Developing Disease Activity and Response Criteria in Connective Tissue Disease-related Interstitial Lung Disease

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ABSTRACT. The interstitial lung diseases (ILD) are a group of heterogeneous diseases that exert significant morbidity and mortality in connective tissue diseases (CTD). There is no consensus on measures of disease activity or therapeutic responsiveness, which hampers effective drug development and regulatory evaluation of candidate therapies. The CTD-ILD Special Interest Group represents an international multidisciplinary effort to identify consensus on criteria to measure disease activity and therapeutic response in CTD-ILD. We summarize the design of the studies we are conducting and progress leading to the OMERACT 10 and 2010 EULAR meetings. (J Rheumatol 2011;38:1514–18; doi:10.3899/jrheum.110281)

Key Indexing Terms:
SCLERODERMA   RHEUMATOID ARTHRITIS   INFLAMMATORY MYOPATHY
INTERSTITIAL LUNG DISEASE   OUTCOME MEASURES   RESPONSE CRITERIA

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Pulmonary involvement is the leading cause of death in systemic sclerosis (SSc) and a major cause of morbidity and mortality in other connective tissue diseases (CTD). For the clinician and the clinical researcher, there is no consensus on measures to use for assessment of disease activity or therapeutic response. Except for scleroderma interstitial lung diseases (ILD), ILD related to CTD has been the focus of relatively little systematic research. Even in regard to scleroderma ILD, addressed by a consortium of experts under the Scleroderma Lung Study Research Group, a consensus core set or composite index for disease activity or therapeutic response has not been developed[1]. This hampers assessment of treatment efficacy, drug development, and regulatory evaluation of candidate therapies.

The Connective Tissue Disease-related Interstitial Lung Disease Special Interest Group (CTD-ILD SIG) set out in November 2008 to address issues of treatment response and outcomes measures in both CTD and ILD by designing a multitiered Delphi process to obtain opinions from a broad base of pulmonary, rheumatology, and cardiology specialists and patients. As traditional measures of disease activity in ILD are easily confounded by the extrapulmonary manifestations of the underlying CTD, the participants were asked to simultaneously provide opinions on treatment response and outcome measures in idiopathic pulmonary fibrosis (IPF), a disease whose clinical characteristics are limited to the lung. During OMERACT 10, the CTD-ILD SIG presented its progress and engaged participants of the meeting in further discussions regarding these challenges. We summarize here the design of the studies we are conducting to develop response criteria and the progress leading up to and following the OMERACT 10 and 2010 EULAR meetings, as well as insights gained from OMERACT participants.

Design. The objective of the work-group study effort is to develop disease activity and response criteria for use in multicenter randomized controlled trials (RCT) in CTD-ILD using IPF as a lung-limited comparator. For study purposes, CTD-ILD includes the parenchymal lung disease associated with idiopathic inflammatory myopathies (IIM), rheumatoid arthritis (RA), Sjögren's syndrome (SjS), and systemic sclerosis (SSc). Two parallel strategies are planned to identify essential descriptors of disease activity in CTD-ILD, as follows:
1. Patient perspective strategy: to identify domains and signs

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and symptoms meaningful to patients with ILD that would be useful in measuring disease activity and assessing response to therapy[2].

2. Expert consensus strategy: to identify consensus on potential outcome measures from a wide base of relevant experts[3].

Data collected from these 2 efforts will be synthesized to identify domains and appropriate instruments to measure those that satisfy the OMERACT filter of truth, discrimination, and feasibility[4]. Domains for which instruments must still be developed, and promising instruments of an exploratory design or "not yet feasible," will be assigned to a research agenda for future investigation.

The patient perspective strategy. Techniques of open interview and focus groups at multiple sites involving patients who have various forms of CTD-ILD will be used to identify potential domains of lung disease outcomes. Using the results of these data, discrete questions will be formulated and directed to patient study participants. The survey is intended for global, Internet distribution to comparatively and quantitatively assess the degree of importance and priority of qualities related to patient experience across disease subgroups and cultures. At this time, data from the first round of the pilot focus groups and interviews have been collected.

