Newer modes of treating interstitial lung disease

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Purpose of review

This review critically discusses recent advances in the treatment of idiopathic pulmonary fibrosis (IPF). Moreover, it also focuses on the practical approach of a patient diagnosed with IPF and uncovers challenges for the future.

Recent findings

Treatment can be divided into three major parts. Firstly, many new agents have been tested, but only the combination of *N*-acetylcysteine with corticosteroids, azathioprine and pirfenidone was able to show some significant effects. In the mean time, many second-generation agents are under development. Lung transplantation has made some major progress by introducing an appropriate allocation system. Finally, as part of best supportive care, several studies show that pulmonary rehabilitation might induce some important effects on quality of life.

Summary

So, it is clear that major progress has been made in the treatment of IPF, but we are convinced that an orchestrated effort will lead to a better understanding and treatment of this devastating condition.

Keywords

best supportive care, idiopathic pulmonary fibrosis, lung transplantation, pulmonary rehabilitation, treatment

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Introduction

Pulmonary fibrosis is the end stage of many different interstitial lung diseases, including interstitial lung diseases of known cause and idiopathic interstitial pneumonias (Table 1). As interstitial lung diseases cover more than 200 different disease entities, we will focus on the archetype of the fibrotic diseases: idiopathic pulmonary fibrosis (IPF). IPF has an estimated incidence of nine per 100 000 person-years and would affect about 500 000 patients in the USA and Europe [1]. For a long time, the pathogenesis of IPF has been considered as chronic inflammation leading to irreversible formation of fibrosis. In the last American Thoracic Society/European Respiratory Society guidelines, IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lungs in association with a usual interstitial pneumonia pattern on histology [2]. It is a relentlessly fibrotic disease, consisting of a deposition of extracellular matrix causing architectural distortion of the lungs. IPF is refractory to current pharmacological intervention and mean survival is about 3 years after diagnosis.

The present review provides a comprehensive overview of recent developments in the treatment of IPF. Many new antifibrotics of the first generation have been tested with mixed results, but second-generation, more powerful agents are in development. Next to drugs, we will also discuss progress in lung transplantation (LTX) and best supportive care. Moreover, we will provide a practical approach for the physician in selecting appropriate treatment for the individual patient. In the final section, we will focus on the future of treating pulmonary fibrosis on the basis of recently published articles.

Treatment

Current treatment of IPF can be divided in three main topics: drug treatment, LTX and best supportive care. A variety of biological factors and complex pathways have been implicated in the pathogenesis of lung fibrosis, and IPF in particular [3]. Upto now, some first-generation agents have been tested with mixed results. Second-generation agents that are more powerful are being developed and clinical trials are under way. There are some promising data on treatment of pulmonary hypertension in IPF and LTX. Unfortunately, not all patients are eligible for LTX and many patients are left with best supportive care, mainly consisting of dyspnoea control and oxygen; however, it becomes clearer that pulmonary rehabilitation is important.

Table 1 Classification of idiopathic interstitial pneumonias

Histological pattern	Clinical–radiological–pathological diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Diffuse alveolar damage	Acute interstitial pneumonia
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Organizing pneumonia	Cryptogenic organizing pneumonia
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia

Key points

- Idiopathic pulmonary fibrosis (IPF) is a relentless disorder in which there is no role for corticosteroids in the treatment.
- A new generation of antifibrotic agents are being tested in clinical trials and many of them look promising.
- Massive progress has been made in lung transplantation for IPF, but timely referral is crucial.
- Palliative care has a broad spectrum of possibilities and should be started in conjunction with the curative approach.

Drug treatment

Currently, drug treatment can be divided into corticosteroids, nonsteroid therapy and treatment for pulmonary hypertension secondary to IPF.

Steroids

For many years, the mainstay of IPF treatment has been corticosteroids; however, it has become clear in the last decade that this induces no proven benefit in this mainly fibrotic disease. A recent Cochrane review has studied the effect of corticosteroids in IPF [4••], but was not able to identify suitable randomized placebo-controlled treatment trials due to inadequate methodologies.

Nonsteroidal therapy

Previously, it has been thought that IPF was the result of a chronic inflammation; in the new paradigm, IPF is considered to be induced by repeated injury which initiates both immunological mechanisms and fibrosis. This change in paradigm has started a new wave of molecules that have been tested in placebo-controlled clinical trials.

Antioxidant therapy

It is clear that oxidative stress plays a role in alveolar epithelial cell injury and fibrogenesis. An extended analysis published by Behr *et al.* [5] confirms and extends the favourable effects of *N*-acetylcysteine (NAC) on lung function in IPF [forced vital capacity (FVC) $4.80 \pm 2.00\%$ predicted, in comparison with placebo] of the primary study of Demedts *et al.* [6]. With NAC therapy, significantly fewer patients suffered a 5% or more deterioration of vital capacity from baseline as compared with placebo (40.8 vs. 61.8%, $P = 0.018$). Most importantly, less progressed disease, as indicated by a composite physiological index of 50 points or lower at baseline, was more responsive to therapy in this study. As a result, the combination of NAC, prednisone and azathioprine has been recommended in the 2008 British Thoracic society guidelines for IPF [7].

