Nintedanib and Sildenafil in Patients with Idiopathic Pulmonary Fibrosis
Echoes of the Past, Lessons for the Future

Pulmonary hypertension (PH) commonly complicates the course of patients with idiopathic pulmonary fibrosis (IPF). It is associated with impaired functional ability and worse survival (1). The prevalence of PH has a variably reported range between 15% in those with mild to moderate restriction and 84% in those with more advanced disease (2, 3). The high end of this range underscores that most patients are likely to develop PH as their disease progresses. The increasing armamentarium of drugs to treat pulmonary arterial hypertension has raised the notion of therapy for PH complicating IPF. It remains uncertain whether the presence of PH is the driver of worse outcomes or whether it is a surrogate for disease severity. If it is indeed an adaptive phenomenon, then ameliorating this may not result in benefit and, worse yet, might result in harm. In contrast, if PH in this setting is a maladaptive response, then targeting it may result in beneficial outcomes.

The INSTAGE (Efficacy and Safety of Nintedanib Co-administered with Sildenafil in Idiopathic Pulmonary Fibrosis Patients with Advanced Lung Function Impairment) study was a prospective, double-blind, randomized clinical trial comparing the benefits of nintedanib with those of nintedanib plus add-on sildenafil in patients with IPF with single-breath DLCO <35% predicted (4). This major inclusionary criterion replicated that of the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) study, which examined the effects of sildenafil versus placebo in patients with IPF (5). Among patients with IPF with DLCO <35%, the prevalence of PH is about 50%, and in this regard, this cutoffpoint represents an enrichment strategy for underlying resting PH (6). The INSTAGE study failed to meet its primary endpoint of a change in the St. George's Respiratory Questionnaire at 12 weeks, but there was a favorable trend in a number of secondary endpoints, including the University of California, San Diego, Shortness of Breath questionnaire, as well as a salutary effect on FVC change. Therefore, although it was a negative study based on the chosen primary endpoint, the INSTAGE study was suggestive of a possible benefit, perhaps best demonstrated in a further enriched population.

In this issue of the Journal, Behr and colleagues (pp. 1505–1512) present a post hoc analysis of the INSTAGE cohort, categorized by the presence or absence of echocardiographic evidence of right heart dysfunction (RHD) (7). This parallels a subgroup analysis of the STEP-IPF study, which demonstrated a significant improvement in 6-minute-walk distance of 99 m in the sildenafil patients who had evidence of RHD on echocardiography (8). Thus, the current subgroup analysis was eagerly anticipated, with the hope that this too might demonstrate a similar difference.
Moreover, a positive result would have further established echocardiography as a complimentary enrichment strategy that, coupled with the \( \Delta V_{\text{FVC}} \), could identify patients with IPF who were likely to benefit from nintedanib. Unfortunately, however, the presence of RHD did not appear to predict benefit from nintedanib plus sildenafil over nintedanib alone. Notably, there was no difference in the effects of combined therapy in those with RHD with regard to the primary endpoint (St. George’s Respiratory Questionnaire score), or secondary endpoints including the University of California, San Diego, Shortness of Breath questionnaire or change in FVC. Indeed, the only difference between the two groups was a change in the B-type natriuretic peptide, with greater stabilization of this biomarker noted in the RHD group receiving combined therapy.

The disappointing message from this subgroup analysis is that those with RHD did not have a magnified response when treated with sildenafil. Why did evidence of RHD on echocardiography not discern an enriched target group for sildenafil therapy? One possible explanation could be insufficient standardization or reader variability between participating centers, as there were no central reads of the echocardiograms. We have certainly learned the value of central adjudication of high-resolution computed tomography scans for inclusion in IPF studies (9). If RHD is to be the target of a subgroup analysis in future clinical trials, then perhaps the same due diligence for echocardiography studies should be applied. This may be especially important in patients with IPF and other forms of advanced lung disease, given the disappointing performance characteristics of echocardiography in determining PH in these patients (10, 11).

