When to start and when to stop antifibrotic therapies

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Today, for the first time, we can use two effective drugs able to reduce the inexorable progression of IPF http://ow.ly/MCS930eOp2b

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ABSTRACT Idiopathic pulmonary fibrosis (IPF) is characterised by progressive changes of the lung architecture causing cough and dyspnoea and ultimately leading to lung failure and death. Today, for the first time, two drugs that may reduce the inexorable progression of the disease are available, suggesting that treatment with specific drugs for IPF should be started as soon as diagnosis is made. This applies to any disease and particularly to IPF, which is marked by a 5-year survival comparable or even worse than many cancers. However, despite common sense and even worse, in spite of scientific data coming from clinical trials, *post hoc* analysis, long-term safety studies and real-life experiences, the question of when to start and when to stop treatment with antifibrotics is still debated. In IPF, particularly when the disease is diagnosed at an early stage, "wait and watch" behaviour is not rare to observe. This is largely due to the lack of awareness of both patients and clinicians regarding the progression of the disease and its prognosis. Another important issue is when treatment should be stopped. In general, there are two main reasons to stop a therapy: unbearable side-effects and/or lack of efficacy. According to current (although preliminary) evidence, antifibrotic drugs should not be discontinued except for safety issues.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease of unknown cause, which is limited to the lungs and associated with the radiological and/or histological pattern of usual interstitial pneumonia. The disease is characterised by progressive morphological changes of the lung architecture, causing cough and worsening dyspnoea and ultimately leading to lung failure and death. Several risk factors have been described to contribute to IPF onset and, despite the recent advances in our understanding of the pathogenesis, the real cause of the disease remains to be determined. IPF is a disease characterised by a very poor prognosis, with a median survival time of 3–5 years from diagnosis. Furthermore, the clinical course is unpredictable, marked in some cases by a relatively slow and gradual progression but in other cases by a rapid and often dramatic clinical evolution [1, 2].

During the last 20 years, many efforts have been made in the search for effective drugs for IPF. After a number of negative clinical trials investigating a variety of potential drugs, first the studies CAPACITY and TOMORROW, and more recently the clinical trials ASCEND and INPULSIS, led to the approval of pirfenidone and nintedanib, the first two antifibrotic drugs with a specific indication for IPF. Since then,

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experience regarding the appropriate use of these drugs has grown progressively. It is clear that they may decrease the functional decline typical of the disease, may prolong survival and, although the data need to be confirmed, are also able to reduce acute exacerbations. The recent data suggesting a reduction in mortality risk will change the mood of both patients and physicians, despite the many papers and websites that still indicate a prognosis of 3–5 years for IPF, which is today not a completely true statement. It is also well known how to deal with the potential side-effects that the two drugs may cause. However, some points, such as when to start and when to stop antifibrotic treatment, maybe because of the limited data available, are still debated and considered as critical issues in the therapeutic scenario for IPF [3].

When to start treatment with antifibrotic drugs

Four common-sense reasons for early treatment

When should treatment with antifibrotic drugs be started? The most logical answer is that treatment with specific drugs for IPF should be started as soon as diagnosis is made. This applies to any disease, and in particular to a disease such as IPF that is marked by a median 5-year survival that is comparable or even worse than many cancers [4]. Nobody would have any doubts about whether to treat cancer, not even in those cases where the diagnosis is made very early. However, in the case of IPF, "wait and watch" behaviour is not rare and is an issue that is still debated. An increasing number of patients are today diagnosed when the disease is at an early stage, when they have preserved lung function at rest and symptoms that become apparent only during exercise. In these cases, because of the potential side-effects that may be induced by antifibrotic drugs, some pulmonologists prefer to "wait and watch" the course of the disease, postponing treatment until the disease worsens. This behaviour is often supported by patients, who are more worried by the potential adverse events caused by the drugs than by a disease that is so far characterised by very mild symptoms. This behaviour can be understood and excused for patients, who are very often not completely aware of the relentless evolution of IPF, but less understandable is a decision to wait taken by the pulmonologist. In fact, the future clinical "scenario" that will distinguish a patient with IPF is already clear at the time of the diagnosis. This "scenario" is characterised by at least four epidemiological and clinical elements that, based on common sense, should be sufficient to induce both pulmonologists and patients to start treatment as soon as possible. These are discussed in the following sections.

