Reconciling Healthcare Professional and Patient Perspectives in the Development of Disease Activity and Response Criteria in Connective Tissue Disease–related Interstitial Lung Diseases

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ABSTRACT. Interstitial lung diseases (ILD), including those related to connective tissue disease (CTD), and idiopathic pulmonary fibrosis (IPF) carry high morbidity and mortality. Great efforts are under way to develop and investigate meaningful treatments in the context of clinical trials. However, efforts have been challenged by a lack of validated outcome measures and by inconsistent use of measures in clinical trials. Lack of consensus has fragmented effective use of strategies in CTD-ILD and IPF, with a history of resultant difficulties in obtaining agency approval of treatment interventions. Until recently, the patient perspective to determine domains and outcome measures in CTD-ILD and IPF had never been applied. Efforts described here demonstrate unequivocally the value and influence of patient involvement on core set development. Regarding CTD-ILD, this is the first OMERACT working group to directly address a manifestation/comorbidity of a rheumatic disease (ILD) as well as a disease not considered rheumatic (IPF). The OMERACT 11 proceedings of the CTD-ILD Working Group describe the forward and lateral process to include both the medical and patient perspectives in the urgently needed identification of a core set of preliminary domains and outcome measures in CTD-ILD and IPF. (First Release Feb 1 2014; J Rheumatol 2014;41:792–8; doi:10.3899/jrheum.131251)

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Background

The Connective Tissue Disease Interstitial Lung Disease (CTD-ILD) Working Group convened as a special interest group (SIG) during the Outcome Measures in Rheumatology 11 (OMERACT 11) conference to examine concurrence of results between the Delphi exercise among healthcare professionals and the focus group sessions with patient participants. The SIG included, in addition to OMERACT participants, 2 patient research partners with ILD (DL, CS), the principal investigator (LAS), a director of the patient expert investigation (SM), a director of the medical expert investigation (ELM), and the representative from the OMERACT executive (VS).

The OMERACT CTD-ILD Working Group is an international multidisciplinary effort to develop consensus on criteria to measure disease activity and therapeutic response in CTD-ILD. The group first met in November 2008 to address outcome measures in CTD-ILD by developing a multitiered Delphi process to obtain opinions from a broad array of expert pulmonologists, rheumatologists, and cardiologists, as well as a patient perspective strategy.

ILD is one of the leading causes of mortality related to underlying CTD pulmonary disease in systemic sclerosis (SSc)[1,2] and is a major cause of morbidity and mortality in CTD such as rheumatoid arthritis (RA), idiopathic inflammatory myopathy, and Sjögren syndrome. Studies suggest that while mortality rates associated with some CTD have declined, mortality rates associated with CTD-associated pulmonary disease have increased[3,4].

Many complexities of CTD-ILD exist; however, presently there is no consensus on measures to use for assessment of disease activity or treatment response in CTD-ILD. Drug development and assessment of treatment efficacy have been diminished by a relative paucity of data on validated outcome measures in CTD.

Traditional measures of disease activity in ILD are easily confounded by extrapulmonary manifestations of underlying CTD, and although instruments are imperfect, even in a disease such as IPF, whose characteristics are limited to the lung, the group embarked on addressing IPF in comparison to CTD-ILD to provide opinion simultaneously on outcome measures for both disease groups. The CTD-ILD SIG is the first working group, to our knowledge, to take an interest in a comorbid manifestation of a rheumatic disease.

During OMERACT 11, the CTD-ILD SIG presented results to date and engaged meeting participants (providers and patients) in further discussions regarding this progress.

We summarize studies conducted to develop response criteria, domains identified, and progress leading up to OMERACT 11.

Medical Expert Consensus

Rheumatology, pulmonary, cardiology, radiology, and pathology specialists with expertise in IPF and/or CTD-ILD, as well as statisticians, advised on construction of and participation in a structured 3-tiered Internet-based Delphi process to develop consensus on outcome measures reflective of disease activity and therapeutic responsiveness.

