http://dx.doi.org/10.4046/trd.2013.74.1.1
ISSN: 1738-3536(Print)/2005-6184(Online)
Tuberc Respir Dis 2013;74:1-6

Review

Recent Advances in Idiopathic Pulmonary Fibrosis

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The concept on idiopathic pulmonary fibrosis (IPF) pathogenesis has progressed from chronic inflammation to aberrant wounding healing and even more to the current paradigms of a multifactorial and heterogeneous disease process. Despite the growth of clinical trials for IPF, most of the results, including N-acetylcysteine combination, warfarin, and bosentan, were disappointing. On the other hand, there have been a number of important developments; the foremost is the licensing of pirfenidone in Europe and Asia. In this article, we briefly review the recent knowledge of pathogenesis of IPF. We also summarize the recent clinical trials regarding the management of IPF.

Key Words: Idiopathic Pulmonary Fibrosis; Etiology; Clinical Trial

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing disease of unknown cause and is limited to the lungs. IPF affects older individuals with a median survival after diagnosis of only 3 to 5 years[1]. The pathogenesis and drug therapy of IPF remains poorly elucidated and controversial. In this review, we summarized several articles regarding the recently published articles focusing on the pathogenesis and clinical trials within 1 to 2 years.

Pathogenesis[2]

Although chronic inflammation has a critical role in most of the interstitial pneumonias, progressive fibrotic manifestation in IPF made an evolution in the concept of disease pathogenesis from chronic inflammation to aberrant wound healing, and to multifactorial and heterogeneous process.

1. Epithelial injury and activation: genetic and environmental interactions

Several environmental and genetic factors such as smoking, chronic microaspiration, viral infection, polymorphism in the promoter region of mucin 5B gene (*MUC5B*), and mutations of telomerase might contribute to the development of IPF. These factors potentially cause an increased endoplasmic reticulum stress in epithelial cells, and consequently trigger epithelial cell apoptosis and epithelial mesenchymal transition (EMT)[3]. Despite type I alveolar epithelial cells (AECs) death, type II AECs covering the honeycombing lesions are activated. Developmental programs are also dysregulated during normal wound repair. Upregulation of Wnt pathway, sonic hedgehog (Shh), and downregulation of phosphatase and tensin homologue (PTEN) in the epithelium and fibroblast suggest a maladaptive repair process.

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Received: Dec. 21, 2012
Revised: Dec. 26, 2012
Accepted: Dec. 28, 2012

2. Profibrotic effects of aberrantly activated AECs in the lung microenvironment

The tissue factor-factor VIIa-factor X complex gathers on the abnormally activated alveolar epithelium, allowing activation of factor X, which consequently stimulates fibroblasts. Additionally, activated factor X induces the activation of thrombin, which in turn differentiates fibroblasts to myofibroblasts via proteinase-activated receptor-I. Myofibroblasts has the higher profibrotic potential than fibroblasts, and therefore these cells lead to the extracellular matrix deposit and destruction of the lung architecture. AECs secret several mediators such as platelet-derived growth factor, transforming growth factor β (TGF-β), tumor necrosis factor α (TNF-α), and endothelin-1, that are contributing to the migration, proliferation, or differentiation of mesenchymal cells. On the other hand, expression of CXCL12 in epithelial cells is markedly increased in IPF lungs, leading to influx of bloodstream-circulating C-X-C chemokine receptor type 4 (CXCR 4) positive fibrocytes toward lung. The epithelium might directly increase the number of fibroblasts and myofibroblasts via EMT.

3. Differentiation of fibroblasts to myofibroblasts

High mechanical stress (mechanotransduction), increment of active TGF-β produced mainly from the epithelial cells, and matrix proteins such as ED-A are the main 3 components for the differentiation from fibroblast to myofibroblast. Myofibroblasts induce excessive accumulation of extracellular matrix, breakdown of basement membrane and epithelial cell death. TGF-β and endothelin-1 are suggested to play a part in resistance of fibroblast against apoptosis; it is still not clear why the epithelial cells are susceptible to death under the identical environment.

