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Proceedings of American College of Rheumatology / Association of Physicians of Great Britain and Ireland Connective Tissue Disease-associated Interstitial Lung Disease Summit: A Multi-Disciplinary Approach to Address Challenges and Opportunities

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Introduction

Interstitial lung disease (ILD), a group of diffuse parenchymal lung disorders classified together based on specific clinical, radiological, and histopathological features, is often associated with significant morbidity and mortality and is a common manifestation in connective tissue disease (CTD) [1].

ILD often arises within the context of a specific exposure or is associated with an underlying CTD. The CTDs are a spectrum of systemic autoimmune disorders with significant clinical heterogeneity characterized by immune-mediated organ dysfunction and the lung is a frequent target. All CTD patients are at risk for developing ILD, and those with systemic sclerosis (SSc), poly-/dermatomyositis (PM/DM), and rheumatoid arthritis (RA) are at particularly high risk [1,2]. ILD may develop at any point in the natural history of CTD, is most frequently identified within the context of an established CTD and may also be the first clinically apparent manifestation of occult CTD. Determining whether a patient has a diagnosis of CTD-associated ILD is important, as this knowledge may impact treatment decisions, guide surveillance for other concomitant clinical features, and help with prognostication [3].

The intersection of CTD with ILD is complex and fraught with areas of controversy and uncertainty. Numerous gaps exist in our understanding of why certain CTD populations are

more likely to develop ILD, but certain phenotypic risk factors have been identified. In RA, these include older age, cigarette smoking, male gender, RF positivity, CCP positivity and more severe articular disease [4-6]. In SSc, autoantibodies serve as the most reliable predictor of ILD, with anti-Scl-70 being one of the strongest [7]. In PM/DM, autoantibody profiles also are useful predictors of ILD; especially anti-synthetase antibodies (e.g. Jo-1, PL-7, PL-12), anti-PM-Scl antibody, and anti-MDA-5 antibody [8-10]. Reliable risk factors for ILD development in other CTDs are lacking. Moreover, since the advent of computed tomography, it has been possible to characterize ILD with greater precision than previously [11,12]. Yet significant gaps exist with respect to reliable determinants of prevalence of ILD in CTD and there is controversy surrounding whether to implement early detection strategies in patients with CTD.

Perhaps the greatest unmet needs for ILD in CTD are in the realm of therapeutics. The reality for CTD-associated ILD is that few effective therapies exist, most decisions about management are based on experience rather than evidence, and there remains a desperate need for well-designed multicenter clinical trials of both existing and novel agents [13].

With a desire to highlight key areas needing scientific and therapeutic focus in CTD-ILD, the Association of Physicians of Great Britain and Ireland and the American College of Rheumatology supported a multidisciplinary panel of international clinician scientists with interests and expertise in ILD from pulmonary, rheumatology, thoracic radiology and lung pathology specialties to convene a one-day "CTD-ILD Summit" in 2017. The goals of the Summit were to highlight key clinical and research aspects of CTD-ILD, identify unmet needs and outline future research goals of this complex intersection of diseases.

In this document, we detail the proceedings of this CTD-ILD Summit, which were anchored around five domains: ***i.) clinical, ii.) biomarkers, iii.) diagnostic imaging and histopathology, iv.) treatment and clinical trials design and outcomes, and v.) translational research.***

Clinical Domain

Statement of the problem and current understanding

Interstitial lung disease (ILD) is amongst the leading causes of morbidity and mortality in patients with connective tissue disease (CTD) [1,2]. Our understanding of patients with ILD in the setting of CTD is challenged by a confluence of factors including the systemic nature of their rheumatologic disease. Patients with CTD-associated ILD (CTD-ILD), compared to those with idiopathic pulmonary fibrosis, present with a greater degree of heterogeneity with marked variability in natural history. Idiopathic pulmonary fibrosis (IPF) is a devastating progressive fibrosing ILD associated with a high burden of morbidity and mortality [14]. A clinical diagnosis of IPF is made only after careful interpretation of integrated clinical, radiologic, and often lung histopathological data. A classification of IPF is restricted to those individuals with a lung injury pattern of usual interstitial pneumonia (UIP) based on high resolution computed tomography (HRCT) scan or surgical lung biopsy, after all known etiologies for UIP – such as underlying CTD – have been evaluated and excluded [14]. Patients with CTD may have a mix of inflammatory and fibrotic ILD along with multicompartment lung involvement including airways, pleural and pulmonary vascular disease, which may confound determining the etiology of their respiratory impairment and potential responses to therapy. Furthermore, the ability to predict progression of ILD in CTD is challenging as some patients develop ILD that is mild and non-progressive, while others have a more progressive course with unrelenting decline in function as seen in IPF.

Optimal care of patients with CTD-ILD requires collaboration and greater interaction by the rheumatology and pulmonology communities. Rheumatologists have begun to improve their surveillance for lung involvement in patients with CTD, though clear guidelines (and training) have been lacking. Pulmonologists evaluating patients with ILD have become more attuned to the demographic, historical, and phenotypic features that may suggest an underlying CTD though their level of expertise with that evaluation varies widely. Our understanding of natural history has been limited mostly to prospective observational studies and retrospective analysis but clinical, physiologic and radiographic data emerging from prospective trials may identify

those patients at highest risk for developing ILD and those who are candidates for treatment and participation in clinical trials [15]. While there has been a greater emphasis on a multidisciplinary approach to patient care and in education of physicians, effective collaboration between pulmonologists and rheumatologists still falls short due to practical reasons including interest, limited expertise in this area, and availability and access of ancillary resources. Collective experience and a recent study demonstrate that collaborative efforts can be effective in enhancing patient care [16,17].