The expert consensus strategy. The strategy to assess expert opinion consists of a modified Delphi exercise (Figure 1) conducted in 2 sequential phases using a customized data collection system[3,5,6], as follows:

1. Tier 0, Brain-storming: including solicitation of suggested qualities (domains) and measures (instruments) from about 250 expert participants (rheumatologists, pulmonologists, and cardiologists) that will form the content of the next phase.

2. Tiers 1, 2 and 3: Three voting rounds will be conducted to rate the measures identified in the Tier 0 exercise on a 9-point Likert-scaled survey instrument. Serial cluster analysis will identify items of consensus[3].

As part of this exercise, measures potentially useful in assessment of outcomes in trials of IPF will be evaluated in parallel to CTD-ILD (Figure 2). The survey will accommodate a simultaneous and identical questionnaire for IPF as for CTD-ILD. This strategy anticipates that comparative investigation will confer an understanding of similarities and differences between these groups, and thus a greater understanding of issues important in assessment of CTD-ILD.

At the time of this submission, Tier 0 has been completed and the items identified are being prepared for the voting survey.

Accommodating variation among disease subgroups. Addressing disease-specific effects on the measurement of disease activity in CTD-ILD presents numerous challenges, such as distinguishing the contribution of accessory muscle weakness in IIM during pulmonary function measurement, or the contribution of severe reflux disease or xerotrachia when assessing cough in SSc-ILD or SjS-ILD, respectively. For practical reasons, the project has focused on 4 disease subgroups in ILD: IIM, RA, SjS, and SSc. Differences among these CTD are expected to affect the utility of any particular instrument within specific CTD disease subgroups. For example, assessment of forced vital capacity (FVC) in IIM may be diminished due to concomitant respiratory muscle weakness, whereas it may be a truer reflection of parenchymal lung disease in SSc-ILD.

To accommodate this expected variation in utility of instruments in different diseases, the expert consensus strategy addresses each of the 4 disease subgroups through Tier 0 and the 3 subsequent voting tiers. In Tier 0, participants were given an opportunity to nominate instruments they perceived
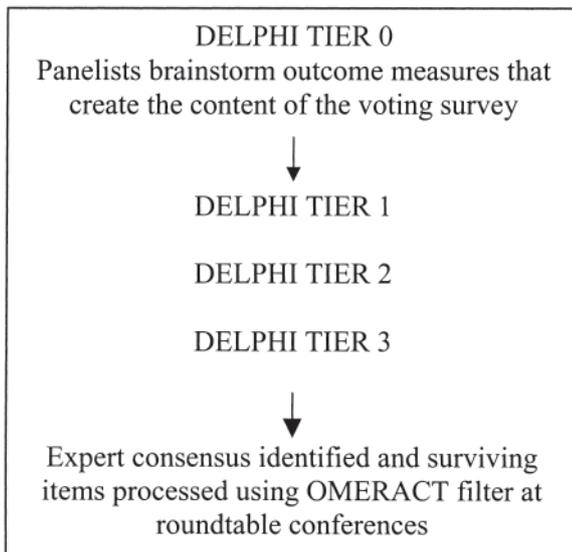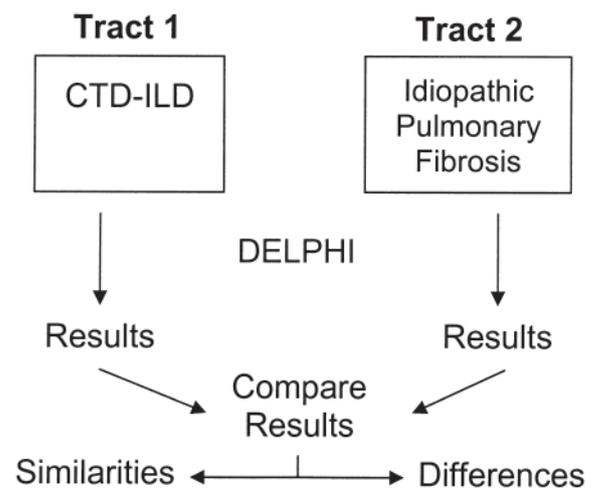

Figure 1. Overview of the Delphi exercise.

