Introduction

Interstitial lung diseases (ILD) represent a large, heterogeneous group of more than 200 different entities, most of which are rare diseases (ATS, 2002; Travis, 2013). ILD are classified together due to similar clinical, radiographic, physiologic and/or pathologic manifestations. These lung diseases affect the pulmonary interstitium in addition to involvement of alveolar structures and small airways. Main categories include ILD related to environmental exposure, connective tissue disease (CTD)-related ILD, sarcoidosis, and the idiopathic interstitial pneumonias such as idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (Ryerson 2013).

The majority of ILD cases are IPF and CTD-ILD (ATS, 2002; Travis, 2013; Kreuter, 2015). IPF is the most common of the constellation of lung diseases that comprise ILD, and includes 24% of all cases (Hyldgaard, 2015). CTD-ILD, on the other hand, comprises 14% of all ILD (Hyldgaard, 2015). The CTDs are a diverse group of systemic autoimmune disorders that includes systemic sclerosis (scleroderma), rheumatoid arthritis (RA), polymyositis/dermatomyositis, Sjogren’s syndrome, systemic lupus erythematosus, or mixed CTD. These disorders often involve end-organ damage, including ILD (Castelino, 2010). The frequency of ILD in these patients varies across the CTDs and is difficult to ascertain given varying criteria and methods of assessment that range from pulmonary function tests, high-resolution computed tomography (HRCT), or lung biopsy.

Differential Diagnosis in ILD

The clinical presentation of ILD often follows a similar pattern, encompassing dyspnea, restrictive pulmonary physiology, and abnormal imaging studies. An accurate diagnosis is paramount to determining a prognosis and selecting therapy for ILD. Yet, many patients report significant delays or a “missed” diagnosis, delaying initiation of appropriate therapy (Durheim, 2015; Hu, 2016; Nair, 2015; Mathai, 2016).

IPF is defined as “a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs” (Raghu, 2011). The incidence and prevalence of IPF between 2001 and 2011 were higher than previous estimates in a 2014 analysis of Medicare beneficiaries (Raghu 2014). Further, the prevalence of IPF increased annually from 2001 to 2011, which has been attributed to an earlier diagnosis, longer survival, and more awareness of IPF.

Unexplained dyspnea, cough, and inspiratory crackles should prompt a suspicion of IPF. A diagnosis of IPF based on the 2011 guidelines from ATS/ERS/JRS/ALAT requires the exclusion of other known causes of ILD, such as environmental exposure, the presence of CTD, or drug toxicity (Raghu 2011). Additionally, confirmation of a diagnosis requires the presence of either a pattern of usual interstitial pneumonia (UIP) on HRCT or a combination of HRCT findings and characteristic results from surgical lung biopsy (Raghu 2011). The UIP pattern on HRCT has characteristic features of basal and subpleural predominance, reticular abnormality, and honeycombing with or without traction bronchiectasis (Figure 1; Raghu, 2011). Patients with atypical signs on HRCT and “probable” or “possible” IPF pose challenges for a prompt, accurate diagnosis, particularly for less experienced teams (Wells, 2013b). Further, some patients may not be candidates for a surgical lung biopsy. The lack of guidance for these cases requires multidisciplinary collaboration and discussion during the diagnostic process.
ILD greatly increases risk for mortality in patients with CTD and it is important to distinguish these patients from other patient subgroups with CTD. Pulmonary manifestations of CTD may precede the onset of systemic disease, and pulmonologists may be confronted with interpreting subtle signs of systemic rheumatic disease and differentiating CTD-related ILD from other conditions, such as idiopathic interstitial pneumonia. Careful interpretation of a patient's medical history, physical examination, and imaging and histologic features is required to detect CTD-ILD. HRCT patterns vary across CTD-ILD, but can be used in the differential diagnosis. Nonspecific interstitial pneumonia is the pattern observed most frequently in CTD-ILD such as systemic sclerosis. However, UIP is the most common pattern observed in patients with RA-associated ILD (Hallowell, 2014; Bahmer, 2016). Patients with RA and a pattern of UIP have a poor prognosis, comparable to that of IPF, compared with RA patients who have other patterns of interstitial pneumonia (Kim, 2010).

