Dancing with DPP-1: The Inflammatory Tango of Bronchiectasis

The need for new therapies in non–cystic fibrosis bronchiectasis (NCFBE) is outlined in a recent special issue of this journal (1–3). Among numerous disappointing failures in phase 3 studies, recent promise is offered by a novel antiinflammatory treatment approach with brensocatib, DPP-1 (dipeptidyl peptidase-1) inhibition. Positive phase 2 data are published, and unpublished phase 3 findings indicate a reduction in exacerbations: 19% in the 25-mg arm and 21% in the 10-mg arm, accompanied by a slowing of lung function decline (4–6).

In this issue of the *Journal*, Johnson and colleagues (pp. 770–778) examine the impact of inhibiting DPP-1 beyond its primary target, restricting the activation of neutrophil serine proteases including NE (neutrophil elastase), Cathepsin-G, and Proteinase 3 (7). They address the broader inflammatory response, including mucin production using clinical samples from the phase 2 (WILLOW) trial, in which 82 patients in the 10-mg group and 87 from the 25-mg and placebo groups had at least two sputum samples obtained at different time points for comparison (4, 7). The study's primary focus was evaluating SLPI (secretory leukoproteinase inhibitor), α-defensin-3, MPO (myeloperoxidase), MUC5AC, and MUC5B, alongside a commercial inflammatory assay panel of 45 cytokines.

Reduced sputum NE by brensocatib is reported in these subjects, and owing to the downstream effects of NE inhibition, including reduction of SLPI, it was unsurprising and largely anticipated to find higher sputum SLPI in treated patients (4). The biology of α-defensin-3 (human neutrophil peptide-3), however, is poorly understood when compared with NE or SLPI but represents one of a number of small related peptides, secreted primarily by neutrophils as antimicrobials and immune regulators (8, 9). The observed increase in α-defensin-3, discovered by Johnson and colleagues, appears to be a direct effect of DPP-1 inhibition through a reduced degradation by NE and other proteases rather than an indirect one. Their demonstration of NE-driven degradation of α-defensin-3 further supports this notion and indicates that brensocatib does not lead to a widespread, nonspecific downregulation of neutrophil secretory products, further supported by the lack of change in MPO levels in sputum between study groups.

Change to MUC5AC with brensocatib is expected, given the established stimulation of its production by NE (10). In contrast, MUC5B levels were unaffected after brensocatib treatment. Interestingly, however, a recent study of inhaled N-acetylcysteine reduced sputum NE in patients with NCFBE, but, in contrast to the findings of Johnson and colleagues, sputum MUC5B significantly increased, implying that NE reduction alone does not explain the full narrative in relation to MUC5B production (7, 11). Although MUC5AC and MUC5B are structurally similar, deletion of the former in mice fails to result in severe lung disease, whereas deletion of the latter results in impaired mucus transport, reduced resistance to infection, and significant accumulation of inflammatory cells in the airways (12, 13). The differing effect on MUC5AC and MUC5B by brensocatib and N-acetylcysteine, respectively, may therefore hold clinical significance, and further dissection of mucin-related pathways in the airway to personalize clinical responses remains an important area for future research.

Interpreting changes to the measured inflammatory cytokines is more complex, owing to the number and variety studied. Although Johnson and colleagues found clear trends toward an upregulation of chemokines enhancing host defenses, even more interesting questions should consider underlying mechanisms driving this phenomenon and if the post-brensocatib inflammatory milieu is more reflective of a "healthy" profile than that of the placebo group (7). With respect to how DPP-1 inhibition drives enhancement of host defenses, a key issue to resolve is whether this occurs directly or indirectly. As brensocatib treatment is associated with fewer exacerbations, and exacerbation events in themselves produce significant inflammatory change, including suppression of adaptive inflammatory responses, an indirect effect is certainly a strong possibility. Although the authors point out that the inflammatory markers demonstrating the greatest responses most closely correlate with baseline NE, this does not confirm that reduced NE activity was indeed responsible for the observed increases. As to the question of which profile is healthier, normal (healthy) individuals do not generally produce sputum, and hence we are left with associations between inflammatory profiles and clinical NCFBE phenotypes, with continuing uncertainty over whether any measured change is maximal or not.

Establishing a biological endpoint that is easily and affordably measurable while serving as a surrogate for long-term therapeutic response is a key goal for the NCFBE field moving forward. Although sputum NE is certainly a leading candidate for this role, our current ability to use it to guide therapeutic decisions is speculative and yet unproven. It therefore remains challenging to determine the optimal brensocatib dose at the individual patient level, and the current study does not provide any fresh data for guidance. For most of the changes observed, there is evidence of an effect favoring the 25-mg dose; however, the effect size remains small and of uncertain significance. Given that the phase 2 and reported phase 3 results show similar effect sizes at both doses with respect to exacerbations, further research is clearly warranted to address this. Although it is likely that many patients will have an adequate treatment response at 10 mg, there is likely a subset of patients who would benefit from the higher 25-mg dose and, equally, a subset who fail to get any therapeutic benefit at either dose. The possibility of additive and/or synergistic effects with other therapies, including N-acetylcysteine and/or inhaled antibiotics, adds additional complexity at the individual

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patient level, further emphasizing the pressing need for a tool to guide individualized therapy and obtain the optimal clinical and health economic benefits that this exciting therapeutic era in NCFBE brings. ■

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Using Symptoms Together with Peak Flow Measurement to Identify Patients Who Require Spirometry to Confirm Chronic Obstructive Pulmonary Disease

The problem of access to spirometry is worldwide, not just in the resource-limited setting of the study reported in this issue of the *Journal* by Checkley and colleagues (pp. 779–788) (1). It is labor intensive in terms of time and technician skill set in all health economies, so efficient case finding is required. Measurement of peak expiratory flow (PEF) is insufficiently well correlated with FEV_1:FVC ratio to be an adequate surrogate, but the development of the Chronic Obstructive Pulmonary Disease Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk showed that PEF, when combined with an assessment of symptoms, provides better sensitivity and specificity to identify patients who may have spirometrically confirmed chronic obstructive pulmonary disease (COPD) (2).

But first, why is case finding needed? COPD is not like hypertension or type 2 diabetes, which remain silent until complications occur. COPD causes symptoms that are directly related to the disease, but these are either ignored or misattributed (e.g., to smoking or age), or their significance is not understood (e.g., exacerbations). In fact, COPD symptoms develop very early in the disease course, as demonstrated in the BEACON (British Early COPD

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