Unmet needs and challenges

One of the challenges in CTD-ILD is that the prevalence of ILD amongst different groups of patients with CTD varies so widely (Table 1), with the highest estimated prevalence rates noted in SSc and with PM/DM [1,2,18]. Severity of disease is most notable in patients where ILD is predominately fibrotic such as patients with usual interstitial pneumonia (UIP) as is seen in RA with mortality rates comparable to IPF [6,19,20]. While prevalence may define the frequency of ILD in any given CTD, focusing on the severity of disease based on features on chest imaging with pathologic correlation when histology is available may offer greater insight into prognosis compared to a focus on any specific CTD and thus guide decision making for treatment and inclusion into treatment trials.

Efforts to identify CTD patients with ILD or those who are at risk of developing it requires an approach to screening that has the dual objectives of identifying early stage disease and more specifically those with greatest risk for progression and functional decline. Our present approaches do not allow us to fulfill either of those screening goals effectively though emerging evidence suggests a framework for screening. In RA for example, as highlighted in a recent high-level review [6], the pattern of UIP predominates in most series [6,20,21] and certain phenotypic features (age, male smoking history and CCP antibody status) have been identified in retrospective cohorts that may predict a higher risk for ILD but prospective data is only now being gathered to test and validate predictive models that may allow selective and targeted screening efforts [22-26]. In RA there is a suggestion that physiologic data can predict decline

though it is unclear whether it can serve as the sole screening strategy [27]. In SSc and PM/DM, retrospective studies have identified phenotypic, autoantibody, radiographic and physiologic data that identify those at higher risk for ILD and greater risk for mortality [28-30]. Such understanding has led to the development of algorithms utilizing a combination of HRCT and physiologic data to assess severity of disease and offers insights into prognostication [28-30]. Screening strategies that identify ILD are important in light of evidence supporting a modest benefit in outcome with immunosuppressive treatment. Data on utilizing antifibrotic drugs approved for use in IPF are not available but are undergoing investigation in ongoing prospective trials.

Proposed future directions

A clearer understanding of long term historical data will require multicenter cooperation using prospective databases that encompass phenotypic, physiologic, radiographic, genomic and proteomic data that may help elucidate those factors that can best predict which patients are at risk for ILD and for progressive disease. Heightened awareness and recognition that lung disease is common among patients CTD should lead to creative and sustained efforts to improve education of rheumatologists regarding clinical features of lung disease and utilization of physiologic data to facilitate prompt and appropriate referral and to forge closer collaborations with pulmonary colleagues. For the pulmonologist, dedicated education and training is needed to aid in recognizing important clinical and historical features that point toward a diagnosis of a CTD and to gain better understanding of autoimmune serologies in the evaluation in patients with ILD. Much of this can be accomplished by greater cooperation between the academic societies of the two disciplines by utilizing existing educational opportunities but also to create additional learning modalities such as case based educational online modules. Finally, enhanced fellowship training in both disciplines with elective rotations in each other's specialty during fellowship and encouraging collaborative pulmonary and rheumatology fellowship opportunities will also enhance greater recognition of these disorders and will hopefully enhance the care of patients with CTD-ILD.

Biomarker Domain

Current understanding and unmet needs

Biomarkers refer to a category of objective medical signs that correlate with certain aspects of normality or abnormality and may be defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [31]. Given the heterogeneity of ILD complicating CTD, the development of biomarkers is an important endeavor. However, to date there are no validated biomarkers for CTD-ILD.

The diagnosis of CTD-ILD is currently limited by the use of clinical data including history, physical examination, pulmonary function testing, and data from lung imaging and histopathology. In order for biomarkers to become important tools for clinical practice, the specific measures should be accessible, reproducible, accurate – and be useful clinically. The risk for sampling must be acceptable and feasible. While biomarkers in ILD studies may be obtained from lung tissue and bronchoalveolar (BAL) fluid, biomarkers obtained from peripheral blood would be far more ideal given ease of access, convenience and cost factors. At the same time, tissue or BAL fluid analysis at the site of pathophysiological action in the lungs is a potentially more promising route than analyses from the blood for discovering ILD-relevant biomarkers. This is especially the case where other organ involvement in a systemic disease contributes to the overall heterogeneity of measured signals in the blood, thereby potentially confounding or limiting interpretation of a serologic test (e.g., rheumatoid factor, anti-nuclear antibody, erythrocyte sedimentation rate).

Several challenges need to be met before the acquisition of valid CTD-ILD biomarkers becomes a reality. A systematic review using an NCBI search strategy employing terms of "interstitial lung disease", "connective tissue disease" and "biomarker" was employed in preparation for this meeting. Case reports, case series, studies with inappropriate design or patient populations, juvenile studies and studies with fewer than 20 cases were excluded from the

analysis. The OMERACT filter was applied to evaluate papers for truthfulness, feasibility and discriminatory ability [32,33]. Papers were also subjected to analysis of whether the instrument biomarker measured an appropriate target domain [34]. There were only 23 papers that passed these initial stages.

