Idiopathic pulmonary fibrosis: from clinical trials to real-life experiences

Sergio Harari and Antonella Caminati

Affiliation: U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria, Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe, MultiMedica IRCCS, Milan, Italy.

Correspondence: Sergio Harari, U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria, Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe, MultiMedica IRCCS, Via San Vittore 12, 20123 Milan, Italy. E-mail: sharari@ilpolmone.it

ABSTRACT Randomised controlled clinical trials are fundamental in medicine to develop new effective drugs and new therapeutic regimens and are the strength of evidence-based medicine. These studies allow us to avoid the repetition of misleading experiences that have been reported in the past, where drugs or associations were utilised without compelling evidence and ultimately proven to be ineffective. In recent years, randomised clinical trials have been conducted and concluded for many rare diseases, including idiopathic pulmonary fibrosis. However, clinical trials do not always reflect the real-life scenario. Patients selected for clinical trials present fewer comorbidities, they fall between certain age limits, and the severity of their disease is defined; therefore, they do not always reflect the whole of the population affected by a specific disease. These are the reasons why we also need data that mirror real-life experience. The limitations that these kind of studies present are always several and the studies should be interpreted with caution, although they can fill the important gap between efficacy and effectiveness. In this article, we will review the existing clinical data on real-life treatment of idiopathic pulmonary fibrosis.

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Introduction

Randomised controlled clinical trials are fundamental in medicine to develop new effective drugs and new therapeutic regimens. The importance of demonstrating the efficacy of any new treatment through randomised double-blind controlled studies is witnessed by the number of misleading experiences registered in the past, looking at drugs that were ultimately proven to be ineffective, or worse, detrimental. Just to give a recent example in the respiratory field, there was the case of the use of immunosuppressive agents for the treatment of idiopathic pulmonary fibrosis (IPF), recommended for years on the basis of very limited scientific data, drugs that we now know to be completely ineffective or harmful [1–4].

However, clinical trials do not always reflect the real-life scenario. It is like in fashion, where high fashion does not correspond to the way we dress in everyday life. Patients selected for clinical trials present fewer comorbidities, they fall between certain age limits, the severity of their disease is defined, *etc*., and, for all these reasons, they do not always reflect the whole of the population affected by a specific disease.

Patients randomised in clinical trials for IPF have less severe disease, are aged ≤80 years and do not have any other significant associated disease. This means that they are slightly different from those whom we normally observe in clinical practice. While in actual fact mortality due to IPF is very high (~20% per year), in the placebo arms of the most recent trials the mortality ranged from 2.3% to 7.8%, which is much lower

Received: May 15 2015 | Accepted after revision: July 11 2015

Conflict of interest: Disclosures can be found alongside the online version of this article at err.ersjournals.com

Provenance: Publication of this peer-reviewed article was sponsored by F. Hoffman-La Roche Ltd, Basel, Switzerland (principal sponsor, *European Respiratory Review* issue 137).

than expected [5–7]. In recent studies, selection criteria for randomisation were so strict that one-third to two-thirds of the patients considered were not randomised and were considered as screening failure [8, 9]. These are the reasons why we also need data that actually mirror real-life experience. The limitations that this kind of study presents are always several and, therefore, these studies should be interpreted with caution, although they can fill the important gap between efficacy and effectiveness. By efficacy we mean proof in a carefully controlled trial and by effectiveness, success in the circumstances of everyday life.

In 2011, pirfenidone, a novel antifibrotic agent, was the first drug to be approved for the treatment of IPF in Europe [10]. Pirfenidone has been available in Japan since 2008 [11, 12]. The approval by the European Medicines Agency (EMA) was based on key clinical studies supporting the efficacy of pirfenidone in reducing lung function deterioration in IPF patients [12, 13]. More recently, results from the ASCEND study, an additional trial requested by USA authorities to confirm the CAPACITY studies (as one of them did not reach the primary end-point) [13], established that pirfenidone reduced disease progression in patients with IPF, as reflected by lung function, exercise tolerance and progression-free survival [8]. The treatment was associated with an acceptable side-effect profile and fewer deaths.

