Interstitial Lung Diseases: Respiratory Review of 2013

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Interstitial lung diseases are heterogeneous entities with diverse clinical presentations. Among them, idiopathic pulmonary fibrosis and connective tissue disease-associated interstitial lung disease are specific categories that pulmonologists are most likely to encounter in the clinical field. Despite the accumulated data from extensive clinical trial and observations, we continue to have many issues which need to be resolved in this field. In this update, we present the review of several articles regarding the clinical presentation, prognosis and treatment of patients with idiopathic pulmonary fibrosis or connective tissue disease-associated interstitial lung disease.

Keywords: Lung Diseases, Interstitial; Idiopathic Pulmonary Fibrosis; Connective Tissue Diseases; Therapeutics; Clinical Trial

Introduction

Interstitial lung diseases (ILD) represent a large number of conditions that involve the parenchyma of the lung. These disorders are heterogeneous and there is little consensus regarding the best treatment of most of them. In this review, we summarized several articles published from January 2012 to present regarding clinical aspect of ILD. This review restrict summary to the articles that deals with idiopathic pulmonary fibrosis (IPF) and connective tissue disease associated interstitial lung disease.

Clinical Presentation and Prognosis in IPF

IPF is a progressive fibrotic lung disease with an overall poor prognosis and patients with IPF demonstrate widely variable clinical courses and survival. Limited data suggest selected features commonly observed in clinical practice are associated with increased mortality. These features are well summarized on the document of evidence-based guidelines. However, the accuracy of these predictors is limited by the retrospective nature of some of these studies and variations in study design and there is a need for multivariable predictive models combined with these predictors.

Combined pulmonary fibrosis and emphysema (CPFE) has been increasingly recognized since it was proposed as an important phenotype of pulmonary fibrosis. But the definition of CPFE is not clear and the heterogeneous nature of fibrotic lung diseases in CPFE makes it difficult to understand its clinical aspect, including prognosis.

A Multidimensional Index and Staging System for IPF

Predicting prognosis in patients with IPF is a challenge for clinicians. The objective of this study was to develop a multidimensional prognostic staging system for IPF by using com-
monly measured clinical and physiologic variables. A clinical prediction model was developed and validated by using retrospective data from 3 large, geographically distinct cohorts (558 IPF patients from interstitial lung disease referral centers in California, Minnesota, and Italy). Four variables were used in the final model: gender (G), age (A), and 2 lung physiology variables (P) (forced vital capacity [FVC] and diffusing capacity of carbon monoxide [DLCO]). This model was assessed by the c-index, and calibration was assessed by comparing predicted and observed cumulative mortality at 1, 2, and 3 years. A model using continuous predictors (GAP calculator) and a simple point-scoring system (GAP index) worked similarly in derivation (c-index of 70.8 and 69.3, respectively) and validation (c-index of 69.1 and 68.7, respectively). Three stages (stages I, II, and III) were identified based on the GAP index with 1-year mortality of 6%, 16%, and 39%, respectively. In conclusion, this staging system for IPF was useful and may improve prognostication, help guide management, and facilitate research.

Clinical Features and Outcomes in CPFE in IPF

The syndrome of CPFE is defined by the presence of emphysema and parenchymal fibrosis in the same patient. Some studies have shown that patients with CPFE have distinct clinical features and inconsistent impact of CPFE on survival. But most of previous studies of CPFE have important limitations, including imprecise definitions of CPFE and heterogeneous patient populations. In this study, 365 only IPF patients who were diagnosed based on multi-disciplinary review according to established criteria were characterized. CPFE was defined as ≥10% emphysema on high-resolution computed tomography (HRCT). The prevalence of CPFE is 8% (29 of 365 patients). Patients with CPFE had less fibrosis on HRCT and higher FVC, but greater oxygen requirements (p≤0.01). These features were maintained with adjustment for fibrosis severity. Therapies for chronic obstructive pulmonary disease were used in 53% of patients with CPFE. It means that potential therapies for this CPFE population remain underutilized. There was no significant difference in mortality comparing CPFE to non-CPFE IPF patients (hazard ratio, 1.14; 95% confidence interval [CI], 0.61–2.13; p=0.69). The similar mortality in CPFE and IPF without emphysema might be a reflection of the approximately balanced mortality risk factors in CPFE (worse oxygenation and pulmonary hypertension) and IPF without emphysema (more fibrosis). This study did not answer a question is whether CPFE represents a biologically distinct disease or is just IPF and emphysema in the same patient. Future research in this field will need evaluation of underlying biological pathways for CPFE and explain why same risk factor, smoking result in the different outcome such as emphysema, IPF, and CPFE.

Treatment of IPF, Clinical Trials

IPF is a chronic, progressive lung disease of unknown cause and the median survival of patients with IPF after diagnosis is 2 to 5 years. Recent study suggested pirfenidone might be effective in slowing the decline of lung function on early-stage IPF patients. However, despite multiple recent clinical trials, no definitive therapy is known to alter survival.

Prednisone, Azathioprine, and N-Acetylcysteine (NAC) for Pulmonary Fibrosis

The use of a combination of prednisone, azathioprine, and NAC glucocorticoids has been the conventional approach to the treatment and recommended by international guidelines though the evidences are weak. But the safety and efficacy of this three-drug regimen is unknown. In this randomized, double-blind, placebo-controlled trial, mild to moderate IPF patient were assigned to one of three groups—receiving a combination of prednisone, azathioprine, and NAC (combination therapy), NAC alone, or placebo in a 1:1:1 ratio. The primary outcome was the change in longitudinal measurements of FVC during of a 60-week period. When approximately 50% of data had been collected, a planned interim analysis was done and this analysis revealed that patients in the combination-therapy group, as compared with the placebo group, had an increased rate of death (8 deaths in combination group vs. 1 death in placebo group, p=0.01) and hospitalization (23 in combination group vs. 7 in placebo group, p<0.001). Assessment of safety showed that serious adverse events occurred more frequently in the combination-therapy group than in the placebo group (24 vs. 8, p=0.001). These results, coupled with no evidence of physiological or clinical benefit for combination therapy, added strong evidence against the use of this combination treatment. But the precise reasons for the increased rates of death and hospitalization are unknown on the basis of results in this trial design. Though combination therapy in this trial was terminated immaturesly, the study with NAC alone and placebo groups is ongoing.

A Placebo-Controlled Randomized Trial of Warfarin in IPF

Animal and human studies suggest a role of the coagulation cascade in pulmonary fibrosis and a previous clinical trial showed survival benefit of anticoagulation in IPF patients who required hospitalization. One hundred forty-five progres-