Respiration 2015;90:352
DOI: 10.1159/000436980

New Treatments for Idiopathic Pulmonary Fibrosis: 'Die Another Day' if Diagnosed Early?

Katerina M. Antoniou^a Emmanouil K. Symvoulakis^b
Dimitrios Anyfantakis^c Athol U. Wells^d

^aLaboratory of Cellular and Molecular Pneumology, Department of Thoracic Medicine, Medical School, University of Crete, and ^bPrivate Family Practice Unit, Heraklion, and ^cPrimary Health Care Centre of Kissamos, Chania, Crete, Greece; ^dRoyal Brompton Hospital, ILDU, London, UK

Idiopathic pulmonary fibrosis (IPF) is a severe, underdiagnosed pulmonary disease limited to the lungs, occurring mostly in older adults and affecting both daily activity and life expectancy [1, 2]. Survival from the time of diagnosis is comparable to that of inoperable pulmonary malignancy, with retrospective longitudinal studies suggesting a median survival of 2–3 years after diagnosis [1, 2]. IPF is characterized by an irreversible and evolving loss of the lung capacity, leading inexorably to respiratory failure [2]. The only care options endorsed by guidelines published in 2011 were pulmonary rehabilitation, long-term oxygen therapy, lung transplantation, and enrolment in a clinical trial [3].

However, after decades of therapeutic disappointment, three recent phase 3 placebo-controlled trials of two oral antifibrotic drugs have demonstrated that slowing disease progression with drug therapy can be achieved in IPF patients with mild-to-moderate disease [4–6]. In all three trials, pirfenidone or nintedanib therapy prevented about 50% of the decline in forced vital capacity typically seen in IPF [4, 5].

The fact that positive findings in both studies were seen in IPF patients with mild-to-moderate disease [2] highlights the importance of early clinical suspicion, diagnosis, and expert evaluation [1, 7]. However, earlier diagnosis is unlikely to occur without the active involvement of primary physicians, who are in a position to achieve earlier referrals, based on awareness of the clinical significance of inspiratory velcro-like crackles on auscultation and restrictive patterns on spirometry [1, 7]. In this direction, a suggestion how to improve early diagnosis deserves attention. It needs to fill the gaps in both undergraduate and postgraduate educational curricula by increasing the exposure to pulmonology and improving the teaching of the basics of lung auscultation and spirometry.

There are other important unanswered questions, including the value of antifibrotic agents in 'real-world', nonpharmaceutical IPF cohorts, the question of whether treatment benefits attenuate in the longer term, and the possibility that combination regimens might provide add-on and synergistic benefits or increased toxicity without any benefits. Only time will provide further insights into these issues [8], and there is no guarantee that the answers will be clear-cut. Our one certainty is that the treatment benefits that have electrified the specialty have been achieved in patients diagnosed whilst disease is still mild-to-moderate. In the seminal treatment trials of 2014 [4, 5], the efficacy of antifibrotic therapy in severe IPF was not explored. It is widely accepted that in chronic progressive disorders in general, treatment tends to be less effective when disease is advanced. In severe IPF, secondary pulmonary hypertension is a highly prevalent malignant prognostic determinant. It appears to be intuitively unlikely that antifibrotic therapy, in isolation, will have a major impact on the outcome in this scenario. Thus, in IPF, diagnostic delays may be deadly and need to be confronted.

References

- 1 Antoniou KM, Symvoulakis EK, Margaritopoulos GA, Lionis C, Wells AU: Early diagnosis of IPF: time for a primary-care case-finding initiative? *Lancet Respir Med* 2014;2:e1.
- 2 King TE Jr, Pardo A, Selman M: Idiopathic pulmonary fibrosis. *Lancet* 2011;378:1949–1956.
- 3 Raghu G: Idiopathic pulmonary fibrosis: new evidence and an improved standard of care in 2012. *Lancet* 2012;380:699–670.
- 4 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.
- 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 Jones MG, Fletcher S, Richeldi L: Idiopathic pulmonary fibrosis: recent trials and current drug therapy. *Respiration* 2013;86:353–363.
- 7 Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ: Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. *Am J Respir Crit Care Med* 2011;184:842–847.
- 8 Oltmanns U, Kahn N, Palmowski K, Träger 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.