Candidate biomarkers have been identified in a number of the studies fulfilling the search criteria and passing the OMERACT filter. Chen and colleagues reported a strong association between the presence of ILD in Rheumatoid arthritis (RA) patients and elevated levels of peripheral blood matrix metalloproteinase-7 (MMP-7)and interferon-γ inducible protein-10 (CXCL10) by multiplex enzyme-linked immunosorbent assay (ELISA) . This association was confirmed in two independent Chinese RA cohorts. The authors subsequently validated their findings using a different quantitative platform (sandwich ELISA) in a separate cohort of RA patients from the United States.al[22]. Further work by Doyle and colleagues reported that a regression model composed of several clinical variables was capable of identifying both clinically evident ILD and sub-clinical ILD in two independent RA cohorts [25]. This association was significantly improved with the addition of peripheral blood biomarkers MMP-7, surfactant protein D (SP-D) and activation regulated chemokine (PARC)/CC-chemokine ligand-18. In the Scleroderma Lung Study (SLS I), analysis of serum Krebs von den Lungen 6 (KL-6) and SP-D in peripheral blood demonstrated significant associations with parenchymal lung disease in SSc-ILD patients [35]. BAL also has proven utility in the assessment of alveolitis in Systemic sclerosis (SSc). Schmidt *et al* compared the levels of alveolar cytokines by multiplex ELISA between in 32 SSc patients [36]. They found higher levels of IL-7, IL4, IL-6, IL-8 and CCL2 in BALF from SSC-ILD patients. However, their observations were limited by the small sample size of the cohort. Potential CTD-ILD biomarkers from different matrices including peripheral blood and BAL have been studied in patient cohorts, however, clinical practice has failed to engage these biomarkers in every day practice to date. Further prospective studies are clearly required.

Overall, the evidence to date consists predominantly of limited retrospective or cross sectional studies to support candidate biomarkers with limited power and sample size. Most published

studies are undertaken in single center academic institutions and results may not be broadly applicable. Furthermore, given the clinical heterogeneity of CTD-ILD, it is likely that no single biomarker will have utility in diagnosis and prognosis, nor act as a measure of disease progression and response to therapy.

Future directions

A number of future directions are proposed to address these unmet needs and challenges in CTD-ILD biomarker development (Figure 1):

Ideally, biomarkers will be employed to achieve a number of specific aims in CTD-ILD. Biomarkers may be employed to facilitate screening or diagnosis to identify individuals at high risk of developing ILD, or alternatively to identify those with early, pre-clinical disease. In addition, biomarkers may be used to risk stratify patients at baseline and predict prognosis. They may provide data on disease progression and/or responses to therapy. Furthermore, biomarkers may be employed as surrogate markers for use as clinical trial endpoints or as tools to provide mechanistic pathophysiological insight. Biomarker studies in other forms of ILD, namely IPF, have led to significant ongoing improvements in our understanding of the pathophysiology of pulmonary fibrosis and these data exemplify the types of studies that may be considered in future CTD-ILD studies [37-39].

In conclusion, the development of accurate and feasible biomarkers for the diagnosis, prognostication, analysis of disease progression and therapeutic responses is an important research endeavor with considerable clinical practice and clinical trial implications. Further deliberations are required from multidisciplinary stakeholders to determine the best course for the future development of CTD-ILD biomarkers.

Diagnostic Imaging / Histopathology Domain

Imaging

Current understanding

Computed tomography (CT) imaging of the chest has a critical role in identifying and characterizing CTD-ILD and in longitudinal follow-up of ILD when present. Its use must also be balanced against longer-term risk associated with radiation exposure. In addition to ILD, clinically important features that may be identified on CT include evidence of airways, pulmonary vascular, or pleural diseases. Any pattern of ILD may occur in any of the CTDs and the estimated prevalence of specific patterns varies by disease (Table 1) [40-42].

CT can detect asymptomatic lung disease in a substantial proportion of patients with CTD, and these changes may progress slowly over time (Figure 2).

Unmet needs

The utility of CT in screening for early CTD-ILD is unknown. If ILD is present, we do not know how to predict which patients will progress, and optimal follow-up and management of patients with early changes remains unclear. Quantitative methods are increasingly used for determining the extent of disease on CT, and have been used to document decrease in extent of disease in CTD-ILD treatment trials [43,44]. However, a standardized quantitative approach has not yet been developed, and the sensitivity of these techniques to identify short-term longitudinal change is unknown.

Future directions

There is a critical need for development of prospective cohorts of well-characterized subjects with SSc, RA, and PM/DM/anti-synthetase syndrome who would undergo CT at enrollment, with follow-up scans at specific intervals. This could be achieved through a multi-institutional network, and perhaps by the collaboration with industry to share CT scans performed in the context of clinical trials. Specifically, the following issues could yield valuable insights: i.) relationship between CT phenotype (UIP, NSIP, OP, LIP) and progression of CTD-ILD or response to treatment, ii.) relationship between baseline extent of abnormality on quantitative CT and

both short-term and medium-term outcome (death, progression, improvement), and iii.) development and validation of techniques for phenotyping and quantifying CTD-ILD.

Histopathology

Current understanding

The decision of whether histologic examination of the lung would be useful in cases of CTD requires an analysis of potential benefit versus risk of an invasive procedure. Microscopic examination of surgical lung biopsies from patients with CTDs often shows histologic clues which support an autoimmune etiology over idiopathic or other disease (Table 2) [45-47]. Some of these histologic features have been shown to be related to prognosis (e.g., fibrosis), but none have been influential in determining treatment decisions [48-50]. These cases often do not fit into a single histologic category when using the criteria for idiopathic interstitial pneumonia, and instead show overlapping features of two or more entities [51]. The risk of mortality from surgical lung biopsy has been recently evaluated [52,53]. In two large series in the United States and the United Kingdom, the 30-day mortality rate was 1.5% and 1.0%, respectively, for elective surgical lung biopsies. However, in the US series, the risk of death was 6.0% in patients with CTDs. The odds ratio for 90-day mortality in patients with CTD was similar to that of the overall cohort in the United Kingdom study. There was increased risk of mortality in patients being treated with glucocorticoids.

