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Systemic Sclerosis Trial Design Moving Forward

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Abstract

The 2013 ACR–EULAR classification criteria for systemic sclerosis (SSc) have shifted the construct of SSc. The new reality is that patients recruited for trials may not be so severe and not so advanced. We can now look for therapeutics that might stop disease evolution and/or prevent organ involvement. This article highlights recent advances in research methodology, and broadens the potential range of design and analytic considerations when planning a SSc trial.

Keywords

Systemic sclerosis; scleroderma; randomized controlled trials; Bayesian; cross-over trial; enriched enrolment randomized withdrawal design; randomized placebo phase design

Our understanding of the vascular, immunologic and fibrotic domains in the pathogenesis of systemic sclerosis (SSc) is increasing in depth and scope. Clinical trials and observational studies in SSc are broadening to the vascular and immunologic domains, but continue to

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primarily study the fibrotic mechanism and manifestations of the disease. The 2013 American College of Rheumatology–European League Against Rheumatism classification criteria for SSc(1) have shifted the construct of SSc, and provides a new opportunity to look at different stages of disease evolution. These criteria allow classification of more patients with early manifestations and patients with limited skin involvement, thus allowing their inclusion into research studies.(1) Similarly, the Very Early Diagnosis of Systemic Sclerosis criteria facilitate the identification and diagnosis of patients with very early signs; some of whom have not yet been classified as SSc.(2) The new reality is that patients recruited for trials may not be so severe and not so advanced.

Therefore, we can now look for therapeutics that might stop disease evolution/progression and/or prevent internal organ involvement. Indeed, a recent position paper from the World Scleroderma Foundation outlined research priorities for future SSc clinical trials.(3) The SSc paradigm of treatment could include: reversal, stabilization, slowing down disease, prevention of new organ involvement and cure.(3) Clinically meaningful outcomes are preferred, including outcomes that matter to patients: fatigue, pain, quality of life, appearance, and hand function.(3) Yet, we still must address many research challenges.(4, 5) In fact, SSc remains a rare disease with limited numbers of patients for study recruitment. Unconscious bias and chance can still threaten the validity of estimates of treatment effect. Recent advances in research methodology can rise to some of these challenges and these novel strategies have been successfully applied in other areas of rheumatology.(4, 6–9) Moving forward, SSc investigators could consider these methodologic advances when designing SSc trials.

At the time that study hypotheses, patient populations and outcomes are considered, the study design and accompanying analysis, too, needs to be planned.(5) This short introduction is aimed at broadening the potential range of design and analytic considerations when planning a SSc trial.(4) Because some of these are designs which are not fully proven in SSc, they may best be initiated during Phase 2 or 4 of therapy development.

Sampling frame

This means rethinking the kinds of patients we include and exclude from trial participation. Past clinical trials for skin fibrosis have preferentially selected patients with current diffuse involvement. This was done as the disease is active in the early phase, and intervention may be effective in a shorter time period. The reality, however, is that patients affected by the limited subset have been completely excluded from clinical trials despite the fact that the majority of SSc patients have limited disease. A smaller proportion of new patients will have primarily fibrotic manifestations and more will succumb to complications of vasculopathic manifestations, gastrointestinal and/or lung involvement. Without ignoring diffuse disease, the classification of patients with earlier disease may require de-emphasizing the traditional concept of reversing fibrosis as the primary outcome and, instead, emphasize prevention of progression or emphasize other aspects like remission in SSc. Furthermore, sampling will still need to consider disease duration, prior disease course, disease acuity, prior internal organ involvement and differentiating early disease from longer duration disease. Increased rigor and attention to these factors may be needed. Innovative, yet untested, strategies to

consider may include biomarker based patient selection.(10) Cohort enrichment strategies may be implemented to select patients who are most likely to respond to therapy.(11)

Outcome measures

A recent consensus report on ‘Points to Consider in Systemic Sclerosis Clinical Trials’ provides guidance on choice of outcome measures for clinical trials. Ideally, an outcome measure should be feasible, have demonstrable validity, reliability, and be responsive to change. Evaluation of the psychometric properties for some outcome measures in SSc trials have been evaluated.(12, 13) In addition, composite indices may provide more discriminatory power to separate an active agent from placebo and such efforts are underway in SSc.(12, 14) Likewise patient response outcomes will be required, and consideration should be given to including patient relevant outcomes in core sets.(14)

Study design: challenges

Fully statistically powered, randomized, controlled, double-blind trials (RCT), accounting for all appropriate confounders, are the acknowledged gold standard.(5) However there are problems when trying to use the traditional RCT for generating evidence in SSc. In rare diseases, a significant challenge relates to difficulties in accruing sufficient numbers of patients into clinical trials. The inability to recruit sufficient numbers of patients into clinical trials affects the ability to detect statistically significant, small-to-moderate treatment effects; and the ability to account for factors that may distort the estimated treatment effect. Current successful strategies, such as larger number of centers, and international collaborations, have overcome this issue. However, these strategies may be costly and require political will.

Study design: potential solutions

One solution is allowing standardized background medications and adding test medication or placebo, that is, use of an **active comparator**.(15) Physicians are more likely to encourage their patients to enroll into active-controlled trials.(16) This is often acceptable but requires additive effects with the background medication(s) (at least) and increased numbers of subjects because the effect size of treatment is decreased relative to the standard placebo-controlled trial. An example of an active comparator is the mycophenolate versus cyclophosphamide trial in SSc lung disease (ClinicalTrials.gov NCT00883129).

