Current Status of Idiopathic Pulmonary Fibrosis Treatment

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Idiopathic pulmonary fibrosis (IPF) is a disease with a poor prognosis, causing progressive fibrosis of the lungs.

idiopathic pulmonary fibrosis | lipid metabolism | lysophosphatidic acid

1. Idiopathic Pulmonary Fibrosis Outline

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive respiratory disease classified as idiopathic interstitial pneumonia. Its prognosis is poor, with the medial survival of patients reported to be 3–5 years after diagnosis [1][2]. The annual incidence is reported to be 6.8–17.4/100,000, with the prevalence being 42.7–63 per 100,000 population [3][4]. It causes progressive interstitial fibrosis, and patients die of acute exacerbation, progressive respiratory failure, lung cancer, and so on [1][2][5].

As far as the etiology is concerned, several genetic abnormalities have been found in some cases of this disease (reported as “familial pulmonary fibrosis”), including abnormalities of SP-C gene [6], ABC-A3 gene [7], and telomere-related genes (TERT, TERC) [8]. However, the exact cause remains unclarified. Involvement of various environmental factors and genetic polymorphisms (e.g., mucin composition: MUC5B, MUC2) and diverse views have been reported about the pathogenesis of this disease [9].

IPF is the most frequent in the Interstitial Lung Diseases (ILD); idiopathic ILDs include nonspecific interstitial pneumonia (NSIP), pleuroparenchymal fibroelastosis (PPFE), cryptogenic organizing pneumonia (COP), acute fibrinous and organizing pneumonia (AFOP), acute interstitial pneumonia (AIPOP), and acute pneumonia in the lungs, fibroelastosis (PPFE), cryptogenic organizing pneumonia (COP), acute fibrinous and organizing pneumonia (AFOP), acute interstitial pneumonia (AIP), respiratory bronchiolitis interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), and others. Autoimmune-related ILDs, hypersensitivity pneumonitis (HP), radiation-related ILD, and sarcoidosis are also considered ILDs [10].

Recent ILD guidelines have defined progressive pulmonary fibrosis (PPF) as ILD with progressive fibrosis. PPF includes not only IPF but also all fibrosing ILD. PPF is defined as at least two of the following three criteria occurring within the past year: (i) Worsening respiratory symptoms. (ii) Physiological evidence of disease progression (a. Absolute decline in FVC > 5% predicted within 1 year; b. Absolute decline in DLCO > 10% predicted within 1 year). (iii) Radiological evidence of disease progression (a. Increased extent or severity of traction bronchiectasis and bronchiolectasis; b. New ground-glass opacity with traction bronchiectasis; c. New fine

reticulation; d. Increased extent or increased coarseness of reticular abnormality; e. New or increased honeycombing; f. Increased lobar volume loss) [10]. Nintedanib is recommended for PPF [10].

At the tissue level, this disease begins with sustained injury to the alveolar epithelium and microvascular endothelium (e.g., injury due to smoking, air pollution, microaspiration, and occupational exposure), resulting in inflammation and abnormal wound healing in the stroma. Then, there occurs transformation of fibroblasts, pericytes, epithelial cells, vascular endothelial cells, and fibrocytes into myofibroblasts which play a central role in fibrosis. Fibroblastic foci are formed from myofibroblasts, followed by excessive extracellular matrix formation and lung tissue remodeling. As a result, hardening and hypoxia occur in the tissue, leading to enhanced profibrotic cytokine formation and the activation of myofibroblasts. Thus, fibrosis advances in a loop-like manner [5][11][12][13][14][15].

Fibrosis involves various cytokines, chemokines, and growth factors such as interleukin (IL)-1β, tumor necrosis factor-α (TNFα), CTGF, TGFβ, IL-13, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) [16][17]. The alveolar epithelial cells and vascular endothelial/mesothelial cells which have been injured by chronic stimuli produce diverse cytokines, of which TGFβ plays a central role in fibrosis [11][18]. TGFβ is known to be produced by alveolar epithelial cells (AECs), endothelial cells, fibroblasts, myofibroblasts, macrophages, and neutrophils [19][20]. The TGFβ secreted into the extracellular matrix (ECM) and stored there forms a complex with latency-associated peptide (LAP) and latent TGF-β binding protein (LTBP) to yield latent form TGFβ. The latent form TGFβ is activated via integrin αv (αv) [21][22] and thus the activated TGFβ binds to TGFβRII, followed by dimerization with TGFβRI and subsequent phosphorylation to enable signal transduction. The binding of this ligand activates many different downstream pathways, leading to the expression of fibrosis-related genes and induction of injury of airway epithelial cells, their transformation into myofibroblasts, epithelial-mesenchymal transition, and extracellular matrix deposition in tissues [20][23].