The question of whether to obtain a surgical lung biopsy is dependent upon the clinical situation. There are several scenarios often encountered: i.) A patient has known CTD, has been shown clinically and/or radiographically to have ILD (Figure 3), and the ILD is progressing typically. In this case, the members of the panel choose not to biopsy because results of a biopsy would not alter the treatment strategy. ii.) A patient has certain clinical or serologic features suggesting possible CTD-ILD but does not meet established criteria for a CTD. In this case, a biopsy may be performed to assess whether certain histologic features support an autoimmune ILD (e.g. “interstitial pneumonia with autoimmune features”) that might impact

treatment strategies. Iii.) A patient has known CTD but has an atypical clinical scenario suggesting hypersensitivity pneumonitis, drug-induced lung toxicity or has an atypical radiographic pattern. In this case, a biopsy may be indicated to differentiate hypersensitivity pneumonitis, drug-toxicity or an infectious etiology (Figure 4) rather than CTD-ILD.

The availability of anti-fibrotic therapies raises the question of whether a biopsy may contain certain histologic features that would guide therapy (e.g. whether a CTD patient with UIP pattern of fibrosis should be offered anti-fibrotic therapy). However, there are currently no data available to answer this question.

Future directions

The recent advances with the technique of cryobiopsy [54] – and wider application of this innovative procedure – may provide valuable insights into lung histopathology in CTD-ILD. However, as recently emphasized by an international cryobiopsy working group [55], the technique has not yet been standardized and its place in the diagnostic algorithm of ILD remains to be defined. In part, this reflects concerns over the diagnostic yield and safety of the procedure, along with the rapid spread of the technique without safety or competency standards [55]. Furthermore, another limitation and concern regarding cryobiopsy is the substantial procedural variability among centers and interventional pulmonologists [55]. As usual practice is not to obtain surgical lung biopsy in "typical" scenarios as discussed above, the advent of cryobiopsy may change this paradigm by providing a safer and easier approach to obtaining parenchymal lung tissue. Time will tell whether cryobiopsy becomes a common procedure in the evaluation of ILD, but if it does, we would anticipate that access to far greater numbers of histopathologic samples in CTD-ILD will allow for a greater understanding of the correlations between lung injury patterns on HRCT and histopathology. Furthermore, cryobiopsy might also lead to insights into whether specific autoimmune histopathology features are more predictive of underlying CTD and could help with refining of the histopathologic criteria for interstitial pneumonia with autoimmune features (IPAF) [45]. We anticipate a need for approaches based on imaging or histopathology to optimize treatment

approaches, i.e. anti-inflammatory vs. anti-fibrotic therapies – and having more access to lung tissue, should enhance such strategies as tissue remains the gold standard to define presence of fibrosis.

Treatment / Clinical Trials Domain

Current understanding and statement of the problem

The clinical management of CTD-associated ILD is challenging as i) the natural history remains poorly understood though with significant recognized disease and individual patient heterogeneity, ii) there are no licensed therapies and iii) with the exception of recent clinical trials in SSc-ILD [44,56,57],there have been a paucity of interventional clinical trials. A similar dilemma existed in IPF, but over the last decade the performance of multiple large multicenter clinical trials in IPF led to a much better understanding of the disease trajectory, and licensed antifibrotic therapy. There are significant challenges to embarking on large clinical trials in CTD-ILD, but the substantial unmet need, especially in RA-ILD and SSc-ILD are a powerful incentive for overcoming these obstacles.

Phenotypic heterogeneity

Clinical trials strive to recruit subjects with diseases of uniform pathobiology and natural history (i.e. homogeneity). The CTD-ILDs have complex systemic manifestations, multi-compartment pulmonary disease and a highly variable natural history. Their interstitial component can be classified according to the recognized pathologic patterns of the idiopathic interstitial pneumonias (IIP) [58]. The most common histological patterns associated with CTD are non-specific pneumonia (NSIP) and UIP, but any of the pathologic patterns can occur. Given that the systemic disease in CTD is immune-driven, there is a rational reason to believe that humoral and T-cell directed inflammatory processes contribute to the lung injury. However, many subjects with CTD-ILD develop progressive ILD despite treatment with a variety of immunomodulatory agents that control the underlying disease.

Future directions

One option to improve study subject homogeneity is to pool subjects based on the underlying pathologic pattern of the ILD rather than the specific CTD, (e.g., grouping patients with a UIP pattern of disease regardless of the underlying CTD). One limitation to this approach is that biopsy is infrequently performed in CTD-ILD so the pathologic pattern cannot always be confirmed. Even when a biopsy is performed, a 'classic' UIP histologic pattern is relatively uncommon, and 'mixed' patterns are frequent. The radiographic pattern seen on high-resolution computerized tomography (HRCT) of the chest is often used as a 'surrogate' for lung biopsy, and thereby to classify the type of CTD-associated ILD. This is common practice in the IIPs based on consensus criteria and it seems intuitively attractive to extrapolate this HRCT classification to CTD-ILD. However HRCT patterns have not been as robustly correlated with pathology in CTD-ILD. The relationship between HRCT patterns and disease progression is reasonably well established in idiopathic disease (e.g., a UIP pattern is associated with a worse outcome than a non-UIP pattern), but comparative studies in CTD-ILD are scarce. There is a pressing need for longitudinal HRCT-based studies in CTD-ILD. Presently, it may be more practical to perform trials according to the underlying CTD and subsequently stratify according to HRCT pattern.

