Connective Tissue Disease-associated Interstitial Lung Diseases (CTD-ILD) — Report from OMERACT CTD-ILD Working Group

Dinesh Khanna, Shikha Mittoo, Rohit Aggarwal, Susanna M. Proudman, Nicola Dalbeth, Eric L. Matteson, Kevin Brown, Kevin Flaherty, Athol U. Wells, James R. Seibold, and Vibeke Strand

ABSTRACT. ***Objective.*** Interstitial lung disease (ILD) is common in connective tissue disease (CTD) and is the leading cause of mortality. Investigators have used certain outcome measures in randomized controlled trials (RCT) in CTD-ILD, but the lack of a systematically developed, CTD-specific index that captures all measures relevant and meaningful to patients with CTD-ILD has left a large and conspicuous gap in CTD-ILD research.

Methods. The CTD-ILD working group, under the aegis of the Outcome Measures in Rheumatology (OMERACT) initiative, has completed a consensus group exercise to reach harmony on core domains and items for inclusion in RCT in CTD-ILD. During the OMERACT 12 meeting, consensus was sought on domains and core items for inclusion in RCT. In addition, consensus was pursued on a definition of response in RCT. Consensus was defined as ≥ 75% agreement among the participants.

Results. OMERACT 12 participants endorsed the domains with minimal modifications. Clinically meaningful progression for CTD-ILD was proposed as ≥ 10% relative decline in forced vital capacity (FVC) or ≥ 5% to < 10% relative decline in FVC and ≥ 15% relative decline in DLCO.

Conclusion. There is consensus on domains for inclusion in RCT in CTD-ILD and on a definition of clinically meaningful progression. Data-driven approaches to validate these results in different cohorts and RCT are needed. (First Release March 1 2015; J Rheumatol 2015;42:2168–71; doi:10.3899/jrheum.141182)

Key Indexing Terms:
LUNG DISEASES INTERSTITIAL LUNG DISEASE OUTCOME ASSESSMENT OMERACT

From the Department of Internal Medicine, Division of Rheumatology, University of Michigan Scleroderma Program, University of Michigan, Ann Arbor, Michigan, USA; University of Toronto, Toronto, Ontario, Canada; University of Pittsburgh, Pittsburgh, Pennsylvania, USA; Royal Adelaide Hospital and University of Adelaide, Adelaide, Australia; University of Auckland, Auckland, New Zealand; Mayo Clinic, Rochester, Minnesota; National Jewish Hospital, Denver, Colorado, USA; Royal Brompton Hospital and National Heart and Lung Institute, London, UK; Scleroderma Research Consultants, Litchfield, Connecticut; Vibeke Strand, MD, Stanford University, Palo Alto, California, USA.

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D. Khanna, MD, MSc, Associate Professor of Medicine, Director, University of Michigan Scleroderma Program, University of Michigan; S. Mittoo, MD, MHS, University of Toronto; R. Aggarwal, MD, MS, Assistant Professor of Medicine, University of Pittsburgh; S.M. Proudman, MBBS, Royal Adelaide Hospital and Associate Professor Discipline of Medicine, University of Adelaide; N. Dalbeth, MD, FRACP, University of Auckland; E.L. Matteson, MD, Mayo Clinic; K. Brown, MD, National Jewish Hospital; K. Flahery, MD, MSc, Professor of Medicine, University of Michigan; A.U. Wells, MD, Royal Brompton Hospital and National Heart and Lung Institute; J.R. Seibold, MD, Scleroderma Research Consultants; V. Strand, MD, Stanford University.

Address correspondence to Dr. D. Khanna, Division of Rheumatology/Department of Internal Medicine, 300 North Ingalls St., Suite 7C27, Ann Arbor, Michigan 48109-5422, USA.
E-mail: khannad@umich.edu

