Severe idiopathic pulmonary fibrosis: what can be done?

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Patients with severe IPF require a global approach similar to patients with advanced cancer disease
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ABSTRACT Idiopathic pulmonary fibrosis (IPF) remains a challenging disease to manage. Two drugs are now available that can slow disease progression in patients with mild-to-moderate IPF. This means that early diagnosis is mandatory, because there are no proven effective therapies for severe IPF. This lack of proven therapies may be at least partially due to the fact that severe IPF patients are usually not enrolled in randomised, prospective, multicentre, international trials. Clinical observation experiences and preliminary results of long-term, open-label extensions of clinical trials suggest that both pirfenidone and nintedanib may also slow or decrease progression in patients with severe IPF. However, data are sparse and obtained from a relatively small number of patients. Lung transplantation should be taken into account early and discussed with patients, when indicated. Rehabilitative strategies are important and effective supportive therapies. The needs of patients with severe IPF are similar to those of patients with an advanced neoplastic disease. Palliative care and psychological support play an important role in the relief of symptoms of anxiety and depression. Accordingly, these therapeutic approaches should start early in IPF patients.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare and serious disease that is characterised by poor survival. IPF can be considered, in its prognostic features, to be a malignant, cancer-like disease [1, 2]. Until the last few years there were no effective treatments, so IPF was also considered an orphan lung disease [3]. The 2011 guidelines and consensus statements did not endorse specific medical therapies, and enrolment in clinical trials and evaluation for lung transplantation have been until recently the only recommended treatment options [1]. The revision of the 2011 guidelines released a conditional recommendation for the use of nintedanib and pirfenidone for the treatment of IPF [4]. A great number of clinical studies have been performed on this specific field of medicine in recent years, many of which led to unsuccessful or inconclusive results, but, thanks to this great effort, two drugs (pirfenidone and nintedanib) have been approved for the treatment of this devastating fibrotic chronic disease [5–8]. Both molecules are approved therapies for reducing the progression of the disease and stabilising lung function. However, although these drugs represent a major advance in the treatment of IPF patients, they cannot halt or reverse the

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lung damage and are not a "cure". Therefore, a number of ongoing prospective, multicentre and controlled clinical trials are ongoing, with the aim of selecting more active treatments and investigating combined therapies, as has already been done successfully for therapy of pulmonary arterial hypertension, which is another rare and serious pulmonary disease [9, 10]. Not much is known about the characteristics of patients with IPF outside clinical trials, their management under everyday clinical practice conditions, or their long-term outcomes. Real-life data (*e.g.* registry data) can complement results from randomised controlled trials, providing much needed information on antifibrotic drug utilisation and allowing their effect in patients with more comorbidities or with more severe disease to be evaluated [11–16].

First, understanding the real meaning of the terms "moderate", "severe", "early" or "advanced" disease is a fundamental step. There is no standardised definition and the very same term has often been used to refer to patients with different functional impairment. However, according to the pulmonary function parameters currently used in clinical trials, patients with a forced vital capacity (FVC) >50–55% of predicted and a diffusing capacity of the lung for carbon monoxide (*D*LCO) >35–40% of predicted are typically diagnosed as having mild-to-moderate disease, while patients with severe or advanced disease present with FVC and *D*LCO values lower than the abovementioned thresholds [17–23]. In many countries, pirfenidone and nintedanib are approved with reimbursement for the treatment of patients with mild-to-moderate disease, who therefore present with well-defined impairments of lung function. Patients with severe IPF and in particular those with FVC <50% and/or *D*LCO <30% of predicted, who are not enrolled in large clinical trials, have no prospect of therapeutic approaches. These patients, despite substantial efforts towards achieving early diagnosis [24] and a prompt and more effective treatment, still represent a considerable subgroup of the real-life IPF population (figure 1). For instance, according to the INSIGHTS-IPF (Investigating Significant Health Trends in Idiopathic Pulmonary Fibrosis) registry in Germany [12], after introduction of the new international guidelines on IPF in 2011 [1], patients categorised as GAP stage III (the GAP index is a stratification model for risk based on age, sex, FVC and *D*LCO, with stage III being the highest [19]) represented 21.3% of the population [12]. Mean±SD FVC was 72±20% of predicted and mean±SD *D*LCO was 35±15% of predicted in the entire registry population. According to the percentage of predicted *D*LCO, INSIGHTS-IPF patients had more severe disease compared with those in randomised controlled trials.

The aim of this article is to review the possible therapeutic interventions in patients with severe IPF.

Pirfenidone and nintedanib: what role in severe IPF?

Pirfenidone is a drug with antifibrotic, anti-inflammatory and anti-oxidant effects, and it has been demonstrated that the treatment of IPF patients with pirfenidone can significantly slow the rate of disease progression [25–27]. An abundance of data supports its use in mild-to-moderate IPF [25–27]. A pre-specified pooled analysis including the ASCEND and CAPACITY trials showed that pirfenidone reduced the risk of death at 1 year by 48% [6].

