Update in Diffuse Parenchymal Lung Disease 2011

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Over the past year, we have witnessed considerable progress in the clinical evaluation/management of diffuse parenchymal lung diseases (DPLDs) and in the elucidation of pathobiological mechanisms. Studies in idiopathic pulmonary fibrosis (IPF), sarcoidosis, and other less common DPLDs, published in this journal and elsewhere, have advanced our understanding of these complex lung diseases. Clinical trials have aided in understanding the natural history of the disease, defining clinical (sub)phenotypes, and informing better study design. Several studies explored the pathophysiologic underpinnings in the development of lung inflammation and fibrosis. A joint consensus statement from multiple international medical societies on the diagnosis and management of IPF was published in 2011. In this update article, we highlight important clinical and basic research advances made over the past year, with a primary focus on those published in this journal.

CLINICAL UPDATES IN IPF

Clinical Guidelines

A noteworthy accomplishment in 2011 was the publication of the revised guidelines for the diagnosis and management of IPF (1). This was the culmination of a joint effort of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society, and the Latin American Thoracic Association. The guidelines were formulated on evidence- and consensus-based recommendations by a group of 24 pulmonologists, 4 radiologists, 4 pathologists, and 4 methodologists (1). This statement replaces the ATS/ERS consensus statement from 2000 (2); therefore, a systematic literature search was not performed for publications before 1996. For the current document, pragmatic evidence-based methodology was applied to answer questions considered relevant by the committee using a stringent and transparent system to determine the quality of the published evidence (3). The major criteria established in the 2000 consensus statement have been eliminated; in the appropriate clinical context, a pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography scan is sufficient to make a diagnosis of IPF. Surgical lung biopsies may be required in uncertain cases, and a multidisciplinary discussion among experienced clinicians, radiologists, and pathologists improves diagnostic accuracy. The committee did not find any proven benefit of pharmacotherapy, reflecting the lack of any drug therapy that has been validated in an unequivocally positive clinical trial with a unanimously accepted, clinically “important” end point(s).

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Clinical Trials

Despite a number of recent negative clinical trials in IPF, we have learned much of the natural history of the disease (4, 5). The BUILD-3 study evaluated the efficacy of bosentan, an endothelin receptor antagonist, in a large, randomized, and placebo-controlled clinical trial (6). The primary end point of the BUILD-3 trial was time to occurrence of IPF worsening, defined as either a worsening of pulmonary function tests (a combined decrease from baseline in FVC of >10% and in diffusing capacity of carbon monoxide of >15%, >4 wk apart), acute exacerbation of IPF, or death (6); this predefined end point was not met. A phase III trial studying the effects of warfarin in IPF, Anticoagulation Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF), was stopped early in 2011 due to ineffectiveness and potential harm to patients with IPF (7).

Tyrosine kinase inhibitors are a promising class of drugs for the treatment of IPF, as they have the potential to target profibrotic mesenchymal cell phenotypes (8). A phase II clinical trial of the safety and efficacy of BIBF-1120, a tyrosine kinase inhibitor that inhibits a number of receptor tyrosine kinases, was recently published (9). The primary end point was the annual rate of decline in FVC. Secondary end points included acute exacerbations, quality-of-life measurements, and TLC. At the highest dose tested of 150 mg twice daily, BIBF-1120 was associated with a trend toward a reduction in the decline in lung function, with fewer acute exacerbations and preserved quality of life. Based on the results of these studies, a larger multicenter phase III clinical trial of BIBF-1120 in IPF has been initiated.

The search for novel antifibrotic agents will gain additional momentum in the face of accumulating evidence against the use of antiinflammatory agents. Triple therapy with prednisone, azathioprine, and N-acetylcysteine was recommended in the 2008 guidelines on IPF of the British Thoracic Society (10), based largely on a 2005 study that demonstrated benefit when N-acetylcysteine was added to a combination of prednisone and azathioprine (11); however, more recent studies suggest a worse outcome of triple therapy when compared with placebo (PANTHER-IPF; NCT00650091). The triple arm of this study was stopped due to higher mortality rates, hospitalizations, and adverse events (NIH news, October 21, 2011) (12). We await publication of these data to provide additional insights and to probe explanations for this finding.

