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Authors
Khanna, Dinesh
Seibold, James
Goldin, Jonathan
et al.

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Interstitial lung disease points to consider for clinical trials in systemic sclerosis

Dinesh Khanna[1], James Seibold[2], Jonathan Goldin[3], Donald P. Tashkin[4], Daniel E. Furst[5] and Athol Wells[6]

Abstract

Interstitial lung disease causes major morbidity and mortality in patients with systemic sclerosis (SSc-ILD). Large randomized clinical trials in SSc-ILD have provided important information regarding the feasibility, reliability and validity of outcome measures. Forced vital capacity percentage predicted should be considered as a primary outcome measure, with inclusion of appropriate radiological and patient-reported measures. We provide practical recommendations for trial design in SSc-ILD.

Key words: scleroderma, lung disease, interstitial lung disease clinical trials

Rheumatology key messages

- Interstitial lung disease is a major cause of morbidity and mortality in SSc patients.
- The OMERACT Working Group recently endorsed domains and a clinically meaningful progression definition for SSc-interstitial lung disease trials.

Introduction

Pulmonary disease is the major cause of morbidity and mortality in patients with SSc [1]. Lung involvement in SSc is typically separated into two distinct entities: pulmonary arterial hypertension and interstitial lung disease (ILD), although many patients may have elements of both.

Large randomized clinical trials in SSc-ILD have provided important information regarding the feasibility, reliability and validity of outcome measures [2–4]. In addition, recent review articles have discussed the pathogenesis and future trial design in SSc-ILD, and readers can consult these articles for detailed information [5–7]. We provide a brief overview in this review.

[1]Department of Medicine, University of Michigan Scleroderma Program, University of Michigan, Ann Arbor, MI, [2]Scleroderma Consultants LLC, Litchfield, CT, [3]Department of Radiological Science, [4]Department of Medicine-Pulmonology, [5]Department of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, USA and [6]Department of Medicine, Royal Brompton Hospital, Faculty of Medicine, London, UK

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Correspondence to: Dinesh Khanna, University of Michigan Scleroderma Program, Division of Rheumatology, Department of Internal Medicine, Suite 7C27, 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109, USA.
E-mail: khannad@med.umich.edu

Background

A key consideration in trial design is that in order to have true clinical significance, end points need to be relevant to the two outcomes that matter to patients: improved survival and improvement in symptoms (dyspnoea or quality of life). The precept that underpins many oncological treatment trials [8, 9], that these two goals are equally valid, applies equally to clinical trials in SSc-ILD. In principle, the primary end point should capture one of these two goals directly.

However, there are cogent arguments against this ideal scenario. Mortality is an impracticable primary end point in SSc-ILD because the disease has insidious decline in pulmonary physiology over a period of 1 year [5]. Dyspnoea and quality of life scales are, in isolation, unsatisfactory as primary end points because they are influenced equally by palliative therapies and, potentially, by radical interventions that slow disease progression. In patients with severe dyspnoea and/or major impairment of quality of life [10], morphine and CS therapy may reduce dyspnoea and improve quality of life without influencing disease progression. Furthermore, if a wide range in disease severity is represented in a therapeutic trial, the realistic symptomatic goals vary greatly with disease severity. In mild to moderate disease, dyspnoea and impairment in quality of life may be minimal, and an improvement with treatment is not feasible. Thus, the use of patient-centred outcomes as primary end points, although desirable in

REVIEW

trials of palliative agents, is difficult to justify in studies of radical interventions.

The necessary compromise, applying equally to malignant disorders and progressive chronic non-malignant diseases such as SSc-ILD, is to select a primary end point that captures chronic disease progression and has demonstrable linkage to patient-centred outcomes. The validation of such an end point requires the separate evaluation of both properties (as well as the satisfaction of the general validation of end points, including ease and accuracy of measurement, reproducibility and the other generally accepted measures of end point validity).

Regarding the first goal, it can be argued that, in principle, changes in a proposed end point should have been shown to predict longer-term mortality consistently in clinical series (validating the use of that end point as a measure of chronic disease progression). As information of this nature is not available in SSc-ILD, it is necessary to turn to studies of idiopathic pulmonary fibrosis (IPF), the chronic progressive pulmonary fibrotic disorder that has been most widely studied. In IPF, the forced vital capacity (FVC) is the only current serial measure that both satisfies this criterion and stands up to scrutiny as an end point on general validity grounds [11]. However, although the adaptation of IPF data to SSc-ILD is a necessary extrapolation at present, it must be stressed that SSc-ILD is a more slowly progressive disease. Even in IPF, change in FVC has proved to be a somewhat insensitive primary end point. Therefore, the group highlights the need for studies in which FVC change is integrated with morphological change on serial high-resolution CT (HRCT), in order to improve end point sensitivity, while recognizing that a composite FVC/HRCT end point has not been established.