Nintedanib is a small molecule that was originally designed as an ATP-competitive inhibitor of fibroblast growth factor receptor-1 and vascular endothelial growth factor receptor-2. Both of these receptors are pro-angiogenic receptor tyrosine kinases and nintedanib was designed as an anti-angiogenic drug for cancer indications [14, 15]. Two phase III, international, placebo-controlled, double-blind clinical studies with identical designs (INPULSIS-1 and INPULSIS-2) [9] investigated the efficacy and safety of nintedanib in patients with IPF, after a phase II proof-of-concept study [16]. In the INPULSIS trials, a total of 1066 patients were randomised three to two to receive nintedanib 150 mg twice daily or placebo for 52 weeks, followed by a 4-week follow-up period. The primary end-point was the annual rate of decline in forced vital capacity (FVC): nintedanib consistently slowed disease progression by reducing the rate of decline in FVC compared with placebo [9].

In October 2014, both pirfenidone and nintedanib were approved by the US Food and Drug Administration for the treatment of IPF [17]. However, the European and Japanese experience in the clinical use of pirfenidone started some years before, meaning that some real-life data regarding its use are already available. In this article, we will review the existing clinical data on real-life treatment of IPF.

Real-life clinical experience with pirfenidone in IPF

Several studies have been published reporting real-life experience with pirfenidone (table 1). Most are single-centre experiences. A real-life experience with pirfenidone in Japanese patients with IPF has been described by Okuda *et al.* [19]. This retrospective study investigated the safety and efficacy of pirfenidone in 76 patients with mild-to-severe IPF in clinical practice. The mean±SD FVC at the initiation of pirfenidone therapy in this study was 2.04±0.61 L and the mean change in FVC during the 6-month period prior to the therapy initiation was −188 mL, which improved to −19 mL during the 6-month period after therapy. Significant attenuation in % predicted diffusing capacity of the lung for carbon monoxide (*D*LCO) decline was also achieved after pirfenidone therapy initiation (*D*LCO increase of 0.6% from starting therapy). The degree of disease progression showed that patients who had experienced the most severe decline in FVC during the 6-month period prior to the therapy initiation were those who could benefit the most from the treatment. Among adverse events, the most frequent was anorexia, although it was mild in most cases. Dose reduction of pirfenidone improved anorexia in >80% of affected patients, allowing a high medication compliance rate.

The study by Arai *et al.* [20] is also from Japan. This study investigated possible predictors of response to therapy with pirfenidone in 41 patients with IPF: diagnosis by a surgical lung biopsy and milder disease were predictors of good, short-term responsiveness. In 10 patients with milder disease (out of 21 patients evaluated), the change in vital capacity (VC) 3 and 12 months before and 3 and 6 months after initiation of pirfenidone therapy was significantly decreased (p=0.0039), although this was not the case in the other, more severe patients (n=11). Additionally, Arai *et al.* [20] suggested that patients taking acid-secretion inhibitors, including proton pump inhibitors and histamine H2-receptor antagonists, showed less anorexia, less nausea or both.

Oltmanns *et al.* [21] reported their findings from an observational cohort study conducted at a German tertiary referral centre for interstitial lung disease. In this real-life experience, data from 63 patients with mild-to-moderate IPF treated with pirfenidone were reviewed. 66% of the patients were treated with pirfenidone monotherapy and 34% of the patients received pirfenidone combined with corticosteroids and/or *N*-acetylcysteine (NAC). There was a nonsignificant reduction in mean decline of % predicted FVC after the beginning of treatment (0.7±10.9%; follow-up time after initiation of treatment of 11±7 months) compared with the pre-treatment period (6.6±6.7%; p=0.098). 62% of the patients had stable disease on