On the flip side of this negative subgroup analysis, a potentially heartening message is that if sildenafil does indeed benefit patients with \( \Delta V_{\text{FVC}} < 35\% \), then everyone may be a candidate, not just those with RHD. Indeed, although there may not be evidence of PH at rest, many of these patients with \( \Delta V_{\text{FVC}} < 35\% \) likely do have exercise-induced PH (12). Another possible reason for the failure of echocardiography to discern a target group is that perhaps the quality-of-life benefit suggested by the INSTAGE study was not a result of the vasodilatory properties of sildenafil but, rather, the synergistic antibiotic properties of sildenafil coupled with nintedanib, suggested by the lack of deterioration in the FVC in the dual-therapy group (4).

Whether the suggested benefits of sildenafil together with nintedanib will be seen in a broader population of patients with IPF (e.g., \( \Delta V_{\text{FVC}} > 35\% \)) remains uncertain. Similarly, whether similar or more robust results will be seen with the combination of pirfenidone and sildenafil remains unknown but is eagerly anticipated (13).

The encouraging news from the INSTAGE study, reinforced by this current subgroup analysis, is that patients with IPF with severe disease are a worthy study population. These patients have typically been excluded from prior pharmaceutical clinical trials and have limited options. They are therefore readily available, recruitable, and retainable with a clinical course that is inevitable. In addition, patients with more severe disease do not appear to be at unduly heightened risk for treatment-related adverse events. The inclusion of patients with more severe disease may be a valuable enrichment strategy when evaluating future pharmacologic therapies for IPF. This is especially important in the current era, in which antifibrotic therapy is the established standard of care resulting in a more attenuated disease trajectory. In the phase 3 INPULSIS studies, 30% of patients with mild to moderate disease when receiving nintedanib had a 10% FVC decline at 52 weeks, whereas in the INSTAGE study of patients with more advanced IPF, 36.8% of patients receiving nintedanib met the endpoint of a 10% relative FVC decline or death at 24 weeks (7, 9). Patients with IPF with more advanced disease therefore have a higher event rate, which may enable shorter studies with fewer patients required to power a difference (14). There is often a silver lining and much to be gained from negative studies; in this regard, it is hoped that the INSTAGE study and the current subgroup analysis will help set the stage for future studies focusing on the later part of the IPF journey.

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References
1. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2008;133:746–752.
2. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J 2015;46:1370–1377.
3. Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005;128:2393–2399.
4. Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, et al.; INSTAGE Investigators. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. N Engl J Med 2018;379:1722–1731.
5. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW; Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010;363:620–628.
6. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest 2007;131:657–663.
7. Behr J, Kolb M, Song JW, Luppi F, Schinzel B, Stowasser S, et al.; INSTAGE Trial Investigators. Nintedanib and sildenafil in patients with idiopathic pulmonary fibrosis and right heart dysfunction: a prespecified subgroup analysis of a double-blind randomized clinical trial (INSTAGE). Am J Respir Crit Care Med 2019;200:1505–1512.
8. Han MK, Bach DS, Hagan PG, Yow E, Flaherty KR, Toews GB, et al.; IPFnet Investigators. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest 2013;143:1699–1708.
9. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–2082.
10. Nathan SD, Shlobin OA, Barnett SD, Saggar R, Belperio JA, Ross DJ, et al. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2008;102:1305–1310.
11. Arcasoy SM, Christie JD, Ferrari VA, Sutton MSJ, Zisman DA, Blumenthal NP, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735–740.
12. Arun J, King CS, Shlobin OA, Brown AW, Wang C, Nathan SD. Pulmonary hemodynamic responses predict outcomes in patients with fibrotic lung disease undergoing exercise right heart catheterization testing. Eur Respir J 2018;52:1.
13. Behr J, Nathan SD, Harari S, Wuyts W, Mogulkoç Bishop N, Bouros DE, et al. Baseline characteristics of all patients randomized in a phase
Patterns of VC Decline in Amyotrophic Lateral Sclerosis
A More Robust Prognostication?

