Idiopathic Pulmonary Fibrosis
—Possible new treatments and recent clinical trials—


Arata AZUMA

Assistant Professor, Fourth Department of Internal Medicine, Nippon Medical School

Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronically progressive fatal disease. However, as there are no prospects of successful prognostic improvement by currently available methods, the development of effective new treatments to improve prognosis is eagerly awaited throughout the world. Although much remains to be elucidated as to the pathology of IPF, it is understood according to two processes: lung injury resulting from preceding inflammation and fibrosis caused by abnormal repair. Most conventional therapies, including steroid therapy, have focused on the inhibition of inflammation. However, the inhibition of fibrosis itself has been attracting recent attention, and clinical applications are evolving. This paper describes the current status of clinical trials of interferon therapy ongoing in Western countries, with an explanation of its mechanism of action. In addition, the progress of a clinical trial of pirfenidone, the first randomized placebo-controlled study on the drug treatment of IPF in Japan, is described. Various treatment strategies for IPF suggested by basic research are also introduced.

Key words: Idiopathic pulmonary fibrosis; Anti-fibrotic therapy; Anti-inflammatory therapy; Pirfenidone; Interferon; N-acetylcysteine

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic type of idiopathic interstitial pneumonia. Currently about 2,300 patients in Japan are receiving medical subsidies for this condition, but the actual number of patients with the disease is estimated to be 5,000 to 10,000, including those who have not sought medical consultation. Since IPF is a progressive, fatal disease for which no spontaneous cure exists, elucidation of its pathology and the development of therapies are urgently needed, even though it is a rare disease. The current situation is such that some physicians are reluctant to treat patients when a diagnosis of idiopathic...
pulmonary fibrosis is made, since no effective treatment to improve prognosis is available.

The existing treatment for IPF aims only at temporary improvement of symptoms and pulmonary functions, because no effective measures are known for improving the prognosis. Therefore, future treatments are being sought both in Japan and other countries.

**Treatment Rationale** (Fig. 1)

Idiopathic pulmonary fibrosis (IPF) is considered to be a condition in which inflammation precedes tissue injury and results in fibrosis in lung tissue that is unable to carry out normal restoration. The cause of inflammation is unknown, and the subsequent repair process may be insufficient or abnormal, leading to fibrosis. Another feature of IPF is that it develops and progresses with aging. Therefore, it is important to elucidate the mechanisms of aging. Conventional treatments have been restricted to the inhibition of various factors in the inflammatory process. However, the efficacy of immunosuppressive treatment including steroid therapy is limited to temporary symptomatic relief.

In recent years, the propriety of these treatments has been reconsidered, and the lack of reliable clinical trials and absence of established criteria for the evaluation of treatment have been cited as faults of previous evaluations.

In light of these circumstances, we have categorized the therapeutic interventions for IPF into the following five areas: (1) inhibition of aggravation caused by acute exacerbation, (2) inhibition of chronic inflammation, (3) inhibition of chronic progressive fibrosis, (4) transplantation, and (5) regenerative medicine.

Ongoing development of new treatments focuses primarily on items (1) to (3). These devel-
Development of New Treatments

The following paragraphs describe the status of recent European and North American clinical trials concerning IPF (Table 1).

In 1999, a European group reported the efficacy of interferon (IFN)-γ in 9 patients with IPF. The incremental benefit of IFN-γ 200µg (given three times per week subcutaneously) combined with prednisolone for 12 months was examined in comparison with prednisolone monotherapy. Results showed significant improvement in lung function in terms of %FVC, alveolar-arterial oxygen gradient (A-aDo2), and total lung capacity (TLC) (Fig. 2).4

In the same year, an open-label trial of the oral antifibrotic agent pirfenidone ended, achieving inhibition of deterioration in lung function.5

In 2000, the protocol of a double-blind randomized controlled study of IFN-β in North America was presented at the annual meeting.
of the American Thoracic Society (ATS) in Toronto, and the progress of the long-term study, which extended over 2.5 years, was reported. However, at the 2001 ATS meeting, Professor Raghu, G. from the University of Washington reported that IFN-\(\gamma\) therapy showed no benefit either for lung function or survival time. In his overall comments, he concluded that therapeutic potential cannot be expected from IFN-\(\alpha\) or -\(\beta\), whereas IFN-\(\gamma\) appears promising.