TABLE 1 Real-life experience with pirfenidone in observational studies

First author [ref.]	Country	Patients n	Patient characteristics	Efficacy outcome	Adverse events		Treatment discontinuation due to adverse events %
					GI	Skin	
Bonella [18]	Germany	45	Age: 69±7 years Baseline FVC (% pred): 61±15 Baseline *D*LCO (% pred): 48±14	Stable lung function in 28 (70%) out of 40 patients; subjective improvement in cough in 12 (33%) out of 36 patients	17 (38)	10 (22)	13
Okuda [19]	Japan	76	Age: 70.5±8.3 years Baseline FVC (% pred): 65.3±16.1 Baseline *D*LCO (% pred): 55.9±17.8	Reduction in FVC and *D*LCO decline	18 (24)[#]	19 (25)[¶]	18
Arai [20]	Japan	41	Age: 70 (65.5–75.5) years Baseline VC (% pred): 66.7 (54.8–77.8)	Significant reduction in VC decline in patients with severity grades I–II (Japanese Respiratory Society criteria)	24 (59)[+]	5 (12)[§]	15
Oltmanns [21]	Germany	63	Age: 68±7 years Baseline FVC (% pred): 70±19 Baseline *D*LCO (% pred): 40±14	Stable lung function in 62% of patients	N/A	N/A	13
Chaudhuri [22]	UK	40	Age: 65.8 (48–80) years Baseline FVC (% pred): 77.3 (range 46–146) Baseline *D*LCO (% pred): 42.4 (14–81)	Reduction in FVC and *D*LCO decline at 9 months	87	10	15
Loeh [23]	Germany and Italy	197	Age: 69.8±0.6 years Baseline FVC (% pred): 65±18.8 Baseline *D*LCO (% pred): 39.8±17	Decrease in annual decline in FVC; greater effect was observed in progressive IPF	N/A	N/A	N/A
Harari [24]	Italy	128	Age: 69±7 years Baseline FVC (% pred): 75±18 Baseline *D*LCO (% pred): 47±15	Decrease in annual decline in FVC[f]; greater effect in patients with more severe disease (GAP II–III and FVC at baseline ≤75% pred)	N/A	N/A	N/A

Data are presented as mean±SD, mean (range) or n (%), unless otherwise stated. GI: gastrointestinal; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; VC: vital capacity; N/A: not applicable; GAP: GAP severity index (a simple point-scoring system based on gender (G), age (A) and two lung physiology (P) variables (FVC and *D*LCO). [#]: gastric distress (n=9) and nausea (n=9); [¶]: photosensitivity (n=14) and rash (n=5); [+]: anorexia and/or nausea; [§]: photosensitivity; [f]: relative change in FVC. Reproduced and modified from [25] with permission from the publisher.

DOI: 10.1183/16000617.0042-2015

pirfenidone treatment. Adverse events affected 85% of the patients, leading to discontinuation of pirfenidone in 20% of the cases. Adverse events and treatment discontinuation were seen more frequently in patients treated with pirfenidone and concomitant therapies (*i.e.* NAC and/or steroids). It is important to note that among these 63 patients, 11 had IPF and coexistent emphysema and 30% had echocardiographic evidence of pulmonary hypertension. Lastly, mortality was higher than in clinical experimental trials, with 11% mortality.

In the German journal *Deutsche medizinische Wochenschrift*, Bonella *et al.* [18] reported their experience with 45 IPF patients with mild-to-moderate IPF treated with pirfenidone, 28 of whom were participating or had participated in clinical trials. The mean duration of treatment per patient was 48 weeks (range 3–321 weeks). 16 (35%) patients received pirfenidone as monotherapy and 29 (65%) in combination with corticosteroids and/or NAC, as in the study by Oltmanns *et al.* [21]. At the end of the follow-up period, 28 (70%) out of 40 patients with treatment duration >3 months were considered stable while 30% (12 patients) progressed. The mean±SD VC reduction after treatment with pirfenidone was 132±36 mL. The majority (58%) of patients suffered from side-effects, mostly gastrointestinal. Pirfenidone was discontinued by six (13%) patients because of side-effects.

Chaudhuri *et al.* [22] described their results on pirfenidone tolerability and its effects on the decline of % predicted FVC and % predicted *D*LCO in UK patients involved in the Named Patient Programme. This programme, which was supported by the company (InterMune Inc.) involved in the development and commercialisation of pirfenidone in Europe, allowed qualified physicians to make the newly approved drug available to their IPF patients, provided that pre-specified medical criteria and conditions were met, before it was commercially available in Europe. The drug was made available to patients free of charge. 6 and 9 months before and after pirfenidone commencement, a reduction in the decline of mean percentage change of FVC and *D*LCO was observed. After 9 months there was a difference in the gradient of slope of decline before and after pirfenidone commencement from −1.043±1.605 to −0.197±0.231 for FVC and from −1.427±1.568 to 0.1±0.367 for *D*LCO. 23 out of 40 patients experienced predominantly gastrointestinal adverse effects. Improved adherence and compliance was achieved over time by improving the learning curve and patient education.

The more recent study by Loeh *et al.* [23], which was also conducted in a real-life setting, considered in a retrospective analysis 197 IPF patients followed in an Italian centre and a German centre. It confirmed that patients with a clear progression of disease before pirfenidone therapy showed an even more favourable course under pirfenidone treatment, in agreement with the data previously published by Okuda *et al.* [19]. In this European experience, the FVC annual decline significantly decreased under pirfenidone treatment. A striking therapeutic effect was registered in patients with progressive disease (loss of >10% of FVC per year before starting therapy). Pirfenidone gave a major advantage and, in some cases, even improved the FVC. In an intra-individual analysis of change in FVC decline, 47.4% of patients were in progression before starting pirfenidone, only 20.6% thereafter.

