# *Novel treatments for idiopathic pulmonary fibrosis: doubts and certainties*

Idiopathic pulmonary fibrosis (IPF) is a serious disease that usually affects middle-aged and older adults. IPF varies from person to person. In some people, fibrosis happens quickly. In others, the process is much slower. In some people, the disease stays the same for years. IPF has no cure yet. IPF represents an important public health problem. Recently, new antifibrotic drugs became available.

**BY: PROF. PAOLO SPAGNOLO**

Idiopathic pulmonary fibrosis (IPF) is a chronic, irreversible and inexorably progressive disease that affects mainly 60- to 70-year-old ever smokers (figure 1).[1] In the last two decades, our understanding of disease pathobiology has greatly improved. Indeed, contrary to the initial "inflammatory" hypothesis, we now know that IPF is characterized by an exuberant and uncontrolled reparative process (with relatively little inflammation) following chronic alveolar epithelial microinjury. The abnormal reparative process results in excessive deposition of collagen, progressive scarring of the lung and irreversible loss of function.[2] While IPF is by definition "idiopathic" (i.e., of unknown cause), the list of potential fibrogenic triggers that have been associated with IPF includes, among others, cigarette smoking, chronic microaspiration of gastric content and chronic infection. In the US only, IPF affects between 150,000-200,000 people, and as many as 40,000 people die from this disease each year.[3] Similar incidence, prevalence and mortality rates have been reported in Europe.[4] With a 5-year survival rate of approximately 20%, which is worse than that of several types of cancer (e.g., breast, ovarian, and colorectal), IPF represents an important public health problem, particularly in elderly people.

In the last two 25 years, a multitude of compounds have been tested in clinical trials of IPF, but with almost invariably negative results.[5] Such high rate of failure was probably due to both incomplete knowledge of disease pathogenesis and the multitude and redundancy of mediators, growth factors and signalling pathways likely to be involved in the fibrotic process.[2] Accordingly, the only care options endorsed by the 2011 guidelines were pulmonary rehabilitation, long-term oxygen therapy, lung transplantation and enrolment in a clinical trial.[1] Our sense of frustration is finally alleviated as two compounds with antifibrotic properties and pleiotropic mechanisms of action (e.g., pirfenidone by Hoffmann-La Roche) and

*Professor Paolo Spagnolo is an Associate Professor of Respiratory Medicine at the University Hospital of Padua, Italy. He started his carrier in Respiratory Medicine at the University Hospital of Bari (Italy). In 2002 Dr Spagnolo joined the Interstitial Lung Disease (ILD) Unit of the Royal Brompton Hospital (London). In 2008 he completed his PhD with a thesis on "Genetic predisposition to clinical phenotypes of sarcoidosis". Between 2010 and 2013 he was lecturer in Respiratory Medicine at the University Hospital of Modena where he joined the Center for Rare Lung Diseases lead by Professor Luca Richeldi. Subsequently, he joined the Medical University Clinic of the Canton Hospital Baselland in Liestal (Switzerland). His main research interests include sarcoidosis and ILD, with emphasis on genetic predisposition, prediction of disease behavior and clinical trials of novel therapies. He (co)authored approximately 100 journal articles, review articles, editorials and book chapters. He is the current treasure of WASOG. e-mail: paolo.spagnolo@unipd.it.*

nintedanib (by Boehringer Ingelheim) have consistently proven effective in reducing functional decline (as assessed by forced vital capacity [FVC], a measure of "lung size") and disease progression in IPF.[6,7] Actually, pirfenidone had already been approved for patients with "mild to moderate" IPF in Japan (October 2008) and in Europe (February 2011) but not by the Food and Drug Administration (FDA) because two large studies (e.g., the CAPACITY 1 and 2 trials) had provided inconsistent evidence of efficacy.[8] Pirfenidone and nintedanib will soon become standard of care worldwide. However, there are some key points that need to be addressed and clarified.

## Who should be treated?

Pirfenidone and nintedanib are approved and recommended for patients with IPF. Therefore, clinicians should be familiar with the diagnostic criteria for IPF and follow the recommendation provided by the evidence-based guidelines.[1] Importantly, pirfenidone and nintedanib should not be used to treat fibrotic interstitial lung diseases other than IPF as their effect in this setting has never been formally tested and is unknown.

## When should we start treatment?

IPF is an inexorably progressive disease. Therefore, it conceptually makes sense to start treatment as early as possible in order to preserve pulmonary function and prolong survival. In support of early treatment, there are data showing that a large minority of patients with FVC greater than 80%, therefore not eligible for pirfenidone, decline significantly over time.[9,10] In support of early treatment, there are data showing that even patients with an FVC within normal range at baseline decline significantly over time. Yet, in many European countries, both pirfenidone and nintedanib are recommended only for IPF patients with a FVC between 50% and 80% of the predicted value. In a small minority of patients who are asymptomatic and have marginal or no lung function impairment, however, it may not be unreasonable to refrain from starting treatment and adopt a close clinical/functional surveillance after careful evaluation of the risks and benefits of such approach and considering the unpredictable course of IPF.