Natural history diversity

Some CTD patients have clear symptoms of lung disease at the time of ILD diagnosis. Others have 'subclinical' disease i.e. radiological abnormalities of ILD in the absence of symptoms, and some have no evidence of lung disease at the time of the CTD diagnosis, but are at risk of developing ILD. There are no consensus guidelines that define either subclinical or clinically overt ILD in this context. Any potential definition would have to include subjective (symptoms scores), chest imaging with qualitative and quantitative HRCT scoring and pulmonary physiology. For instance, subclinical CTD-ILD could be defined by a threshold in extent and pattern of abnormality on HRCT in the setting of normal pulmonary physiology and the absence of respiratory symptoms. Clinically overt CTD-ILD could be defined as HRCT abnormality plus lung function impairment or decline and/or respiratory symptoms. This potentially offers a

unique opportunity to initiate clinical trials for all 'stages' of disease and therein generate much needed natural history data.

Future directions

An attractive model would be to enroll unselected patients with CTD into a multicenter longitudinal observational cohort, in which both incident and prevalent patients of all stages could be studied (Figure 5). In isolation, unbiased observational cohort studies, though informative, can be difficult to perform and fund. A therapeutic intervention is more likely to be attractive, and is easy to justify in clinically overt CTD-ILD, but in patients with subclinical or 'at risk' of ILD the justification is more nuanced. A number of these 'at-risk' patients will develop ILD, but the proportion and time-scale is uncertain. In fact, such trial design was recently instituted in a phase 3 trial of anti-IL-6 antagonist in patients with early SSc with elevated acute phase reactants [59]. Moreover, some of these patients are likely to be receiving treatment for extra-pulmonary features of their CTD. Treatment, in the context of a trial, could only be justified if the intervention was known to have low risk of harm. Mycophenolate mofetil (MMF) is a commonly used immunosuppressant in various CTD-ILDs. In early diffuse SSc, MMF is used for management of skin fibrosis, although there are practice differences. Consideration can be given to case control or longitudinal observational cohorts to assess the incident cases of ILD in those treated with MMF versus not, accounting for covariates such as duration of disease, ethnicity, autoantibody status, and geographic distribution. The safety profile is good and it may be ethically justifiable for a randomized controlled trial of MMF for primary prevention of ILD in at-risk patents with CTD.

Addressing systemic manifestations

Well-executed clinical trials demand a defined standard of care. For subjects 'at-risk' of CTD-ILD and with subclinical ILD, this would be 'no-treatment' for the underlying ILD. While there are currently no approved drugs for the treatment of CTD-ILD, there are ongoing late phase trials with pirfenidone and nintedanib, drugs currently licensed for IPF, that include subjects with clinically significant CTD-ILD. Many clinicians use glucocorticoids and/or other

immunomodulatory drugs, commonly cyclophosphamide (CYC), MMF or azathioprine, for CTD-ILD. In rapidly progressing CTD-ILD, which can occur, for example, in dermatomyositis, these and other agents are accepted as appropriate therapy. A similar case may be made for SSc-ILD where there is some prospective trial evidence of efficacy for CYC and MMF [44,57], especially in specific subgroups. Thus, while placebo-controlled studies may still be ethically viable for patients with CTD-ILD, the fact that routine care often includes immunomodulatory therapies makes such trial design more difficult to successfully implement and recruit. Trial stratification methodology could be employed to ensure the veracity of the results.

Endpoints for clinical trials in CTD-ILD

Trial endpoints are often dependent on the phase of study and study aims. For subjects recruited into a trial of CTD at risk of ILD, the end point would be the development of subclinical or clinically overt ILD, as defined *a priori*. There have been few efficacy trials in the setting of clinically overt CTD-ILD and primary endpoints are not well established. In IPF, mortality, while clinically relevant, does not appear to be a feasible primary end-point [60]. Because the association between decline in forced vital capacity (FVC) and subsequent death is high, change in FVC is now the established primary endpoint in IPF efficacy trials and has been recognized as a surrogate for mortality by regulatory agencies. In contrast to IPF, our understanding of the behavior of CTD-ILD within a trial setting, in terms of mortality, change in lung function and hospitalizations is very limited. It is unlikely that studies in CTD-ILD powered on a mortality endpoint could be practically performed. There are data to confirm that change in FVC correlates with mortality in CTD-ILD as it does in IPF [27,61] but hospitalization rate is unknown. Tools, such as blood biomarkers and/or 'risk scores' to enrich recruited subjects with a higher rate of predicted 'events' during the period of observation would be invaluable.

In the absence of an established relevant single end-point, a composite 'event-driven' endpoint may be a tempting solution, comprising for example ≥10% decline in FVC, ≥15% decline in DLCO, hospitalization or death [62,63]. However composite endpoints present their own difficulties that may limit interpretation of the data [64]. Lastly, patient-reported outcomes (PROs) including

dyspnea, cough or quality of life should be considered in all efficacy trials. The OMERACT workshop recently provided consensus based domains and PROs for use in clinical trials. Although some PRO-related instruments, such as the Mahler dyspnea index and St. George's Respiratory Questionnaire have been validated via clinical trials (SLS-I and II)[65] and observational cohorts, many have not. Therefore ongoing and future trials should proactively validate outcome measures. Table 3 summarizes ongoing clinical studies in CTD-ILD submitted to ClinicalTrials.gov.