To assess the efficacy and safety of pirfenidone in patients with more severe lung function impairment (*i.e.* FVC <50% and/or *D*LCO <35%), a *post hoc* exploratory analysis of data from the open-label extension study of the pirfenidone phase III trial (RECAP study; patients with IPF who completed one of the ASCEND or CAPACITY phase III trials) was performed. The number of study patients in the subgroup

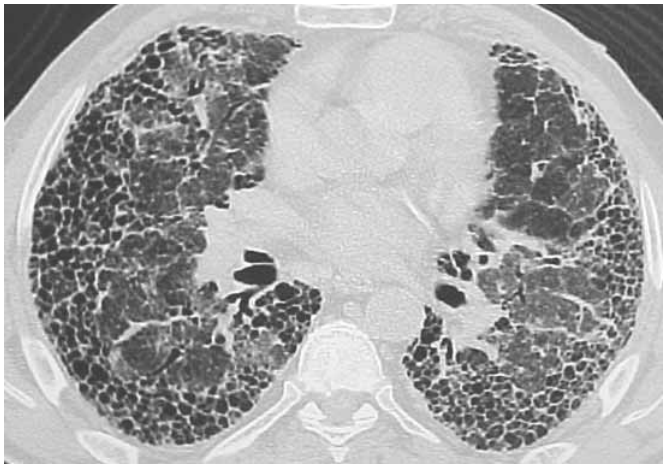

FIGURE 1 High-resolution computed tomography image in a case of severe idiopathic pulmonary fibrosis. Diffuse honeycombing and traction bronchiectasis are present.

with severe disease was rather small (187 patients). Long-term treatment with pirfenidone resulted in similar rates of decline in lung function in patients with more severe lung function impairment compared with patients with more preserved lung function. Safety profiles were comparable between the two patient populations (U. Costabel, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany; personal communication). Furthermore, preliminary data from observational studies by other groups have suggested a similar efficacy of pirfenidone in severe IPF [28–33]; however, the results were quite preliminary.

Nintedanib, an intracellular inhibitor of tyrosine kinases [34, 35], is approved for the treatment of IPF in several countries, including the USA, Europe and Japan. Nintedanib slows disease progression by reducing the annual rate of decline in FVC by ~50% [7, 8].

In the INPULSIS studies (which investigated the efficacy and safety of nintedanib in IPF), results obtained in patients who were stratified into two categories of disease severity based on the GAP classification (GAP I *versus* GAP II/III) showed that the efficacy in reducing the progression of disease was comparable between subgroups. Moreover, similar results were obtained in patients stratified by D_{LCO} values (>40% or ⩽40%). A greater proportion of patients at GAP stage II/III at baseline had an acute exacerbation compared with patients at GAP stage I; likewise, a greater proportion of patients with D_{LCO} ⩽40% of predicted than those with D_{LCO} >40% of predicted at baseline had an acute exacerbation, but the treatment effect of nintedanib remained consistent between the subgroups (T.M. Maher, National Institute for Health Research Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust, and National Heart and Lung Institute, Imperial College, London, UK; and C.J. Ryerson, University of British Columbia, Vancouver, BC, Canada; personal communications).

In the INPULSIS-ON study (the open-label extension of the INPULSIS trials), a *post hoc* exploratory subgroup analysis was carried out in patients with FVC ⩽50% and >50% of predicted at the start of the extension phase [36]. Only 24 patients had FVC ⩽50% of predicted, and a similar effect of nintedanib on disease progression was observed [36]. In the subgroup of patients with severe disease, the progression of disease and fatal events were more frequent than in patients with a less severe disease, although the difference was not statistically significant. In view of the small number of severely ill patients, these data should be interpreted with caution [36].

In conclusion, there are some data suggesting that both drugs might also be effective at later stages of the disease; however, these data are preliminary and more solid evidence is required. It seems reasonable to suppose that earlier rather than later initiation of a treatment that reduces disease progression would lead to better benefit. Both drugs have small effects on patient symptoms. In particular, no data currently exist on the effect of nintedanib on cough, but there are some observations on a possible effect on cough by pirfenidone [37, 38].