A unique national study describing the experience of all Italian IPF referral centres (n=12), looking at 128 patients, was recently published [24]. This unsponsored experience considered patients who entered straight onto the Named Patient Programme and also patients who had been previously enrolled in the CAPACITY trials and subsequently entered this programme. To be eligible for this retrospective study, patients had to have a medical history documented up to at least 1 year prior and 1 year after initiation of pirfenidone therapy. Stratifications of patients based on FVC % predicted values and GAP severity index (a simple point-scoring system based on gender (G), age (A) and two lung physiology (P) variables (FVC and *D*LCO) [26]) at treatment initiation were performed. Most of the patients were men (75%), ex-smokers (75.8%), had a clinical-radiological diagnosis of IPF (75%; 25% having a histological diagnosis) and aged >65 years (71.1%). Many patients had been previously treated with corticosteroids (58%), NAC (41%) or azathioprine (24%), sometimes in combination. Over the 1-year pre-treatment period, patients experienced a mean decrement of 6.3% in the % predicted FVC: the average FVC dropped from 80% (95% CI 77–84%) to 75% (95% CI 72–79%) of predicted. Over the pirfenidone period (1 year), an attenuation of FVC decline was observed, with a mean decrement of only 1.3% in the % predicted FVC, from 75% (95% CI 72–79%) to 74% (95% CI 70–77%).

During the treatment with the new antifibrotic drug pirfenidone, the difference in percentage changes of FVC compared with the pre-treatment observational time (1 year) was 4.9% (p=0.065) [24]. No significant variation in *D*LCO or in 6-min walking distance (6MWD) before and after starting therapy was detected. Additionally, the efficacy of pirfenidone in attenuating the degree of FVC decline was significantly higher in the group of patients with more severe disease at baseline (FVC ≤75% of predicted): in fact, these patients experienced a mean decrement of 12.7% in % predicted FVC over the pre-treatment period, while no decrement was registered over the follow-up period (p=0.006). With regard to attenuation of decline in

FVC, the results of the analysis according to the GAP index staging system confirmed that, compared with patients with less advanced disease (GAP stage I), those with more advanced disease (GAP stages II and III) could benefit the most from the administration of pirfenidone (p-value for homogeneity of difference between strata of 0.041). Ultimately, in this trial, as already reported by Loeh *et al.* [23], 16 (12.5%) out of 128 patients improved their FVC by >10% during therapy with pirfenidone [24]. Only 22 (17.1%) patients out of 128 were treated with lower than the standard dose of the drug (2403 mg·day^{-1}); however, such dose reduction did not influence the outcomes.

International collaborative experiences

PASSPORT is a post-authorisation safety registry required for pirfenidone by the EMA. Safety data are recorded in routine clinic visits for 2 years. A preliminary analysis was presented in 2014 at the European Respiratory Society annual meeting held in Munich (Germany), reporting data from 530 patients enrolled by 68 sites in seven different countries [27]. The study achieved full recruitment in September 2014, with a total of 1009 patients having been enrolled from >100 active sites in 10 countries: Austria, Denmark, Finland, France, Germany, Ireland, Italy, Norway, Sweden and the UK. The population in this preliminary report was typical of IPF: the mean±SD age was 69±8.8 years, 81% of patients were men, the median time in study was 5.5 months and total exposure was 284 person-years. Out of 311 patients with adverse drug reactions (ADRs), 85 discontinued due to ADRs and 41 discontinued for other reasons. Approximately one-third of patients with ADRs had their dose adjusted. Among those who experienced ADRs, 55% of patients without a dose adjustment were able to continue treatment, while 69% of those who did undergo a dose adjustment were able to continue treatment. 20% discontinued due to the ADR after having a dose adjustment, but 31% discontinued due to the ADR without a dose adjustment. When ADRs were managed by dose adjustment, dose adjustment was associated with continuing treatment. The authors concluded their preliminary analysis by suggesting that ADRs in real-life scenarios are comparable to those in clinical trials, that no new safety issues emerged and that dose adjustment may influence long-term tolerability of pirfenidone. The PASSPORT study is expected to be completed in September 2016 and the final results will be published shortly thereafter.