Antifibrotic therapy

Antifibrotic agents decrease fibroblast proliferation and collagen synthesis, at least *in vitro* and in animal research. Unfortunately, most of these first-generation agents did not lead to a major breakthrough in IPF. In a recently published trial, it has been shown that interferon-γ, which inhibits formation of inflammatory and angiogenetic markers, showed no effect in IPF [8]. Etanercept, which inhibits binding of tumour necrosis factor (TNF)-α to its receptor, showed no significant effect on FVC nor on diffusing capacity (DLCO) after 48 weeks [9]. A further potential target is endothelin-1, which as well as being a pulmonary vasoconstrictor is a mitogen of (myo)fibroblasts. With bosentan, a dual endothelin receptor antagonist, no effect was found on the 6-min walking test, although a trend was observed in time to death or disease progression [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.33–1.14] [10]. This was more pronounced in the subgroup diagnosed by surgical lung biopsy (post-hoc analysis, HR 0.31; $P = 0.009$) and these results led to the start of a larger study: Bosentan Use in Interstitial Lung Disease-3 (BUILD-3), results of which are not yet published.

Pirfenidone inhibits the progression of fibrosis in animal models. A recent Cochrane review [11••] has analysed two large randomized controlled trials (RCTs; CAPACITY 1 and 2) and Taniguchi 2010 [12]. Significant differences were observed in progression-free survival time between pirfenidone and placebo for two of three studies (CAPACITY 2 and Taniguchi 2010), a nonsignificant effect was observed for CAPACITY 1. The summary of these studies suggests that pirfenidone reduces the risk of progression by 30% (HR 0.70, 95% CI 0.56–0.88). Although encouraging there is still doubt about the long-term effect [13•]; therefore, it is not clear whether the effect justifies the toxicity.

Other targets for therapy

Transforming growth factor (TGF)-β plays a major role in the development of pulmonary fibrosis; therefore, many inhibitors are in development. A first approach can be direct inhibition of the action by antibodies against TGF-β such as GC 1008 (Genzyme Corporation, Framingham, USA). A phase I trial has finished and

publication of the results is awaited. Moreover, TGF-β signal transduction can be affected by an inhibitor of the high-affinity serine/threonine kinase receptor (TGF-βRI activin-like kinase receptor 5), which is in development. The blockade of the TGF-β activation process can lead to the development of many new high potential agents.

The most prominent cell in bronchoalveolar lavage of patients with IPF is the macrophage, attracted by CCL2/MCP1. At present a randomized double-blind placebo-controlled trial is being performed to investigate the safety and efficacy of CNTO888 (Centocor, Horsham, USA), an inhibitor of CCL2/MCP1.

Another potential agent is QAX576 (Novartis, Basel, Switzerland) an anti-IL13 which is being studied in a phase II trial in IPF.

Angiotensin-converting enzyme (ACE) came recently into the scope of potential therapies for IPF, as in-vitro and in-vivo data showed a decreased ACE activity in pulmonary fibrosis. This attractive hypothesis is being tested in a pilot trial evaluating the effect of losartan on FVC.

The coagulation cascade has been shown to have a role in the formation of pulmonary fibrosis by the tissue factor-dependent extrinsic pathway orchestrating the interplay among coagulation, inflammation and lung fibrosis [14••]. One study treated 56 patients with anticoagulation in a nonblinded, prospective randomized manner [15]. Patients were treated with warfarin, or low molecular weight heparin during acute exacerbations. There were significantly fewer deaths in anticoagulated patients, but the study had many flaws, such as selective dropouts in the anticoagulant group, not one single agent, nonblinded nature of the study and criteria to diagnose IPF. Nevertheless, this study points to the high potential of anticoagulation and warrants urgent new studies.

Next to fibrosis, there might be a role for angiogenesis in the development of fibrosis. A large phase II trial with BIBF1120 (Boehringer Ingelheim Pharmaceuticals, Ingelheim, Germany) targeting vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor has finished, but results are not published yet.

Possible new targets for the future

It is clear that there is an emerging need for new agents in the future. Development will be based on recently identified novel targets and pathways [16]. Lysophosphatiditic acid has been identified as an important mediator in wound repair and tissue fibrogenesis, but also Wnt signalling pathways, involved in regulation of epithelial and mesenchymal development via autocrine and paracrine signals, open a whole new world. Moreover, the Jagged/Notch pathway and lysyl oxidase-2 might represent another set of targets with high potential.

Treatment of pulmonary hypertension in idiopathic pulmonary fibrosis

The prevalence of pulmonary hypertension in IPF ranges from 32 to 85%; moreover, pulmonary hypertension is associated with increased (early) mortality. Vasodilators have been shown to worsen gas exchange and hypoxemia. In contrast, in a placebo-controlled study, sildenafil was associated with a significant improvement in DLCO, Pa_{O_2} and quality of life at 12 weeks [17]. However, as always, further trials are needed.

