Pirfenidone in Idiopathic Pulmonary Fibrosis “RECAP-itolating Safety into the Real World”

Argyris Tzouvelekis^{a,b} Evangelos Bouros^a Vasilios Tzilas^a
Demosthenes Bouros^a

^aFirst Academic Department of Pneumology, Hospital for Diseases of the Chest “Sotiria,” Medical School, National and Kapodistrian University of Athens, and ^bDivision of Immunology, Biomedical Sciences Research Center “Alexander Fleming,” Athens, Greece

Idiopathic pulmonary fibrosis (IPF) is a devastating chronic lung disease that is characterized by progressive lung scarring, ultimately leading to respiratory failure and death within 2.5–3 years of diagnosis [1]. With a gradually increasing incidence, its clinical course being largely unpredictable and the pathogenesis elusive, IPF treatment still represents a major bottleneck for clinicians and researchers [2]. Pirfenidone was the first drug to be approved for the treatment of IPF in the European Union [3]. Pirfenidone is a pleiotropic molecule with antifibrotic, anti-inflammatory and antioxidant properties. It has been demonstrated to inhibit major antifibrotic signaling pathways including those of transforming growth factor- β 1, fibroblast growth factor and interleukin-1 β [4]. Importantly, pirfenidone has been clinically evaluated and has shown beneficial effects in patients with IPF in 5 randomized controlled trials comprising an overall of 1,710 patients [5–7]. In particular, it was shown that pirfenidone was able to slow down the annual functional decline and reduce the risk of death at 1 year by 48% in a prespecified pooled analysis including data from 3 independent cohorts of patients with IPF [5, 6]. In addition, a recent study showed that pirfenidone significantly re-

duced respiratory-related hospitalizations indicating a beneficial impact on acute exacerbations of the disease [8]. Major drug-related side effects were nausea, respiratory tract infections, photosensitivity, and diarrhea [9].

Although phase 3 clinical trials set the basis for marketing authorization approval and commercial availability of the drug, they present with inherent limitations on generalizability of the results since they cannot map risks in the real-world setting. Moreover, thorough knowledge that we have about well-established therapeutic agents is acquired after the drug has been approved and marketed and thousands of patients have been exposed to it.

In this issue of *Respiration*, Costabel et al. [10] report longitudinal safety outcomes of the RECAP study, a large simple trial in a cohort of patients with IPF who had previously completed a phase 3 randomized controlled trial. The study enrolled 1,058 patients who had been followed up for almost 5 years. Almost all patients reported at least one treatment-related adverse event. The majority of those were associated with disease progression (33.6%) and respiratory tract infections (52.5%). Cough and dyspnea were also reported in about 1/3 of participants. On the other hand, the most frequent adverse reactions were

nausea (21.6%), diarrhea (12.3%), and rash (11.6%). Treatment discontinuation due to adverse reactions occurred in almost 1/10 of patients with only 1/100 of patients dying due to an adverse reaction of pirfenidone. Death as an outcome of a treatment-related adverse event was reported in about 1/5 of patients and IPF progression was the most common cause (15.3%).

The RECAP study exhibited a number of major attributes that should be highlighted. (1) It is the first study of an antifibrotic agent that reports longitudinal safety in a large cohort of IPF patients of the real-world clinical practice. The RECAP study represents the antechamber of a postmarketing surveillance phase 4 clinical trial where safety is evaluated in a naturalistic setting and in line with current practice at each study site. (2) The striking similarities of the safety profile between the RECAP study and the phase 3 clinical trials further establish an already acceptable safety profile. Discontinuation rates due to drug adverse reactions were similar between the RECAP study and the phase 3 trials, indicating that prolonged exposure to the drug does not increase the risk of adverse reactions. Particular safety aspects that should be noted are the finding that anorexia, weight loss, and insomnia, 3 major adverse reactions that have been previously reported in almost 10% of patients in the parent studies and are closely related to quality of life, have not been reported in the RECAP study. This could be associated with adaptation of patients to treatment following the first year of administration or it could indicate early and careful management of adverse events further reinforcing the safety and tolerability profile. In addition, the finding that discontinuation rates due to adverse events occurred most frequently in patients of the placebo arm of the phase 3 trials (newly initiating pirfenidone) may suggest a more favorable safety profile during early disease stages. (3) Finally, the RECAP study, though designed to address the safety of pirfenidone, also provides important and longitudinal efficacy data in real-world conditions [11]. The evidence that the annual rate of lung function decline over 5 years is comparable to what was observed in the parent studies (144 vs. 164 mL, respectively) represents the first indication of an antifibrotic drug that exemplifies the difference between efficacy and effectiveness. This observation is based on the fact that efficacy is judged within the “sterilized” and controlled environment of a clinical trial over a short period of time with strict inclusion criteria and ensured compliance while effectiveness is the real test of a drug when it is administered in the everyday clinical practice for a prolonged period of time. Safety and efficacy data derived

from real-world observational studies in small cohorts of patients with IPF are also in line with the RECAP study, reinforcing the beneficial profile of pirfenidone [12, 13].