The healthcare professional (HCP) Delphi exercise was designed to identify domains and instruments perceived as important outcomes in the context of a 1-year multicenter randomized controlled trial (RCT) of a promising treatment for IPF and/or CTD-ILD. This consensus process included 254 medical experts (physicians with research and clinical expertise in ILD) from 36 countries and 6 continents. In an effort to representatively reflect the views and maintain the true voice of the expert community, the process was initiated with an unrestricted collection of domains and instruments suggested by the HCP. This method of data collection created the voting survey. Throughout the consensus process, the Delphi addressed both CTD-ILD and IPF in parallel tracts, to identify commonalities and differences among outcome measures between these 2 entities.

The Delphi process used a Web-based data collection system that featured links to original publications and subsequent articles addressing validation of all instruments that were identified by a comprehensive Medline literature review. An "Inter-Expert Educational Component" allowed participants to upload commentary, articles, and links for review, as well as challenge or defend inclusion of a domain or instrument.

Using cluster analyses, the 3-part Delphi resulted in selection of 5 domains each for IPF and CTD-ILD that were further supported by high mean and median ratings (Table 1). Surviving instruments, also analyzed by cluster analysis, are shown in Table 2, with supporting high median and mean scores. In addition, surviving instruments of "increasing or decreasing steroids and/or immunosuppressive medications" survived as a marker of disease activity in the "Medications" domain. Please see discussion under "OMERACT 11 Proceedings" below.

Patient Perspective Investigation

The patient-centered investigation was planned with the following objectives: to collect information relevant to the patient experience to determine domains important to patients in assessing disease activity and its effect, provide their perspective on currently used instruments in IPF/CTD-ILD, and to recognize aspects of these diseases relevant to patients potentially not considered by investigators. This strategy was intended to promote understanding of the disease based on the priorities, central experiences, and subtle day-to-day challenges faced by patients that investigators rarely witness.

The investigative team included 3 rheumatologists with expertise in CTD-ILD, a pulmonologist, a patient research partner, and a senior qualitative researcher. All members engaged in study design, implementation, analysis, and interpretation of the results. No preconceived themes or codification were imposed upon the data collected for deductive analysis. Rather, the team adopted an inductive methodology to preserve views expressed by the patients within their own frames of reference, whereby data collected through focus group interviews underwent iterative analyses from which a codification system emerged. Each transcript from each focus group was

Table 1. Results of cluster analysis of the 3-tiered healthcare professional Delphi process. Five domains each were identified for connective tissue disease–related interstitial lung disease (CTD-ILD) and idiopathic pulmonary fibrosis (IPF). Values are ratings on a 9-point scale.

Domain Name	CTD-ILD median/mean	IPF median/mean
Dyspnea	8.0/7.8	8.0/8.1
Health-related quality of life	8.0/7.7	8.0/7.8
Lung imaging	9.0/8.3	9.0/8.3
Lung physiology/function	9.0/8.7	9.0/8.7
Survival	8.0/8.2	9.0/8.4

Table 2. Instruments yielded by cluster analysis and their corresponding domains, with median/mean scores reported. Values in square brackets signify items no longer considered relevant to that disease.