Transplantation in idiopathic pulmonary fibrosis

LTX is the only treatment that improves survival in IPF. However, mortality of IPF patients on the waiting list is high owing to limited organ supply and the unpredictable natural course, with acute exacerbations that are often fatal.

Recently, it has been shown that the use of lung allocation score (LAS), is able to predict mortality 1 year after LTX [18]. The LAS is a standardized score ranging from 0 to 100, calculating the difference between expected 1-year posttransplant survival and the likelihood of dying on the waiting list. Furthermore, two studies have investigated the difference between single and bilateral LTX. One study showed that in patients at highest risk based on LAS score, bilateral LTX was associated with a 14.4% decrease in mortality at 1 year [19]. Another article has shown no difference in survival after adjustment for baseline differences, but bilateral LTX seemed to result in a greater risk in the first year, but survival benefit thereafter [20].

Best supportive care

Recent data show that quality of life in patients with IPF is poor, so improving palliative care in patients with IPF is necessary [21]. Owing to the unpredictable natural course of IPF, the classical model of palliative care that starts where curative care ends is not applicable. In the recent Official American Thoracic Society clinical policy statement, an individualized integrated model of palliative care concurrent with curative care for patients with respiratory diseases and critical illnesses is recommended [22].

Treatment of dyspnoea

The treatment of dyspnoea can be established using oxygen treatment or pharmacological treatment.

Oxygen in idiopathic pulmonary fibrosis

Current guidelines recommend the prescription of long-term oxygen therapy for patients who are hypoxic at rest, especially if pulmonary hypertension is present. Ambulatory oxygen is recommended for patients who

desaturate to less than 90% during exercise if a clear beneficial effect on exercise capacity or dyspnoea is seen [7]. However, to date, it is not known whether there are survival or quality-of-life benefits from oxygen therapy.

Pharmacological treatment of dyspnoea

For severe dyspnoea, the use of opioids such as morphine should be considered. The available data, although sparse, are reviewed in Spruit *et al.* [23].

Rehabilitation in idiopathic pulmonary fibrosis

It has been shown that exercise limitation has a profound effect on the quality of life of patients with interstitial lung diseases. Recently, it has been shown that the main reason for exercise limitation is impaired gas exchange, but also an effect of peripheral and respiratory muscle dysfunction [24]. Two randomized controlled trial (RCTs) have reported positive effects in 8–10 weeks of exercise training in different types of interstitial lung diseases [25] or only IPF [26]. In IPF, improvement was smaller than in mixed interstitial lung diseases, but still associated with significant improvement in health-related quality of life. A study looking at longer term effects of exercise training could not show a benefit at 6 months [25], probably because no formal after care programme was initiated. Therefore, it is recommended that patients with interstitial lung diseases have access to a multidisciplinary pulmonary rehabilitation programme [7].

Practical approach

Once the diagnosis of IPF is made, the major problem is choosing the right treatment at the right time. This decision is difficult, as interpretation of published studies is difficult and for many agents results are awaited. Major elements that should be balanced are activity of the disease, effect of treatment and side-effects. Therefore, we propose a three-step approach.

Immediately after diagnosis, the physician must consider whether this patient is eligible for transplantation, based on age and medical history. If the patient is potentially eligible, the patient should be referred to a highly experienced transplant centre. Thereafter, appropriate treatment should be initiated as soon as possible. It is clear that the best current practice is to enrol as many IPF patients as possible in high-quality multicentre trials with new agents [27]. Unfortunately, not all patients fit the inclusion criteria of those trials. At this present time, the most evidence is for either the combination of corticosteroids with azathioprine and NAC or the novel antifibrotic pirfenidone. The first option is criticized, as it has only been shown in one study and there was no placebo group. Therefore, a conformational study is under the way (prednisone, azathioprine, and NAC: A Study That Evaluates Response in IPF: PANTHER trial). For pirfenidone, more studies have been done, but not all of them are convincing.

Challenges for the future

Despite major efforts that have been made, the results of new drug development in IPF are rather poor. An earlier diagnosis might lead to a more effective treatment, but this is hardly possible. The future will also be in focusing on multiple profibrotic pathways, as seen in the new generation of antifibrotics. Another important element is the choice of end points in clinical trials. Survival is the most appropriate end point; however, an adequate powered trial for mortality is impossible in this rare disorder. A 10% decline in FVC has been used as a surrogate end point for a long time, but smaller changes may be also clinically significant [28••,29].

Conclusion

After realizing that IPF is mainly a fibrotic disorder, many new antifibrotic agents have been developed, but many have been disappointing. Although another generation of antifibrotics are being tested, the tendency exists to treat with NAC, corticosteroids and azathioprine, or more recently pirfenidone. Apart from drug treatment, substantial progress has been made in LTX. Timely referral in IPF is crucial, although difficult as individual evolution is different and acute exacerbations can induce an abrupt deterioration. Therefore prognostic factors such as LAS score should be further elaborated. If transplantation is not an option, best supportive care and, especially, pulmonary rehabilitation should be considered in an attempt to improve quality of life and decrease shortness of breath.

So, it is clear that the efforts upto now have not been in vain, but an orchestrated effort will lead to a better understanding and treatment of this devastating condition.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 399).

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