Despite relative enthusiasm arising from the above observations, the RECAP study exhibited a number of caveats that should be treated cautiously. (1) The RECAP study presents inherent weaknesses of an open-label extension study including dependence upon appropriateness of the design and control for bias. In particular, the study included patients with mild-to-moderate disease severity as assessed by a mean DLCO %pred of 41% and FVC %pred of 71% and, therefore, may have missed a significant proportion of patients with more severe disease that could potentially be in greater need for therapeutic interventions. (2) In line with this, patients included in the RECAP study were white Caucasians (90%), suggesting a potential selection bias. In fact, pirfenidone trials have been characterized by high screening failure rates (64%), similar to those observed with nintedanib trials, and this evidence should be taken into consideration [14]. (3) Regarding safety and tolerability, the RECAP study included only patients that completed phase 3 clinical trials indicating a potential selection bias towards those patients with an acceptable tolerability profile. However, a recently published integrated analysis of 1,299 patients from 5 studies (including RECAP) that had been followed up for almost 10 years clearly demonstrated that prolonged exposure to pirfenidone is safe and well tolerated [15].

Prospective observational studies in the context of registries that collect well-defined supporting data over time can provide a real-world view of pirfenidone in clinical practice and answer residual questions on safety and efficacy of the drug in a broad spectrum of patients with IPF irrespective of disease severity, race, and gender. The RECAP study represents the first step in this direction.

References

- 1 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis: 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 Bouros D, Tzouvelekis A: Idiopathic pulmonary fibrosis: on the move. *Lancet Respir Med* 2014;2:17–19.
- 3 Tzouvelekis A, Tzilas V, Papiris S, Aidinis V, Bouros D: Diagnostic and prognostic challenges in idiopathic pulmonary fibrosis: a patient “Q and A” approach. *Pulm Pharmacol Ther* 2017;42:21–24.
- 4 Oku H, Shimizu T, Kawabata T, Nagira M, Hikita I, Ueyama A, Matsushima S, Torii M, Arimura A: Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. *Eur J Pharmacol* 2008;590:400–408.
- 5 King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, ASCEND Study Group: A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–2092.
- 6 Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, Lancaster L, Sahn SA, Szwarzberg J, Valeyre D, du Bois RM, CAPACITY Study Group: Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011;377:1760–1769.
- 7 Bouros D: Pirfenidone for idiopathic pulmonary fibrosis. *Lancet* 2011;377:1727–1729.
- 8 Ley B, Swigris J, Day BM, Stauffer JL, Raimundo K, Chou W, Collard HR: Pirfenidone reduces respiratory-related hospitalizations in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2017, Epub ahead of print.
- 9 Noble PW, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, Lancaster L, Lederer DJ, Leff JA, Nathan SD, Pereira CA, Swigris JJ, Valeyre D, King TE Jr: Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J* 2016;47:243–253.
- 10 Costabel U, Albera C, Lancaster LH, Lin C-Y, Hormel P, Hultner HN, Noble PW: An open-label study of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (RECAP). *Respiration* 2017;94:408–415.
- 11 Costabel U, Albera C, Bradford WZ, Hormel P, King TE Jr, Noble PW, Sahn SA, Valeyre D, du Bois RM: Analysis of lung function and survival in RECAP: an open-label extension study of pirfenidone in patients with idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;31:198–205.
- 12 Loeh B, Drakopanagiotakis F, Bandelli GP, von der Beck D, Tello S, Cordani E, Rizza E, Barrocu L, Markart P, Seeger W, Guenther A, Albera C: Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2015;191:110–113.
- 13 Oltmanns U, Kahn N, Palmowski K, Trager A, Wenz H, Heussel CP, Schnabel PA, Puderbach M, Wiebel M, Ehlers-Tenenbaum S, Warth A, Herth FJ, Kreuter M: Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a german tertiary referral center for interstitial lung diseases. *Respiration* 2014;88:199–207.
- 14 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herzeg R, Disse B, Collard HR; INPULSIS Trial Investigators: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
- 15 Lancaster L, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, King TE Jr, Lederer DJ, Lin Z, Nathan SD, Pereira CA, Swigris JJ, Valeyre D, Noble PW: Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Respir Res* 2016; 3:e000105.