4. The absent type I pneumocytes

Type I pneumocytes that surround more than 90% of the alveoli are mainly decreased in IPF lungs. It is not clarified how the decrease of type I pneumocyte contributes to the fibrosis in IPF, but decline of antifibrotic molecules (e.g., caveolin-1) and receptor for advanced glycation end product may lead to a barrier of epithelial regeneration.

5. Matrix metalloproteinases (MMPs) and the abnormal lung remodelling

MMP7, MMP1, and MMP2 expressions are reported to increase from gene-expression signatures of IPF patients. MMP1, MMP8, and MMP9 are also reported. MMP9 is usually expressed in epithelial cells, some discovered from the fibroblastic foci. MMP1 and MMP7 facilitate migration of the epithelial cells.

6. Angiogenesis and vascular remodelling

Although the exact role of angiogenesis has not been verified yet, neovascularisation is essential in regeneration of tissue after injury. New vessel formation is scarcely seen in the fibrotic tissue such as fibroblastic foci, whereas non-fibrotic tissues are characterized of abundant neovascularisation, showing an abnormal vascular remodelling.

7. Processes that link ageing with IPF

Telomeres normally shorten as the cell division goes on, and this phenomenon is commonly noted in ageing-related disorders such as chronic obstructive pulmonary disease (COPD). However, IPF, related to a mechanism opposite to that of COPD, also shows an accelerated telomere shortening. Ageing is also related to an increase of oxidative stress. A deficiency of extracellular glutathione leads to a redox imbalance, and this stress directly evokes DNA damage and inactivation of enzymes. Besides, senescence participates in epigenetic mechanisms and induces several changes: epigenetic silencing via hypermethylation of Thy1 that inhibits the differentiation of fibroblast into myofibroblast, decrease of cyclooxygenase 2 expression by change of histone acetylation, or suppression of target messenger RNA expression via dysregulation of microRNA expression are the representative examples.

8. Pericytes and mesothelial cells as possible sources of myofibroblast[4]

Pericytes are the mesenchyme-derived cells existing in the basement membrane and perivascular lining, known as the source of myofibroblast by some investigations. Consistently, there are previous reports that pleural mesothelial cells show EMT via induction of TGF-β.

Clinical Trials

1. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. Idiopathic Pulmonary Fibrosis Clinical Research Network et al. N Engl J Med 2012;366:1968-77[5]

Mild to moderate IPF patients were enrolled to one of three groups: a group receiving a combination of prednisone, azathioprine, and N-acetylcysteine (NAC; combination group), NAC alone group, or placebo group. Primary outcome was the change in forced vital capacity (FVC) during of 60 weeks. This study reported the result of the combination group compared with placebo group at the time of planned midpoint interim analysis (combination group, 77 patients; placebo group, 78 patients). Patients in the combination group had an increased rate of death (8 subjects in combination group vs. 1 in placebo group, p=0.01) and hospitalization (23 in combination group vs. 7 in placebo group, $p<0.001$) without any evidence of physiological or clinical benefit as compared with the placebo group. According to these results, combination therapy was terminated immaturely, and the study is ongoing with the remaining two groups. This article added another strong evidence of not to use a combination therapy to IPF patients.

2. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. Homma et al. Respirology 2012;17:467-77[6]

A study performed for 2 years from 2005 at 27 centers in Japan completed 76 cases of investigation from one hundred enrollments with mild to moderate IPF ($PaO_2 \geq 70$ mm Hg at rest, $SpO_2 > 90\%$ on six-minute walking test), assessing the efficacy of NAC inhalation. There was no significant difference between the two groups in terms of FVC change at week 48 and secondary variables. However, NAC solitary inhalation therapy revealed a slowdown of FVC decrement in a subgroup of patients with initial FVC < 95% of predicted and diffusing capacity for carbon monoxide (DL_{CO}) < 55%. There are several drawbacks in this study such as a study design with no double-blinding, omission of evaluating survival, and dropout rate of 24%; however, further investigation is expected as this therapy may confer a benefit to a specific group of IPF patients.

3. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. Horton et al. Ann Intern Med 2012;157:398-406[7]

This is a double-blind, crossover trial for 23 subjects with IPF, who were coughing for more than 8 weeks, treating with low-dose of thalidomide and placebo for 12 weeks respectively with a washout interval for 2 weeks. Thalidomide administration revealed to improve not only the quality of life regarding cough but also the St. George's Respiratory Questionnaire (SGRQ). Although this study has limitation with short treatment duration of only 12 weeks and a small number of patients from a single centre, value should be noticed as this investigation is the first randomized controlled trial (RCT) evaluating cough, an important symptom of IPF.

4. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Noth et al. Am J Respir Crit Care Med 2012;186:88-95[8]

One hundred forty five IPF patients were enrolled to warfarin and placebo group. Progressive IPF was defined when dyspnea is aggravated or physiologic signs are worsening (i.e., more than 10% of FVC decrease, more than 15% of DL_{CO} decrease, more than 5% decrease of arterial oxygen saturation, or radiologic aggravation). Primary endpoint was death, admission or time to decrease of more than 10% of FVC. It was ini-

tially designed as an event-driven study with a period of 144 weeks, but as the registration was slow and other IPFnet study showed a high rate of event, study period was shortened to 48 weeks. However, there were unexpected surplus of death cases in the warfarin group, leading to early termination of this study on May 2011 with an interim analysis. All-cause mortality and hospitalization were increased in warfarin group, but the well-known bleeding complication was not related to these deaths. This investigation is the first double-blinded RCT study utilizing warfarin, with a strength of using an encrypted home international normalised ratio monitoring.

5. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. King et al. Am J Respir Crit Care Med 2011;184:92-9[9]

Inspired by the Bosentan Use in Interstital Lung Disease (BUILD)-1 study of improving the quality of life (QoL) and retarding secondary endpoints (e.g., death and disease progression) of IPF subjects especially confirmed via histology, 616 patients established with biopsy without extensive honeycombing on high-resolution computed tomography were enrolled for investigation. However, there was no significant difference of primary endpoints (i.e., simultaneous FVC decrease of more than 10% and DL_{CO} decrease, or acute exacerbation) or secondary endpoints such as health-related QoL and transition dyspnea index. Administration of bosentan was tolerable.

6. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Noble et al. Lancet 2011;377:1760-9[10]

Pirfenidone is known as suppressing TGF-β and TNF-α, leading to an overturn of fibroblast and collagen synthesis. The CAPACITY trial is consisted of two studies of 004 and 006, with the 004 trial constructed with three study groups of high-dose pirfenidone, low-dose pirfenidone and placebo group. Meanwhile, the 006 trial had two study groups, i.e., high pirfenidone group and placebo group. Primary endpoint was the change of FVC (%) at week 72; 004 trial showed a result of significant decrease of FVC% in the high-dose group compared with placebo group (−8% vs. −12.4%, p=0.001), whereas the 006 trial revealed no discrete difference between the two study groups (−9% vs. −9.6%). The reason for the difference among two trials are speculated as follows: there is no apparent difference between the two high-dose pirfenidone groups of two trials, but the FVC% change of placebo group of 006 trial is relatively small than expected. Recently diagnosed IPF cases were more enrolled into the 006 than the 004 trial, and considering that a larger number of cases with obstructive airway disease was included in the placebo group, baseline imbalance or intrinsic variability of FVC change may influenced the change of FVC. Meanwhile, merging the data of 004 and 006 trials revealed a result favoring the effect of pirfenidone. Based on the phase 3 trial performed to 275 subjects with mild to moderate IPF published in 2010, pirfenidone has been under license in the Japanese market on 2008. Pirfenidone was subsequently released to patients of mild to moderate IPF in Europe after the result of CAPACITY trial.

7. Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. Azuma et al. Respir Res 2011;12:143[11]

A post-hoc analysis was performed to find out the specific subpopulation with benefit from pirfenidone, with 275 subjects of mild to moderate IPF showing a favorable effect to pirfenidone. Group A (subjects with baseline percentage predicted vital capacity [%VC] ≥ 70% and SpO_2 < 90%) revealed a significantly lower VC decrement compared with the placebo group in both high- and low-dosages. Main symptoms of coughing and dyspnea were also considerably improved. When dividing subjects according to PaO_2 at rest and lowest PaO_2 on exercise, group B (PaO_2 > 70 mm Hg at rest and the lowest PaO_2 after exercise of < 90%) showed a tendency of lowering of VC decrease, albeit statistically insignificant. Group A was consisted of subjects

who had an early stage of IPF, with a relatively intact pulmonary function test but V-Q mismatch on exercise due to inflammatory edematous change on interstitial septa in advance of established fibrosis. This study showed that pirfenidone might be effective on these early-stage IPF patients. However, further investigation is needed as being a post-hoc analysis with small size of sample in each study group.

8. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. Richeldi et al. N Engl J Med 2011;365:1079-87[12]

Efficacy and safety was assessed using four different dosages of tyrosine kinase inhibitor BIBF1120 and a placebo group for 12 months among groups. Primary end point was annual decrease of FVC. Four dosages of BIBF1120 groups (50 mg/day, 50 mg bid, 100 mg bid, and 150 mg bid) and a placebo group were enrolled with 432 subjects *in toto*. The annual rate of decline in FVC was 0.06 L/yr in BIBF1120 150 mg bid group whereas placebo group was 0.19 L/yr, showing a 68.4% decrease by administering BIBF1120 (p=0.06 when adopting closed testing procedure for multiplicity correction, p=0.01 when adopting hierarchical testing procedure). This dosage group showed a lower incidence of acute exacerbations compared with the placebo group (2.4 vs. 15.7 cases per hundred case-years, p=0.02), also proving a better QoL via SGRQ scores. BIBF1120 150 mg bid group revealed to have a higher rate of gastrointestinal side effects leading to discontinuation of administration compared to the placebo group, also with a higher rate of serum hepatic aminotransferase elevation. Two 3-phase studies are being performed for evaluating the effectiveness of BIBF.

9. Treatment of idiopathic pulmonary fibrosis with losartan: a pilot project. Couluris et al. Lung 2012; 190:523-7[13]

Angiotensin II receptors are known to induce expression of TGF-β, promote lung fibroblast proliferation, and engage in the synthesis of procollagen. This study was performed from April 2009 to October 2010 toward 20 subjects with IPF. The primary endpoint was FVC% change after 12-months of losartan administration, and 17 subjects were included in the response evaluation. Of these 17 patients, 12 (71%) revealed stable (i.e., FVCs within 5% change) or improved (i.e., FVC increase of more than 5%). Secondary endpoints such as FEV1% change in 1 year, DLco% change, and 6-minute walk test distance (6MWD) were also stable or improved in 58%, 71%, and 65%, respectively. There was no incident of commonly anticipated hypotension. This investigation is a small-number pilot study, necessitating a phase 2 and RCT.

10. Stem cell therapy for idiopathic pulmonary fibrosis. Tzouvelekis et al. J Transl Med 2011;9:182[14]

Twelve subjects with mild to moderate IPFs were enrolled for intratracheal instillation of autologous adipose stem cells via bronchoscope to both lower lobes of lung monthly for three times; this non-randomized phase 1 trial is still ongoing for 12-months safety and toxicity evaluation. According to the interim findings, this study has been performed with no serious side effects such as infection, allergic reaction, acute exacerbation, institutional admission or neoplasm, showing a tendency of improvement of 6MWD and FVC. Second and third phase investigation that has been hesitated in fear of safety problem are expected based upon this trial.

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