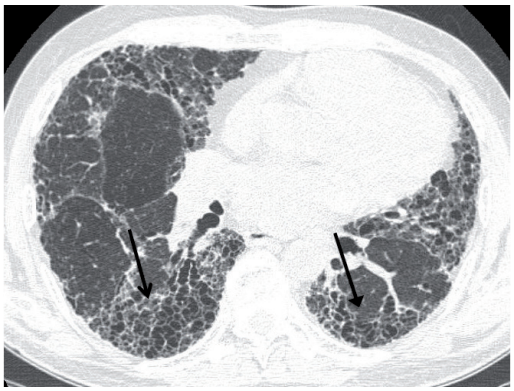

***Figure 1.*** *Idiopathic pulmonary fibrosis. Chest high-resolution computed tomography showing a characteristic combination of subpleural reticular abnormalities with associated bibasilar honeycombing (arrows).*

## Which agent should be used as first line treatment?

Pirfenidone is a small molecule inhibitor of several pathways implicated in fibrosis, including transforming

growth factor beta (TGFβ), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF). Nintedanib is a tyrosine kinase inhibitor that blocks the profibrotic pathways mediated by PDGF, FGF and vascular endothelial growth factor (VEGF). Despite substantial differences in the mechanism of action of these two compounds, treatment effect (e.g., the reduction in FVC decline) is strikingly similar, around 100 ml/year. Therefore, when deciding which agent to start, a careful discussion with each patient should involve dosing, potential side effects and expected outcomes of therapy. The most common side effects of pirfenidone are skin rash, nausea and dyspepsia, but they were not a common cause of drug discontinuation in clinical trials.[6,8] Similarly, while more than 60% of patients receiving nintedanib in the INPULSIS trials experienced diarrhoea, this was often adequately controlled with dose reduction or anti-diarrheal medication, with <5% of them having to discontinue the medication completely.[7] Elevation of liver function tests (LFT) also occurred in a small number of patients with both drugs.[6-8] Therefore, it is recommended to check LFTs monthly for the first three months after starting either therapy, then every three months thereafter. Pill burden may also factor into the decision, as pirfenidone is administered as three tablets three times a day, while nintedanib is given as one tablet twice daily.

## How long should we treat IPF patients for?

Ideally, a progressive and almost invariably deadly disease like IPF should be treated indefinitely, unless there is clear evidence of lack of response to treatment. While it is difficult to establish what constitutes treatment failure in an individual patient, according to many European national guidelines antifibrotic treatment (e.g., pirfenidone or nintedanib) should be stopped if the disease gets worse, that is, if the FVC falls by 10% or more in 12 months. However, the assessment of treatment response in IPF is complicated by its variable clinical course, and it cannot be excluded that the extent of functional decline would be even higher without antifibrotic treatment. In fact, recent data suggest a potential benefit of continued treatment with pirfenidone in patents with IPF who experience clinically meaningful progression during treatment.11 In the case of "treatment failure" (e.g., FVC decline ≥10% predicted), clinicians should also consider switching to the other drug.

## Should we combine pirfenidone and nintedanib?

Having two drugs available will lead many physicians to consider combination therapy, an approach that has been successfully applied to various respiratory diseases such asthma, chronic obstructive pulmonary disease, pulmonary arterial hypertension and lung cancer. In addition, the co-administration of pirfenidone and nintedanib is appealing given the large number of fibrotic pathways likely to be involved in disease pathobiology and the potential synergistic effects. However, at present, there are no robust data on the safety and efficacy of pirfenidone and nintedanib in combination in IPF. As with any combination therapy, four scenarios are possible: 1. synergy; 2. add-on; 3. a weaker effect than expected (either because the mechanism of efficacy is targeted by both drugs and a ceiling effect is achieved, or because there is a blocking interaction); and 4. unpredictable interaction that drives disease progression or produces unacceptable side effects. Combination therapy should therefore be avoided until data demonstrating its efficacy and tolerability/safety in patients with IPF become available.

## The updated 2011 Clinical Practice Guideline

Since the publication of the American Thoracic Society/ European Respiratory Society/Japanese Respiratory

*Table 1. Key recommendations on pharmacological treatment of IPF according to current guideline.*

| Therapeutic agent | 2015 Guideline | 2011 Guideline |
|---|---|---|
| Pirfenidone | Conditional recommendation for use* | Weak recommendation against use |
| Nintedanib | Conditional recommendation for use | Not addressed |
| Antiacid therapy | Conditional recommendation for use | Weak recommendation for use |
| Phosphodiesterase-5 inhibitor (sildenafil) | Conditional recommendation against use | Not addressed |
| Dual endothelin receptor antagonists (bosentan, macitentan) | Conditional recommendation against use | Strong recommendation against use |
| N-acetylcysteine (NAC) | Conditional recommendation against use | Weak recommendation against use |
| Azathioprine + corticosteroids + NAC | Strong recommendation against use | Weak recommendation against use |
| Warfarin | Strong recommendation against use | Weak recommendation against use |
| Imatinib | Strong recommendation against use | Not addressed |
| Selective endothelin receptor antagonist (ambrisentan) | Strong recommendation against use | Not addressed |