In 2011, pirfenidone was approved for the treatment of IPF in Europe. Two concurrent, randomized, placebo-controlled trials (CAPACITY) measured the change in percentage of FVC after 72 weeks of pirfenidone treatment. The first trial (004) demonstrated a significant reduction in the rate of decline in FVC with an effect size of 4.4% with fewer patients in the treatment group having greater than 10% decline in FVC (20% vs. 35%). The second trial (006) did not demonstrate a statistically significant difference in decline in FVC between the treatment and placebo groups at 72 weeks, but a consistent treatment effect was seen up to 48 weeks (13). A review of the Cochrane Database in 2010 did show improved progression-free survival and improvement

in FVC of 0.08 L with pirfenidone (14). Also, exploratory subgroup analysis of a phase III trial with pirfenidone in Japan demonstrated that patients with vital capacities greater than 70% and a baseline oxygen saturation by pulse oximetry less than 90% were most likely to benefit from treatment with pirfenidone (15). This drug, which had already been approved in Japan in 2008, has not yet received approval by the U.S. Food and Drug Administration. The 2011 ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association guidelines give a recommendation for the use of pirfenidone only in select IPF cases due to the side effect profile and the small treatment effect observed in clinical trials (1, 16). It remains to be seen what impact pirfenidone will have in the future treatment of pulmonary fibrosis, but it is one of the few potential treatments either alone or in combination that has shown potential therapeutic benefit.

Minimal Clinically Important Difference

There is growing recognition of heterogeneity in the clinical course of IPF. This heterogeneity and the lack of surrogate biomarkers to distinguish between different clinical phenotypes make it difficult to effectively design clinical trials. Ley and colleagues (4) analyzed the decline of FVC in seven placebo-controlled trials and concluded that this decline is approximately 150 to 200 ml/yr in patients with IPF. What constitutes a “minimal clinically important difference” (MCID) in relation to absolute or percent-predicted FVC has remained unclear.

The concept of MCID, as originally defined by Jaeschke and colleagues (17) was developed as an approach to elucidating the significance of changes on scores in quality-of-life instruments by comparing them to global ratings of change and thus determining the smallest difference in these scores that patients would perceive to be sufficiently important to warrant a change in the patient’s management. The MCID concept has evolved to incorporate the smallest change in a physiologic function (or other measured end point) that would warrant medical intervention or change in therapy. Two studies by du Bois and colleagues evaluated the MCID in changes of FVC and 6-minute walk test by analyzing cohorts of patients enrolled in previously reported clinical trials (18, 19). An estimated MCID of 2 to 6% decline in FVC was found to be a reliable and responsive measure of clinical status in patients with IPF (18); this notion is also supported by recent studies from the United Kingdom and Japan (20, 21). Similarly, a 24-week decline of 24 to 45 m was associated with a fourfold increase in risk of death at 1 year (19). Because these MCIDs are close to, or even within, the range of inpatient variation, they should not be used for decision making in individual patients; however, they may prove to be valid end points in large clinical trials.

Interferon- γ and bosentan have been investigated in large phase III trials for their potential to slow IPF progression after *post hoc* analysis of preceding trials identified subcohorts of patients who had a survival benefit (5). Both studies failed to meet their primary end points (6, 22), which included the strict criteria of reduction in FVC decline to less than 10%. The application of MCIDs may aid in resolving the conundrum of “positive” results of *post hoc* analysis using quality of life or 6-minute walk test (23, 24) and “negative” results in phase III trials (6, 22). MCIDs may also allow for risk stratification (e.g., by identification of a subset of patients with rapid progressive IPF), thereby enhancing the chances of identifying treatment effects in smaller cohorts. Consensus among clinical investigators on the most appropriate clinical trial design and end points for phase III trials in IPF will be critical in expediting drug development for this disease (25).

Natural History and Risk Stratification of IPF

Data from the clinical trials (noted above) and a Cox proportional hazard model were used to identify independent predictors of 1-year mortality in patients with IPF (26). A risk scoring system comprising four easily obtainable predictors was developed to produce estimates of 1-year mortality risk consistent with observed mortality during the course of these studies; the four predictors were age, respiratory hospitalization, percent predicted FVC, and 24-week change in FVC (26). The applicability and accuracy of this scoring system awaits validation in prospective studies.