The near future

Patients with severe IPF are patient "orphans" of therapy, mainly because they are usually excluded from large clinical trials on IPF. Thus, it is of utmost importance to offer therapeutic options for the treatment of these patients. The prospective, randomised, controlled STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) study was one of only a few trials that enrolled patients with severe IPF (D_{LCO} ⩽35% predicted). The aim of this trial was to evaluate the effect of therapy with sildenafil (20 mg three times daily) in patients with advanced IPF [39]. The primary end-point of the study (20% improvement in the 6-min walk distance (6MWD)) was not achieved; however, some improvements were observed for the secondary end-points, such as D_{LCO}, dyspnoea, oxygen saturation and quality of life of patients. A *post hoc* analysis showed that patients with right ventricular systolic dysfunction receiving sildenafil experienced a 99-m lower decline in the 6MWD and an improved quality of life compared with those who received placebo [40]. However, this study was not designed to evaluate the presence of pulmonary hypertension in the group of patients with severe IPF, and haemodynamic assessments were not performed at the start and end of the study. Thus, the conclusion that the positive effect on secondary end-points could be related to some effect on pulmonary hypertension (which was likely to be present in these patients) could not be drawn [40].

Pulmonary hypertension is a common complication of IPF [41, 42]. Its occurrence increases in more advanced stages of the disease and can affect patients' symptoms and prognosis [43–45]. Pulmonary hypertension secondary to IPF falls under group III of the pulmonary hypertension classification, and no therapy is approved for its treatment [46]. Therefore, patients with pulmonary hypertension secondary to advanced IPF represent a group with a high unmet medical need. For this reason, clinical studies are currently being conducted with the aim of evaluating the efficacy and safety of sildenafil in association with either pirfenidone or nintedanib in patients with severe IPF and a high probability of pulmonary hypertension.

Rehabilitation and palliative care

Pulmonary rehabilitation is recommended in the IPF guidelines as a possible supportive therapy [1]. Pulmonary rehabilitation is beneficial to patients with chronic obstructive pulmonary disease (COPD) in order to improve functional capacity as assessed by the 6MWD, reduce dyspnoea and improve the quality of life [47]. In fact, it is an established supportive therapy for these patients [48]. Despite the distinct pathophysiological mechanisms of COPD and IPF, some symptoms (such as exertional dyspnoea, fatigue and depression) that are seen in patients with IPF are similar to those seen in COPD patients [49]. The progressive reduction of exercise tolerance and loss of independence in daily life activities has a great impact on the quality of life of these patients [49]. Therefore, because the current therapeutic options are limited, even a very small benefit gained from pulmonary rehabilitation can certainly represent a therapeutic added value and play an important role. In fact, it should be taken into consideration that the two medications currently approved for the treatment of IPF (pirfenidone and nintedanib) can slow the progression of the disease but provide inadequate symptom relief (especially for cough and dyspnoea). A pulmonary rehabilitation programme carried out in IPF patients for 8 or 12 weeks can improve exercise tolerance, dyspnoea and quality of life [50–53]. These positive effects are due not only to the exercise component of the rehabilitative programme, but also to a comprehensive approach to patient care. Holland *et al.* [52] studied the effects of a long-term rehabilitation programme on 34 patients with IPF. After 6 months of discharge from pulmonary rehabilitation, there was no difference in outcome between the treatment and control groups, suggesting that the beneficial effects of the rehabilitation programme were lost. This may be due in part to the fact that IPF is a chronic and progressive disease. Therefore, it is crucial to educate and prompt patients to keep to a regular exercise schedule in order to maintain the benefits over time [53–55]. Rehabilitation programmes may represent a unique opportunity to inform patients about their prognosis and discuss hypothetical end-of-life scenarios. It has been shown that participation in rehabilitation programmes may reduce the high levels of anxiety and depression in patients with IPF, even in the absence of specific psychological interventionist techniques [56].

Patients with severe IPF currently have many unmet healthcare needs [57]. Palliative care is defined as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [58].

The 2011 and 2015 guidelines for the diagnosis and treatment of IPF released fundamental recommendations for the management of IPF, but provided little information on the treatment of the advanced stage and palliative care. According to the guidelines, palliative care should be started at the occurrence of symptoms. Palliative care should begin at diagnosis, and then be continued (and tailored) through treatment, follow-up care and the end of life [1, 56]. In clinical practice, the delivery of palliative care approaches may vary considerably between countries because of the differences in cultural background and healthcare systems. Patients with severe IPF have communication needs similar to those of cancer patients, so the IPF care team should spend time with these patients and their families to provide them with understandable information on IPF diagnosis, disease severity, prognosis, palliative care and all related issues. Patients with IPF, as well as those with severe IPF, are quite uncomfortable talking about death and end-of-life issues with healthcare specialists [56]. There are many reasons for the late transfer to palliative care programmes: one of these is the embarrassment of physicians, in particular for non-IPF specialists, in having a conversation about death with the patient and family. Caregivers and family members may also feel awkwardness in discussing end-of-life issues. Last, but not least, delays in the initiation of palliative care may be due to the fear that the patient's end-of-life discussion would eventually jeopardise hope for recovery [59, 60]. However, a recent study instead has shown that patients appreciate having these conversations [61].

