel molecular and cellular biology underpinning the disease process[46,47] but it is not currently known whether any of the profiles or regulators identified will improve prediction. This is an area of active research.

It is worth highlighting that recent successful clinical trials that have led to regulatory approval in different regions of nintedanib, tocilizumab and rituximab have each targeted quite different study populations. This is a challenge in defining prognostic or predictive markers. Recent studies have attempted to integrate lessons from a clinical trial and a real-world cohort[48*], and reinforce the relevance of general characteristics as well as autoantibody and other markers such as elevated acute phase markers. However, it seems that differences in pathogenic mechanisms that overlap make it difficult to extrapolate across the stages and subgroups of SSc-ILD. It does, however, seem that immunomodulatory therapies are most likely to impact in the earlier phase of disease whereas antifibrotic agents are more impactful in later or more extensive SSc-ILD where pathogenic mechanisms are more like idiopathic pulmonary fibrosis[49]. Thus, as well as enrichment it is critical to have balance across treatment arms in prospective parallel group trials and to link the target population to putative mechanism of action of a new therapy. Adaptive trial designs that will generate comparative data across treatments and potentially allow combination of placebo arms to generate future comparator cohorts offer a way of overcoming the increasing challenge of having multiple competing trials in a rare and heterogeneous disease [see e.g. CONQUEST https://srfcure.org/research/conquest].

OVERALL CONCLUSIONS

There are major challenges for trials in both early dcSSc skin disease and SSc-ILD as discussed, but robust and valid measurement of disease severity in skin and lung are available and improved trial design with enriched cohorts should improve performance of current and emerging endpoints[50]. Cohort enrichment may increase the group level response in trials to differentiate active drug from placebo with a smaller sample size. However, whilst this is critical to success it also has potential limitations. Firstly, it will limit generalisability of the findings if a trial only includes a subgroup of the disease population. Secondly, it may result in a trial that is slower to recruit due to stringent eligibility criteria and so take longer than a more open trial. Thirdly, if assumptions are incorrect about responsiveness than there is a high risk of type 2 error. Recommendations for future clinical trials will vary depending upon the mechanism of action of the drug in question, and continued development of potential new enrichment strategies.

KEY POINTS

Clinical trials in patients with early dcSSc-related skin fibrosis and with SSc-ILD are challenging, yet both conditions are areas of unmet clinical need.

Effective enrichment strategies to identify 'progressors' would ensure that future clinical trials focus on patients most likely to benefit, at the same time taking feasibility, and also generalisability of results, into account.

Study design (including selection criteria) needs to consider drug mechanism of action.

For skin fibrosis, current enrichment strategies are mainly clinical and include disease duration, extent of skin thickening, tendon friction rubs and anti-RNA polymerase III positivity: gene expression signatures may play a role in the future.

For ILD, current enrichment strategies (degree of lung involvement as assessed by pulmonary function and HRCT) have proven unsatisfactory: other strategies are being researched.

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CONFLICTS OF INTEREST

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This study provided further support of the concept that in the future, it may be possible to select patients for inclusion into clinical trials on the basis of laboratory variables (in this case high peripheral blood B cell counts) implicated in the mechanism of action of the drug under investigation.

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Table 1 – Recent examples of studies in which mRSS was an outcome measure (usually the primary outcome)

Study	Key inclusion criteria[a]		Primary end-point	Comment
	mRSS	Disease duration (months)		
Tocilizumab vs placebo phase II (FaSScinate)[17]	15-40	≤ 60	Change in mRSS at 24 weeks (not met)	No significant improvement in mRSS on tocilizumab. although trend in favour, and less decline in FVC
Tocilizumab vs placebo phase III (FocuSSed)[3]	10-35	≤ 60	Change in mRSS at 48 weeks (not met)	No significant improvement in mRSS on tocilizumab. Changes in FVC (significant) in favour of tocilizumab.
Abatacept vs placebo[18]	≥10 ≤ 35 or ≥15 ≤ 45	≤ 18 >18 ≤ 36	Change in mRSS at 12 months (not met)	No significant improvement in mRSS on abatacept (although there was for the inflammatory and normal-like gene expression subsets), but significant improvement in HAQ-DI and ACR CRISS on abatacept.
Riociguat vs placebo[19]	10-22	≤18	Change in mRSS at 52 weeks (not met)	No significant improvement in mRSS on riociguat
Romilkimab vs placebo[20]	10-35	<36	Change in mRSS at 24 weeks (met)	mRSS improved more on romilkimab

				than on placebo
Lenabasum vs placebo[21]	Proximal or truncal involvement or ≥16 (or ≥12 with increase ≥ 5 in previous 6 months)	≤ 36 >36 ≤72	No single primary efficacy outcome, but outcomes included change in mRSS	No significant improvement in mRSS on lenabasum, but trend in favour. Other measures significantly improved including SSPRO and itch score

a. For full details, see full publications

ACR CRISS: American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis

FVC: Forced vital capacity

SSPRO: Scleroderma Skin Patient Reported Outcome