REVIEW

http://dx.doi.org/10.4046/trd.2013.75.2.47
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2013;75:47-51

TRD
Tuberculosis and Respiratory Diseases

Interstitial Lung Diseases: Respiratory Review of 2013

Yong Hyun Kim, M.D. and Soon Seog Kwon, M.D., Ph.D.
Division of Allergy and Pulmonology, Department of Internal Medicine, The Catholic University of Korea School of Medicine, Seoul, Korea

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.

Address for correspondence: Soon Seog Kwon, M.D., Ph.D.
Division of Allergy and Pulmonology, Department of Internal Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea School of Medicine, 327 Sosa-ro, Wonmi-gu, Bucheon 420-717, Korea
Phone: 82-32-340-7010, **Fax:** 82-32-340-2669
E-mail: sskwon@catholic.ac.kr
Received: May 29, 2013
Revised: Jun. 5, 2013
Accepted: Jun. 14, 2013

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[1-4]. 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[5]. 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[6]. 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[7]

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[8]

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[9-11]. 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 ($p \leq 0.01$). 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[12,13]. However, despite multiple recent clinical trials, no definitive therapy is known to alter survival.

Prednisone, Azathioprine, and N-Acetylcysteine (NAC) for Pulmonary Fibrosis[14]

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 immaturely, the study with NAC alone and placebo groups is ongoing.

A Placebo-Controlled Randomized Trial of Warfarin in IPF[15]

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[16]. One hundred forty-five progres-

sive IPF patients were randomized in a 1:1 ratio to warfarin or matching placebo for a planned treatment period of 48 weeks. Targeting of warfarin therapeutic doses is an international normalized ratio of 2.0 to 3.0. Progressive IPF was defined as a history of worsening of dyspnea, or physiologic deterioration defined as an absolute decline of either FVC greater than or equal to 10% or DLCO greater than or equal to 15%, a reduction in arterial oxygen saturation of greater than or equal to 5%, or progression of radiographic finding. The primary outcome was the composite outcome of time to death, hospitalization (nonbleeding, nonelective), or a 10% or greater absolute decline in FVC. This study was terminated because an increase in mortality was observed in the patients randomized to warfarin group (14 warfarin vs. 3 placebo group deaths; p=0.005), but this increased mortality was not associated with the well-known bleeding complication of warfarin. The mechanism of excess mortality in warfarin group was unknown but the excess mortality in the warfarin group appeared to be due to respiratory worsening (exacerbation or progression). This study did not show a benefit for warfarin in the treatment of patients with progressive IPF. Accordingly warfarin should not be used for the treatment of progressive IPF.

Treating IDF with the Addition of Co-trimoxazole: A Randomized Controlled Trial[17]

IPF is a fatal condition with limited treatment options. On the basis of a previous small study that showed co-trimoxazole was beneficial, the efficacy and safety of the addition of 12 months of oral co-trimoxazole to standard treatment for fibrotic idiopathic interstitial pneumonia was assessed. 181 patients with fibrotic idiopathic interstitial pneumonia (89% diagnosed as definite/probable IPF) were randomized to receive co-trimoxazole 960 mg twice daily or placebo for 12 months in addition to usual care. Primary endpoint was FVC and DLCO, EuroQol (EQ5D)-based utility, 6-minute walk test (6MWT) and Medical Research Council (MRC) dyspnea score were secondary endpoints. All-cause mortality and adverse events were recorded as tertiary endpoints. Co-trimoxazole had no effect on FVC, DLCO, 6MWT, or MRC dyspnea score (intention-to-treat analysis). The per-protocol analysis were the same except that co-trimoxazole treatment resulted in a significant improvement of overall health-related quality of life (EQ5D-based utility, mean difference 0.12; 95% CI, 0.01–0.22), a reduction in the percentage of patients requiring an increase in oxygen therapy (odds ratio, 0.05; 95% CI, 0.00–0.61) and a significant reduction in all-cause mortality (co-trimoxazole 3/53, placebo 14/65; hazard ratio, 0.21; 95% CI, 0.06–0.78; p=0.02) compared with placebo. The survival benefit by co-trimoxazole, if real, could be due to its antimicrobial activity as there was a significant reduction in the number of respiratory tract infections in co-trimoxazole group. The use of cotrimoxazole increased the incidence of nausea and rash. But this study had been started before the results from the study of prednisolone, azathioprine and NAC for pulmonary fibrosis released. Consequentially, most of study patients were on immunosuppressive treatment at recruitment. This suggests co-trimoxazole treatment may be ineffective under circumstance of abandonment of immunosuppressive agent in treating IPF because co-trimoxazole may have acted by preventing immunosuppression-related infections.

Treatment of Connective Tissue Disease Associated Interstitial Lung Disease

The pathogenesis of connective tissue disease associated interstitial lung disease (CTD-ILD) is complex, and it is believed that underlying immune system dysfunction and immune-mediated pulmonary inflammation are critical to CTD-ILD development. Immunosuppression is a frequent treatment strategy for clinically significant CTD-ILD but there are no evidences of the safety or efficacy of this therapeutic approach supported by ample systematic, prospective studies. Additionally, there are substantial differences in the clinical presentations and management of each specific CTD. This heterogeneity has complicated the conduct of prospective multicenter treatment trials and establishment of treatment guideline for CTD-ILD.

