If All That You Have Is a Hammer … : Can We Phenotype Our Patients with Chronic Obstructive Pulmonary Disease?

It took more than a century to move spirometry past its rudimentary beginnings, but in 1947, Tiffeneau and Pinelli described the FEV_1 and its relationship to VC, thereby allowing clinicians to distinguish obstructive from restrictive processes (1). As predictive equations became available and standards for measurement were codified, the FEV_1 not only came to define a broad family of obstructive pulmonary diseases but also became the variable most often chosen to evaluate therapies. This has had far-reaching implications to our approach to a diverse group of pulmonary disorders. In guideline documents of the late 20th century, asthma and chronic obstructive pulmonary disease (COPD) were lumped together despite our awareness that these disorders were different in their manifestations and underlying mechanisms (2). Inhaled medications shown to improve FEV_1 in patients with asthma were assumed by regulators and clinicians to be useful in COPD. The consequences of this "one-size-fits-all" approach can be seen today in the continued overprescription of inhaled corticosteroids for patients with COPD (3, 4).

Tailoring our interventions to specific pathophysiological processes has enjoyed greater progress in asthma than in COPD. The development of mepolizumab for severe asthma nearly foundered until investigators learned to target exacerbation-prone patients whose eosinophil counts in sputum or blood were elevated (5). In the clinical setting, choosing the correct monoclonal for a given asthma phenotype can yield dramatic results. In COPD, the outcome of our tailored therapies is less dramatic. Inhaled steroids yield the best results in COPD when reserved for the exacerbation-prone patient with an elevated blood eosinophil count (6). Roflumilast works best in the "chronic bronchitic" patient with exacerbations (7). But there is one clearly defined COPD phenotype where a tailored intervention is well studied and impactful. Weekly infusions of alpha-1 antitrypsin have been shown to slow the loss of lung function and to preserve lung parenchyma in the small subset of patients with COPD with emphysema secondary to a severe deficiency of alpha-1 antitrypsin (8, 9). Classically, this would be patients with genotype ZZ, the most common severe northern European variant of the disease. Although we have recognized that the MZ carriers of the deficiency with mildly reduced serum levels of alpha-1 antitrypsin are at increased risk for developing emphysema, this has not been factored into day-to-day phenotyping or clinical decision-making.

In this issue of the *Journal*, Ghosh and colleagues (pp. 313–323) report findings that should cause us to reconsider the role of alpha-1 antitrypsin genetics in our phenotyping of COPD (10). Using three large cohorts of well-characterized individuals with COPD, they found that MZ carriers for the deficiency differed in important ways from individuals with normal alpha-1 antitrypsin genetics and obstructive lung disease. Carriers of the deficiency had worse lung function and more emphysema on computed tomographic scans when compared with those without deficiency. Moreover, carriers exhibited more rapid decline in lung function in the one cohort with sufficient longitudinal data to address the matter. Gene expression in the lung also differed between the groups with evidence of heightened peroxisome pathway activity in the alpha-1 antitrypsin carriers.

Like all good research, this large study raises at least as many questions as it answers. What is the mechanism for the findings reported? The most obvious explanation is that the mild antiprotease deficiency in the carriers has led to parenchymal loss via relative protease excess. This apparently plausible explanation ignores our long-standing faith in the 11 micromole protective threshold for alpha-1 antitrypsin. More than a quarter-century after the introduction of augmentation therapy to maintain alpha-1 antitrypsin levels above this threshold, it is difficult to find the evidence underlying this benchmark. Indeed, pharmacodynamic modeling suggest that higher serum levels afford more protection to the severely deficient patient and at least one large scale trial is underway to test that hypothesis (11, 12). But the authors also note that abnormal alpha-1 antitrypsin is proinflammatory and that this may contribute to the negative impact of this otherwise mild deficiency state.

There are limitations to the study, of course. Was there elevation of elastin breakdown products in subjects with mildly reduced alpha-1 antitrypsin levels? Was the accelerated loss of lung function linear or intermittent and related to exacerbations? Did carriers of the deficiency achieve the same acute phase response elevation of alpha-1 antitrypsin levels as their nondeficient counterparts? These and many other questions are beyond the scope of the published study and should stimulate further research.

Will this paper change our clinical approach to COPD? I hope so. This study reminds us once again that there is no single disease called COPD but a variety of injuries and pathophysiologic pathways that can produce persistent airflow limitation. The phenotype described by Ghosh and colleagues is associated with more emphysema and might therefore prompt us to assess oxygen requirements earlier than we might otherwise (13). This risk of unopposed protease activity might prompt increased vigilance to address exacerbations early. But there is no evidence that augmentation therapy plays a role in these mildly deficient patients with COPD. Alpha-1 antitrypsin purified from pooled blood donations remains a scarce and expensive resource. Perhaps the small molecule chaperones or recombinant alpha-1 antitrypsin now in development will become feasible and testable interventions for the carrier with COPD. For now, the study should remind us to screen routinely for the alpha-1 antitrypsin deficiency in all of our newly diagnosed patients with COPD, so as to detect the severely deficient individuals who are usually diagnosed late or not at all. As we do so, we will come to recognize the more common mildly deficient carrier, a distinct phenotype of COPD. ■

Originally Published in Press as DOI: 10.1164/rccm.202111-2663ED on December 15, 2021

Author disclosures are available with the text of this article at www.atsjournals.org.

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Making Sense of Phase II Trials for Investigational Agents in COVID-19

The Case of Ilomedin in Mechanically Ventilated Patients

Feasibility trials are underappreciated, although they are an essential part of building a solid evidence-based practice (1). Such studies are designed to test important aspects of future larger clinical trials, including plausible inclusion rate, logistic procedures (drug supply and data collection), site monitoring, and early safety in the population of interest, among others. By their own nature and comparatively small sample size, feasibility trials can be challenging to interpret for preliminary efficacy results. A "positive" finding from a small trial can be overinflated ("winners curse" [2] or publication bias), whereas a "neutral" result is frequently only the reflex of low power. Reckless interpretation of data leads to euphoria or deception, and the former inevitably leads to the latter.

In this issue of the *Journal*, Johansson and colleagues (pp. 324–329) present the results of a well-conducted feasibility/phase II trial that excels at being exactly what it was designed to be. The authors randomized 80 patients with coronavirus disease (COVID-19) on mechanical ventilation and with high (>4 ng/ml) thrombomodulin to receive intravenous prostacyclin or placebo (3). The trial's rationale is based on the premise that prostacyclin could attenuate endotheliopathy, mainly through local vasodilatation and platelet adhesion inhibition; therefore, the use of a serum thrombomodulin threshold for inclusion is a clever predictive enrichment strategy used by the authors. The primary endpoint was days alive and free of mechanical ventilation, an endpoint that is patient-centered, may maximize power owing to greater granularity

Originally Published in Press as DOI: 10.1164/rccm.202111-2593ED on December 15, 2021