Figure 2. Expert comparison of CTD-ILD and IPF during the Delphi exercise.

as being particularly helpful or unhelpful in measuring ILD activity in any of the 4 diseases. A comprehensive list of instruments potentially useful as outcome measures in CTD-ILD in general and the discrete disease subgroups was developed. These instruments will subsequently be assembled into subsections of the voting survey. Participants who do not feel they possess sufficient expertise in a particular disease-specific subgroup may decline to vote in that section.

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Presented data. At the time of OMERACT 10, the CTD-ILD SIG had closed participation for Tier 0 and reported 98% participation from solicited specialists, of which 74% declared "interstitial lung disease" and 69% "rheumatologic lung disease" as their primary field of investigation. A total of 137 pulmonary, 102 rheumatology, and 4 cardiology specialists from 32 countries participated. We presented a raw count of 133 suggested domains and 6700 instruments that were streamlined to 616 after processing for duplications.

Establishing preliminary domains. The next step is to establish preliminary disease "domains" or "qualities that are important to measure" in CTD-ILD. We are now in the process of provisionally identifying which of the 133 domains suggested by the Delphi participants are meaningful and necessary to characterize the breadth of ILD activity.

Domains of function. The International Classification of Functioning, Disability and Health (ICF) has been approved by the World Health Organization (WHO) as a universal framework and classification system for the bio-psycho-social mode of functioning[7]. Participants suggested interfacing with the ICF as a reference to identify and investigate relevant facets of physical activity level and global assessment. Along with the detailed question-banking of the National Institutes of Health (NIH) initiative, the Patient-Reported Outcomes Measurement Information System (PROMIS), the ICF may add further information to assessment of the influence of extrapulmonary disease in patients with CTD-ILD.

Patient-reported outcomes. As discrete descriptors of domains, patient-reported measures are increasingly recognized as equal to or more important than traditional measures of disease activity[8,9]. For example, in patients with IPF, patient-reported dyspnea is recognized as an accurate and robust prognosticator of death[10]. In order to develop and select valid patient-reported outcome measures, investigators must incorporate patient perspective measures into the bank of individual measures that, alone or alongside traditional measures, supply crucial information to a domain.

CTD-ILD as a disease construct. Unlike the majority of diseases considered by OMERACT work-groups, CTD-ILD lacks a clear concept of what actually constitutes clinical worsening of disease. Historically, suppression of "inflammation" or "alveolitis" was considered a logical endpoint for clinical trial design. However, these measures correlate poorly with outcomes of pulmonary function, radiographic change, or survivorship used in RCT of diseases like SSc-ILD[1,11]. Assessment of disease activity and damage in the lung is further confounded by multiple factors, such as prior parenchymal damage, infection, aspiration, reflux or decreased function, and fatigue related to the underlying CTD, making it challenging to distinguish between measures that reflect activity of the lung disease and those that reflect exacerbation of symptoms and objective findings related to the underlying CTD and unassociated with lung disease. With these confounders, it is unsurprising that universally accepted standards for therapeutic responsiveness in the lung diseases have not been agreed upon. As a result, a provisional core set may initially be dominated by comparative descriptors that describe "lack of damage," "stabilization," "no deterioration," "time to clinical worsening," or "survival" (including mortality and its surrogates such as time to transplantation, hospitalization, decline in lung function, etc.) as measures of activity.

Cohort enrichment. Patient selection is an important element for design of RCT. Trials provide significantly more information when patients with clinically active and potentially therapeutically responsive disease are enrolled. This requires the ability to recognize clinically insignificant disease, for which no or little treatment effect can be detected. Other considerations include consistency and reliability of interpretation of high-resolution computed tomography and surgical lung biopsy for revealing the distribution, features, and patterns of parenchymal involvement. Because the performance of a core set of selected measures for use in trial design is affected by these considerations, we advocate that consensus panels of experts be used in RCT to address specific areas of uncertainty. In summary, a useful core set of outcome measures should provide guidance in optimal patient selection for RCT purposes and be able to measure and discriminate between variables of clinical importance related to lung disease.

Length of RCT. How long should a RTC of CTD-ILD be? Certainly the answer depends on the underlying disease, its features, and the measures used to assess the lung disease. Participants voiced the opinion that while a 3-year multicenter randomized clinical trial would yield important natural history and therapeutic responsiveness data, a trial of this length would not be feasible in light of the currently known event rates, desired time to demonstrate efficacy of the candidate therapeutic, and cost of performing the trial. At this point, the one-year multicenter randomized clinical trial is preferred.

