Editorial

Adjunctive therapies in idiopathic pulmonary fibrosis—where do we stand?

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A rationale for combined therapy in idiopathic pulmonary fibrosis (IPF)

IPF is a restrictive lung disease that is characterized by dyspnea, non-productive cough and progressive loss of lung function. Some patients with IPF will have a slow and steady decline in their lung function, while others can experience a more rapid deterioration in their health and documented lung functions (1). The pathogenesis of IPF [histologically referred to as usual interstitial pneumonia (UIP)], is incompletely understood. However, it may involve a number of genes including surfactant protein C and telomerase mutations, resultant pneumocyte senescence, and aberrant repair pathways hallmarked by progressive pulmonary fibrosis (2,3).

Numerous anti-inflammatory therapies such as corticosteroids, N-acetylcysteine, azathioprine, Etanercept, and Imatinib have all been prospectively assessed without meaningful impact on progression of fibrosis or survival (4). Similarly, the utility of pulmonary hypertension medications has historically been of little utility in improving clinical outcomes in IPF. The Build-3 IPF trial examined the utility of Bosentan, a pulmonary hypertension medication, in >600 patients with an IPF diagnosis for less than 3 years without extensive honeycombing on high-resolution computed tomography (HRCT) over an average of 19.9 months (5). They assessed for time to IPF worsening as a primary endpoint, and secondary endpoints included: change in healthcare related quality of life, transition dyspnea index, time to IPF worsening, and time to death by end of study. None of these endpoints were meaningfully impacted by treatment with Bosentan (5).

However, the two currently approved therapies for IPF are the "anti-fibrotics", pirfenidone and nintedanib (6,7). These drugs have both been shown to abrogate decline in forced vital capacity (FVC). This editorial will focus on nintedanib as well as its recent combination with sildenafil, another pulmonary hypertension medication, in the INSTAGE trial.

Nintedanib—an overview

Nintedanib, a tyrosine kinase inhibitor, has been approved for the treatment of IPF (7-9). In two parallel, randomized placebo-controlled trials, INPULSIS 1 and INPULSIS 2, nintedanib was evaluated for safety and efficacy of 52 weeks of treatment (7). Eligibility criteria included patients who were 40 years and older with a diagnosis of IPF with an FVC >50% predicted, and a diffusion capacity of carbon monoxide (DLCO) between 30–79% predicted. HRCT of the chest findings had to include the following if a surgical lung biopsy was not available: (I) definite honeycomb lung destruction with basal and peripheral predominance; (II) presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance and/or (III) atypical features being absent, specifically lung nodules and consolidation. Ground glass opacity could be present, but had to be less extensive than reticular opacity patterns. A single radiologist was used to confirm the radiological diagnosis. Only 20–25% of patients had a surgical biopsy confirming

UIP/IPF prior to enrollment. Another important feature was that patients could be on concomitant therapy with daily dose of Prednisone 15 mg if the dose had been stable for ≥8 weeks before screening. Higher dose of steroids, the use of azathioprine, or N-acetylcysteine were exclusionary factors. After 52 weeks Nintedanib had less adjusted annual rate of change in FVC compared to placebo. A divergence in the difference starts at around 6 weeks and continued to 52 weeks. The impact on acute exacerbations was not as robust however. It is only after adjudication was there a statistically significant reduction in the acute exacerbation rate (10). The serious adverse event rate was 31.1 in the treatment arm of INPULSIS 1 and 29.8 in the treatment arm of INPULSIS 2. Common adverse events are diarrhea and liver function test elevation. Myocardial infarction has been reported, but it is not clear if this is causally related to nintedanib exposure. The safety and tolerability of the medication remained the same when evaluated in the 64-week open-label extension study, INPULSIS-ON (11). Nintedanib appears to blunt pulmonary function decline, though the optimal start time for this drug had not fully been delineated (4). As part of the INPULSIS-ON interim analysis (at 48 weeks), the decline in FVC and safety of nintedanib was assessed between 690 IPF patients with FVC >50% and 41 IPF patients with FVC ≤50% predicted (12). Patients either continued nintedanib or initiated it. In both subgroups, the relative change to the FVC from baseline to 48 weeks was to the same degree as the combined INPULSIS 1 and 2 trials (–3%) (12).

Targeting pulmonary hypertension in IPF

By its nature, IPF is a restrictive lung disease owing to the expansion of fibroproliferative foci. This leads to impairments in both ventilation and gas exchange as the total lung capacity is reduced and alveolar-capillary interface is obliterated. As a result, ventilation-perfusion matching can be markedly impaired, and though an important driver of hypoxemia in IPF is an increase in PAO_2-PaO_2 gradient, it is not the only source of hypoxemia or dyspnea.

Hypoxia leads to pulmonary vasoconstriction, elevated pulmonary vascular resistance, pulmonary vascular remodeling, potential intrapulmonary shunt, and right heart dysfunction in a large number of IPF patients (13,14) The development of World Health Organization (WHO) group III pulmonary hypertension is one of the most important predictors of mortality in IPF (15). Approximately 30–40% of individuals with IPF ultimately develop WHO group III pulmonary hypertension. Within this paradigm also lies the nidus for the commonly observed reduction in DLCO, afflicting virtually all patients with IPF (16). Intriguingly, TGF-beta appears to be important in both the fibrotic evolution of IPF as well as the consequent pulmonary vascular remodeling (8,17). Nintedanib abrogates TGF-beta signaling and in turn blunts pulmonary fibrosis (8). Sildenafil may attenuate TGF-beta signaling as well in addition to phosphodiesterase (PDE) 5. In murine Bleomycin models, Sildenafil has been shown to not only act as a vasodilator, but also as an anti-fibrotic via inhibition of the RhoA/ROCK pathway (18,19). As such, a combined approach of interrupting fibrogenesis and vascular remodeling, mitigating hypoxic vasoconstriction, and assuaging the right heart burden of advanced IPF are tempting and logical therapeutic endpoints. Despite initial negative trial results with the BUILD-3 IPF trial, IPF-associated pulmonary hypertension remains a desirable therapeutic target (5).

The Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary (STEP-IPF) trial assessed the potential utility of sildenafil, dosed at 20mg three times daily, in individuals with advanced IPF with DLCO <35% predicted compared with placebo. The primary endpoint of this 12-week trial was the proportion of patients with ≥20% in the distance on the 6-minute walk test. The treatment group did not meets the primary endpoint. In a subgroup analysis, however, sildenafil did improve patient quality of life as assessed by the St. George's Respiratory Questionnaire (SGRQ), improved DLCO and oxygenation at rest. This benefit was greater in patients with confirmed evidence of right ventricular systolic dysfunction (18.6% of a cohort of 119) (20,21). This finding prompted investigators in the INSTAGE trial to assess the utility of combining sildenafil 20mg three times daily with nintedanib 150 mg twice daily over 12 and 24 weeks with the primary endpoint of assessing changes in SGRQ (22).

The INSTAGE trial overview

The INSTAGE trial was a randomized, double-blind, parallel-group trial of 274 patients with IPF with a DLCO ≤35% who were randomized in a 1:1 fashion, receiving nintedanib at a dose of 150 mg twice daily plus sildenafil at a dose of 20 mg three times daily (137 patients) or nintedanib at a dose of 150 mg twice daily plus placebo three times daily for 24 weeks (136 patients). The primary endpoint was the change from baseline in the SGRQ total score at week

12 and 24. Enrollment required patients to be older than 40 years of age with a diagnosis of IPF per the 2011 American Thoracic Society (ATS) consensus criteria and concurrent DLCO ≤35% predicted. Similar to the INPULSIS 1 and 2 trials, HRCT chest was required and surgical biopsy, if available, to demonstrate a diagnosis of IPF. Baseline demographics were no different between the two groups. Approximately 40% in ear arm had echocardiographic sign of right heart dysfunction (44.5% nintedanib-sildenafil *vs.* 41.2% nintedanib-placebo). Right heart dysfunction, which was defined as right ventricular systolic dysfunction, right ventricular hypertrophy, right ventricular dilation, right atrium enlargement or paradoxical septum motion. 32 patients (23.4%) in the nintedanib-sildenafil and 33 (24.3%) patients in the nintedanib-placebo discontinued medications prematurely, with 105 treatment and 103 placebo patients completing the prescribed regimen. The trial was largely a negative study, and did not achieve the primary endpoint of improvement in SGRQ (22).

Importantly, there is high degree of discordance between the INSTAGE trial design when compared to the predecessor trials. Approximately one-third of the patients had demonstrated emphysema (37.2% nintedanib-sildenafil *vs.* 33.1% nintedanib-placebo) in the INSTAGE trial. As noted above, presence of emphysema was not an inclusion criterion for the INPULSIS 1 and 2 trials. The INSTAGE trial was under-powered based on the size of patient population, and shorter duration of the trial compared to INPULSIS 1 and 2. Notably, the SGRQ will not change as much in more advanced cases of IPF, and the window of assessing a determinable effect of treatment on SGRQ may not have been available within the trial window. This is evident by the adjusted mean change in SGRQ being lower in the nintedanib-placebo arm in the INSTAGE trial compared to nintedanib arm of the INPULSIS 1 and 2 trials. This trial also had higher fatal adverse events in the nintedanib-placebo arm compared to the nintedanib arm of the INPULSIS 1 and 2. Even with the study participants (61 treatment arm and 56 placebo arm) who had echocardiographic evidence of right ventricle (RV) dysfunction, it is not clear the role of nintedanib-sildenafil. The study evaluated B-type natriuretic peptide (BNP) as a surrogate as opposed to echocardiographic parameters like the size of the right atrium, size of the right ventricle or TAPSE. However, it is not indicated from the analysis what percentage of these individuals completed the trial. This is an important consideration given that the individuals with IPF and RV dysfunction are the ones that appear to benefit from adjunctive sildenafil therapy (20). Combination therapy remains a potential therapeutic intervention in IPF management, but it has yet to be adequately assessed by available clinical trial data.

Future directions

There are at least three IPF phenotypes that have been proposed, each of which may portend to a unique clinical course and treatment algorithm (23). These phenotypes, rapidly progressive IPF, combined emphysema and IPF, as well as disproportionate pulmonary hypertension and IPF may be worth considering when designing clinical trials. Likewise, the genome-wide association study (GWAS) data surrounding IPF suggests that in addition to the above noted phenotypic heterogeneity, there is genotypic variability as well (2). Collectively, this data suggests that the applicability of different therapies may vary between patients. Given the paucity of patients available for clinical trials and the urgency often surrounding IPF diagnosis, it is difficult to implement such nuanced consideration when recruiting for clinical trials. Larger scale, multi-center studies are needed in order to sufficiently assess the best therapeutic algorithm for individuals with IPF irrespective of phenotype. Lung transplantation remains the only treatment modality to meaningfully reduce mortality within a select IPF population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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