Poor prognosis

IPF is characterised by a very poor prognosis, which differentiates this disease from other interstitial lung diseases. The median survival at the time of diagnosis is 3–5 years, and its 5-year survival is worse than many cancers, with the only exceptions being pancreatic and lung cancer, which, based on data from the US National Cancer Institute, have a survival only slightly lower than IPF [5, 6].

IPF behaviour is unpredictable

To further complicate the matter, IPF has a heterogeneous clinical course characterised by different phenotypes. A good number of patients show a relatively slow course with a progressive decrease in lung volumes, diffusing capacity of the lung for carbon monoxide and exercise tolerance. This slow course, together with the late onset of symptoms, often favour an underestimation of the disease, resulting in a delay in diagnosis and unavoidably to a late starting of antifibrotic treatments. Other patients may show a more rapid progression of the disease, and in some, the clinical course, regardless of its speed, can be interrupted at any time by unpredictable events (acute exacerbations) [7].

Forced vital capacity tends to decline

One of the terms that characterise IPF behaviour is "progressive". The best, most easy and reproducible way to measure this progression is to evaluate pulmonary function through the assessment of forced vital capacity (FVC). This evaluation is widely accepted as the most reliable measure of disease progression, demonstrating less intra- and inter-subject variability [8]. For this reason, FVC has been commonly used as the primary end-point in clinical trials [9–11]. The most important and recent clinical trials have shown that the mean annual rate of FVC decline in placebo groups is ~200 mL, as compared to 20–30 mL for a normal individual [1, 12–14].

Change in FVC is associated with increased mortality

The longitudinal change in FVC has been widely studied as a reliable measure of disease progression. Several retrospective and prospective studies have shown that a 10% decline in FVC within either 6 months or 12 months is associated with a significant increase in mortality [9, 10, 15]. According to Zappala *et al.* [16], a decline in % predicted FVC of 5–10% is related to a two-fold increase in the risk of mortality at 24 weeks, while a decline $\geqslant$10% is associated with a nearly five-fold increase in the risk of mortality over the subsequent year. It has also been shown that smaller declines in FVC may predict a

worse prognosis [16]. DU BOIS *et al.* [17] have demonstrated that small changes in FVC (2–6%) are predictive of clinically relevant changes in disease status.

Milestones from clinical trials

The very poor prognosis that marks IPF, the unpredictable clinical course, the relentless decline of lung function and the association of this decline with mortality should be by themselves very good common-sense reasons to start antifibrotic therapies as soon as diagnosis is made, even in patients with early disease. "Common sense" is important, but cannot be enough in taking a decision so crucial as when to start a demanding treatment such as antifibrotic therapy. Fortunately, in the case of IPF, a range of scientific evidence provides support for this decision. Indeed, antifibrotic treatments may significantly reduce the decline of FVC, ultimately prolonging survival and improving the prognosis of this dreadful disease. Pirfenidone was the first drug approved for the treatment of mild to moderate IPF. It is an orally administered drug with antifibrotic, anti-inflammatory and antioxidant effects. After promising preclinical studies, a first Japanese double-blind, randomised, placebo-controlled phase III trial and the following two CAPACITY trials (studies 004 and 006) involving, respectively, 348 and 344 patients, demonstrated with pooled analysis a significantly slower rate of FVC decline in the pirfenidone group than in the placebo group [18, 19]. After these positive results, pirfenidone was licensed in Europe for the treatment of mild to moderate IPF patients. However, because of the conflicting results from the 006 trial, the US Food and Drug Administration requested an additional study testing the efficacy of pirfenidone. This study involved 555 patients and the results were published in 2014, demonstrating again the effectiveness of pirfenidone in reducing FVC decline but also in reducing the decline of the 6-min walk distance and improving progression-free survival [20].

The finding of specific pathogenic pathways being activated in cancer, and interestingly also involved in the pathogenesis of IPF, has led to the development of a new effective drug derived from oncology. Nintedanib is the second drug approved for the treatment of IPF. This drug, already used in the treatment of nonsmall cell lung cancer, is an intracellular inhibitor that targets multiple tyrosine kinases, including the vascular endothelial growth factor (VEGF), fibroblast growth factor and platelet-derived growth factor receptors. It was initially tested in a randomised, double-blind, placebo-controlled, phase II dose-finding study involving 432 patients with IPF, and was shown to lead to a reduced decline in FVC in the treated group compared to placebo [21]. Two subsequent parallel 52-week, randomised, double-blind, phase III studies (INPULSIS-1 and INPULSIS-2), involving 1066 patients, evaluated the efficacy and safety of nintedanib (at a dose of 150 mg twice daily), confirming the previous results [22], and thus leading to the licensing of this second effective drug for IPF.