Serological testing has been recommended to aid in making these distinctions; however, clinical application of autoantibodies and other tests varies (Fischer, 2015). In 2016, a group of clinicians proposed a diagnostic algorithm for pulmonologists to guide a rational and stepwise approach to serological testing for ILD (Bahmer, 2016). This algorithm includes laboratory screening for autoantibodies against Ro/SSA, La/SSB, Jo-1 and CCP, such as an ANA, ANCA and RF test to screen for myositis, Sjogren's syndrome, RA, and other potential CTD (Figure 2). Guidance on more advanced serologic testing is included if initial screening fails to identify a cause, and the importance of multidisciplinary approaches and early consultation with an experienced rheumatologist are emphasized (Bahmer, 2016). It is also possible that some patients with idiopathic interstitial pneumonia possess features suggestive of CTD, but do not fully meet established criteria for a CTD. A recent task force proposed the term interstitial pneumonia with autoimmune features for such patients (Fischer 2015).
Guiding ILD Patients Through the Diagnostic Process

As noted above, the differential diagnosis of ILD may be clinically challenging, and patients often report misdiagnoses or delays in receiving a confirmed diagnosis. Not surprisingly, ILD patients report frustrations and significant emotional consequences of their disease; approximately 43% of respondents in one survey felt that their family and friends did not understand what they were going through during the diagnostic process (PFF, 2015). As such family and caregivers should be involved in the diagnostic process and counseled that ILD is a heterogeneous group of disorders with a variable disease course, and that an accurate diagnosis is important to not only guide treatment selection, but also provide information on prognosis.

Management of ILD: Focus on IPF

Until recently, numerous clinical trials conducted in IPF patients reported disappointing results despite plausible biologic rationales and preliminary positive results. Some agents were even demonstrated to cause harm and altered long-standing treatment paradigms. These findings also instigated changes in clinical trial design and selection of efficacy endpoints for IPF.
For example, the PANTHER-IPF clinical trial examined a combination of prednisone, azathioprine, and N-acetylcysteine widely used as a treatment for IPF. However, in this prospective clinical trial, a planned interim analysis revealed that patients in the combination-therapy group had increased rates of death and hospitalization compared with the placebo group. These observations and the lack physiological or clinical benefit for combination therapy, prompted termination of the combination therapy group at a mean follow-up of 32 weeks (IPFCRN, 2012). Subsequent analyses indicate that subpopulations of patients who participated in the PANTHER IPF trial who have specific IPF genotypes may benefit from this regimen, warranting further study (Oldham, 2015).

In late 2014, two therapies received approval for use in IPF. The tyrosine kinase inhibitor nintedanib received approval based on two randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) that evaluated the efficacy and safety of nintedanib versus placebo. These studies revealed that nintedanib reduced the decline in in forced vital capacity (FVC) (Richeldi, 2014). The most frequently reported adverse event in these trials was diarrhea; however, this led to discontinuation of study drug in less than 5% of the patients. Analysis of data from the clinical trials with nintedanib indicates that this agent has beneficial effects on slowing disease progression (Richeldi, 2016).

The anti-fibrotic and anti-inflammatory agent pirfenidone demonstrated conflicting results in initial clinical trials, with one trial showing significant reductions in the decline in FVC and another failing to demonstrate a benefit over the placebo arm (Noble, 2011). The beneficial effect of pirfenidone was confirmed in a subsequent phase 3 trial (ASCEND) that revealed that pirfenidone reduced disease progression (as measured by lung function) and exercise tolerance, and improved progression-free survival (King, 2014). Pirfenidone was associated with a favorable safety profile in these trials. A meta-analysis of data from the ASCEND and CAPACITY trials also confirmed that use of pirfenidone results in a significant reduction in all-cause mortality (Nathan, 2015).

Patients with IPF also have a significantly increased risk for comorbidities compared with age-matched controls. Common comorbidities include pulmonary hypertension, emphysema, gastroesophageal reflux disease, obstructive sleep apnea, ischemic heart disease, thromboembolic disease, and mood disorders such as depression (Collard, 2012). The presence of these comorbidities may result in an atypical presentation. An accurate diagnosis and comprehensive management of IPF requires recognition of these comorbidities and implementation of steps to treat them simultaneously. In fact, addressing these comorbidities may improve clinical outcomes.

The positive clinical trial results and approval of new therapies prompted a release of updated guidelines for IPF. These include conditional recommendations for the use of nintedanib and pirfenidone and strong recommendations against other therapies such as warfarin and prednisone, azathioprine, and N-acetylcysteine (Table 1) (Raghu, 2015). Studies of additional therapies for IPF, including an antibody that interferes with the action of connective tissue growth factor and agents that target immune activation (interleukin-13) or collagen cross-linking are ongoing. Unfortunately, a recent study with simtuzumab, a monoclonal antibody against lysyl oxidase-like-2, a catalyst of collagen cross-linking, failed to demonstrate an effect on progression-free survival in IPF (Raghu, 2017).