Interstitial lung disease (ILD) induces overwhelming morbidity and is the leading cause of mortality in patients with connective tissue disease (CTD)[1,2]. Certain CTD are more likely to be associated with ILD [e.g., systemic sclerosis (SSc), idiopathic inflammatory myopathy (IIM), and rheumatoid arthritis (RA)], but all patients with CTD are at risk for developing ILD, and ILD may be the first or only manifestation of a CTD[3]. There are currently no approved treatments for CTD-ILD, and drug development for CTD-ILD is challenged by its variable presentation, heterogeneous disease course, devastating morbidity, and considerable mortality[3]. There have been very few randomized controlled trials (RCT) in CTD-ILD, and further advances are adversely affected by the lack of well-defined, consensus-driven outcome measures[4,5]. In a well-designed RCT of cyclophosphamide versus placebo in SSc-ILD (Scleroderma Lung Study-1), modest changes were evident in lung physiology [forced vital capacity (FVC) and total lung capacity] and in patient-reported outcomes (PRO)[5]. This is reminiscent of the 1980s, when RA trials were being conducted without consensus on a group of core set outcome measures to assess efficacy. The lack of uniform outcome measures impedes drug development and hampers metaanalyses to assess

efficacy. This has been a major obstacle to the conduct and interpretation of RCT in CTD-ILD. Similar challenges were present in idiopathic pulmonary fibrosis (IPF), but there have been some successes with positive trials[6,7].

Because of the above issues, there is a keen and growing interest in the rheumatology and pulmonary communities to identify and test promising therapies that target CTD-ILD. Investigators have used certain outcome measures in RCT in CTD-ILD, but the lack of a systematically developed, CTD-specific index that captures all measures relevant and meaningful to patients has left a large and conspicuous gap in CTD-ILD research. Although the CTD where ILD develops are complex and heterogeneous, manifestations of ILD share similar symptomatic, physiologic, and radiographic features, suggesting that development of a single response index may be possible. The CTD-ILD working group, under the aegis of the Outcome Measures in Rheumatology (OMERACT) initiative, completed a consensus group exercise to reach harmony on core domains and items for inclusion in RCT in CTD-ILD. The exercise involved patient partners in well-structured focus groups to develop themes that are important to patients; the group also initiated analyses in large international cohorts of CTD-ILD.

Background Information

Consensus methodology to develop outcome measures for RCT in CTD-ILD. The CTD-ILD working group has completed consensus development [including a detailed Delphi process, patient focus groups, and a nominal group technique (NGT) meeting among participating healthcare providers and patient partners] to propose and select domains and items (outcome measures) for multicenter RCT in CTD-ILD and IPF; and their report is published elsewhere[8]. Briefly, this initiative included an international interdisciplinary network comprising rheumatology, pulmonary, thoracic radiology, and pathology experts in ILD; patients with CTD-ILD or IPF participated at each stage of this initiative. There was a 4-tier Web-based Delphi exercise for identification of domains and items followed by the NGT to reach consensus[8]. A core set including the domains pulmonary physiology (including function), pulmonary imaging, survival, dyspnea, cough, and health-related quality of life was proposed as appropriate for consideration for use in a hypothetical 1-year multicenter RCT for CTD-ILD (Table 1)[7]. Existing items (instruments) were proposed and voted on during the NGT exercise (see dyspnea and cough domains) with careful evaluation of the proposed items as they relate to the OMERACT filter 2.0 (reviewed in Vancheri and du Bois[7]). In addition, there was discussion regarding the need to develop ILD-specific instruments (which are included in the research agenda).

Table 1. Consensus domain and instrument for CTD-ILD and IPF groups. Modified from Saketkoo LA, et al. Thorax 2014;69:428-36; with permission.

Domains and Instrument	CTD-ILD Consensus, %	IPF Consensus, %
Dyspnea		
MRC chronic dyspnea scale	75	92
Dyspnea 12	88	70
UCSD-SBQ	NA	80
Cough		
Leicester cough monitor	79	82
HRQOL		
Short Form–36	100	82
SGRQ	87	82
VAS-PtGA	96	NA
Lung imaging		
Overall extent of ILD on HRCT	92	100
Lung physiology		
Forced vital capacity	100	100
Diffusion capacity of lung	91	100
Survival		
All-cause mortality	100	100

CTD-ILD: connective tissue disease–associated interstitial lung disease; HRCT: high-resolution computed tomography; HRQOL: health-related quality of life; IPF: idiopathic pulmonary fibrosis; MRC: Medical Research Council; PtGA: patient's global assessment; SGRQ: St. George's Respiratory Questionnaire; UCSD-SBQ: University of California San Diego Shortness of Breath Questionnaire; VAS: visual analog scale; NA: not applicable.