2. Current Status of IPF Treatment

Steroids, which are most frequently used for anti-inflammatory therapy, are poor in their effects against IPF, and there are few reports endorsing the effectiveness of their use in combination with immunosuppressors. Thus, it has been recommended to avoid the use of steroids in the treatment of IPF [24][25]. For the treatment of this disease with a poor prognosis, only two drugs, i.e., pirfenidone (PFD) and nintedanib (NTD), are now available clinically [10]. The effects of these drugs are confined to the suppression of disease progression and are unlikely to improve the once-reduced lung function. This chapter will describe PFD and NTD currently available for use.

2.1. Pirfenidone

Pharmacology

PFD is the first drug shown to alleviate the reduced respiratory function and to extend the survival of patients with IPF [26][27]. Through the suppression of TGFβ production (a major action mechanism) [28][29][30], PFD inhibits

fibroblast-myofibroblast transformation and cell proliferation mediated by TGFβ1/SMAD3 signals [31], reduces the levels of tenascin-c and fibronectin (extracellular matrix proteins) [32], and reduces the formation of collagen-specific chaperone of heat shock protein (HSP) 47 involved in procollagen secretion [33]. PFD is additionally known to suppress fibrosis through affecting platelet-derived growth factor (PDGF) [34] and basic fibroblast growth factor (bFGF) [35]. Macrophages on the airway are known to produce diverse cytokines and chemokines, thus contributing to wound healing and inducing immune reactions [36]. PFD has been reported to suppress the inflammatory cytokines produced by macrophages (IL-1, TNFα, TGFβ, PDGF [34][37]) as well as MCP1 (a chemokine produced by macrophages) [38]. PFD is considered to manifest antifibrotic effects via these mechanisms.

Clinical Trials on Pirfenidone

The first clinical trial was conducted in Japan. When the clinical usefulness was evaluated in that trial, patients treated with PFD showed improvement in the 6 min exercise test (primary endpoint), accompanied by suppression of vital capacity (VC) reduction (the secondary endpoint). [26]. In the phase 3 clinical trial subsequently conducted in Japan, the reduction in vital capacity (VC) at Week 52 (the primary endpoint) was suppressed significantly by PFD, accompanied by an extension of the progression-free survival (PFS), evaluated as the secondary endpoint [39]. Later, similar clinical trials (CAPACITY 004 and 006 Studies) were conducted overseas [40]. In the CAPACITY 004 Study (NCT00287729), 435 patients were allocated at random to a high-dose PFD group, a low-dose PFD group, and a placebo group. In the CAPACITY 006 Study (NCT00287716), 344 patients were allocated at random to a high-dose PFD group and a placebo group. The primary endpoint in these trials was the absolute change in percent predicted forced vital capacity (FVC) at week 72. In the CAPACITY 004 Study, FVC reduction was suppressed significantly by this drug (high-dose group −8.0% vs. placebo group −12.4%, $p = 0.001$), whereas no significant inter-group difference in FVC reduction was noted in the CAPACITY 006 Study ($p = 0.501$, high-dose group −9.0% vs. placebo group −9.6%) [40].

Thereafter, the ASCEND Study (NCT01366209) was conducted, allocating 555 patients at random to a high-dose PFD group and a placebo group [27]. In that trial, the change in percent predicted forced vital capacity (%FVC) or death at week 52 was set as the primary end point. When patients showing 10% or more reduction in FVC were defined as “decreased FVC” cases, the number of patients satisfying this definition or leading to death was significantly smaller in the high-dose PFD group than in the placebo group ($p < 0.001$; 46 patients, 16.5% vs. 88 patients, 31.8%).

Later, pooled post hoc analyses of these three clinical trials were conducted, revealing that the number of cases showing 10% or more reduction in FVC or leading to death was reduced by 43.8% (95%CI 29.3–55.4%) in the PFD treatment group, accompanied by significant alleviation or improvement in the secondary endpoints, i.e., reduction in 6 min walking distance, PFS, and the San Diego Shortness of Breath Questionnaire (SOBQ) score [41]. On the basis of these results, the clinical use of PFD was approved.

Also, in the phase 2 trial designed to evaluate the effects of PFD on progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, the potential of this drug in manifesting a certain efficacy was reported [42][43].

As adverse reactions to this drug, eruption (29.2%) and gastrointestinal symptoms, such as nausea (35.5%), anorexia (12.4%), dyspepsia (17.8%), and diarrhea (24.6%), were often noted [41].