Time to efficacy. In order to preserve patient, public, and private sector interest in development of new therapeutics, timing of a therapeutic intervention is likely an important consideration in a disease entity like CTD-ILD, in which treatments are often offered late in the disease course and treatment response is often poor. Additionally, limits on the numbers of patients with the disease of interest who might be eligible for enrollment in such trials certainly influence the ability to experiment with various dosing schedules. These considera-

tions affect aggressiveness of the dosing regimen, time to achieve an early treatment response, and the time necessary to assess safety and survival. Lack of attention to these issues can affect the ability of investigators to sustain interest in CTD-ILD as a potentially treatable disease indication.

Patient-partners. Patients as consultants and advisers will be included early in the process of response criteria development as recommended by patient advocacy groups, investigators, and organizations such as OMERACT, WHO, US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). To this end, each of the CTD-ILD work-group subcommittees for IIM, RA, SSc, and SjS have been charged with identifying at least one patient-partner to be part of the process.

Research agenda. Validated measures for response are scarce in ILD. In light of this, we anticipate identification of promising measures that are not currently validated, and support ongoing investigation and validation of such measures within the context of clinical trials.

Regulatory support. Real-time involvement from regulatory agencies such as the FDA and the EMEA in review and discussion, as well as predistribution guidance and approval for the provisional core-set and plan of implementation, will be important in ensuring acceptance of any proposed outcome measures and response criteria.

Post-OMERACT 10 proceedings. In the month following OMERACT 10, in preparation for Tier 1, members of the CTD-ILD executive committee participated in a series of exercises and group reviews of candidate domains and instruments, and identified 23 preliminary domains to be tested in subsequent Delphi tiers and into which the 616 instruments suggested in Tier 0 would be populated (Table 1).

Summary. Through this multidisciplinary international consensus effort, we believe that a core set of outcome measures can be developed that has broad applicability to parenchymal lung disease in general and the ILD that affect rheumatologic conditions. The complexities of trial design in SSc-ILD have been addressed[12] and progress is apparent on many fronts in IPF[13]. The high level of participation in the first phase of this effort reflects the need for a systematic approach to ILD and a collective interest in establishing criteria for this group of diseases. This is a promising and robust platform for the next phases of this consensus study. A broad panel of measures relevant to all related syndromes seems within our reach.

APPENDIX

List of study collaborators: The Connective Tissue Disease-related Interstitial Lung Disease Special Interest Group includes Paul Dellaripa, Brigham and Womens Hospital, Boston, MA; Kevin Flaherty, University of Michigan, Ann Arbor, MI, USA; Dörte Huscher, German Rheumatism Research Centre, Charité – Universitätsmedizin, Berlin, Germany; Dinesh Khanna, Division of Rheumatology, University of California at Los Angeles, Los Angeles, CA; Chester V. Oddis, Rheumatology/Clinical Immunology, University of Pittsburgh, Pittsburgh, PA; Kristine Phillips, University of Michigan, Ann Arbor, MI, USA; David Pittrow, University of Dresden, Dresden, Germany; Athol Wells, Royal Brompton Hospital and National Heart and Lung Institute, London, UK; Christopher Denton, Centre for Rheumatology, Royal Free Hospital, London, UK; Oliver Distler, Centre for Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland; Aryeh Fischer, Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; Otylia Kowal-Bielecka, National Jewish Health Center, Denver, CO, USA; Shikha Mittoo, Department of Internal Medicine, University of Toronto, Toronto, Ontario, Canada; Jeffrey Swigris, Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

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Table 1. Final 23 domains emerging from Tier 0 for the Delphi voting rounds.

Survival	Mental health
Biomarkers	Sleep
Imaging	Global assessment
Lung physiology/function	Health-related quality of life
Lung parenchyma	Functionality
Lung vascular	Participation
Cardiac function	Employment
Composite scores	Extrapulmonary/connective tissue disease features
Gastroesophageal reflux	Medication
Cough	Comorbidities
Dyspnea	Barriers to care
Fatigue	

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