Patients may be more willing to participate in trials if they are offered **post-trial provision of beneficial treatment** (open label extension) when the trial is done compared to a previously proven treatment and the proven treatment is the offered post trial. This strategy is implemented in the clinical trial of tocilizumab compared to placebo in diffuse SSc for a year, followed by 1-year of open label therapy (ClinicalTrials.gov NCT01532869). When the treatment is offered at the end of the trial, patients may feel rewarded and recruitment will be enhanced.(15)

Cross-over trials compare two or more treatments by allocating each participant to all compared treatments in a randomly selected sequence. Since patients act as their own control, between patient variability is removed, increasing the precision of the estimated

treatment effect and reducing the needed sample size. Cross-over trials have been widely used in pediatrics, oncology, pharmacology and psychiatry.(17) The carry-over effects from the first treatment may confound the trial and must be guarded against which generally requires between crossover washout periods. Appropriate outcomes must be selected where short-term changes are expected.

The **enriched enrolment randomized withdrawal design** enrolls study participants into an open label trial where all patients receive treatment (enrichment phase).(15) Once the responders are identified, they are enrolled into the randomized withdrawal phase where they are randomly allocated to continue receiving treatment or switch to control. The trial endpoints are the return of symptoms or the ability to continue receiving the treatment.(18) Subjects who have their therapy withdrawn can re-start treatment when they have flared. Thus, the time on placebo is limited. This study design was successfully used in the evaluation of etanercept in juvenile rheumatoid arthritis.(6) This design is hampered by the lack of validated endpoints of 'flare' in SSc, which are thus far not available.

The **randomized placebo phase design** (RPPD) is another design that reduces the time on control (often placebo) medication.(4) Patients in the RPPD are randomly allocated to either treatment or control. After a short, fixed time period (placebo phase) patients in the control group are blindly switched to the treatment. The design is based on the assumption that if the treatment is effective, patients who receive it sooner will respond, on average, sooner. At the end of the trial, average response times of the groups are compared, most often using time-to-event analysis.(19, 20) This design has been successfully used in the evaluation of rituximab in inflammatory myositis.(8)

Applied Bayesian methods are a solution that facilitates *maximizing information* from studies. Bayesian inference has 3 components: the prior, the likelihood and the posterior distributions. The prior is the probability of hypothesized treatment effects, based on information independent of the study (i.e. previous evidence). The likelihood summarizes the data from a new study. The posterior is the end result: the probability of hypothesized treatment effect based on data from the new study and prior evidence.(21) It is calculated using Bayes Theorem, which states that the posterior is directly proportional to the product of the likelihood and the prior. These are frequently illustrated using a Bayesian triplot. (Figure 1.)

The Bayesian approach confers a number of pragmatic advantages. First, applied Bayesian methods allow for the explicit incorporation of pre-existing knowledge/data into the estimation of treatment effect.(22) Previously published evidence and expert knowledge are usually ignored in the interpretation of a new trial. Bayesian inference quantitatively incorporates this external information when deriving the probability of a therapeutic benefit. (21) Using this approach, warfarin was demonstrated to have a low probability of improving survival in SSc-associated pulmonary arterial hypertension(23), and confirmed in a recent multicenter cohort study.(24) The ability to include external information improved the precision of the estimated treatment effect. The incorporation of experts' beliefs about the treatment effect of an intervention may be incorporated in the analysis (statistical models) through applications such as www.UntappedKnowledge.org. This approach is currently

being used to evaluate the effect of lung transplantation in SSc (Canadian Institutes of Health (CIHR) grant 301574).

Second, investigators can directly estimate of the probability of there being a meaningful treatment effect of a particular magnitude. This is true, irrespective of the sample size. More data will yield a more precise estimate of treatment. For example, in the cohort study evaluating the effect of warfarin in SSc-PAH, the probability of warfarin improving survival by 6 months or more was only 23.5%. Figure 2. A second example is the randomized controlled trial of methotrexate in SSc. Despite the trial's inability to recruit patients to the trial's targeted sample size, using this approach, methotrexate was demonstrated to have a high probability of a beneficial effect on skin score.(25)

Third, Bayesian meta-analysis of *multiple n-of-1 studies* can use small number of patients to generate estimates of the population effect and the likelihood of treatment benefit. Multiple n-of-1 studies are randomized clinical trials, with multiple crossovers, in single subjects.(26) By combining subjects who have had n-of-1 studies, it is possible to estimate the treatment effect in the population.(27) This approach has been used to evaluate the efficacy of amitriptyline for pain in juvenile idiopathic arthritis.(9) Using small numbers of patients (n=6), the investigators demonstrated a low probability of a beneficial treatment effect. This data was valuable to preventing the initiation of a large, potentially expensive, futile trial.

Conclusions

The paradigm for SSc research is shifting. Improved insight into the pathogenesis and manifestation of SSc, classification of patients at an earlier point in their disease, changing focus of the primary target of therapy, measuring the appropriate outcome, choice of the appropriate study design and analytic strategies, are all critical points to consider. Researchers will need to choose wisely and this article is meant to introduce the reader to a broader range of study designs than usually considered.

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Figure 1.

Bayesian triplot. The Bayesian triplot illustrates the prior probability distribution (pre-existing information, in green), the likelihood (new data, in red) and the posterior probability distribution (revised estimate based on pre-existing information and new data, in blue). Hazard ratio >1 indicates increased mortality, hazard ratio <1 indicates decreased mortality. Reprinted with permission from The Journal of Rheumatology. JOHNSON, S.R. et al. *J Rheumatol* 2012;39(2). All rights reserved

Figure 2.

Density plot for difference in median survival times in patients with systemic sclerosis-associated pulmonary arterial hypertension untreated and treated with warfarin, using an informative group prior. Differences in median survival > 0 indicate improved survival associated with warfarin exposure. Differences in median survival < 0 indicate worsened survival associated with warfarin exposure. Y-axis indicates relative probability.

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