

Idiopathic Pulmonary Fibrosis: The dawn of a new era

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Idiopathic pulmonary fibrosis (IPF) is devastating, progressively fatal chronic pulmonary disease of unknown cause that is characterized by the histopathological or radiological patterns of usual interstitial pneumonia in a typical clinical setting. To date no pharmacologic therapies have been shown to improve survival. Half of the patients die within three years, a prognosis worse than many cancers. Lung transplantation, in the eligible minority, extends to a five-year survival only in 60%^{1,2}.

Pharmacotherapy with prednisone, azathioprine and NAC, suggested by previous experts' opinion^{3,4}, proved to be detrimental. Indeed, the long-standing idea that the underlying pathogenetic cause of IPF is inflammation and the goal for medical treatment had been to decrease inflammation, led to a trial⁵ that compared a three-drug combination of immune suppression – prednisone, azathioprine and an antioxidant, N-acetylcysteine – to placebo, and to acetylcysteine alone (PANTHER-IPF). The primary outcome was the change in measurements of forced vital capacity (FVC) during a 60-week treatment period. The study was stopped early in the interim analysis as the group of IPF patients in the three-drug trial arm were more likely to die (8 vs. 1, $P=0.01$) and hospitalized (23 vs. 7, $P<0.001$) than those receiving either acetylcysteine or placebo⁵. These findings provide evidence against the use of this combination in such patients.

Recently three papers have been published in the NEJM that offer new promise for medical treatments and clarify which therapies are not effective.

The first one⁶ answers to the question of whether acetylcysteine alone could yield a benefit in patients with mild to-moderate impairment in lung function. After stopping the three-drug study arm of the PANTHER-IPF trial, investigators had continued to enroll patients in the acetylcysteine versus placebo trial. However, at 60 weeks patients randomly assigned to receive acetylcysteine did no better – by lung function (-0.18 liters and -0.19 liters, $P=0.77$), rate of exacerbation (2.3% in each group, $P>0.99$) or death (4.9% vs. 2.5%, $P=0.30$ by the log-rank test) – than those assigned to receive placebo.

On the other hand the two other IPF trials (the IMPULSIS and the ASCEND trials), published simultaneously, are promising. The IMPULSIS trials⁷ were two randomized, double-blind, placebo-controlled, phase 3 trials that were conducted simultaneously to evaluate the role of nintedanib, as compared with placebo, in patients with IPF. Nintedanib (formerly called BIBF-1120) is a tyrosine kinase receptor antagonist thought to have a benefit in IPF in

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a previous study⁸ by acting against various pro-fibrotic growth factors, including platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor that have been implicated in the pathogenesis of idiopathic pulmonary fibrosis⁹. The investigators randomly assigned 1066 patients to receive either nintedanib or placebo. Patients receiving nintedanib had significant reductions in the rate of decline in forced vital capacity (FVC) at 1 year, the primary end point of the two studies. The adjusted annual rate of change in FVC was -114.7 ml with nintedanib versus -239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; $P < 0.001$) in INPULSIS-1 and -113.6 ml with nintedanib versus -207.3 ml with placebo (difference, 93.7 ml per year; 95% CI, 44.8 to 142.7; $P < 0.001$) in INPULSIS-2.

In one of the studies of this drug, there was a longer time to first IPF exacerbation but this wasn't replicated in the other. The most frequent adverse event in the nintedanib groups was diarrhea, which led to discontinuation of the study medication in <5% of patients (rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively). In both studies, there was no significant difference in the self-reported scores for respiratory symptoms. Although these trials were not powered to detect statistically significant differences in mortality, there was a trend toward a reduced mortality among the patients taking nintedanib.

The ASCEND trial randomized 555 patients with centrally-confirmed IPF to receive either oral pirfenidone (a total of 2,403 mg divided into three doses daily) or placebo for 1 year¹⁰. Pirfenidone is a drug with antifibrotic properties that has been approved for use in patients with IPF, but not yet by the FDA. The primary end point was the change in FVC or death. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from IPF. Patients who received pirfenidone had a slower decline in FVC than those with placebo (22.7% versus 9.7%, $P < 0.001$), and more of them had no decline at all over one year. Key secondary endpoints also improved with the drug compared with placebo [decline in the 6-minute walk distance ($P = 0.04$) and improved progression-free survival ($P < 0.001$)]. There was no change in respiratory symptom scores, nor in rates of death. However, when these results were pooled with prior studies of pirfenidone in IPF¹¹ a total of 1,247 patients, pirfenidone reduced the risk of death at 1 year by a relative 48% overall and by 68% for death from IPF ($P = 0.01$ and $P = 0.006$, respectively).

The most common serious adverse event was wors-

ening IPF. But excluding these events, serious adverse event rates were about similar between pirfenidone and placebo (18.7% versus 20.2%). Gastrointestinal and skin-related adverse events were more common with pirfenidone group than placebo, but these rarely led to treatment discontinuation and none were grade 4. Clinically significant elevations in aminotransferase levels occurred more with pirfenidone but occur in less than 3% of patients, are reversible, and did not have clinically significant consequences.

As it is noted in an accompanying editorial by Gary Hunninghake¹², while these results represent "a major breakthrough for patients with IPF," we should be "cautious" in extrapolating the findings to all patients. Namely, neither study enrolled patients with severe disease, and neither study tracked patients for longer than one year. Furthermore, we don't know how the drugs would work together or whether they might benefit patients with other kinds of fibrotic lung disease, or pre-clinical stages of IPF. However, still remain many pathogenetic ways in the development of IPF to be treated, including immunoregulation¹³, oxidative stress⁹, apoptosis¹⁴, gastroesophageal reflux¹⁵, microbiome¹⁶, etc. Combination pharmacologic treatment in an "oncologic approach" and the role of stem cell treatment should be pursued aggressively¹⁷⁻¹⁹. Combined pulmonary-fibrosis emphysema needs its pathogenetic and treatment investigation²⁰.

In conclusion, for the first time there is really good news and a "New Era" in the medical management of idiopathic pulmonary fibrosis. IPF patients can hope they can live with their disease longer and avoiding detrimental treatments²¹.

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