Amyotrophic lateral sclerosis (ALS) is a progressive disease of the upper and lower motor neurons that leads to skeletal (including respiratory) muscle weakness. The decrease in respiratory function is commonly assessed by the FVC or slow VC (1), depending on the magnitude of skeletal muscle denervation (2). Complications of functional decline include hypoventilation, pneumonia, and respiratory failure, necessitating initiation of assisted ventilation (3). There have been few descriptions of the different patterns of respiratory function decline in ALS. In this issue of the Journal, Ackrivo and colleagues (pp. 1513–1521) describe the creation of a group-based trajectory model (GBTM) that identified three distinct trajectory groups of FVC in ALS, termed “stable low,” “rapid progressor,” and “slow progressor” (4). Patients were followed until they developed respiratory insufficiency, were lost to follow-up, or completed the study. Five variables were found to have a significant association with the trajectory groups: diagnosis delay, body mass index, bulbar-onset disease, ALS Functional Rating Scale-Revised (ALSFRS-R) orthopnea score, and ALSFRS-R total score. The authors found that compared with the slow progressors group, rapid progressors tended to have longer diagnosis delays, a lower body mass index, more bulbar-onset disease, lower ALSFRS-R total scores, and an orthopnea score. The potential clinical value of this analysis of functional decline is that it can predict the initiation of noninvasive ventilation or tracheostomy, or death. The study is based on an earlier investigation in which Ackrivo and colleagues created and validated a model to be used at baseline “at the bedside” to discriminate patients at high risk of developing respiratory insufficiency at 6 months (5).

A few points regarding the computational model used by the authors should be noted. GBTM involves a procedure in which individuals are gathered into meaningful subgroups that show statistically similar trajectories (6). It is facilitated by use of the Bayesian information criterion, a criterion for model selection among a finite set of models that is based, in part, on the likelihood function. In this study, the authors selected the model in which all groups had stable or declining FVC values while following significantly different trajectories. This strategy left out groups with increasing FVC values (which would be highly unlikely in ALS) while it preserved the least number of groups, which would suggest separate phenotypes. The source population used to derive the group-based trajectory model was a University of Pennsylvania cohort of patients (n = 873). The source population for the validation cohort was a clinical trial database (PRO-ACT [Pooled Resource Open-Access ALS Clinical Trials]) from 23 phase II/III clinical trials (n = 7,461). The pattern of overall functional decline was approximately the same in the derivation and validation cohorts. The main finding was that there were distinct differences between the patterns of VC decline and the curves depicting the proportion of patients who were free of respiratory insufficiency.

Could the different trajectories of VC decline represent genetic variants among ALS patients? Technological advances in gene mapping and DNA analysis have led to the identification of multiple ALS genes. More than 120 genetic variants had been identified as of 2016 (7) and have been reported to be involved in protein homeostasis, RNA homeostasis, and cytoskeletal dynamics (2). Among these, SOD1 (superoxide dismutase 1) and C9ORF72 (chromosome 9 open reading frame 72) are the most common in familial and sporadic cases (2). Skeletal muscle integrity is facilitated by genes that encode proteins that are important for normal cytoskeletal dynamics, including DCTN1 (dynactin 1), PFN1 (profilin 1), TUBA4A (tubulin 4A), and possibly the modifier gene EPHA4 (ephrin type-A receptor 4), all of which are involved in aspects of axonal structural maintenance and transport. Diminished expression of the latter is associated with longer survival in ALS. This finding may account for the longevity of the slow progressors in this study. Other genes have been implicated in protein degradation and neuroinflammation, depositions of intranuclear RNA, impaired nuclear membrane transport, and perturbations of gene transport, all of which contribute to motor neuron degeneration (2). Environmental factors such as a remote history of head trauma (8) and smoking (9) have also been implicated in an increased risk for ALS.

In any analysis of disease onset and rate of progression in different cohorts, a concern may be raised regarding the issue of lead time to diagnosis and first measurement of VC. The time when the patient is first assessed may not be related to the disease itself but rather to social and financial considerations such as distance from the referral center, referral patterns, and insurance coverage, with the result that different time points are designated for individual patients at different stages of their disease. The authors accounted for this potential source of analytical error by using the initial clinic presentation as time zero (as opposed to the date of diagnosis), by controlling for diagnosis delay, and by indicating the time from symptom onset to the first visit and survival since symptom onset. They concluded that the GBTM model’s ability to separate trajectories regardless of when the functional decline was first observed attested to its reliability.