

Positioning dipeptidyl peptidase-1 inhibitors in bronchiectasis: no drug is an island

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Bronchiectasis is a chronic inflammatory airway disease characterized by daily symptoms and irreversible bronchial enlargement. Bronchiectasis management has historically relied on off-label therapies, reflecting decades of insufficient evidence.¹ Lack of approved treatments has led to global variability in clinical practice, longstanding dissatisfaction among patients, and challenges, including limited regulatory oversight, clinical ambiguity due to the absence of robust evidence, ethical uncertainty for clinicians, and safety concerns due to scarce long-term data. Our understanding of bronchiectasis has evolved significantly in recent years, driven by both large-scale epidemiological data from international registries^{2,3} and advances in the understanding of disease mechanisms. Neutrophilic inflammation has lately emerged as a key marker of disease activity and severity.⁴ Innovative therapeutics targeting neutrophilic inflammation, such as oral dipeptidyl peptidase-1 (DPP-1) inhibitors, demonstrated promising results in patients at risk for exacerbations despite optimized clinical management and airway clearance techniques in well-designed, multinational, phase 2 and 3, randomized controlled trials.^{5–8} The recently published ASPEN trial confirmed that the DPP-1 inhibitor brensocatic significantly reduces the frequency of exacerbations and attenuates lung function decline in frequent exacerbators, while maintaining a favorable safety profile.⁶ Similarly, the phase 2 trials AIRLEAF and SAVE-BE confirmed the efficacy of 2 other DPP-1 inhibitors in modulating neutrophilic inflammation and reducing exacerbation rates in patients at risk for future exacerbations, supporting the therapeutic potential of this drug class.^{7,8} With the recent decision by the U.S. Food and Drug Administration (FDA), brensocatic has become the first drug approved for bronchiectasis, offering renewed hope to the global bronchiectasis community.⁹

The approval of a DPP-1 inhibitor marks a pivotal milestone in bronchiectasis management, but also underscores the forthcoming complexities clinicians will inevitably face in therapeutic decision-making. The major challenge lies in strategically positioning new in-label drugs into an existing off-label treatment landscape that will likely be dominated by long-term macrolides and inhaled antibiotics even in the near future. This exciting yet unpredictable scenario raises several key considerations.

First, factors such as drug availability, national regulatory decisions, cost allocation, and health system policies will critically shape access to DPP-1 inhibitors worldwide. These disparities may

affect treatment equity, exacerbate regional imbalances in clinical care, and even drive health-related migration in some countries as patients seek therapies unavailable in their own healthcare settings. Optimizing the positioning of DPP-1 inhibitors will, thus, require not only solid clinical evidence but also coordinated health policy efforts to ensure equitable access.

Second, DPP1 inhibitors effectively reduce the rate of bronchiectasis exacerbations regardless of baseline characteristics or subgroup stratification.⁶ The absence of identifiable phenotypes or biomarkers predicting differential benefit prevents, to date, identification of specific patient categories such as “responders,” “super-responders,” or “non-responders.” While broad efficacy is undoubtedly advantageous, it simultaneously complicates the strategic positioning of DPP-1 inhibitors in clinical practice, raising questions on their optimal use. This challenge is not exclusive to DPP-1 inhibitors but also extends to both macrolides and inhaled antibiotics, where predictors of success or failure remain lacking in large patient populations. From this perspective, the development of predictive tools or biomarkers, ideally derived from real-world studies, becomes essential to enhance patient selection and ensure cost-effective, individualized therapies.

Third, once long-term treatments—whether DPP-1 inhibitors, macrolides, or inhaled antibiotics—have been initiated, clinical decision-making should consider patient’s response. Although effective, these interventions may leave residual disease activity, prompting both patients and physicians to consider switching to an alternative long-term therapy, adding a second intervention, or continuing the current regimen with dose adjustments. Evidence suggests that adding a DPP-1 inhibitor to ongoing macrolide or inhaled antibiotic treatment can further reduce exacerbation rates.⁶ For such reason, a minimum period of 12 months of treatment should be considered before assessing response. However, sub-population analyses from the ASPEN trial showed no interaction between DPP-1 inhibitors and macrolides, suggesting that these 2 interventions may act through independent, non-overlapping mechanisms. Evaluating the safety and efficacy of adding a macrolide or inhaled antibiotic to ongoing DPP-1 inhibitor therapy in cases of partial response is a clinical priority. This question should be addressed in future real-world studies enrolling patients with persistent disease activity after initiation of one intervention to

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avoid practice variability and minimize the risk of suboptimal patient outcomes.

Fourth, as bronchiectasis enters its therapeutic era, a shifting paradigm may parallel that observed in heart failure management. In cardiology, clinicians have long adopted a strategy of layered pharmacotherapy, combining ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and SGLT-2 inhibitors in the same patient despite the absence of tools predicting individual response.¹⁰ While combining treatments in patients at high risk of exacerbations is likely to be beneficial, our view is that such combinations should ultimately be guided by precision approaches based on patient endotypes rather than applied uniformly. The sequential or combined use of multiple agents in bronchiectasis without predictive biomarkers risks fostering prescribing practices driven primarily by exacerbation frequency rather than by well-defined, personalized treatment strategies. Without validated tools for phenotyping or endotyping, bronchiectasis management may mirror cardiology's layering model without clarity on individual or synergistic effects. The approval of brensocatib by the FDA should therefore be seen not only as a major treatment milestone in bronchiectasis but also as a catalyst for the development of therapeutic algorithms and robust real-world effectiveness data.

In light of these considerations, a pressing question emerges: how will future international guidelines provide recommendations on the positioning of the 3 long-term interventions (brensocatib and other DPP-1 inhibitors, macrolides, and inhaled antibiotics) in bronchiectasis, given that the FDA is not directly responsible for regulating the practice of medicine? Based on our clinical experience and the data available from clinical trials, we would consider brensocatib primarily for bronchiectasis patients who are frequent exacerbators despite optimized standard care (including respiratory physiotherapy, management of underlying bronchiectasis etiologies and comorbidities). However, both patients and guideline task forces should critically evaluate multiple factors when formulating recommendations on the positioning of the 3 aforementioned long-term interventions, including the robustness of the evidence, costs, potential interactions, underlying phenotypes, endotypes and microbiology, antibiotic stewardship, and, importantly, patient preferences. Most crucial will be understanding how these 3 therapies interact in real-world practice. After all, to borrow from John Donne, and later echoed by Ernest Hemingway, no drug is an island.

Author contributions

MN and SA contributed to the conception of the viewpoint. MN drafted the initial version of the manuscript. MN and SA critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as [supplementary material](#).

Artificial intelligence disclaimer

No artificial intelligence tools were used in writing this manuscript.

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