Pirfenidone in idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a severe, chronic, irreversibly progressive fibrosing disease of the lungs, which leads to death in all patients affected and for which there is no effective treatment[1,2]. The most recent guidelines for the diagnosis and management of IPF conclude that there is no effective treatment and recommend avoidance of the use of steroids and immunosuppressants, which are commonly administered by physicians, but that could be toxic for the lung parenchyma or predispose to severe infections[1,3]. Immunosuppression may be responsible for the most devastating of complications in the clinical course of IPF, which is the acute exacerbation of IPF,i.e., the development of acute lung injury and acute respiratory distress syndrome (RDS), presenting histologically as diffuse alveolar damage on the substrate of usual interstitial pneumonia (UIP)[4].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone, PFD) is a substance with proven antioxidant, anti-inflammatory and antifibrogenic properties. Its mechanism of action is by inhibition of tumour necrosis factor α (TNFα) and tumour growth factor β (TGFβ), through inhibition of collagen synthesis and release of reactive oxygen intermediates, and through activation of collagenases and matrix metalloproteinases[5]. PFD has been used successfully in animal models of fibrosis and thus appears promising for the treatment of IPF.

Raghu and coworkers published in 1999 the findings of the first phase II study of PFD in 54 patients with advanced IPF, which showed some encouraging results regarding control of the rate of decline of respiratory function and the degree of oxygenation[6]. In 2002 Nagai and coworkers published a similar study of 10 patients, 8 with IPF and 2 with UIP caused by systemic sclerosis[7].

Azuma and coworkers reported in 2005 the first double blind, placebo controlled, phase II study of PFD in 107 patients with IPF[8]. The primary endpoint was defined as the lowest oxygen saturation by pulse oxymetry (SpO_2) during a 6-minute exercise test (6MET). The study was aborted prematurely because the Data Safety Monitoring Board (DSMB), in an interim analysis, found a significant difference in the incidence of acute exacerbations between the PFD and placebo groups: 14% in the placebo group and none in the PFD group during the first 9 months of the study ($p = 0.0031$). In addition, at 9 months the difference in decline of vital capacity (VC) between the placebo group (-0.13 L) and the PFD group (-0.03 L) was statistically significant ($p = 0.0366$). Neither the other secondary endpoints nor the primary endpoint were validated. This study was criticized for its choice of

primary endpoint which is unvalidated and not of proven value in the assessment of IPF, and for the methodology that required the patients to perform a 6MET which is a non-standardized variant of the 6-minute walk test.

Taniguchi and coworkers published in 2010 the first double blind, randomized, placebo controlled, phase III study of PFD in 275 patients with IPF[9]. The patients were divided into 3 groups, a high-dose and a low-dose PFD group, and a placebo group. The primary endpoint, which was the change in VC, was -0.16 L in the placebo group, -0.09 L in the high-dose PFD group (p = 0.0416) and -0.08 L in the low-dose PFD group (p = 0.0394). Progression-free survival time (PFS), one of the secondary endpoints, was also validated between the high-dose and the placebo groups (p = 0.028). The rate of acute exacerbations was similar in all 3 groups. The major criticism of this study was the change of the prespecified primary endpoint, which had originally been decided to be the lowest SpO_2 during a 6MET (as in the Azuma study)[10]. This change was recommended by the DSMB while the trial was ongoing, after a discussion of blinded interim comparative data[11]. This means that the members of the DSMB had knowledge of whether there were significant differences between study groups with respect to the primary and secondary endpoints). In addition, the handling of the missing data by the authors (incomplete data were obtained for a full one-third of subjects) was by the method of last observation carried forward analysis, which may underestimate the true variability of the missing data and inflate the type 1 error rate (i.e., finding a statistically significant difference when a difference does not truly exist)[11]. In studies such as this, with a small treatment effect and marginal p-value, estimated significance may hinge on the method of statistical adjustment used.

In 2011 the findings of the most recent trials of the use of PFD in IPF were published. These were the CAPACITY trials, two concurrent, double blind, randomized trials, the 004 and the 006 trials[12,13]. The 004 trial involved 435 patients with IPF randomized into high-dose PFD, low-dose PFD and placebo groups, while in the 004 trial 344 patients with IPF were randomized into high-dose PFD and placebo groups. These two trials had the same design and endpoints and their data were analysed and presented both separately and pooled. The primary endpoint was the change in percentage predicted forced vital capacity (FVC). In the 004 trial the mean decline of percentage predicted FVC was 8% in the high-dose group and 12.4% in the placebo group (p= 0.001). In the 006 trial there was no such significant difference between groups. In the pooled data a mean decline of percentage predicted FVC of 8.5% was observed in the combined high-dose group, while in the combined placebo group the decline was 11% (p= 0.005). Regarding the secondary endpoints that were validated, in the 004 trial there was a significant difference in the proportion of patients presenting a categorical change in FVC (>10% decline) between the high-dose group and the placebo group (p =0.001) and also in the PFS time (p = 0.023). In the 006 trial no differences were observed, but in the pooled data the same differences were validated, with p-values of 0.003 and 0.025 respectively.