In conclusion, the unmet need for therapy in CTD-ILD combined with a plethora of potential 'antifibrotic' drugs in industry pipelines demands a new age of clinical trials. Lessons learned from studies in IPF suggest that recruitment to well-designed studies can both increase the understanding of the natural history of disease and lead to the discovery of effective treatments. Recruitment of CTD patients from the full spectrum of disease, from 'at-risk' of ILD to clinically overt CTD-ILD is ambitious and would require multicenter cooperation, but offers the potential for dramatically increasing our knowledge in these under-studied disorders.

Translational Research Domain

The purview of translational research in CTD-ILD is exceptionally broad. In this section we focus on several themes identified by this panel as of particular relevance due to high levels of future promise as well as addressable barriers to progress. The discussion will be divided into i.) Databases/Bioregistries, ii.) Technology for Precision Medicine, iii.) Quality of Life and iv.) Animal Models.

i. Databases and Bioregistries

Statement of problem

While randomized control trials remain the gold standard of hypothesis driven clinical research questions on treatment efficacy, the information contained in clinical registries and biorepositories offers unique opportunities for advancing our understanding of CTD-ILD. Particularly in the context of rare diseases, like CTD-ILDs, maximizing the use of existing

registries and biorepositories will be necessary to form the groundwork for targeted clinical trials.

Current understanding

The accumulation of real-world registry data over time provides a more dynamic and evolving picture of disease course, which is more generalizable and relevant to the 'real-world' patient population [66]. Targeted biological sample repositories, particularly when aligned to clinical registry information, may be used with maximal effect both to specifically inquire into the connected contributions of genetic susceptibility, environmental and lifestyle factors in influencing disease pathogenesis, and the development of a future individualized precision medicine approach.

Challenges/Unmet needs

Significant barriers to data sharing exist, where clinical and biological registries are designed within disconnected, institutional 'silos of information' or where no available technological platform exists for data sharing between institutions, at a national or international level. Differences in defining the terms of reference of diseases for inclusion into disease registries or in the precise domains of clinical information stored, prevent clinical equivalence between registry data sets that in turn prevent the merging of information between research groups. For biological samples, variations in sample collection and processing can lead to variations in the quality of available bio-banked material and may affect their suitability for sample collaboration between groups. This is of particular importance with rare diseases, where larger populations are required to enable sufficient collection of relevant material.

Proposed future directions

A more collaborative approach from the research community is required to maximize scientific output, with an emphasis on improved sharing of available data and on the standardization of future data collection through the formation of national and/or international disease registries. One such effort has been recently launched by the Pulmonary Fibrosis Foundation (PFF) with

the creation of a large network of PFF Care Centers around the United States. Within the PFF Care Network a collaborative PFF Registry was established and now has over 2000 patients with diverse forms of ILD enrolled. High-quality clinical data are being collected, there is an accompanying biorepository, and a potentially valuable research database will be able to be accessed by independent investigators (https://www.pulmonaryfibrosis.org/medical-community/pff-patient-registry).

ii. Technology for Precision Medicine

Statement of problem and current understanding

In pursuit of truly personalized medicine, the capacity to monitor individuals in their unique environments should be paramount. While a number of technologies have emerged to assess physiology (e.g., heart rate, blood pressure), mobility (accelerometer) and even to measure PROs on a daily basis, this technology has not adequately evolved to include outcomes relevant in CTD-ILD nor has it been adopted in CTD-ILD research. The thoughtful proactive development and implementation of technology will provide a powerful new tool for research, including the assessment of therapy and potentially direct therapeutic interventions for CTD-ILD.

Challenges and unmet needs

Technological barriers to progress exist. The pace of technological advancement in information systems, including mobile technologies, has outstripped the rate of progress seen in healthcare information sharing. The academic healthcare community runs the risk of losing opportunities to improve and shape the quality and quantity of data platforms that may be used to further enrich the information available for research.

Proposed future directions

Significant opportunities exist for the research community to influence the development of research technology, including mobile technologies to enhance the type and quality of data-collection. This could be achieved through partnership with bio-technological and engineering research communities, and through engagement with patient-centered organizations to ensure

that both the research community and the patients themselves benefit from future partnerships.

iii. Quality of Life Outcome Measures

Statement of problem and current understanding

Little is understood about the impact of CTD-ILD on daily living, including quality of life (QOL). Challenges to studying and understanding the effects of CTD-ILD on health related QOL include the differing organ manifestations and effects of specific CTDs and teasing out the pulmonary and extra-pulmonary contributions to quality of life. Nonetheless, how our patients experience disease is critical to understand as we assess the impact of our treatments and interventions. PRO questionnaires are designed to assess the impact of disease on patient function and individual subjective life experience. They remain an important outcome measure, both through their reproducibility in quantifying the impact of disease severity and by their sensitivity to change.

Challenges and unmet needs

The evaluation of how a specific disease impacts QOL for patients with simultaneously overlapping symptoms of both ILD and systemic disease manifestations, presents clear challenges. While some rheumatic disease specific QOL instruments including the Systemic Sclerosis QOL questionnaire (SYSQ) contain domains which are specific for respiratory manifestations of disease, others including the Rheumatoid Arthritis Quality of Life (RA QOL) questionnaire, which was validated using RA patients without ILD, have not been designed to determine the specific impact of RA-ILD on health related QOL [67,68]. Although efforts have been made to validate lung-specific QOL measures such as the King's brief ILD questionnaire (K-BILD) for ILD other than IPF, other measures including the St. George's Respiratory Questionnaire, which was initially designed for patients with chronic obstructive pulmonary disease, have been subsequently validated for patients with IPF, but not those with CTD-ILD [69,70].