Patient Perspective

Since the last OMERACT CTD-ILD workshop, qualitative interviews have been completed of 45 patients in 6 types of CTD-ILD across the US and Canada. Cough and dyspnea were found central to the CTD-ILD experience, and patients considered both as very important measures to be evaluated in RCT. Further, the patient participant focus groups provided ILD-specific content, context, and language essential for development and validation of PRO measures[8]. The effect of CTD-ILD on various life areas such as activity, participation, patients' perceptions, family/caregivers, work, and overall health-related quality of life was explored. Psychosocial themes related to effect on life included self-efficacy, living with uncertainty, and struggle over self-identity. Living with uncertainty was a theme where patients described confusion regarding their diagnosis and prognosis; discussions emphasized the need for improved communication to aid patients' perceptions and understanding of their health/health condition (submitted)[9].

Developing Definitions of Response

Candidate measures of efficacy have been proposed for IPF that attempt to address the inconsistent relationship between pulmonary function trends (i.e., serial measures such as FVC) and outcomes important to patients, especially survival and changes in symptoms. A "time to worsening" definition has been proposed in IPF that measures time to occurrence of clinically meaningful events including acute IPF exacerbation, IPF-related death, lung transplantation, and/or hospitalization for respiratory decompensation. The excellent

short-term survival in SSc-ILD (the most studied CTD in RCT) and other CTD-ILD (such as RA) and the rarity of performance of lung transplantation reduce the utility of this definition of outcome and response in CTD-ILD. For example, there were only 7 deaths over 2 years in the Scleroderma Lung Study and none in the first year[10]. An intermediate measure of poor clinical course is termed "progression-free survival;" specifically, characteristics proposed as a possible composite outcome index for CTD-ILD include time to first occurrence of either ≥ 10% relative decline in FVC predicted or ≥ 5% to < 10% relative decline in FVC predicted; and ≥ 15% relative decline in DLCO predicted; or death[11].

OMERACT 12 Workshop Presentations

Three brief presentations highlighted data on the topics discussed above: results from the consensus process and NGT meeting, patient participant focus groups, data-driven approaches in each CTD-ILD to validate proposed domains/items, and a proposal for a clinically meaningful definition of progression as an endpoint in 1-year CTD-ILD RCT. These were followed by 3 breakout sessions: 2 groups focused on core domains/items for a 1-year multicenter RCT, and a "progression-free survival" definition and 1 breakout group focused on patient perspectives. The patient perspective group focused on the benefits and limitations of standardization of patient/physician communication protocols and whether coping and self-efficacy should be captured in the context of a 1-year RCT and observational studies.

Discussion on core domains/items and "progression-free survival" definition. There was consensus on the preliminary core set of domains and research agenda (Figure 1)[8]; 45 of 46 (98%) voters concurred. It was suggested to separate functional status from lung physiology and to include this as a separate domain in the inner core. It was also acknowledged that some existing core items (instruments), especially for cough and dyspnea, do not meet the OMERACT 2.0 filter[12], and research should be conducted to develop CTD-ILD PRO for their assessment [98% concurred (45 of 46 attendees), with 1 abstention]. Further there was consensus [98% with 1 abstention] that a disease-specific measure of health-related quality of life and instrument(s) to assess effect on life should be included in the research agenda.

Regarding progression-free survival, participants recommended that survival be separated from disease progression because it is difficult to demonstrate a relationship between the 2 in a clinical trial. The breakout groups suggested the term "clinically meaningful progression" and agreed with the proposed definition of ≥ 10% relative decline in FVC predicted or ≥ 5 to < 10% relative decline in FVC predicted and ≥ 15% relative decline in DLCO predicted; 87% agreed, with 6 abstaining (out of 46 votes). Several points were