Management of ILD: Focus on CTD-ILD

Therapeutic approaches for CTD-ILD depend on the type and standard therapies for a given CTD. Advancing treatment for patients with CTD-ILD has been complicated by a lack of validated outcome measures and by inconsistent use of endpoints in clinical trials. A core set of measures in the domains of lung physiology, lung imaging, survival, dyspnea, cough and health-related quality of life has been proposed for use in clinical trials of potential treatments for CTD-ILD (Saketkoo, 2014a; Saketkoo, 2014b).

ILD is among the extra-articular manifestations associated with RA, and a contributor to morbidity and mortality in this population. Patients with RA receive non-biologic disease-modifying drugs (DMARDs) such as methotrexate, or biologic DMARDs such as the anti-tumor necrosis factor (TNF) inhibitors or rituximab for their joint symptoms. Induction or exacerbation of ILD is a rare complication of the DMARDs, and a causal relationship has not been established (Roubille, 2014). Severity of disease, age, and prior use of DMARDs may increase the risk. Additionally, some small case series have demonstrated improvements in lung function in patients receiving anti-TNF therapy or rituximab (Antoniou 2007; Sharp 2016). Therefore, clinicians must conduct a careful risk-benefit assessment with their RA patients when initiating a DMARD, and pulmonary safety should be monitored (Roubille, 2014).
Lung fibrosis is a significant driver of mortality in systemic sclerosis; therefore, several clinical trials have been conducted in this population. In the randomized Scleroderma Lung Study (SLS) I, cyclophosphamide was demonstrated to stabilize or improve lung function, yet with short-lived benefits and tolerability issues (Tashkin, 2006; Iudici, 2015). Further, long-term use of cyclophosphamide is precluded by its potent immunosuppressant properties and risk for treatment-related malignancies. Clinical trials also indicate that mycophenolate mofetil has improved efficacy and tolerability compared with cyclophosphamide, and can be used for longer periods of time, prompting investigation in SLS II. In this study, patients with symptomatic scleroderma-related ILD were randomized to either mycophenolate mofetil for 2 years or cyclophosphamide for 1 year (Tashkin, 2016). Both agents improved lung function and, while mycophenolate mofetil was better tolerated, it did not demonstrate greater efficacy compared with cyclophosphamide (Tashkin, 2016).

There is a need for additional therapies and trials across the spectrum of CTD-ILD (Chartrand, 2015; Volkmann 2015). Given the progress in the treatment of IPF, it is reasonable to investigate nintedanib and pirfenidone for other ILD. For example, nintedanib demonstrated antifibrotic effects in an animal model of systemic sclerosis, suggesting a potential role for management of this therapy (Huang, 2016). In fact, a phase 3 clinical trial of nintedanib was recently initiated in patients with systemic sclerosis and CTD-ILD (NCT02597933), and nintedanib was granted orphan status for the treatment of systemic sclerosis in 2016. Case reports also indicate that pirfenidone improves lung function in patients with ILD and systemic sclerosis. The phase 2 LARIAT trial of bardoxolone in patients with pulmonary artery hypertension (PAH) was recently expanded to include patients with PAH associated with certain types of ILD, including CTD-ILD, since preliminary data indicated that the most significant effects were observed in patients with PAH and CTD-ILD (Reata Pharmaceuticals, 2016). These trials will provide information on whether novel approaches improve outcomes in patients with CTD-ILD.

Guiding ILD Patients Through Selection and Initiation of Therapy

Clinical decisions for ILD require shared decision-making with the patient and caregiver. Available therapies for IPF have comparable benefits on lung function, but there are differences between the dosing frequency and side effect profiles that require patient input. Evidence-based therapies for patients with CTD-ILD are limited, with disease heterogeneity and a lack of consensus further challenging management. Patients and the multidisciplinary CTD-ILD care team should perform a comprehensive risk-benefit assessment when selecting therapy for the underlying CTD and its pulmonary manifestations. Patients and their caregivers also require counseling on symptom management in ILD, including the roles of oxygen supplementation and pulmonary rehabilitation.

Patients and their caregivers should also have realistic expectations about available therapies, their potential adverse events, and the importance of adherence. For example, available therapies slow, but do not stop, disease progression, and patients will eventually experience exacerbations or progressive worsening. Difficult decisions on cessation of therapy, palliative care of symptoms, and comfort care will eventually be required with disease progression.

Conclusions

An accurate diagnosis is needed to guide clinical decisions and counsel ILD patients on their prognosis, but there are clinical challenges in the differentiation of ILD. Clinicians require knowledge of the heterogenous ILDs and up-to-date information on their clinical presentation and the role of imaging, histology and, serologic testing. Although progress has been made in the management of IPF, additional approaches and disease-modifying therapies for ILD are needed. Multidisciplinary collaboration across the disease ILD spectrum—from diagnosis to management—can assist clinicians and enhance patient satisfaction.

References