Another predictor of mortality is the delay between first IPF symptoms and access to tertiary care; however, the reason for this is unclear, as delayed access did not influence age, lung function at the time of initial evaluation, or likelihood of undergoing lung transplantation (27). Comorbidities might have resulted in false attribution of dyspnea or cough to preexisting conditions that may have influenced mortality. Similarly, IPF may present with uncommon radiographic manifestations, as illustrated by a case of progressive fibrotic cavity mimicking pulmonary malignancy (28).

Gastroesophageal Reflux

A significant proportion of patients with IPF suffer from gastroesophageal reflux (GERD), and acid/alkaline reflux may be a cause or cofactor in IPF, which has led to the evaluation of medical and/or surgical therapy against GERD as a potential therapy for IPF (29). Lee and coworkers retrospectively analyzed the course of IPF in patients with/without GERD and demonstrated that the use of antireflux therapy or a Nissen fundoplication are independent predictors of longer survival; acid suppression was also found to be associated with a lower radiological fibrosis score (30). There have not been any prospective, randomized trials evaluating either medical or surgical treatment for GERD in IPF. Because IPF is a heterogeneous disease that may result from diverse types of chronic lung injury, it is not known to what extent the association with GERD is cause versus effect.

PATHOBIOLOGICAL UPDATES IN PULMONARY FIBROSIS

Infection and Immune Responses

Several reports in 2011 investigated the potential roles of infection, autoimmunity, and other immune mechanisms in lung fibrosis.

Infections. There is growing interest on the role of viral infection(s) in the pathogenesis and/or progression of IPF. Acute exacerbations of IPF (AE-IPF) share many characteristics of viral infection, such as fever, myalgias, and diffuse lung injury, and this has led to the hypothesis that AE-IPF may be precipitated by viruses. Wootten and colleagues (31) analyzed bronchoalveolar lavage (BAL) samples in a cohort of Korean and Japanese patients with AE-IPF, stable IPF, and acute lung injury. They did not observe an increase in common respiratory viruses or herpesviruses infection in patients with AE-IPF when compared with stable IPF control subjects. Torque teno virus was found more commonly in patients with AE-IPF when compared with stable control subjects, but this was present at a similar rate in patients with acute lung injury, suggesting that it may represent a nonspecific marker of lung injury (31). Despite limitations of this study, such as geographical considerations, the possibility that BAL might not be the most appropriate compartment of the lung to survey for viruses, and whether timing was ideal for detecting all viruses (32), this study highlights our general lack

of understanding of the pathogenic mechanisms in AE-IPF. Interestingly, there is mounting evidence for an association between herpesviruses and IPF. A study by Pulkkinen and colleagues (33) demonstrated an increased incidence of Epstein-Barr virus DNA in lung tissue from patients with IPF as compared with control subjects (92 vs. 0%), adding to existing data that herpesviruses likely play a role in pathogenesis and progression of at least a subset of patients with IPF. A potential mechanism by which viruses contribute to IPF pathogenesis is by the induction of endoplasmic reticulum stress in alveolar epithelial cells (34, 35).

Autoimmunity. Several studies have reported the presence of autoantibodies to matrix and cellular components in patients with IPF, and patients with connective tissue disease associated-DPLD have autoantibodies that likely play a role in the pathogenesis of fibrosis. However, it is yet to be determined whether autoimmunity is pathogenic in IPF. At a minimum, identification of autoantibodies may serve as a biomarker in these patients. Taille and colleagues (36) reported that 40% of patients with IPF carry autoantibodies to periplakin (detected in BAL and serum) compared with 0% of control subjects and patients with COPD; importantly, the presence of antibodies to periplakin was found to correlate with disease progression (36). Periplakin is a protein found in intracellular adhesion junctions; it regulates cytoskeletal organization and migration of epithelial cells (36, 37). Because periplakin is cleaved by caspase 6 during apoptosis, and anti-periplakin antibodies are found in paraneoplastic pemphigus with severe alveolitis, Feghali-Bostwick and Wilkes suggest that alveolar epithelial injury may uncover this antigen and expose it to the immune response (37). Thus, while the search for pathogenic role(s) for autoantibodies in IPF continues, these studies provide evidence for the potential usefulness of autoantibodies as biomarkers of disease severity/progression.