### Clinical Trials in Japan

1. Pirfenidone

Pirfenidone, which was examined in an open-label study in the US, is one of the most promising agents for IPF (Table 2). This agent exerts inhibitory activity on the production of a number of inflammatory cytokines, including tumor necrosis factor (TNF)-\(\alpha\),\(^6\) and also inhibits the collagen synthesis.\(^5\) Therefore, a clinical trial of this drug as an antifibrotic agent was carried out in the US, targeting IPF.\(^5\) In Japan, a double-blind randomized controlled study of pirfenidone for IPF was begun in November 2000 to verify its efficacy and safety.\(^8\)

Pirfenidone was developed by MARNAC, Inc., of the US. In Japan, Shionogi & Co., Ltd., acquired a license for production from MARNAC, and a clinical trial was initiated. After about six months of study using a daily oral dose of 1,200–1,800 mg, an interim analysis was performed in 2001. Because of the decrease in acute aggravation among patients on pirfenidone therapy, the agent was assessed as effective. Adverse effects such as photosensitivity and gastrointestinal symptoms were noted, as in the clinical trial in the US. These effects, however, were considered to be controllable by adjusting the dosage. On the basis of these clinical trial data, an application for the approval of pirfenidone’s use in Japan was sent to the Ministry of Health, Labor and Welfare.

One of the special features of the above study was its attempt to provide an exploratory evaluation of drug efficacy (Table 3). In previ-
ous clinical studies on the treatment of IPF, a period of 1 or 2 years was required for investigation, and drug efficacy was evaluated in terms of improvement in static lung function. IPF is a chronic progressive disease with an extremely slow course.

Because of this limitation, we attempted to more sensitively detect changes in lung function by quantifying the decrease in blood oxygen saturation during exercise as an area and using it as a primary endpoint (a modification of the original method developed by N. Tsuboi and K. Nakata, Respiratory Division, Toranomon Hospital). The conventional six-minute walk test is associated with individual changes in walking speed and walking distance along with improvement of lung function, making it difficult to compare pre- and post-treatment status accurately. In contrast, exercise with constant speed loading before and after treatment in the above study allowed more accurate evaluation of therapeutic efficacy. Although there is room for improvement in this method of evaluation, it is expected to be applied more widely as a sensitive, objective method of evaluating the efficacy of new drugs.

2. Interferon (IFN)

Owing to the circumstances referred to previously, IFN-β therapy for IPF was judged to be ineffective at the 2001 ATS meeting. In light of this evaluation, clinical trials of IFN-β therapy were abandoned in Japan. However, since IFN-γ is expected to be effective in preclinical studies and the results of an earlier pilot study were promising, the introduction of clinical trials employing this therapy is now under consideration in Japan, awaiting the publication of results of an ongoing large-scale clinical trial of IFN-γ in North America.

3. N-acetylcysteine (NAC)

The Research Committee on Diffuse Pulmonary Disease of the Ministry of Health, Labor and Welfare is in charge of clinical investigations of NAC inhalation therapy as well as other therapies. This therapy is expected to inhibit injury to the alveolar epithelium through its antioxidant properties. NAC attracted general attention in 1997, when Behr et al. in Germany reported improvement in lung function after high-dose oral NAC therapy (1,800 mg/day in 3 divided doses). In Japan, an inhibitory effect on the progression of pulmonary fibrosis is expected from inhalation therapy with nebulized injectable NAC.

In an open-label trial in Japan, inhaled NAC provided improvement in clinical symptoms in comparison with the baseline in 30% of patients who were on this therapy for at least one year and was rated “effective” in about 40% of the patients. In addition, no particular adverse effects occurred after prolonged use, demonstrating its safety (Ishii et al., Ministry of Health and Welfare Research Project).

In Europe (7 countries), a large-scale clinical trial of NAC therapy is underway in about 150 patients with IPF, using vital capacity and DLco as primary endpoints, based on the data reported to date.