Regarding the second goal, serial FVC trends, in common with all other shorter-term outcome measures, cannot be viewed as a surrogate for mortality at present. The definition of a surrogate for mortality requires that changes in an end point with therapy must be shown to lead to changes in survival, even if trends in that end point are strongly and consistently linked to longer-term mortality in non-interventional clinical series [12, 13]. A therapeutic intervention may have clearly beneficial effects on such an end point but may increase mortality through unexpected adverse effects, as seen with an anti-arrhythmic therapy that suppresses ventricular tachycardia (a highly malignant prognostic determinant), but increases mortality by reducing ventricular function. Other examples of improvement of a surrogate with treatment, but increased mortality, are well recognized [14]. Furthermore, a shorter-term intervention with beneficial effects on measures such as FVC may, in the longer term, drive pathogenetic pathways towards a more progressive phenotype. At most it can be argued that if there is strong linkage to mortality in clinical series, as seen with FVC trends in IPF, the variable in question is probably a surrogate for mortality, and therefore linkage of this sort is desirable. However, even this conclusion can be questioned in the absence of open treatment data following a controlled treatment trial.

Progression-free survival has been advocated as a surrogate for mortality, but even in studies of advanced malignancy, in which there is arguably the greatest chance of demonstrating mortality linkage, progression-free survival has been disappointing in this regard [8, 9]. In shorter-term treatment trials of mild to moderate SSc-ILD (with severity thresholds used to exclude patients), a progression-free FVC/mortality end point will be dominated by FVC. Moreover, it appears counter-intuitive that mortality in such a study, which can be viewed as unexpected mortality, can possibly be viewed as a surrogate for the expected longer-term mortality that occurs as a logical consequence of long-term disease progression. Thus, at present, linkage between serial FVC trends and mortality in SSc-ILD are not sufficiently robust, either in principle or based on current data, to satisfy the precept that the primary end point should be linked to patient-centred outcomes.

However, if survival linkage is not practicable at present, a very different picture emerges when dyspnoea and quality of life are considered. In IPF, cohort change in FVC with treatment has been shown to be correlated with cohort change in dyspnoea [15]. Similar cohort relationships were seen in the placebo-controlled trial of oral CYC in SSc-ILD [2]. In the placebo-controlled trial of oral CYC, a treatment effect on FVC was mirrored by improvements in health-related quality of life, dyspnoea and skin softening. It should be stressed that these observations are not synonymous with establishing that the prevention of FVC decline is directly relevant to the level of dyspnoea or quality of life in individual patients in an interventional study. The ideal primary end point should establish that treatment effects on FVC have individual linkage to patient-centric end points; the average cohort effects are insufficient but do at least establish that this is a practicable end point goal.

Based on these considerations, we believe that it remains appropriate to continue to base the choice of primary end point on the measurement of chronic disease progression at present, as defined by FVC change (see below). However, we strongly recommend that future research should be focused on refinement of the measurement of disease progression by integrating FVC change with a morphological measure of disease progression (such as serial HRCT) and exploration of strategies to integrate best measures of disease progression with changes in dyspnoea and quality of life in individual patients. The challenge in SSc-ILD is exactly analogous to oncological interventional studies, in which change in tumour bulk is now the most widespread primary end point, but establishing the relevance of this outcome measure to survival and patient symptoms is an enduring challenge.

We consider evidenced-based recommendations for points to consider in conducting clinical trials to improve or stabilize SSc-ILD.

Outcome measures

The primary outcome measure is usually FVC% predicted, although other pulmonary measures meeting OMERACT criteria may be considered (Table 1).

Table 1 Items proposed in trial design for SSc-associated interstitial lung diseases[a]

Measure	Truth				Discrimination		Feasibility	Ready for use in clinical trials as primary/secondary outcome?
	Face validity	Content validity	Construct validity	Criterion validity	Reliability	Sensitive to change		
Pulmonary function test								
FVC, % predicted [5, 7, 16]	Y	Y	Y	Y	Y	Y	Y	P
Total lung capacity, % predicted [5, 7]	Y	Y	Y	Y	Y	Y	Y	S
DLCO, % predicted [5, 7, 16]	N	Y	Y	Y	Y	N	Y	S
High-resolution chest tomography [5, 7, 17, 16]	Y	Y	Y	Y	Y	Y	Y	S
Exercise oxygen desaturation [18]	Y	Y	NR	Y	NR	NR	Y	N
Dyspnoea indices							Y	
Mahler dyspnoea index [5, 7, 16, 19]	Y	Y	Y	NR	NR	Y	Y	S
VAS breathing [5, 20]	Y	Y	Y	NR	NR	NR	Y	S
6MWT [5, 7, 16, 21]	Y	Y	Y	NR	Y	N	Y	N

[a]This does not include all domains/items proposed during a recent consensus meeting [22] because some do not meet the OMERACT filter. Generic health-related of life should also be assessed in addition to dyspnoea. DLCO: diffusing capacity of carbon monoxide; FVC: forced vital capacity; 6MWT: 6-min walk test; N: not ready; NR: not reported; P: Primary; S: secondary; VAS: visual analog scale.