Severe Interstitial Lung Disease in Connective Tissue Disease: Rituximab as Rescue Therapy[18]

The aim of the present study was to test whether rituximab, a chimeric monoclonal antibody with a high affinity for the CD20 surface antigen expressed on pre-B and B-lymphocytes, is effective as rescue therapy in very severe CTD-ILD, unresponsive to conventional immunosuppression. Eight patients with severe and progressive CTD-ILD treated with rituximab were assessed retrospectively. (polymyositis/dermatomyositis in five patients, undifferentiated CTD in two patients and systemic sclerosis in one patient). In six patients, change in pulmonary function tests compared with pre-rituximab levels, was assessed at 9–12 months post-treatment. In two patients, who were mechanically ventilated at the time of treatment, clinical and HRCT changes were assessed. Seven out of eight patients had a favorable treatment response to rituximab, while in one patient disease severity did not change. In contrast with previous progression, rituximab treatment showed a median significant improvement of 22% in diffusing capacity for carbon monoxide (from a median baseline of 25%; range, 16–32%; p=0.04), and a median significant improvement of

18% in FVC (from a median baseline of 45%; range, 37–59%; p=0.03), in the 9–12 months following treatment with rituximab. Two patients who were mechanically ventilated succeeded in weaning and extubation. In very severe CTD-ILD unresponsive to conventional immunosuppression, rituximab may represent an effective, potentially life-saving rescue therapy. But the patients in this study used other immunosuppressive agents concurrently or shortly before Rituximab treatment. This should be considered as a potential confounding factor and we should keep in mind that Rituximab can induce adverse pulmonary reactions, including interstitial pneumonia itself[19].

Mycophenolate Mofetil Improves Lung Function in Connective Tissue Disease-Associated Interstitial Lung Disease[20]

In 2 controlled trials of cyclophosphamide (CYC) for scleroderma-associated ILD, CYC was associated with stability or modest improvement in lung physiology (FVC)[21-23]. However, the use of CYC for CTD-ILD is related to serous toxicity. Mycophenolate mofetil (MMF) is an immunosuppressive medication that is recently used as an alternative to CYC for the treatment of CTD-ILD. In this retrospective study, diverse cohort of patients with CTD-ILD treated with MMF was examined. The 125 patients with CTD-ILD who had available baseline and at least 6 months of follow-up data were analyzed. The diagnosis of ILD was made using multidisciplinary review, including surgical lung biopsy or chest HRCT scan result. This study evaluated safety and tolerability of MMF and used longitudinal data analyses to examine changes in pulmonary physiology over time, before and after initiation of MMF. MMF was associated with significant improvements in estimated percentage of predicted FVC (%) from MMF initiation to 52, 104, and 156 weeks (4.9±1.9%, p=0.01; 6.1±1.8%, p=0.0008; and 7.3±2.6%, p=0.004, respectively); and in estimated percentage predicted diffusing capacity (DLCO%) from MMF initiation to 52 and 104 weeks (6.3±2.8%, p=0.02; 7.1±2.8%, p=0.01). In the subgroup without usual interstitial pneumonia-pattern injury, MMF significantly improved FVC% and DLCO%, and in the subgroup with usual interstitial pneumonitis-pattern injury, MMF was associated with stability in FVC% and DLCO%. MMF was discontinued in 13 subjects due to adverse events or disease progression. The actual median daily prednisone dose at MMF initiation was 20 mg, and the median daily prednisone dose after 9–12 months on MMF was 5 mg (p<0.0001 for difference between doses). This study shows that MMF appears to be a promising therapy for the spectrum of CTD-ILD and allowed for corticosteroid tapering.

Refrerences

1. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199-203.
2. Fernandez Perez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest 2010;137:129-37.
3. Kim DS, Collard HR, King TE Jr. Classification and natural history of the idiopathic interstitial pneumonias. Proc Am Thorac Soc 2006;3:285-92.
4. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005;142(12 Pt 1):963-7.
5. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.
6. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26:586-93.
7. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012;156:684-91.
8. Ryerson CJ, Hartman T, Elicker BM, Ley B, Lee JS, Abbritti M, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest 2013;144:234-40.
9. Jankowich MD, Rounds S. Combined pulmonary fibrosis and emphysema alters physiology but has similar mortality to pulmonary fibrosis without emphysema. Lung 2010;188:365-73.
10. Mejia M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso D, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136:10-5.
11. Akagi T, Matsumoto T, Harada T, Tanaka M, Kuraki T, Fujita M, et al. Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis. Respir Med 2009;103:1209-15.
12. Azuma A, Taguchi Y, Ogura T, Ebina M, Taniguchi H, Kondoh Y, et al. Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. Respir Res 2011;12:143.
13. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;377:1760-9.

14. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968-77.
15. Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012;186:88-95.
16. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest 2005;128:1475-82.
17. Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, Wilson EC, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax 2013;68:155-62.
18. Keir GJ, Maher TM, Hansell DM, Denton CP, Ong VH, Singh S, et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Respir J 2012;40:641-8.
19. Liote H, Liote F, Seroussi B, Mayaud C, Cadranel J. Rituximab-induced lung disease: A systematic literature review. Eur Respir J 2010;35:681-7.
20. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol 2013;40:640-6.
21. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-66.
22. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026-34.
23. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962-70.