Proposed future directions

Future work is needed to determine whether a new QOL tool should be designed, tested and validated in collaboration with CTD-ILD patients to fully reflect all disease specific impacts on QOL. Alternatively, consideration should be given as to whether an existing, generic, and/or symptom specific tool, which has previously validated in IPF or a CTD can be tested and validated in the CTD-ILD population. The establishment of a QOL outcome measure working group is required to reach a consensus on whether such instruments should be (a) symptom-specific, (b) disease specific or (c) generic, such as the use of the short-form 36 QOL questionnaire. Validation testing of candidate QOL outcomes, with engagement of patient-centered organizations, to assess their accuracy in determining their association with disease severity and sensitivity to change, should be performed.

iv. Animal Models

Statement of problem, current understanding, unmet needs

Animal models provide a critical tool in identifying relevant biological pathways in disease as well as providing a model to test therapeutic agents. To better understand the pathogenesis of fibrotic lung diseases, a number of animal models have been developed. Recent advances have allowed for the development of models to study targeted injuries of Type II alveolar epithelial cells, fibroblastic autonomous effects, and targeted genetic defects [71]. However, there are few models of CTD-ILD. Although a recently described RA-ILD mouse model in SKG has been described, other animal models for CTD including tight-skinned mice, either have not been characterized for lung disease or do not manifest lung disease [72,73]. It remains uncertain whether murine models of fibrotic lung disease, which including bleomycin induced, radiation induced or adoptive cell transfer models of lung fibrosis [71], are sufficiently similar to human CTD-ILD to be of use in identifying molecular targets for drug development [74].

Proposed future directions

An inventory of currently existing animal models of ILD, documenting their disease equivalence to specific manifestations of human CTD-ILD, as well as any known overlap of the known molecular mechanisms of human and murine disease is needed. Where adequate animal models do not currently exist, funding and research efforts will be required to develop better animal models of CTD-ILD, which more closely reflects the human condition and are therefore relevant for disease pathway evaluation and drug development in pre-clinical studies.

Summary

This document summarizes the proceedings of a recent CTD-ILD Summit that consisted of a multidisciplinary panel of international clinician scientists with expertise in CTD-ILD. Key clinical aspects are outlined, and a variety of research initiatives are proposed (Table 4) with hopes of addressing the many unmet needs and challenges within the complex intersection between CTD and ILD. Our hope is that further multidisciplinary collaboration around the care and research of patients with CTD-ILD will lead to greater disease awareness, earlier disease detection and diagnosis, implementation of interdisciplinary treatment approaches with novel therapeutic agents – and ultimately improved quality of life and outcomes for those afflicted with these diseases.

Table 1. Connective tissue disease–associated interstitial lung disease: Estimated prevalence rates, lung injury patterns, and clinical presentation

Connective Tissue Disease	Estimated Prevalence of ILD [1,2,6,18,45,75,76]	ILD Pattern	CTD is Occult
Dermatomyositis Polymyositis Antisynthetase syndrome	40%	NSIP with OP NSIP OP UIP	Often
Rheumatoid arthritis	10% clinical, 30% subclinical	UIP NSIP OP	Less often
Sjogren's syndrome	40%	NSIP UIP LIP	Less often
Systemic sclerosis	30-40% clinical 80% subclinical	NSIP UIP	Less often

Systemic lupus erythematosus	8-12%	DAH, NSIP	ILD is infrequent
Interstitial pneumonia with autoimmune features	100%	NSIP OP NSIP/OP UIP, LIP	Always

CTD: Connective tissue disease; ILD: Interstitial lung disease; LIP: Lymphocytic interstitial pneumonia; OP: Organizing pneumonia; UIP: Usual interstitial pneumonia; DAH: Diffuse alveolar hemorrhage

Table 2. Histologic features associated with underlying connective tissue disease

Prominent lymphoid aggregates with germinal center formation
Increased lymphocytic inflammation with plasma cell infiltrates
Overlapping features of peripheral honeycombing with central fibrosis
Involvement of multiple pulmonary compartments (interstitial disease with additional small airway, vascular, or pleural disease)
Nonspecific interstitial pneumonia pattern with additional organizing pneumonia

Table 3: Pending or currently recruiting clinical trials in CTD-ILD (as of September 2018)

TRIAL NAME	ClinicalTrials.gov Identifier:	STUDY TYPE	DISEASE ENTITY	PARTICPANTS (TARGET or ESTIMATED)	ENDPOINTS
Abatacept in RA-ILD (APRIL)	NCT03084419	Interventional (Phase 2 open label)	RA-ILD	30	Number of participants without significant decrease (≥ 10%) in Forced Vital Capacity (FVC) measurements following abatacept treatment
Phase 2 Study of Pirfenidone in Patients With RA-ILD	NCT02808871	Interventional (Phase 2)	RA-ILD	270	Incidence of the composite endpoint of decline in percent predicted FVC of