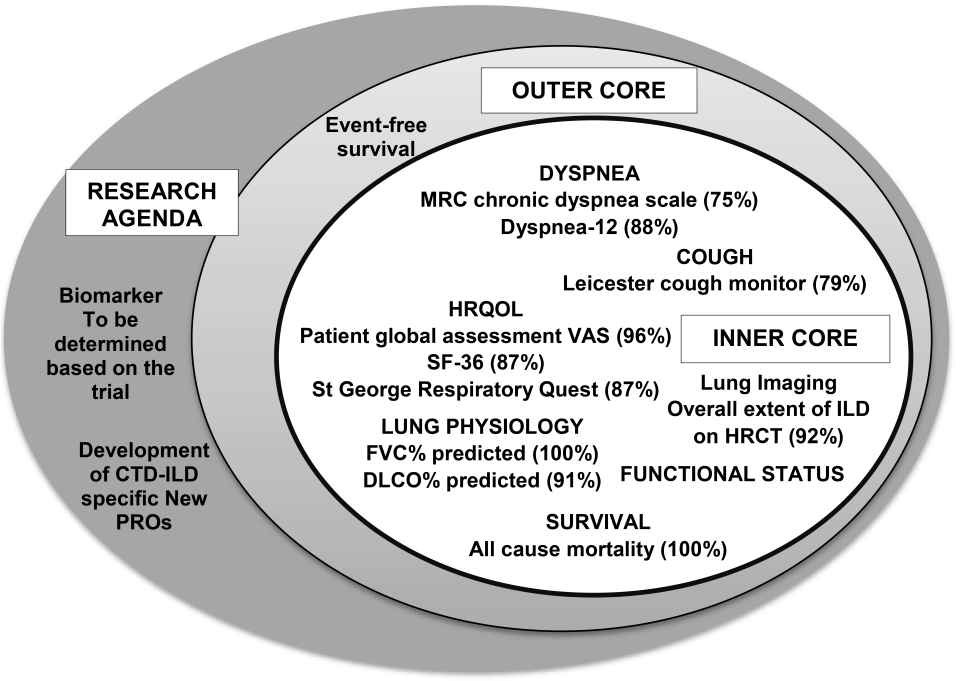

Figure 1. Core domains/items for CTD-ILD as presented and discussed at OMERACT 12. MRC: Medical Research Council; CTD-ILD: connective tissue disease–interstitial lung disease; PRO: patient-reported outcome; HRQOL: health-related quality of life; SF-36: Medical Outcomes Study Short Form-36 (questionnaire); HRCT: high-resolution computed tomography; FVC: forced vital capacity.

emphasized: a clear distinction should be made between a surrogate and a clinical outcome measure; moreover, progression should not be synonymous with decline because future therapies may stabilize and/or even improve pulmonary physiology. For RCT, it was emphasized to standardize the outcome measures (e.g., the American Thoracic Society/European Respiratory Society recommendations on performance/evaluation of pulmonary function tests[13]). The next steps are to validate this definition and assess psychometric properties of core domains and items (Figure 1) in large observational studies and RCT already under way in cohorts of RA, SSc, and IIM-associated ILD. The overall goal is to develop composite indices in different CTD-ILD, but we acknowledge that the heterogeneity of CTD-ILD may impede applying a single measure across different CTD-ILD. Different CTD-ILD may have different composite indices such as a composite for change in disease bulk (decline in FVC, decline in DLCO, change on high-resolution computed tomography), clinically significant events (severe decline/hospital admissions/mortality), or combination of both. This will largely depend on the underlying ILD. For example, a patient with SSc-usual interstitial pneumonia may have (1) overtly irreversible disease; (2) CTD-ILD with definite organizing pneumonia that is reversible; and (3) indeterminate ILD (such as IIM-non-specific interstitial pneumonia), i.e., reversibility is possible but unlikely. The differences in endpoints potentially may need multidisciplinary review by a rheumatologist, a pulmonologist, and an experienced radiologist to determine whether a patient falls into a key subgroup, which might influence the choice of the primary endpoint and use of a composite index. This type of data-driven approach will inform such decisions.

Discussion in the patient-perspective breakout group. Self-efficacy and coping were discussed as separate, but related, aspects of how patients manage their ILD. Coping referred to a patient's behavioral or cognitive efforts related to managing ILD, whereas self-efficacy referred to a patient's self-perception and judgment of how a situation can be managed. OMERACT attendees agreed that coping and self-efficacy were not unique to patients with CTD-ILD and that a special interest group to discuss these aspects across multiple chronic rheumatologic diseases should be established.

Communication between providers and patients living with CTD-ILD was discussed to identify aspects at the time of diagnosis of ILD that would provide the basis for a meaningful understanding regarding prognosis and management decisions. Patients with a CTD-ILD expressed the need for a timely discussion at diagnosis of ILD and provision of sufficient information related to ILD; particularly discussions concerning results such as pulmonary function tests because knowledge of disease activity/severity has an important effect on self-efficacy.

Important advances have been made by the CTD-ILD group in the past 2 years. Next steps include validation of consensus-driven definitions of domains/items and clinically meaningful progression.

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