2.2. Nintedanib

Pharmacology

NTD was initially developed as a drug for the treatment of solid cancer. Later, it was found to suppress the proliferation of fibroblasts and began to be used for the treatment of IPF. This is a multi-tyrosine kinase inhibitor, with a major function estimated as inhibiting the receptors involved in fibroblast activation such as platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1–3, and vascular endothelial growth factor receptor (VEGFR) 1–3. To put it concretely, this drug binds to the ATP binding pocket and thus inhibits phosphorylation, leading to the inhibition of downstream cascade signals such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), mitogen-activated protein kinase 1/2 (MEK1/2), and protein kinase B (Akt) [44][45][46].

There is a report that the PDGFR and FGFR expression levels in fibroblasts are higher in IPF patients than in controls, suggesting that these receptors may serve as critical targets for IPF treatment [47]. NTD has been reported to reduce PDGFR activity, fibroblast proliferation, and the transformation of fibroblasts into myofibroblasts [46]. In a study of fibroblasts derived from IPF patients, fibroblast proliferation was stimulated by each of PDGF, VEGF, and FGF administered separately, and treatment with NTD resulted in the dose-dependent suppression of fibroblast proliferation [47]. NTD has additionally been reported to reduce collagen production by fibroblasts stimulated with TGFβ [47]. The cascade involved in this activity has been reported to include mitogen-activated protein (MAP) kinase, extracellular signal regulated kinase (ERK), protein tyrosine kinase, and c-Abelson (c-Abl) [47]. Here, the TGFβ-Smad2/3 cascade (often studied in connection with IPF) was not found to be involved [47].

In addition, inhibitory activity against Flt3 and Src family (Src, Lyn, and Lck) has also been reported. The drug did not inhibit the other tyrosine kinase receptors (EGFR, HER2, InsR, IGF-IR, CDK1,2,4) [45].

Src is important as a target of NTD. TGFβ activates Src kinase, stimulating the transformation of fibroblasts into myofibroblasts. The Src inhibitor AZD0530 (saracatinib) inhibited the TGFβ signals, thus suppressing the transformation into myofibroblasts and the induction of collagen or fibronectin expression [48]. Resembling that report, Src inhibition by NTD has the potential of manifesting antifibrotic activity via a similar mechanism.

Clinical Trials on Nintedanib

The first large-scale clinical trial on NTD was a phase 2, randomized, double-blind, placebo-controlled trial (TOMORROW Study: NCT00514683). In that trial, 432 patients with IPF were allocated at random to NTD 300, 200, 100, and 50 mg groups and a placebo group, with the primary endpoint set as percent FVC reduction at 12 months. FVC reduction was suppressed by 68.4% in the NTD 300 mg group compared to the placebo group, although this difference was not statistically significant (NTD 300 mg group 0.06 L/year vs. placebo group 0.19 L/year) [49]. Later, INPULSIS I Study (NCT01335464) and INPULSIS II (NCT01335477) Study were carried out with

a similar design, enrolling 515 and 551 patients with IPF, respectively. FVC reduction differed significantly between the NTD group and the placebo group in both INPULSIS I Study (NTD: −114.7 mL/year, placebo −239.9 mL/year; $p < 0.01$) and INPULSIS II Study (NTD: −113.6 mL/year, Placebo −207.3 mL/year; $p < 0.01$) [50]. On the basis of these results, the clinical use of NTD was approved.

Clinical trials on NTD have also been conducted in patients with progressive fibrosing interstitial lung disease (PF-ILD) other than IPF patients. In the phase 3 INBUILD Study (NCT02999178), percent annual FVC reduction until week 52 of treatment (mL/year) was set as the primary endpoint and compared between the NTD group and the placebo group. It was −80.8 mL in the NTD group and −187.8 mL in the placebo group ($p < 0.0001$), thus endorsing the drug's effectiveness on PF-ILD in addition to IPF [51].

Gastrointestinal symptoms, including diarrhea (61.5–63.2%), nausea (22.7–26.1%), and vomiting (12.9–10.3%) were often seen as adverse reactions to NTD [50].

2.3. Combined Therapy

Combined PFD + NTD therapy was evaluated in INJOURNEY Study (NCT02579603). Of the 105 patients with IPF initially treated with NTD, 53 patients were additionally treated with PFD (the add-on PFD group) and 5 patients continued to receive uncombined NTD therapy. These two groups were evaluated for 12 weeks. The primary endpoint was the percentage of patients with on-treatment gastrointestinal adverse events from baseline to Week 12. The exploratory endpoints were the absolute and relative FVC changes from baseline to Week 12 and the rate of decline in FVC. The incidence of gastrointestinal adverse events was 69.8% (37/53) in the add-on PFD group and 52.9% (27/51) in the NTD alone group. The mean change in FVC at 12 weeks was −13.3 (S.E. 17.4) mL in the add-on PFD group and −40.9 (S.E. 31.4) mL in the NTD alone group. The combined use of PFD and NTD was shown to be tolerable and safe in this study and the other [52][53]. Further evaluation is needed about the efficacy of this combined therapy.

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