The following should be considered for secondary outcome measures: total lung capacity percentage predicted, diffusing capacity of carbon monoxide percentage predicted (DLCO% predicted), thoracic HRCT extent (in either the whole lung or zone of maximal involvement) of global ILD [23] (fibrosis, ground glass opacity and honeycombing) [17] or the extent of fibrosis or ground-glass appearance separately, and dyspnoea indices (Table 1). In certain trials, quality-of-life measures can also be included as secondary outcomes.

Exploratory outcome measures

Consideration should be given to analysis for clinically meaningful progression defined as the time to first occurrence and proportion of subjects achieving either $\geqslant$10% sustained relative decline in FVC% predicted, $\geqslant$5 to $<$10% decline in relative FVC predicted and 15% sustained relative decline in DLCO% predicted or all-cause mortality [16, 24].

Composite end point

Although a change of $\geqslant$10% FVC% predicted is clinically meaningful, exploratory analyses can be considered, such as the following: lesser relative changes in FVC; marginal sustained reductions in FVC (5–10% as relative change); and composite measures, including FVC along with changes in dyspnoea, changes in skin score (as a surrogate of lung fibrosis) and changes in HRCT extent.

Study design and duration

The study should be double blind, randomized, placebo controlled or an active comparator trial (e.g. oral CYC or MMF). It may be difficult to conduct a placebo-controlled trial given the recent Scleroderma Lung Study-II (SLS-II) showing efficacy of oral CYC and MMF [25]. There are different trial designs that may be considered, as follows: first, placebo-controlled trials with allowance of standard-of-care treatment if the subject has a pre-defined decline in pulmonary physiology [16]; second, stable background immunosuppressive therapy for every subject; and finally, no background therapy or stable background immunosuppressive therapy and stratification during randomization to the background immunosuppressive therapy.

Study duration should be at least 1 year, although a longer trial (such as the recently completed SLS-II) may provide additional outcomes, such as morbidity and mortality. Trials of longer duration, with a focus on clinically meaningful morbidity and mortality, are difficult to perform in SSc-ILD because of the slowly progressive nature of the underling ILD, requirement for a large sample size and high attrition rate. Owing to variability in the conduct of PFT and HRCT, standardization of these measures should be considered and was successfully included in SLS-I and SLS-II.

Inclusion and exclusion criteria

Inclusion criteria

Apart from general inclusion and exclusion criteria as outlined in the overall points to consider [26], specific

inclusion and exclusion criteria are as follows: the 2013 ACR/EULAR classification of SSc with limited or dcSSc; relatively short disease duration (defined as first 7 years after onset of signs or symptoms attributable to SSc from first non-Raynaud's signs or symptoms); the presence of ILD should be based upon the detection of appropriate abnormalities on HRCT (subject to quality control [7]) and FVC <85% predicted. This trial design was used in the SLS-I and SLS-II and allowed more rapid recruitment. Occasionally, patients with >7 years of disease duration develop progressive ILD. This is rare, and it is not clear whether the pathophysiology in these patients is similar to those with earlier progressive disease. Aspiration attributable to progressive upper gastrointestinal dysmotility may be a cause for late progressive ILD.

Cohort enrichment

We strongly recommend selecting patients at greater risk of progression, based upon disease severity, observed progression or a short duration of systemic disease. Although cohort enrichment might be based on any single one of the criteria, it is recommended that patients attain a severity threshold based on HRCT {>20–25% maximal HRCT fibrosis score (the score in the zone with the highest score) or global lung involvement attributable to SSc-ILD [2, 27, 28]} and FVC% predicted (e.g. FVC ⩽70%) [23, 26], or both. For an anti-fibrotic drug, one can consider a minimal level of fibrosis on HRCT (based on computer-aided methodology), such as 5–10% [29]. Based on this, consideration should be given to recruitment of patients with FVC 45–70% (because they are likely to progress) or FVC 70–85% with HRCT involvement of ⩾20–25% maximal fibrosis score/lung involvement/computer-aided methodology.

In addition, one could consider observed progression (e.g. >10% relative decline of FVC over the past 3–12 months). Elevated CRP concentrations have been associated with progressive ILD, and observational cohorts suggest that baseline elevated CRP predicts long-term FVC decline [30]. Recent data from the positive phase 2 study of tocilizimab, an IL-6 inhibitor, in early diffuse SSc showed a favourable effect on FVC% [30], supporting elevated CRP as a biological marker for cohort enrichment.