Domain	Instruments	CTD-ILD Median/Mean	IPF Median/Mean
Dyspnea	Borg Dyspnea Index	7.0/6.9	7.0/7.0
	Dyspnea 12	[7.0/6.6]	7.0/6.7
	Medical Research Council (MRC) Breathlessness (Chronic Dyspnea) Scale or the Modified MRC Dyspnea Scale	7.0/7.0	7.0/7.1
	Borg Dyspnea Index, pre- and post-exercise	7.0/7.0	[7.0/7.1]
Health-related quality of life (HRQOL)	Medical Outcome Study Short Form-36 Questionnaire	7.0/7.3	7.0/7.3
	St. George's Dyspnea Respiratory Questionnaire	[7.0/6.6]	7.0/6.8
	Visual analog scale of patient assessment of disease activity	7.0/6.8	7.0/6.7
	Ability to carry out activities of daily living	7.0/6.8	Lost Tier 1
	Health Assessment Questionnaire Disability Index	7.0/7.0	Lost Tier 1
Lung imaging	Extent of honeycombing on HRCT	7.0/7.1	8.0/7.4
	Extent of reticulation on HRCT	[7.0/6.9]	7.0/6.9
	Extent of ground glass opacities on HRCT	7.0/7.2	[7.0/6.7]
	Overall extent of interstitial lung disease on HRCT	8.0/7.7	8.0/7.7
Lung physiology/function	Supplemental oxygen requirement	7.0/7.3	8.0/7.5
	Forced vital capacity on spirometry	8.0/8.3	9.0/8.3
	Diffusion capacity of lung for carbon monoxide	8.0/7.9	8.0/7.9
	6-MWT with maximal desaturation on pulse oximetry	7.0/6.8	7.0/7.0
	6-MWT for distance	[7.0/6.5]	7.0/7.0
Survival	Time to decline in forced vital capacity	7.0/7.3	7.0/7.0
	Progression-free survival	8.0/8.2	8.0/8.3
	Time to death	7.0/7.1	8.0/7.3

6-MWT: 6-minute walk test; CTD-ILD: connective tissue disease-related interstitial lung disease; IPF: idiopathic pulmonary fibrosis; HRCT: high-resolution computed tomography.

individually analyzed by 5 or more independent evaluators (one of whom was a patient research partner) with subsequent comparative analysis across transcripts. Throughout the process, the patient-research partner provided expert guidance in interpretation and theme development, and prioritization of themes.

Following the focus groups, patient partners completed a questionnaire to rate and prioritize the importance of a series of domains presented in lay terminology. The question was asked "On a scale from 1 to 7, how much do you care about the following item as it relates to your lungs?" Some examples included: "How much do you cough?" and "How good are the results of your chest x-ray or CT scan?"

At the time of OMERACT 11, data from 6 focus groups including 45 English-speaking participants were available. Two groups included patients with various underlying CTD: 1 with rheumatoid arthritis and ILD, 1 with idiopathic inflammatory myositis and ILD, and 2 with SSc and ILD. Moderation of focus groups necessitated knowledge of ILD, using both script and guiding discussions of lung disease as a primary topic or a comparator topic to the underlying disease. From these groups a preliminary set of congruent themes and issues important to inform synthesis with the HCP Delphi process for identifying domains and outcome measures emerged:

Cough. Cough, originally lost in HCP Delphi process, was found to (1) be central to the experience of patients with ILD; (2) impair physical functional, sleep, and social aspects of health-related quality of life (HRQOL); and (3) be well articulated by patients who could (i) describe its quality and distinguish between types of cough; (ii) recognize various triggers of cough; and (iii) identify changes in cough that are relevant to difficulty breathing (dyspnea).

Dyspnea. Dyspnea, a central experience to patients (although it had survived the HCP Delphi process) revealed important areas of discordance with concepts of "difficulty in breathing," i.e.: (1) It rarely referred to the act of breathing itself; (2) descriptors such as "shortness of breath" were rarely used to describe difficulty in breathing; rather descriptors such as "winded", "wind cut," trouble "getting a deep breath in," "can't catch a breath," "losing your breath" were used; (3) it was described in the context of the ability to carry out a central life activity, such as: (i) not being able to finish reading or singing a song to children/grandchildren; (ii) not being able to accomplish activities of daily living, care for others and surroundings; (iii) length of recovery time between tasks. The limitations arising from dyspnea generate (1) feelings of frustration, shame, anger, and isolation; (2) sleep disturbances; and (3) loss of connectedness/participation in family, employment, social, and pleasurable activities.

Distinct components of HRQOL affected were described, including mental health, fatigue, sleep, participation, etc. Such distinction had not been identified in the HCP Delphi

process. Cough, dyspnea, and HRQOL have been identified as important health areas for IPF[6].