Immune regulation of fibrosis. There are considerable data supporting a role for innate and adaptive immunity in experimental lung fibrosis, although its role in IPF is not well understood. Gibbons and colleagues provide convincing evidence for the importance of lung macrophages in the development and progression of pulmonary fibrosis (38). They demonstrate that although depletion of macrophages in the lung has no effect on the early inflammatory phase of bleomycin-induced lung inflammation, it results in decreased fibrosis during the fibrotic phase of lung injury and influences the reversibility of fibrosis in this animal model. These investigators provide intriguing data supporting a role for alternatively activated macrophages in IPF by demonstrating that more than 90% of lung macrophages from patients with IPF express CD163, a marker for alternative activation; this marker was not expressed on lung macrophages from elderly control subjects (38).

Lo Re and colleagues studied the effects of CD4⁺ Foxp3⁺ regulatory T cells and CD4⁺ effector T cells on a silica model of pulmonary fibrosis in mice (39); they demonstrated that Foxp3⁺ regulatory T cells are recruited to the lung during lung fibrogenesis and, through the secretion of platelet-derived growth factor B and transforming growth factor (TGF)- β , increase fibroblast proliferation and collagen deposition. These regulatory T cells control the influx of CD4⁺ effector T cells and neutrophils; depleting regulatory T cells results in an increase in effector T cells and production of proinflammatory cytokines that worsens silica-induced pulmonary fibrosis (39). As highlighted by Atamas and Fontenot (40), many questions remain regarding the role of T cells and the adaptive immune system in pulmonary fibrosis, including subsets of regulatory T cells that may promote or protect against pulmonary fibrosis.

In a mouse model of Hermansky-Pudlak syndrome, Atochina-Vasserman and colleagues demonstrate that injury to type 2 alveolar epithelial cells manifested by lamellar body distention and

deposition of phospholipid precedes the macrophage-dominant inflammation that characterizes this disease (41). The production of monocyte chemotactic protein-1 (MCP-1), nitric oxide, and the S-nitrosylation of surfactant protein-D (SP-D) by the alveolar epithelium induces macrophage chemotaxis to the lung. This study illustrates a key role for the alveolar epithelium in the modulation of inflammatory responses to lung injury repair that culminates in fibrosis. This concept may be extended to the more proximal airways, as illustrated by the demonstration that conditional depletion of airway progenitor (Clara) cells in a transgenic mouse model induces peribronchiolar fibrosis (42).

Coagulation

A homeostatic imbalance between the procoagulant and fibrinolytic systems may contribute to fibrogenesis. Protease-activated receptors (PARs) promote the deposition of fibrin in addition to a multitude of other actions (43). A study by Wygrecka and colleagues (43) demonstrate that patients with IPF express increased levels of PAR-2 in type 2 alveolar epithelial cells and fibroblasts, which is further up-regulated by TGF- β . They provide evidence that factor VIIa/tissue factor complexes on the hyperplastic alveolar epithelium activate PAR-2, which then promotes fibroblast proliferation and matrix deposition. These studies highlight the important role of epithelial and mesenchymal cell interactions in the pathogenesis of lung fibrosis (44).

Fibroblasts and Matrix

Work by Hoyles and colleagues highlights a central role of TGF- β signaling by demonstrating that signaling via the high-affinity type II TGF- β receptors is important in fibrocyte recruitment in addition to myofibroblast differentiation and matrix production of lung resident fibroblasts in a mouse model of fibrosis (45). Lin and colleagues demonstrated that the activity of transcription factor Yin Yang 1 (YY1) in fibroblasts promotes fibrogenesis by increasing myofibroblast differentiation and collagen production (46). YY1 is expressed at high levels in fibroblasts from lungs of patients with IPF and in mouse models of lung fibrosis.

The importance of post-translational modifications involving extracellular matrix (ECM) proteins was highlighted by Olsen and colleagues (47); they demonstrated that transglutaminase 2 (TG2), an enzyme important in cross-linking collagen and other ECM proteins, promotes fibrosis and is up-regulated in the lungs of patients with IPF. These investigators also showed that TGF- β induces TG2 expression in fibroblasts, which promotes fibroblast adhesion, differentiation, contractility, and migration. The regulation of fibroblast differentiation and ECM turnover by microRNAs was reviewed by Lawson and colleagues (48). These studies offer novel therapeutic approaches targeting fibroblasts and the ECM in lung fibrosis.