RECAP is a long-term, open-label extension study evaluating the safety of continued therapy with pirfenidone in patients who completed CAPACITY trials. It is almost a real-life study but a major bias is that patients included in this study come from clinical trials, with all the aforementioned limitations of this population. Data from an interim analysis performed in April 2012 have been recently published in the *European Respiratory Review* (*ERR*) [28]. 603 patients (mean age 68.3 years, 72% male, mean 2.6 years since IPF diagnosis) were enrolled in the RECAP study. Data from patients initially randomised to pirfenidone 2403 mg·day^{-1} in CAPACITY studies and subsequently included in RECAP had a follow-up time of almost 5 years (240 weeks) and demonstrated that 50% of patients who originally received pirfenidone in the CAPACITY studies were still alive and remained on treatment for almost 4 years (week 192) and 40% at week 240. Long-term treatment with pirfenidone had a favourable safety profile and was generally well tolerated for up to 4.9 years of therapy (table 2). Costabel *et al.* [30] reviewed the data of 178 IPF patients who entered the RECAP study having been previously in the placebo arms of the CAPACITY studies and having baseline pulmonary function test values that met the original criteria of the experimental trial (median FVC 73.4% predicted and *D*LCO 46.1% predicted). At week 60, 16.3% of these newly treated patients experienced an absolute decline of FVC ≥10%, compared with 16.8% and 24.8% of the pirfenidone and placebo arms of the CAPACITY trials [13]. Also, overall survival was similar (the Kaplan–Meier estimate of survival was 69% at week 228), allowing the authors to conclude that results in this study mirror those of randomised controlled trials. After 5 years of follow-up, almost 50% of the patients initially randomised to pirfenidone and later included in the RECAP study were still receiving therapy.

A comprehensive analysis of safety across four clinical trials evaluating pirfenidone in patients with IPF was published by Valeyre *et al.* [31], including all patients receiving pirfenidone at full dose in the phase III CAPACITY studies [13] and all patients receiving at least one dose of pirfenidone in one of two ongoing open-label studies on patients with IPF (RECAP and a compassionate-use study including patients with IPF and secondary pulmonary fibrosis). They were selected for inclusion and safety outcomes were evaluated. 789 patients were included in the analysis. The median duration of exposure to pirfenidone was 2.6 years (range 1 week to 7.7 years) and the cumulative total exposure was 2059 person exposure years. Gastrointestinal and skin-related events were the most commonly reported adverse events. They were almost always mild-to-moderate in severity and rarely led to treatment discontinuation. Elevations (>3× upper limit of normal) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) occurred in 21 (2.7%) out of 789 patients. The adjusted incidence of AST/ALT elevations was 1.7 per 100 person exposure years. Treatment with pirfenidone in this large cohort of IPF patients seemed to be safe and generally well tolerated.

DOI: 10.1183/16000617.0042-2015

TABLE 2 Long-term observational studies of pirfenidone from international collaborative experiences

Study name	Patients n	Type of study	Patient characteristics	Median length of treatment	Efficacy outcome	Adverse events		Treatment discontinuation due to adverse events
						GI	Skin	
RECAP [25, 28]	603	Ongoing open-label, long-term, follow-up extension study	The baseline characteristics of patients were similar to those in the CAPACITY study in terms of FVC % predicted and *D*LCO % predicted; age: 68.3 years	163.3 weeks (provisional)	FVC and survival outcome were similar to those in the CAPACITY pirfenidone group	Nausea in 30% of cases; diarrhoea in 22%	Rash in 13.3% of cases; photosensitivity in 8.8%	3.3% (due to nausea, diarrhoea, photosensitivity and rash)
PASSPORT [27]	530	Ongoing, post-authorisation safety registry mandated by the EMA following the approval of pirfenidone; prospective, observational, long-term registry with a follow-up period of 2 years	Age: 69±8.8 years; baseline FVC (% pred): 64.5±16.6	5.5 months (provisional)	The longer term safety profile of pirfenidone appears to be consistent with those seen in the clinical trials	Nausea in 15.7% of cases	Rash in 7.5% of cases and photosensitivity reaction in 4.2%	16%
INSIGHTS-IPF [29]	502	Multicentre, non-interventional study (registry)	Age: 68.7±9.4 years; baseline FVC (% pred): 67±18.2	Started in November 2012	Prospectively assessed the characteristics, diagnostic procedures, treatment patterns, quality of life and long-term outcome; 44.2% of patients were treated with pirfenidone			

Data are presented as mean±SD, unless otherwise stated. GI: gastrointestinal; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; EMA: European Medicines Agency.

