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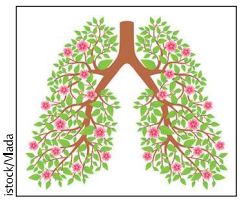
The FLORA study: presenting a novel IPF trial design



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The past decade has seen understanding of the pathobiology, natural history, and clinical relevance of idiopathic pulmonary fibrosis (IPF) progress tremendously. This expansion of knowledge culminated in the establishment of two therapeutic options for IPF patients—nintedanib and pirfenidone[1]—that are now being tested in patients with chronic progressive non-IPF fibrotic lung diseases.[2] Despite these major advances, there is no cure yet and the disease remains progressive and fatal. Identification, development, and delivery of new therapies are urgently needed, but drug development is a long and winding road and progress is slow. One way to speed up the drug development process in IPF is to make early-phase trials faster and cheaper. Initial early-phase clinical trials in IPF have generally been too large, too long, and too dependent on clinical efficacy endpoints, such as decline in forced vital capacity (FVC). Collard and colleagues[3] have suggested that early-phase endpoints should be, whenever possible, biological and mechanistic.

In *The Lancet Respiratory Medicine*, Toby Maher and colleagues[4] report the results of the FLORA study, a phase 2a randomised trial assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of the autotaxin inhibitor GLPG1690 in IPF. The study involved 23 adults with IPF who were not taking pirfenidone or nintedanib. 17 were assigned to receive 600 mg GLPG1690 orally once daily for 12 weeks and the remainder to receive placebo. 11 patients in the GLPG1690 group had treatment-emergent adverse events (two judged to be related to treatment) that were generally mild to moderate, compared with four in the placebo group. One patient in each group stopped treatment because of serious adverse events. No patients died or had acute IPF exacerbations. The pharmacokinetic and pharmacodynamic profiles of GLPG1690 were similar to those previously shown in healthy controls. The results strongly support the hypothesis that autotaxin inhibition alters the fibrotic process in the lungs and support phase 3 studies with this molecule.

This study is a very important, for two reasons: it sets new standards for IPF early-phase trials and it supports the idea that lysophosphatidic acid (LPA), concentrations of which were consistently decreased in recipients of GLPG1690, might be an actionable target for fibrotic disorders.

The design of this early-phase trial is novel and overcomes the limitations of most previous early-phase studies in IPF.[3] The trial was small, fast (treatment duration 12 weeks and total participation 18 weeks), and the primary outcomes included evidence for engagement of the target by assessment of LPA C18:2 concentrations in plasma. It was also probably cheaper to run than most phase 2 studies in IPF, although this is unknown. Moreover, besides measurement of FVC, the investigators used the exploratory efficacy endpoints of home spirometry and functional imaging based on repeated high-resolution CT. Despite the small numbers of participants, the study was highly successful. The investigators were able to show

clearly the biological activity of the molecule tested. The size of the study does mean that it is far too early to judge efficacy, but the curve for change in FVC in the GLPG1690 group, in which values stayed similar to or greater than baseline, separated from that for the placebo group, where values decreased from baseline, with the difference almost reaching significance. Their data also support the use of home spirometry to assess longitudinal lung function changes in IPF patients. Home spirometry might improve the precision of endpoint assessments and the efficiency in clinical trials of therapeutics for IPF.[5,6] Functional lung imaging showed that specific airway volume increased and specific airway resistance decreased in the GLPG1690 group compared with in the placebo group, further supporting the idea that autotaxin inhibition affected the mechanical properties of the lung.

Autotaxin is a secreted enzyme that is abundant in the lung. It converts lysophosphatidylcholine (produced through the enzymatic action of phospholipase A2 on phosphatidylcholine, a major component of cell membranes) to LPA, which has been implicated in various fibrogenic pathways in different tissues, including the lung. LPA acts through specific G-protein-coupled receptors (LPA 1, 2, and 3), is involved in the recruitment of fibroblasts to the fibrotic tissue,[7] and protects the epithelium from acute injury.[8,9] LPA has been involved in the fibrotic process in systemic sclerosis,[10] and preliminary data suggest that plasma lysophosphatidylcholine, a precursor of LPA, could be a biomarker for IPF.[11] Targeting LPA by inhibiting LPA receptors or synthesis is being actively researched in fibrotic diseases. Besides the FLORA study,[4] early-phase trials have been completed with LPA-1 antagonists BMS-986020 in IPF (NCT01766817) and SAR100842 in systemic sclerosis (NCT01651143). The investigators of the FLORA trial should be congratulated on their excellent trial design.

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Disadvantages of set length antibiotic treatment for pulmonary exacerbation

The optimal duration of intravenous antibiotic treatment for an acute exacerbation of cystic fibrosis is an important question because approximately 34% of patients with cystic fibrosis are treated with intravenous antibiotics each year, with the average number of treatment days per year being 29 among those treated.[1] Exacerbations lead to a decline in lung function, poor quality of life, and increased risk of death.[2] Clinicians are attempting to optimise lung function, improve symptoms, and provide long-term stability, while balancing the burden of treatment, the potential for numerous side effects, and costs.

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