The parameters identified above can also be used as stratification factors in a randomized controlled trial. For example, the trialist may consider stratification during randomization to the severity of HRCT involvement, FVC% predicted (e.g. ⩽70 *vs* >70%) and the use or absence of background immunosuppressive.

Exclusion criteria

Strongly consider excluding FVC <45% of predicted or DLCO (Hgb-corrected) <40% of predicted, because this suggests severe, probably irreparable disease. Patients with DLCO values of 30–39% in the absence of evidence of pulmonary hypertension probably should be excluded.

Consider using FEV1/FVC ratio <65% to exclude significant airflow obstruction. Additional exclusions to consider are as follows: clinically significant abnormalities on HRCT not attributable to SSc (e.g. lung mass, cavitary lesion, airspace consolidation, adenopathy); concomitant pulmonary hypertension requiring pulmonary arterial hypertension-specific therapy; and pulmonary hypertension.

When considering the definition of pulmonary hypertension, right heart catheterization (RHC) remains the gold standard. In the absence of RHC, pulmonary hypertension should be strongly suspected if transthoracic echocardiography showing a TR jet >2.8 m/s, right atrial (right atrial major dimension >53 mm) or right ventricular enlargement (mid-cavity right ventricular dimension >35 mm), irrespective of TR velocity, moderate to severe left ventricular dysfunction on transthoracic echocardiography, DLCO <60% predicted and BNP or NT-Pro BNP > 2 times the upper limit of normal [31]. RHC should be strongly considered in any of these circumstances, and if RHC does not show pulmonary hypertension, then the patient should remain eligible for the study. Smoking of cigars, pipes or cigarettes during the past 6 months should usually exclude a patient. Other serious concomitant medical illness (e.g. cancer) or chronic debilitating illness (other than SSc) that might compromise the patient's participation in the trial should also usually exclude a patient.

Statistical analysis

Descriptive statistics should be provided. With respect to sample size calculation, a great deal depends upon whether there is a significant group of patients with reversible disease but with more extensive disease on HRCT. By and large, such patients tend to be under-represented in placebo-controlled studies (as open therapy is preferred); the SLS-I study provides useful information on statistical powering if a placebo-controlled study is planned. A trial consisting of a comparison between two active agents may increase the patient subset with reversible disease, resulting in a reduction in mean FVC decline and an increase in standard deviations of FVC change, making the use of FVC as a continuous variable impracticable and complicating power calculations. One possible solution is to evaluate the prevalence of decline to a pre-specified threshold (e.g. a relative or absolute change in FVC of 10%).

The usefulness of the rate of change in FVC as an end point to describe the effect of a drug may depend on assumptions of linear trends over time. Provisions should be incorporated to examine the time course of trends in FVC over time in each treatment group, as well as the treatment effect on change from baseline in FVC over time, using data collected at multiple time points for each patient.

Relative *vs* absolute change in FVC% predicted

Given the lack of data in SSc-ILD examining linkage between FVC trends and subsequent mortality, it is necessary to extrapolate from IPF data. FVC trends predict mortality in all studies, with relative change examined in

the majority [32]. In a recent analysis, a relative decline of 10% (e.g. 2.0 l drops to 1.8 l) and an absolute decline of 10% predicted (e.g. 60% of predicted drops to 50% of predicted) were equally predictive of mortality, but the use of relative change greatly increased the prevalence of decline signal [33]. For this reason, given the problems with powering SSc-ILD studies, relative decline is preferred as the primary end point. Further data are needed to provide supportive data in SSc-ILD. Change in FVC% predicted adjusting for baseline HRCT fibrosis score (to adjust for different outcomes based on HRCT fibrosis score) and other baseline covariates using a mixed effects model or similar appropriate statistical methodology has also improved discrimination [2, 17]. Exploratory analyses of the decline in FVC% predicted should be adjusted for autoantibody status (anti-RNA polymerase III, anti-SCL-70 and anti-centromere antibody) and FVC% predicted at baseline.

Biomarkers

Consideration should be given to storage of sera to assess for correlates and predictors of SSc-ILD. Surfactant protein D, CRP and Krebs von den Lungen-6 are glycoproteins secreted by type II pneumocytes that have emerged as possible surrogate markers for ILD, including SSc-ILD [34]. Data from SLS-I and other studies will provide further validation of these markers and provide other new markers [2].

Conclusion

We provide practical recommendations to consider for trial design in SSc-ILD. This field is rapidly evolving; a recent consensus exercise defined the domains and items that meet OMERACT filters based on input from experts and patients [35] and endorsed by OMERACT attendees [16].

Supplement

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