In the *ERR*, COTTIN and MAHER [25] recently reviewed the long-term clinical and real-world experience with pirfenidone in the treatment of IPF and concluded their overview by affirming that in clinical trials, observational studies and real-world use, pirfenidone has proved to have a favourable safety profile and has been generally well tolerated over the long term. However, management of adverse events is critical for some patients in order to help them remain on treatment. It is therefore crucial to educate patients about the possibility of adverse events occurring and the prospective provision of instructions on adverse event management.

Discussion

The problem of having real-life studies that reflect clinical practice is more and more evident and some recent data outline its importance in the IPF world. The INSIGHTS-IPF, for example, is a German multicentre, non-interventional study (registry) that documents patients with IPF in routine care [29]. Data regarding a large cohort of >500 patients, who, in contrast to clinical trials, were not pre-selected, were recently published. Comorbidities in this population were frequent, particularly overweight/obesity (47.8%/26.5%), and pulmonary hypertension was suspected on transthoracic echocardiography in 86 (17.2%) patients. On the GAP score (data available for only 348 patients), 21.8% were in stage I, 56.9% in stage II and 21.3% in stage III. Mean±SD FVC was 72±20% predicted, VC was 72±20% predicted and *D*LCO was 35±15% predicted. Multidisciplinary discussion was the diagnostic basis in 108 (21.8%) patients and, in order to obtain adequate lung specimens, histology was performed in 171 (34.1%) patients (as opposed to 25% of the Italian study [24]). The authors compared the data from their national registry to those of recent randomised clinical trials: patients in INSIGHTS-IPF were the same age as patients in ASCEND [8] and PANTHER [32], but were older than those in the two INPULSIS studies [9]. Furthermore, patients from the German study had a longer disease duration than the patients in any of the randomised clinical trials and a much lower 6MWD than the patients in the ASCEND [8] and PANTHER [32] studies. Also, lung function was worse in INSIGHTS-IPF compared with the randomised clinical trials (*e.g.* *D*LCO of 36% *versus* 43–48% predicted, forced expiratory volume in 1 s/FVC of 77% *versus* 81–84% predicted). In particular, the lower 6MWD and lower *D*LCO in INSIGHTS-IPF indicated that in real life, patients presented a more severe disease state compared with those randomised in experimental trials. Mortality in the real-life experience of OLTMANNS *et al.* [21] was slightly higher than in randomised trials (11%), while in the more general German experience it was 9.1% [29].

Some suggestions can be gathered from these real-life studies, such as: 1) pirfenidone could also be effective in patients who are more severe than those randomised in clinical trials (the Italian experience [24] and the German experience of BONELLA *et al.* [18] are significant in that direction); 2) pirfenidone is well tolerated, and the most common adverse events are gastrointestinal, skin-related events and weight loss; 3) to improve compliance it is crucial to manage any adverse event or ADR with the patients [33]; and 4) some studies report that the association of concomitant medications such as NAC and/or corticosteroids could negatively affect tolerability. However, data regarding this last issue will soon be available thanks to the PANORAMA studies evaluating the combination of pirfenidone with NAC [34].

Finally, real-life studies also allow the description of the clinical profile of the population of IPF patients all over the world and give us an idea of their clinical management. The profile of these patients seems to be quite similar all over the world, as does their clinical management. However, some differences can be noted, for example, in the use of lung biopsy: 25% in the Italian experience, *versus* 34% in the German one, although this higher percentage was probably also related to the fact that many of these patients were managed before the release of the 2011 international guidelines on the diagnosis of IPF [2]. In the near future, thanks to the availability of new drugs such as nintedanib, therapy of IPF could change significantly in different countries, according to national rules for prescribing these expensive drugs [35].

Conclusion

Real-life studies support the results of clinical trials performed with pirfenidone and confirm its safety profile, also suggesting possible effects on more severe patients. No real-life studies on nintedanib are available yet. However, the real-life scenario seems to be quite different from the one of randomised trials: patients often have comorbidities, have more severe disease, take concomitant medications and have a higher mortality. For these reasons, it seems important that in the future clinical trials better reflect the general population of patients on whom the drugs will be used and prescribed long term. Surveillance real-life studies, despite several limitations, are useful in following and confirming the experimental data and should therefore be pursued and promoted.

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