"Cough" was clearly important to patients, although it did not survive as a domain in the HCP Delphi process. "Dyspnea," although included as a domain, revealed important areas of discordance between the language and concepts reflected in current instruments and those expressed by patients. Discrete areas of HRQOL were identified as important to patients. Additionally, patient participants identified previously unanticipated and important insights regarding the burden of these diseases: living with uncertainty, challenges in physician communication, struggle over new self, coping strategies, and self-efficacy.

OMERACT 11 Proceedings (Table 3)

At the CTD-ILD SIG at OMERACT 11, data from both the HCP Delphi exercise and the patient focus groups were presented. The main objectives of the meeting were to examine crucial issues arising from the preliminary comparative synthesis of data from both investigations. In addition, an in-depth analysis of data relating to psychosocial concepts that fell outside the primary goal of developing outcome measures in RCT was discussed by Drs. Frankel and Mittoo. Ms. LeSage and Ms. Sarver provided poignant summaries regarding the burden of their disease, issues pertaining to healthcare delivery for the patient with ILD, use of instruments, as well as unique interpretations of the data. This offered unanticipated and significant enhancements to the clinical knowledge of most of the attendees. Dr. Frankel presented results of the patient focus group analyses with interpretations based on careful reconstruction of patient-guided themes — this was expanded and corroborated by Ms. LeSage and Ms. Sarver. These presentations promoted understanding of patient response to the Delphi results and demonstrate lateralization of priorities between the 2 groups and thus an interim consensus.

Results of the patient perspective investigation revealed "cough" to be central to the patient experience, although it did not survive the HCP Delphi process. Patients were able to articulate subtleties indicating that "cough" in ILD is associated with distinct qualities not captured in currently available instruments, especially because current instruments of cough were not developed with patient participation nor specifically for patients with ILD. It was hypothesized by the group that "cough" may have been lost in the medical expert Delphi because of lack of an appropriate instrument. In view of these points, the following received 100% acceptance upon voting:

- Any domain important to either HCP or patient participants should be considered for inclusion in the core sets for CTD-ILD and IPF
- "Cough" should be included in the core sets for CTD-ILD and IPF
- Although appropriate instruments may be used in the interim, new instruments should be developed for "cough" specific for CTD-ILD and/or IPF with patient participation

"Dyspnea" was deemed important in both investigations, although there was important discordance between HCP and patient perspectives. In view of these points, the following received 100% acceptance upon voting:

- Although appropriate instruments may be used in the interim, new instruments should be developed for "dyspnea" specific for CTD-ILD and/or IPF with patient participation

Although HRQOL was collapsed into a single domain during the HCP Delphi process, patient participants identified the clearly defined importance of each of the discrete components of HRQOL. After discussion, the following was supported by an 82% vote for acceptance:

- Recognition of discrete components of HRQOL is essential; however, until these components can be

Table 3. Domains ratified during OMERACT 11 proceedings. Forging consensus between patients and physicians with special considerations.

Domains from Combined Investigations	Special Considerations
Dyspnea	Unexpected language and contextual factors
	Consider need for disease-specific instrument development
Cough	Pervasive effect on dyspnea and HRQOL
	Core set inclusion received 100% endorsement
	Consider need for disease-specific instrument development
Health-related quality of life (HRQOL; also captures patient global assessment)	Consider need for disease-specific instrument development
	HRQOL is affected by uncertainty surrounding disease outcome
	HRQOL may be affected by physician-patient communication
Lung physiology/function	Important to patients and physicians
	Patients are anxious about performance-related results (re: poor result of spirometry because of "effort" or a "bad day")
Lung imaging	Patients and physicians care about this domain
Survival	Important to both groups
	Patients want to communicate about prognosis and handling episodic exacerbations
Medications	Important to both groups
	Incremental increase/decrease may be useful as a disease activity marker but depends on targeted therapy

supported by validated instruments for CTD-ILD and/or IPF, interim instruments designed to measure generic and disease-specific HRQOL may be utilized