A subsequent pre-specified pooled analysis including data from the two CAPACITY and ASCEND studies (1247 patients) confirmed previous results on the efficacy of pirfenidone in reducing the function decline. Moreover, thanks to the relatively large number of patients, it was also possible to assess a major end-point evaluation represented by mortality. Pooled analysis demonstrated a reduction of all-cause mortality at 1 year by 48% (hazard ratio (HR) 0.52, 95% CI 0.31–0.87; p=0.01) in the group treated with pirfenidone compared to placebo, as well as a reduction of the risk in treatment-emergent IPF-related mortality at 1 year by 68% (HR 0.32, 95% CI 0.14–0.76; p=0.006) compared to placebo [23]. These first positive results were also recently confirmed in an article by NATHAN *et al.* [24], which included data from the two CAPACITY trials, from the ASCEND trial and also from two other Japanese studies (Shinogi Phase II and Shinogi Phase III trials). More complex analyses (pooled and meta-analysis) and a different statistical approach were also performed to assess the outcomes, with new landmark results. Both analyses demonstrated a significantly lower risk for all mortality outcomes (all-cause mortality, treatment-emergent all-cause mortality, IPF-related mortality and treatment-emergent IPF-related mortality) at week 52 in the pirfenidone group compared to placebo [24]. Recently, data from the TOMORROW and INPULSIS trials were also pooled (1231 patients), confirming a significant reduction in the annual rate of decline in FVC (112.4 mL·year^{-1} with nintedanib and 223.3 mL·year^{-1} with placebo; p<0.0001). Nintedanib also demonstrated a significant benefit for time to the first investigator-reported acute exacerbation (which in general account for ~40% of IPF mortality causes) [25], with an HR of 0.53 (95% CI 0.34–0.83; p=0.0047) representing a 47% reduction. No significant differences in all-cause mortality and respiratory mortality were observed (HR 0.70, 95% CI 0.46–1.08 (p=0.0954) and HR 0.62, 95% CI 0.37–1.06 (p=0.0779), respectively), but a significant reduction in the risk of on-treatment mortality was described (HR 0.57, 95% CI 0.34–0.97; p=0.0274) [26].

It is interesting to note that subsequent analyses of subgroups of patients considering different demographic variables and baseline measures were performed, and showed similar results regardless of age, sex, ethnicity, *etc*. Both for pirfenidone and nintedanib, the analyses provided further evidence to

support the clinically meaningful treatment benefit and acceptable safety profile of antifibrotic treatments in patients with IPF [25, 27, 28].

Despite the consolidated evidence regarding the severe prognosis of IPF and the current option to treat patients with drugs that are safe, well tolerated and effective in reducing functional decline and improving survival, some physicians still prefer not to treat patients with preserved lung function, choosing instead to adopt a "wait and watch" approach. Furthermore, some patients, not aware of the prognostic picture of the disease, prefer not to be treated because they have no clear symptoms. A recent *post hoc* analysis examined the IPF progression and pirfenidone effects in patients with more preserved lung function and milder disease and compared the results with those with less preserved lung function and more advanced disease. Patients were stratified according to FVC and the GAP (gender, age and physiology) index. Interestingly, no significant differences were found in terms of progression at 12 months (FVC decline ⩾10%) between patients with more preserved (FVC ⩾80% or GAP stage I) *versus* less preserved lung function (FVC <80% or GAP stage II–III) (p=0.2403 and p=0.1175, respectively). In addition, irrespective of the basal FVC or GAP stage values, all outcomes evaluated were also in favour of the treatment with pirfenidone [29]. A similar analysis was also performed using pooled data from the two INPULSIS trials for nintedanib. Patients were stratified according to FVC values (FVC >90% and ⩽90%; FVC >70% and ⩽70%). As for pirfenidone, there were no statistically significant differences between these subgroups in the annual rate of decline in FVC, change from baseline in St George's Respiratory Questionnaire total score, or time to first acute exacerbation [28, 30]. These results showed consistent and meaningful evidence of a similar functional decline in both categories, more preserved and less preserved lung function and, most importantly, that antifibrotic drugs are equally effective in both scenarios. The results thus strongly support the importance of an early diagnosis and the subsequent choice of early treatment in order to slow, as soon as possible, the progression of the disease, making a wait-type approach unacceptable and dangerous for the patient.