4. Cyclosporin A (CYA)

In contrast to the conventional treatment of pulmonary fibrosis by anti-inflammatory drugs, attempts have been made to use cyclosporin A therapy, with a stronger effect expected as a result of its immunosuppressive activity. Its therapeutic efficacy in general cases of pulmonary fibrosis is under investigation, and no decisive conclusion has yet been reached.

However, it appears that some patients with rapidly progressive interstitial pneumonia caused by collagen disease who have not responded to prednisolone (PSL), cyclophosphamide (CPA), or azathioprine (AZP) are rescued by CYA therapy.

On the other hand, steroids have been used to treat the acute exacerbation of IPF, but results have been extremely poor. Accumulated clinical evidence indicates that the combined use of CYA for this condition provides a favorable response, preventing re-aggravation.
as a result of the reduced dosage of steroid therapy (Yoshizawa et al., Ministry of Health and Welfare Research Project).

Future verification by a larger-scale clinical trial is awaited.

**Therapeutic Targets Expected from Molecular Pathological Research**

Although the targets of pulmonary fibrosis treatment are broadly divided into “lung injury” and “fibrosis,” there is a question as to what therapeutic strategies are possible.

Treatment to inhibit lung injury caused by inflammation, i.e., the inflammatory phase, has depended on steroids or immunosuppressants. In recent years, however, gene therapy to supplement the cytokines that are lacking has been tried in an attempt to correct the imbalance of inflammatory conditions in the body.

1. **Inhibitory effect of IL-10 on interstitial pneumonia**

   The inhibitory activity of interleukin (IL)-10 is one of the promising treatment options; *in vivo* gene transfer has achieved inhibition of inflammation and fibrosis of the lung in the bleomycin (BLM)-induced lung injury model.9) In addition, in the *in vitro* setting, IL-10 inhibited transforming growth factor-β (TGF-β)-induced production of collagen in fibroblasts.

   Based on the above findings, it is apparent that IL-10 is an important inhibitory factor for both inflammation and fibrosis of the lung, and the possibility of introducing IL-10 therapy for IPF patients is now being examined from its fundamental aspects.

2. **Anti-fibrotic action of 14-membered ring macrolides**

   Macrolide antibiotics represent a class of drugs that have recently been attracting attention because of their anti-inflammatory effect on airway inflammation. In preclinical studies, this class of antibiotics inhibited tissue infiltration and injury by neutrophils as well as inhibiting airway inflammation, suggesting beneficial effects in the inhibition of fibrosis.10)

   On the other hand, lung tissue in which the existing architecture has been destroyed and replaced by fibrosis can never be restored. Thus regeneration and reconstruction of the alveolar epithelium in the tissue injury phase is considered a critical process in the normal repair mechanism.

3. **Clinical application of gene therapy with hepatocyte growth factor for pulmonary fibrosis**

   Hepatocyte growth factor (HGF) is a promising epithelium-regenerating factor.11) Currently, the development of efficient HGF expression vectors and their introduction to the lung are being attempted in the experimental setting. However, the greatest problem involved in such gene introduction is whether the possibility exists of maintaining gene expression in the right quantity and in the right place. Thus, technical issues remain to be solved.

**Future Perspectives**

ATS indicated in the international consensus statement entitled “Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment” published in its official journal in 2000 that a change from conventional therapeutic strategies is necessary. Attention has already been focused on the inhibition of fibrosis itself rather than the inhibition of inflammation, which has been the key point in conventional treatments. However, for some drugs, the results of clinical and experimental studies have not necessarily been consistent.

Diagnostic issues regarding IPF are also in the process of reevaluation. The pathological condition of IPF may present different clinical pictures according to its temporal phase. Future discussion should be advanced from the stage of drug discovery to that of treatment guidelines based on close investigations.

Although gene therapy has been introduced
for several diseases, the induction of gene expression in appropriate quantities required according to time and place remains a key issue to be solved in gene therapy for IPF in view of the peculiarity of the disease site, namely, the respiratory organ. To this end, it may be important for medical care of the 21st century to examine the possibility of tailored treatment based on full knowledge of the individual patient’s characteristics, including the developmental stage of the lung.

In addition, from the viewpoint of regenerative medicine, it is important to be able to induce regeneration of lost alveolar epithelial cells where it is required. These studies are about to begin, and a vision created on the basis of an international perspective will be needed.

REFERENCES