Strong support in the HCP Delphi for results led to the proposal that strategies in the handling of adjuvant immunosuppressant agents be decided depending on the targeted therapy. It was acknowledged that, in the present state of uncertainty about the benefits of the medication and management of ILD, this is a complex concept. However, after discussion, the following was supported by an 82% vote for acceptance:

- Both strategies: (a) dichotomous treatment failure/success defined by increase or decrease in immunosuppressive agents and (b) incremental increases or decreases in immunosuppressive agents over time be considered as outcome measures, on a protocol specific basis.

At OMERACT 10, discussions during the CTD-ILD SIG included consideration of cohort enrichment, as well as alternative models of efficacy and clinically meaningful endpoints, particularly in a condition that typically results in irreversible damage[5]. Subsequent discussions during OMERACT 11 resulted in 100% voting for acceptance:

- "Lack of progression" should be considered a clinically meaningful endpoint in RCT in CTD-ILD and IPF
- Definitions of "progression free survival" should be a goal of the CTD-ILD Working Group for use in RCT

These points were important for future efforts of this CTD-ILD Working Group.

Future Directions

The next step in the process is a meeting of HCP and patient participants, using nominal group technique (NGT), to identify currently available instruments most appropriate to measure the domains selected from the HCP Delphi process and patient participant focus groups, examine the degree to which they meet the "OMERACT filter"[7], and to outline the research agenda.

The selected domains, which include the reinstatement of "cough," "dyspnea" as voted upon in the OMERACT proceedings, as well as "patient global assessment of disease activity," will be evaluated by a panel of experts: patients, as well as pulmonary, rheumatology, and radiology specialists in the fields of IPF and CTD-ILD. A domain to capture the above called "signs and symptoms" is under consideration.

"Domain teams" including representation from each expert group according to expertise will be assigned to present the most updated information regarding the instruments and how well they fulfill the OMERACT filter; each team will also be responsible for ensuring that patient perspective results are included. As an example, a concept central to the OMERACT Filter 2.0, a core domain of "survival" or death will be considered. Importantly it encompasses not only the length of time a patient lives, but also the concept of "progression free survival." Additional discussion and voting will include addressing whether and how "lung physiology/function" measures should be part of the core set. For each accepted instrument, experts will determine whether they should be considered primary or secondary endpoints and whether a preliminary threshold of change (e.g., > 10% decline in DLCO regarded as significant) can be assigned.

In addition to the pre-meeting endeavors of the "domain teams," pre-meeting educational sessions on the meeting process and OMERACT methodology[7] are planned, allowing for clarification and review of the combined results. A subsequent meeting in San Francisco in May 2012 was dedicated to review the NGT content and process review for the pulmonary experts on the panel. This meeting also provided a forum to discuss the results of these OMERACT proceedings. Patient experts will attend a pre-meeting teleconference/Web series that deconstructs domains and potential instruments' importance as perceived by medical experts as well as a forum devoted to reviewing the patient-centered data, with continual open discussion of experiences and perceptions related to the instruments.

Future directions necessitate a priority-tiered research agenda to guide inclusion and testing of non-core set items that did not survive the Delphi tier-filtered exercise but may nonetheless be considered important for examination within the context of randomized clinical trials, clinical practice, and registry studies. Continued work will necessarily involve non-physician HCP such as nurse specialists in ILD and pulmonary rehabilitation therapists, who provide useful insights into the disease process and care of these patients.

Summary

Perspectives from and results of the HCP Delphi process and patient perspective focus groups will be reconciled in the evaluation of domains and instruments appropriate for their assessment in 1 year RCT in CTD-ILD and IPF at an upcoming NGT meeting. Following this and on completing an outline of the research agenda, the CTD-ILD group will work over time to develop a responder analysis using the core set of domains and recommended and validated instruments.

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APPENDIX 1

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