					10% or greater or death.
BI 1199.247 Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD)	NCT02999178	Interventional (Phase 3)	Progressive fibrosing ILD including CTD-ILD	600	Annual rate of decline in Forced Vital Capacity (FVC; in mL) over 52 weeks
BI 1199.214 A Trial to Compare Nintedanib With Placebo for Patients With Scleroderma Related Lung Fibrosis	NCT02597933	Interventional (Phase 3)	SSc-ILD	520	Annual rate of decline in FVC in mL
Scleroderma Lung Study III - Combining Pirfenidone With Mycophenolate	NCT03221257	Interventional (Phase 2)	SSc-ILD	150	Change from baseline, measured at 3-month intervals, in the mean forced vital capacity
Study to Compare the Efficacy of Mycophenolate Mofetil in Systemic Sclerosis Related Early Interstitial Lung Disease	NCT02896205	Interventional (Phase 3)	SSC-ILD	60	Change from baseline in Forced vital capacity (FVC) at 6 months, after treatment with oral mycophenolate mofetil or placebo
Abituzumab in SSc-ILD	NCT02745145	Interventional (Phase 2)	SSc-ILD	22*	Annual rate of absolute Forced vital capacity (FVC) change in volume

					(milliliter [mL])
Abatacept for Myositis-ILD	NCT03215927	Interventional/ Pilot study	Synthetase-ILD	20	The primary outcome criteria for efficacy will be the FVC% change from the baseline visit to week 24 between the 2 treatment arms (standard of care/placebo vs. standard of care/abatacept/
Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD (RECITAL)	NCT01862926	Interventional	CTD-ILD	116	Absolute change in FVC [Time Frame: 48 weeks]

Table 4. Summary of Proposed Future Directions in CTD-ILD

- *Standardized international criteria for the classification of CTD-ILD*
  Deliver international guidelines that standardize clinical, radiological, histopathology and biological parameters for the diagnosis and classification of CTD-ILD

- *Define the natural history of CTD –ILD*
  Deliver multicenter global clinical networks of well–defined disease groups – encompassing longitudinal integrated collections of phenotypic, physiologic, radiographic, genomic and biological data

- *Clinical Care*

  Deliver multidisciplinary clinics between rheumatology, pulmonary and allied healthcare professionals to enhance patient care

- *Cross-disciplinary clinical training*

  Deliver cross-disciplinary Fellowship clinical training opportunities for medical graduates

- *Biomarker development*

  Deliver biomarker platforms in a precision medicine basis to guide the optimal therapies to the individual patient.

- *Early screening strategies for ILD*

  Deliver early detection strategies that identify ILD earlier and ultimately predict those at highest risk for disease progression

- *Integration of imaging and histopathology*

  Generate ILD imaging repositories across the spectrum of CTD-ILD that correlate with histopathology specimens

  Refining cryobiopsy techniques to enrich the availability of parenchymal lung tissue specimens

- *Clinical Trials of the Future in CTD-ILD*
  - Validation of CTD specific trial end-points
  - Incorporation of novel technologies to validate quality of life endpoints and patient reported outcome measures
  - Develop and incorporate composite end-points specific to CTD-ILD
  - Development of an integrated clinical, radiological, laboratory, biological database solution that aligns large data sets and allows maximum interrogation

- *Translational Research*
  - Formation of shared national/international registries with biological repositories
  - Creation of new, optimization of existing, quality of life measures in CTD-ILD

- Development of animal models of CTD-ILD

Figure legends

Figure 1. CTD-ILD biomarker development: Proposed future directions

Figure 2. Progression of interstitial lung abnormalities over 3 years in a patient with systemic sclerosis

Figure 3. Typical surgical lung biopsy showing mixed pattern of subpleural and centrilobular fibrosis with prominent lymphoid aggregates (scale bar = 1 mm)

Figure 4. Surgical lung biopsy in a patient with rheumatoid arthritis treated with biologics who developed nodular ground-glass opacities on CT. The biopsy shows granulomatous Pneumocystis pneumonia (scale bar = 400 μm)

Figure 5. Suggested clinical trial disease population stratification and corresponding primary trial outcome

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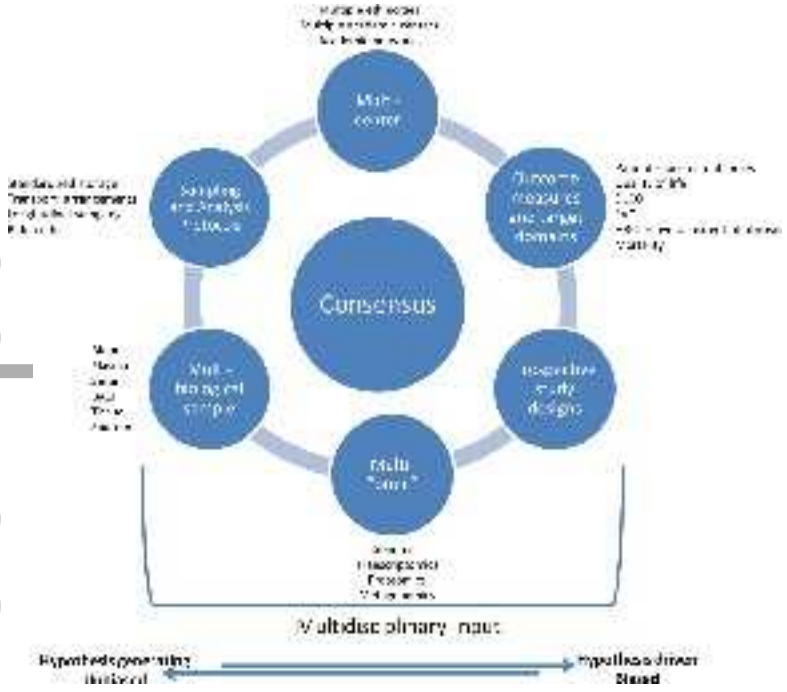

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