The trials of PFD in IPF reveal many of the methodological issues faced by researchers. Some of these are very apparent, such as the choice of an unvalidated primary endpoint in the study of Azuma, and the change of the primary endpoint in the study of Taniguchi while the study was ongoing and after analysis of some of the data[8,9]. In the CAPACITY trials the choice of the change of FVC as a primary endpoint appears to be logical and it was well justified by many studies that have shown a strong relationship between the decline of VC and both the decline of lung function and the prognosis of IPF[14]. A decline of more than 10% in VC is commonly considered to indicate progression of IPF, but more recent data suggest that even a decline of 5-10% should be regarded as a progression of the disease[15,16]. The CAPACITY trials showed a statistically significant difference in the change of FVC between PFD and placebo group (4.4% and 2.5%, respectively) which should not, however, be considered as clinically significant[17,18]. Moreover, the 8% decline of FVC in the high-dose PFD group of the 004 trial does not surpass the threshold of the minimal clinically important difference of either 10% or 5% as described above and cannot possibly be interpreted as evidence of the clinical effectiveness of PFD[17,18].

It is obvious that no convincing data in support of the use of PFD in IPF have yet been documented, and it is quite peculiar that the Japanese and European authorities have approved PFD, in contrast with the US Federal Drug Administration (FDA). The cardinal sin in all IPF studies is the obsession with marginal statistical significances of parameters that sometimes are not even validated endpoints for IPF, instead of using the only reliable and universally acceptable endpoint, which is the overall mortality[19-21]. It is our belief that a truly effective treatment for IPF should prolong the duration of life of patients with IPF, rather than merely attenuating the rate of decline of certain parameters of doubtful clinical significance.

If this is difficult to achieve for a disease such as IPF that has a short median survival and low prevalence, then we should be very careful not to confuse statistical with clinical significance[22].

REFERENCES

1. Raghu G, Harold R, Collard HR, 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. Bouros D. The new ATS/ERS/JRS IPF Guidelines. Pneumon 2008; 21:117-118.
3. Bouros D, Tzouvelekis A. Interferon-gamma for the treatment of idiopathic pulmonary fibrosis. Pneumon 2009; 22:13-17.
4. Papiris SA, Manali ED, Kolilekas L, et al. Idiopathic Pulmonary Fibrosis Acute Exacerbations: Unravelling Ariadne's thread. Crit Care 2010; 14:246.
5. Macías-Barragán J, Sandoval-Rodríguez A, Navarro-Partida J, Armendáriz-Borunda J. The multifaceted role of pirfenidone and its novel targets. Fibrogenesis Tissue Repair 2010; 3:16.
6. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. Am J Respir Crit Care Med 1999; 159:1061-1069.
7. Nagai S, Hamada K, Shigematsu M, Taniyama M, Yamauchi S, Izumi T. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med 2002; 41:1118-1123.
8. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005; 171:1040–1047.
9. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 821–829.
10. Swigris J, Fairclough D. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 36:695–696; author reply 696–698.
11. Collard HR. Idiopathic pulmonary fibrosis and pirfenidone. Eur Respir J 2010; 35:728-729.
12. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377:1760–1769.
13. Bouros D. Pirfenidone for idiopathic pulmonary fibrosis. Lancet 2011 21; 377:1727-1729.
14. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003; 168:531-537.
15. 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.
16. 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; 184:1382-1389.
17. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002; 77:371–383.
18. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study results. J Gen Intern Med 2002; 17: 469–476.
19. D'Agostino RB. Changing End Points in Breast-Cancer Drug Approval — The Avastin Story. N Engl J Med 2011; 365:e2
20. McKee AE, Farrell AT, Pazdur R, Woodcock J. The role of the U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. Oncologist 2010; 15:Suppl 1:13-18.
21. Food and Drug Administration Oncologic Drug Advisory Committee. Transcript of the July 20, 2010, meeting. (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM221998.pdf.)
22. Papiris S, Kagouridis K, Kolilekas K, Triantafillidou C, Tsangaris I, Manali E. Pirfenidone treatment in idiopathic pulmonary fibrosis: too much of a great expectation? Eur Respir J 2012; 39: in press.