Cough, dyspnoea and asthenia are common symptoms of IPF, but IPF patients can also be vulnerable to the effects of psychological stress. Symptoms of psychological distress, such as anxiety and depression, might be heightened by the uncertain trajectory of critical illness and/or a lack of clarity about the prognosis [62]. Not knowing what the future may hold means that patients are unable to mobilise their internal resources and support structures to develop effective coping strategies [63]. The prognosis for people with IPF is quite difficult to define and can vary greatly, so communication about prognosis between the healthcare professional and the patient should not be a one-time occurrence but rather should be repeated and revisited within the continuum of dynamic counselling [64]. Because depressive symptoms are rather common in these patients and may reduce their quality of life, depression should be actively screened in patients with IPF and, if present, therapy with antidepressants should be offered [65–68]. Overall, the care needs of IPF patients and their families are similar to those of late-stage cancer patients [69]. A recent study proposed a new model for continuous care in IPF, "the ABCDE of IPF care":

Assessing patients' needs; Backing patients by giving information and support; delivering Comfort care by focusing on treating symptoms and taking into account Comorbidities; striving to prolong life by Disease modification; helping and preparing patients and their caregivers for the eventual End-of-life events that are likely to occur [69]. Skills in symptom control are needed [70]. However, the use of morphine or its derivatives in end-stage patients with IPF to reduce the severity of dyspnoea and persistent cough remains a taboo subject [71–73]. Also, in severe and advanced stages of disease, it is important to carefully analyse the comorbidities of IPF patients (pulmonary hypertension, sleep apnoea, emphysema, lung cancer, gastro-oesophageal reflux disease, cardiovascular disease, *etc.*), which might negatively affect functional status, quality of life and prognosis. Optimal treatment of comorbidities is a difficult issue: as already mentioned, there is no indication to treat pulmonary hypertension in IPF [46], gastro-oesophageal reflux therapy is a matter of debate [74, 75] and lung cancer treatment is a major problem [76, 77]. Other comorbidities are treated in the same way as patients without IPF [41, 42, 78].

Lung transplantation

Lung transplantation is the only well-documented intervention that prolongs survival in IPF. However, new observations have now suggested that pirfenidone and nintedanib may also improve survival in IPF patients [6, 25, 79]. Due to the long waiting time for surgery, patients with severe IPF should be referred early for lung transplantation assessment. Lung transplantation might be the only therapeutic option in patients with end-stage disease.

Many current organ allocation systems are based on policies that give equal consideration to both severity and prognosis of disease, and this has allowed for timely interventions as well as a dramatic decrease in waiting list deaths in IPF patients [80]. Moreover, since the introduction of the "lung allocation score", IPF has become the most common indication for lung transplantation [80, 81]. Lung transplantation is commonly advised for patients aged <65 years. This procedure should be taken into account and discussed with the patient at the earliest possible opportunity, *i.e.* at the time of diagnosis or at the occurrence of signs associated with disease progression [1]. Transplant suitability should be assessed in stable patients with early-stage IPF. Patients with bad prognostic factors, such as D_{LCO} ⩽40%, desaturation during the 6-min walk test, presence of dyspnoea, honeycombing changes on chest high-resolution computed tomography (HRCT) and pulmonary hypertension, should be promptly assessed for transplant suitability. Other indicators that should suggest opting for a prompt evaluation for lung transplantation include worsening dyspnoea, loss of FVC ⩾10% and D_{LCO} ⩾15% at 6 months and serious honeycombing changes on chest HRCT [1, 82]. Telomerase mutations are the most common identifiable genetic cause of IPF and, at times, the telomere defect manifests in extrapulmonary disease, such as bone marrow failure. A preliminary evaluation of the relevance of this genetic diagnosis for lung transplant management has been performed. The observations supported the feasibility of lung transplantation in telomerase mutation carriers, although some post-surgery complications could occur (*e.g.* requirement for platelet transfusion, which, in some cases, was prolonged, and an abnormal or exaggerated cytotoxic response to commonly used immunosuppressant drugs). Such preliminary results might suggest that, for a subset of IPF patients, a pre-transplant genetic evaluation might be indicated, as it may facilitate risk assessment and inform post-transplant management [83].

Conclusions

Today, therapy for severe IPF is a challenge, and early diagnosis is mandatory. Preliminary data show that pirfenidone and nintedanib are also active in severe IPF. The comprehensive care of patients with severe IPF remains essential, including management of comorbidities and physical debility and timely referral for lung transplantation. Further research is needed to help alleviate or control symptoms of this debilitating condition. In particular, the relevance of programmes of pulmonary rehabilitation, palliative care and end-of-life support for patients with this particular disease is an aspect that has not been studied enough by the scientific community and it deserves more attention. Patients with IPF need effective communication and adequate psychological support. However, detailed guidance on these aspects, whether released in the form of guidelines or based on clinical practice in centres highly skilled in IPF treatment, remains lacking.

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