When to stop therapy

Should antifibrotic treatments following clinically meaningful decline be stopped?

Another important issue, as important as when to start treatment, is when treatment should be stopped. In general, there are two main reasons to stop a therapy: unbearable side-effects and/or lack of efficacy. Patients treated with pirfenidone or nintedanib have reported a number of different side-effects, the vast majority being gastrointestinal (nausea, dyspepsia, diarrhoea) and skin-related events (rash, photosensitivity reaction) in the case of pirfenidone, and mainly gastrointestinal (diarrhoea and vomiting) for nintedanib. Both drugs may also alter liver enzymes, but this rarely leads to definitive drug discontinuation. Clinical trials, *post hoc* analysis, long-term safety studies and real-life experiences have clearly demonstrated that these side-effects are generally mild and rarely result in treatment discontinuation. In most cases, temporary reduction of the definitive dose may also allow the drug to be continued.

The other reason for stopping treatment should be lack of efficacy, but this must be evaluated carefully. Antifibrotic drugs are effective in slowing functional decline but do not represent a definite "cure", forcing the clinician to focus on how to consider a clinical response to treatment. Clinical trials have based their results on the longitudinal evaluation of FVC. It is well known that this parameter, although reliable, demonstrates a certain intra-subject variability, especially in clinical practice. According to clinical trials, it is also considered that an absolute decline of ⩾10% in FVC should be an index of non-adequate response to therapy. On this basis, different local rules and guidelines (such as the National Institute for Health and Care Excellence (NICE; UK) guidelines) recommend discontinuing pirfenidone if there is evidence of disease progression in the previous 12 months [31]. This leads to a dilemma for the clinician. Should the antifibrotic therapy be discontinued during an evident functional decline? What would have been the functional decline in the absence of treatment? A recent article by Nathan *et al.* [32] tried to answer these intriguing questions. They analysed data coming from the pooled pirfenidone clinical trials, focusing on patients who experienced a significant disease progression, both in the pirfenidone and placebo groups. A total of 34 patients (5.5%) in the pirfenidone group and 68 patients (10.9%) in the placebo group experienced a decline of ⩾10% in FVC after 6 months. Interestingly, only a few patients (5.9%) in the pirfenidone group experienced a further decline of ⩾10% in FVC during the subsequent 6 months, compared to 27.9% of patients in the placebo group, with only one death (2.9%) in the pirfenidone group *versus* 14 deaths (20.6%) in the placebo group. These data demonstrate that even patients with an initial decline in FVC of ⩾10% may also benefit from continued treatment with pirfenidone compared with placebo [32]. Accordingly, antifibrotic drugs should not be discontinued other than for safety issues. The presence of two drugs may also provide the possibility to switch between drugs in some cases. Although this may be a possibility, few data are available (and these only cover the switch from pirfenidone to nintedanib). In a recent study, it was found that the intra-individual response to the two drugs may differ,

ranging from stable to unstable depending on the treatment [33]. Therefore, prospective randomised studies are needed to determine the best choice, from keeping the same drug, switching, or opting for a combination therapy, when lung function is declining.

Should antifibrotic treatments be stopped before lung transplantation?

Although antifibrotic drugs have changed the therapeutic approach to the disease, modifying its natural progression, they do not represent a cure, and lung transplantation is the only definitive treatment option. Early referral to the transplant centre still remains a fundamental action to take in selected cases. The advent of antifibrotic drugs may be helpful in improving the general clinical condition of patients awaiting lung transplantation and, most importantly, in reducing mortality while on waiting lists [34]. However, little is known about the safety of their use in this specific context. Because of their antifibrotic action, both drugs may in theory impair post-operative wound healing or cause anastomotic complications. Moreover, nintedanib, because of its action directed at VEGF, may also increase perioperative bleeding risk. According to the most recent clinical trials evaluating antifibrotic drugs (2832 patients), only 11 patients, treated with pirfenidone, received transplants, and specific data on their outcomes are lacking. A recent study by Delanote *et al.* [35] focused on this specific problem, and published the largest clinical series available. Nine patients with IPF treated with pirfenidone (n=7) or nintedanib (n=2) for a mean period of 13.4 months, who underwent lung transplantation, were evaluated for a median post-transplant follow-up of 19.8 months. No major side-effects occurred during the observation period, except for a significant weight loss due to drug-induced anorexia. Moreover, FVC values tended to stabilise after 12 weeks of treatment in most patients, and no post-operative thoracic wound healing problem, bleeding or severe anastomotic airway complications due to prior antifibrotic treatment were described [35]. Therefore, although only evaluated in a very limited number of case studies, antifibrotic drugs have been shown to be safe in IPF patients undergoing lung transplantation.