OTHER DPLDs

Sarcoidosis

Over the last several years, considerable progress has been made in our understanding of the inflammatory process in sarcoidosis. From a clinical point of view, it has become increasingly clear that there are other factors beyond inflammation that burden patients with sarcoidosis, including sarcoidosis-associated hypertension and chronic fatigue. Recent diagnostic and therapeutic approaches are summarized in a concise clinical review on sarcoidosis by Baughman and colleagues (49). An epidemiologic study analyzing causes of deaths in 23,679 U.S. decedents with sarcoidosis demonstrated that from 1988 to 2007, age-adjusted

sarcoidosis-related mortality rates increased 50.5% in women and 30.1% in men (50). Interestingly, regardless of sex or race, mortality rates climbed most in decedents 55 years or older, and the most common cause of death was sarcoidosis itself. This mortality increase was more pronounced in black women; pulmonary and cardiac disease was more frequently a cause of death in young African Americans. These disturbing numbers point to an urgent need for a better understanding of sarcoidosis.

A study by Rastogi and colleagues (51) demonstrated sustained activation of p38 mitogen-activated protein kinase in BAL cells isolated from patients with sarcoidosis, which is mediated, at least in part, to an inability to induce mitogen-activated protein kinase phosphatase-1. Thus, in susceptible individuals, inanimate remnants of bacteria or remote infection may be capable of inducing sustained sarcoid-like inflammation (51, 52). The nature of these disease susceptibilities may be queried in genome-wide association studies, which have identified a number of gene variants associated with sarcoidosis and other granulomatous disorders (53–55). Another approach is the identification of molecular signatures by systems biology approaches using peripheral blood cells or lung tissue. Sarcoidosis-specific miRNA signatures have been identified that may correlate with the genomic location of disease-associated genetic variants (56). A similar approach was used by Koth and colleagues to identify transcriptome (mRNA) signatures in sarcoidosis, which appear to overlap with tuberculosis (57). The use of these techniques allows hypothesis-free identification of pathways that may yield new targets for pharmacological intervention or diagnostic tools.

Hypersensitivity Pneumonitis

Classical hypothesis-driven immunologic research continues to yield exciting results on the pathobiological mechanisms involved in sarcoidosis and other granulomatous disorders. Dendritic cell trafficking is a pivotal mechanism in many inflammatory lung diseases. Blanchet and colleagues (58) demonstrate the requirement for stem cell antigen, CD34, in trafficking of dendritic cells from the circulation into the alveoli and, from there through the lung parenchyma, to draining lymph nodes in a murine hypersensitivity pneumonitis model (58). In this study, CD34-deficient mice are protected from hypersensitivity pneumonitis. This finding lends support to potential therapeutic targeting of CD34, particularly because CD34-deficient mice do not exhibit any obvious phenotype, suggesting that anti-CD34 therapy might be well tolerated.

Connective Tissue Disease

DPLDs associated with connective tissue disease, such as in rheumatoid arthritis (RA), pose difficult clinical management issues and impose a high social burden. This burden is quantified in an epidemiologic study by Olson and colleagues (59). They report that, although mortality rates from RA have fallen over the past 2 decades, mortality rates from RA-DPLD have increased; moreover, clinically significant DPLD occurs in nearly 10% of the RA population (59).

Occupational Lung Disease

Rare causes of DPLD have been reported from environmental and occupational exposures. Titanium-induced giant cell interstitial pneumonitis was identified by mineralogical analysis of lung biopsies with transmission electron microscopy (60); a case of silicosis induced by sandblasting denim jeans to fade the color to a worn look has also been reported (61). Diagnosis of such cases requires a high degree of suspicion and emphasizes the need for a thorough and careful exposure history.

CONCLUSIONS

Although we have continued to make progress in more accurate diagnosis of the DPLDs and in elucidating basic mechanisms of the pathobiology of these diseases, the search for effective treatments, most notably for IPF, has remained elusive. We ought to be encouraged by the ever increasing numbers of randomized clinical trials for IPF; however, defining widely accepted clinical end points and MCIDs will need to occur if we are to move promising drugs to the clinic. Greater attention of governmental funding agencies and the pharmaceutical industry to research support of rare diseases will foster the development of novel therapies. The next several years will uncover many more exciting discoveries that will translate to better health for patients with DPLDs.

Author disclosures are available with the text of this article at www.atsjournals.org.

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