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Chronic Cough in Idiopathic Pulmonary Fibrosis: The Same Difference?

The world is divided into lumpers and splitters, if this is not a *non sequitur*. According to the American Lung Association, "Pulmonary fibrosis (PF) is a form of interstitial lung disease that causes scarring in the lungs. There are over 200 different types of PF and in most cases, there's no known cause." I have sat through many meetings where the "diagnosis" of interstitial lung disease (ILD) has been hotly debated. In an international study, Walsh and colleagues asked seven ILD multidisciplinary team meetings to comprehensively review 70 patients with ILD, and, although agreement on the diagnosis idiopathic pulmonary fibrosis (IPF) was fair (they say good) (weighted $\kappa = 0.71$), other categories fared less well (1). Kolb and Flaherty and others have suggested a simplification with the identification of a progressive fibrotic phenotype of ILD, irrespective of primary diagnosis (2). This view is supported by the INBUILD (Nintedanib in Progressive Fibrosing Interstitial Lung Disease) study demonstrating the beneficial effects of nintedanib in progressive fibrosing ILDs of various supposed etiologies (1). In the therapeutics of ILD, perhaps lumping is preferable to splitting.

In patients with chronic cough, a similar paradigm has unfolded. Chronic cough in the absence of other obvious pulmonary pathology was originally ascribed to three existing diseases: asthma, postnasal drip, and gastroesophageal reflux. However, many patients failed to respond to conventional treatments for these conditions, leading to prolonged morbidity over many years. The concept of cough hypersensitivity syndrome—aberrant vagal and central neuronal activation of the cough reflex—was suggested as the overarching etiology in such patients (3). International guidelines now recognize chronic cough as a disease with different phenotypes (4). Again, the proof of this lumping approach has been demonstrated by the results of COUGH-1 (A Study of Gefapixant [MK-7264] in Adult Participants with Chronic Cough [MK-7264-027]) and COUGH-2 (A Study of Gefapixant [MK-7264] in Adult Participants with Chronic Cough [MK-7264-030]) (5). Here, more than 2,000 patients with the typical demographics of patients with chronic cough (predominantly middle-aged women) were randomized to an entirely novel therapeutic approach: blockade of the ATP receptor. Gefapixant, a P2X3 antagonist, demonstrated significant reductions in objective and subjective cough versus placebo and a greater than 60% reduction in cough from baseline.

Where these two worlds collide is in the cough associated with IPF. Approximately 80% of patients with IPF report cough as a significant symptom, and it is a predictor of morbidity and mortality (6). So, is the coughing in IPF a manifestation of cough hypersensitivity, or is it an epiphenomenon of the disease? Cromolyn

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sodium is widely considered as a stabilizer of mast cells, but it has many other activities on inflammatory cells and afferent C fiber neurones. A novel, concentrated formulation of inhaled cromolyn sodium (PA-101) was developed and tested in a randomized controlled trial (7) in both patients with IPF and those with chronic cough. It reduced patient-reported outcomes and daytime cough frequency by 31% in patients with IPF, but it had no significant effect (6%) in those with the chronic cough. These findings suggested that cough in IPF is of a different etiology from that in chronic cough. The authors proposed that an effect on airway inflammation, as demonstrated by increased numbers of mast cells, neutrophils, eosinophils and their mediators in BAL and in sputum of patients with IPF, may be responsible.

In this issue of the *Journal*, Martinez and colleagues (pp. 1084–1092) present a multicenter, randomized, placebo-controlled phase 2B study of PA-101 (now renamed RVT-1601) in patients with IPF and chronic cough (the SCENIC [A Phase 2b Study of Inhaled RVT-1601 for the Treatment of Persistent Cough in IPF] trial) (8). Unfortunately, the study was terminated early owing to the coronavirus disease (COVID-19) pandemic, but sufficient numbers ($N = 108$) were recruited for the study to be evaluable. The primary endpoint, log-transformed, objectively measured 24-hour cough counts, has become the accepted metric in cough studies. Cough severity visual analog scale and the Leicester cough questionnaire were used to assess patient-reported outcomes.

Unfortunately, the change in the primary outcome of cough counts was similar between placebo (0.66) and the RTV-1601 treatment groups (0.55–0.85). Similar placebo adjusted changes were seen in the patient-reported outcomes. Thus, by conventional statistical thinking, this study fails on the rock of the null hypothesis.

The editors of the *Journal* must be complimented on accepting for publication a negative study. I view negative studies as just as important as ones with a positive outcome. Publication bias bedevils much of the literature, and I am sure I am not the only one to receive a rejection notice for a well-executed study such as SCENIC.

Does this study merit any further consideration? The premature termination of the study severely limited its power, which was at the limits of feasibility even with the planned 180 subjects in a four-way parallel group study. Any treatment effects may have been swamped by the placebo response. Placebo response is well described in studies of neurogenic conditions such as cough, pain, and migraine. Chronic cough phase 2 studies usually report an approximately 30% effect, but such studies are usually performed in centers treating patients with cough who have become accustomed to negative therapeutic trials. In SCENIC, patients were recruited who were naive to cough therapy for their disease. In support of this suggestion, a massive 50% placebo effect was seen in COUGH-1 and COUGH-2 when patients were also recruited from nonspecialist centers. Similar negative results were seen in a trial of gefapixant in IPF (9), where again study numbers were suboptimal.

I hope we have not thrown the baby out with the bathwater, because the potential disease-modifying antifibrotic (10) and antitussive effects of cromolyn sodium cannot be investigated in anything other than a large-scale, long-term trial. ■

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