Should antifibrotic treatments be stopped before surgery?

IPF represents a risk factor for lung cancer development. Several studies demonstrate a prevalence of lung cancer in IPF patients ranging from 2.7% to 48% [36]. The extensive use of high-resolution computed tomography has increased early diagnosis and a better detection of lung cancer in IPF patients, increasing the number of candidates for surgical resection. However, in the case of IPF, surgery may expose the patient to a significant risk of acute exacerbations, which may occur in ~20% of cases. This represents a finding of particular relevance in this setting, because, despite the usual difficulties in identifying acute exacerbations of IPF, the events described in this review can be considered as true acute exacerbations of IPF. As previously described, they are extremely severe and associated with a 50% mortality rate [37–40]. As in the case of lung transplantation, the use of antifibrotic drugs is not well studied and, so far, there has been much reluctance to use them, especially during or after surgery, because of the possible side-effects. In a recent article, Iwata *et al.* [41] suggested a possible role of pirfenidone in reducing post-operative acute exacerbations of IPF in patients with lung cancer. In that study, pirfenidone was orally administered to IPF patients who were candidates for lung cancer surgery. Surgery was performed after at least 2 weeks of 1200 mg·day^{-1} administration. The study demonstrated that acute exacerbations did not occur in 37 out of 39 patients (94.9%, 95% CI 82.7–99.4%; p=0.01) in the full-analysis set and in 38 out of 39 patients (97.2%, 95% CI 85.5–99.9%; p=0.004) in the per protocol set [41]. This study revealed for the first time that the use of pirfenidone before and after surgery is generally safe and significantly reduces the risk of acute exacerbations. Future trials are necessary to confirm these results and to test other drugs such as nintedanib, which have already demonstrated a reduction of acute exacerbations in the general IPF setting.

Conclusion

IPF is a dreadful disease. Many efforts have been made in understanding its pathogenesis, but despite recent advances in research, this disease still represents a dilemma. Today, for the first time, we can use two effective drugs able to reduce the inexorable progression of the disease. However, despite common sense and, even worse, in spite of solid scientific data coming from clinical trials, *post hoc* analysis, long-term safety studies and real-life experiences, the question of when to start and when to stop treatment with antifibrotics is still debated. This is largely due to the lack of awareness on the part of both patients and clinicians on the progression of the disease and its prognosis. It is currently estimated that only 54% of patients with an IPF diagnosis in Europe receive antifibrotic treatment with an approved drug. It is desirable, when faced with evidence of a disease that is not cancer, but looks like a cancer in its behaviour, and moreover with consistent literature supporting the efficacy of antifibrotic drugs in reducing its progression and improving survival, that there should be less doubt about treating IPF (as with any other disease) from the time of diagnosis, and antifibrotic treatment should be stopped only when continuing would be worse than the disease itself.