** Conditional recommendations are synonymous with weak recommendations.*

Society/Latin American Thoracic Association evidence-based guidelines in 2011,[1] a number of large clinical trials of therapeutic interventions have been completed. Therefore, the guideline document has recently been updated.[12] Although these updated guidelines represent a major step forward, they have also fuelled some discussion, related mainly to the same level of recommendation (e.g., conditional recommendation for use) given to antiacid therapy as to antifibrotic agents (e.g., pirfenidone and nintedanib) despite different levels and quality of evidence (Table 1). In fact, contrary to pirfenidone and nintedanib, the data supporting a potential role for antiacid therapy in IPF are, overall, of poor quality (e.g., observational/retrospective studies and post hoc analysis of patients assigned to placebo arms in clinical trials of pharmaceutical interventions). The guidelines however acknowledge the need for further research focusing on efficacy and long-term safety of antiacid therapy as well as interactions with other IPF medications.

## Unanswered questions

Although the approval worldwide of two drugs for IPF represents a breakthrough for patients and treating physicians alike, many unanswered questions remain.

- We do not know whether (and to what extent) pirfenidone and nintedanib remain effective beyond the 52-week clinical trial period. Extension studies of these trials are ongoing to determine the long-term safety and efficacy of these drugs.
- Neither drug showed a clear mortality benefit and it remains to be determined to what extent a beneficial effect on FVC decline translates to a significant effect on survival (measuring survival appears prohibitive due to the number of patients and study duration required for an adequately powered study).[13]
- Neither drug has demonstrated a consistent beneficial effect on quality of life, although the tools available to measure this outcome in IPF may be suboptimal.
- Clinical trials of pirfenidone and nintedanib have limited

their enrolment to patients with mild to moderate functional impairment. Therefore, whether the beneficial effects of these drugs apply also to patients with more advanced disease (e.g., forced vital capacity <50%) is unknown. Nevertheless, the US FDA has approved both pirfenidone and nintedanib with no prescription limitations and regardless of severity of lung function impairment

- Clinical trials of pirfenidone and nintedanib tend to enrol selected patients by means of strict inclusion and exclusion criteria (e.g., those with mild to moderate disease and without significant morbidity). Therefore, how the results of clinical trials translate in daily practice is difficult to forecast.
- Pirfenidone and nintedanib are expensive drugs, which may potentially represent a barrier to receiving these therapies. In addition, their cost-effectiveness remains to be determined.

For all the reasons stated above, pirfenidone and nintedanib should be prescribed by respiratory physicians experienced in the management of IPF patients.

## Practice recommendations

The recent emergence of two drugs of proven efficacy (pirfenidone and nintedanib) represents a significant milestone for patients suffering from IPF. Although we still do not have a cure as many patients continue to progress despite therapy, this is likely to be the beginning of a new era that will witness major advances in our understanding and treatment of IPF and other fibrotic lung diseases. Priority should also be given to the identification of patients that may respond more dramatically to designer therapies thus maximizing treatment effects. This latter concept, often called "personalized medicine", will eventually ensure that the right patient gets the right treatment at the right time.

## References


1. Raghu G, et al. An official ATS/ERS/JRS/ALAT statement: IPF: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.
2. King TE Jr, et al. IPF. Lancet 2011; 378(9807): 1949-56.
3. Raghu G, et al. IPF in US Medicare beneficiaries aged 65 years and older: incidence, prevalence and survival, 2001-11. Lancet Respir Med 2014; 2: 566-72.
4. Navaratnam V, et al. The rising incidence of IPF in the UK. Thorax 2011; 66: 462-27.
5. Spagnolo P, et al. Non-steroid agents for IPF. Cochrane Database Syst Rev 2010; 9: CD003134
6. King TE Jr, et al. A phase 3 trial of pirfenidone in patients with IPF. N Engl J Med 2014; 370: 2083-92.
7. Richeldi L, et al. Efficacy and safety of nintedanib in IPF. N Engl J Med 2014; 370: 2071-82.
8. Noble PW, et al. Pirfenidone in patients with IPF (CAPACITY): two randomised trials. Lancet 2011; 377: 1760-69.
9. du Bois RM, et al. Ascertainment of individual risk of mortality for patients with IPF. Am J Respir Crit Care Med 2011; 184: 459-66.
10. N Chaudhuri, CT Leonard. A quarter of IPF patients not eligible for pirfenidone treatment due to the NICE criteria significantly decline over time. Thorax 2014; 69: Suppl 2 A218.
11. Nathan SD, et al. Effect of continued treatment with pirfenidone following clinically meaningful declines in FCV: analysis of data from three phase 3 trials in patients with IPF. Thorax 2016; 71(5): 429-35.
12. Raghu G, et al. An official ATS/ERS/ JRS/ALAT clinical practice guideline: treatment of IPF. Am J Respir Crit Care Med 2015; 192: e3–e19.
13. King TE Jr, et al. All-cause mortality rate in patients with IPF. Implications for the design and execution of clinical trials. Am J Respir Crit Care Med 2014; 189: 825-33.