References

1 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
2 Puglisi S, Torrisi SE, Giuliano R, *et al.* What we know about the pathogenesis of idiopathic pulmonary fibrosis. *Semin Respir Crit Care Med* 2016; 37: 358–367.
3 Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 2001; 134: 136–151.
4 Vancheri C. Common pathways in idiopathic pulmonary fibrosis and cancer. *Eur Respir Rev* 2013; 22: 265–272.
5 Vancheri C, Failla M, Crimi N, *et al.* Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. *Eur Respir J* 2010; 35: 496–504.
6 National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts. https://seer.cancer.gov/statfacts/ Date last updated: 2014. Date last accessed: April 2017.
7 King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet* 2011; 378: 1949–1961.
8 du Bois RM, Weycker D, Albera C, *et al.* Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med* 2011; 184: 1382–1389.
9 du Bois RM, Nathan SD, Richeldi L, *et al.* Idiopathic pulmonary fibrosis: lung function is a clinically meaningful endpoint for phase 3 trials. *Am J Respir Crit Care Med* 2012; 186: 712–715.
10 Wells AU. Forced vital capacity as a primary end point in idiopathic pulmonary fibrosis treatment trials: making a silk purse from a sow's ear. *Thorax* 2013; 68: 309–310.
11 Nathan SD, Meyer KC. IPF clinical trial design and endpoints. *Curr Opin Pulm Med* 2014; 20: 463–471.
12 Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. *Respir Med* 2015; 109: 661–670.
13 Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.
14 Nathan SD, Shlobin OA, Weir N, *et al.* Long-term course and prognosis of idiopathic pulmonary fibrosis in the modern era. *Chest* 2011; 140: 221–229.
15 Flaherty KR, Mumford JA, Murray S, *et al.* Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 543–548.
16 Zappala CJ, Latsi PI, Nicholson AG, *et al.* Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; 35: 830–836.
17 du Bois RM, Weycker D, Albera C, *et al.* Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 459–466.
18 Taniguchi H, Ebina M, Kondoh Y, *et al.* Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; 35: 821–829.
19 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–1769.
20 King TE Jr, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
21 Richeldi L, Costabel U, Selman M, *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; 365: 1079–1087.
22 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
23 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J* 2016; 47: 243–253.
24 Nathan SD, Albera C, Bradford WZ, *et al.* Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir Med* 2017; 5: 33–41.
25 Natsuizaka M, Chiba H, Kuronuma K, *et al.* Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. *Am J Respir Crit Care Med* 2014; 190: 773–779.
26 Richeldi L, Cottin V, du Bois RM, *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials. *Respir Med* 2016; 113: 74–79.
27 Costabel U, Inoue Y, Richeldi L, *et al.* Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. *Am J Respir Crit Care Med* 2016; 193: 178–185.
28 Fisher M, Nathan SD, Hill C, *et al.* Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. *J Manag Care Spec Pharm* 2017; 23: Suppl. 3b, S17–S24.
29 Albera C, Costabel U, Fagan EA, *et al.* Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function. *Eur Respir J* 2016; 48: 843–851.
30 Kolb M, Richeldi L, Behr J, *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax* 2017; 72: 340–346.
31 National Clinical Guideline Centre (UK). Diagnosis and Management of Suspected Idiopathic Pulmonary Fibrosis: Idiopathic Pulmonary Fibrosis. London, Royal College of Physicians, 2013.
32 Nathan SD, Albera C, Bradford WZ, *et al.* Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. *Thorax* 2016; 71: 429–435.
33 Milger K, Kneidinger N, Neurohr C, *et al.* Switching to nintedanib after discontinuation of pirfenidone due to adverse events in IPF. *Eur Respir J* 2015; 46: 1217–1221.
34 Kistler KD, Nalysnyk L, Rotella P, *et al.* Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. *BMC Pulm Med* 2014; 14: 139.
35 Delanote I, Wuyts WA, Yserbyt J, *et al.* Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series. *BMC Pulm Med* 2016; 16: 156.
36 Karampitsakos T, Tzilas V, Tringidou R, *et al.* Lung cancer in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther* 2017; 45: 1–10.
37 Hyzy R, Huang S, Myers J, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2007; 132: 1652–1658.
38 Hoshikawa Y, Kondo T. Perioperative lung injury: acute exacerbation of idiopathic pulmonary fibrosis and acute interstitial pneumonia after pulmonary resection. *Nihon Geka Gakkai Zasshi* 2004; 105: 757–762.

39 Kumar P, Goldstraw P, Yamada K, *et al.* Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. *J Thorac Cardiovasc Surg* 2003; 125: 1321–1327.

40 Yoshimura K, Miyamoto A, Uruga H, *et al.* A nation-wide survey on prophylaxis for acute exacerbation of idiopathic pulmonary fibrosis following lung surgery for associated lung cancer. Annual Report by the Study Group of the Ministry of Health and Welfare for Diffuse Lung Disease. Diffuse Lung Diseases Research Group from the Ministry of Health, Labour and Welfare of the Japanese Government 2008. 2009; pp. 77–81.

41 Iwata T, Yoshino I, Yoshida S, *et al.* A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: West Japan Oncology Group 6711 L (PEOPLE Study). *Respir Res* 2016; 17: 90.