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PLAIN LANGUAGE SUMMARY

The convergent pathway of obstructive lung disease: the disease-modifying potential of dipeptidyl peptidase 1 inhibition in COPD, asthma and bronchiectasis overlap

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Article available at: https://doi.org/10.7573/dic.2025-11-3

The challenge: overlapping lung diseases and uncontrolled inflammation

For many years, clinicians treated chronic lung diseases like asthma and chronic obstructive pulmonary disease (COPD) as separate problems. However, we now know that these conditions often overlap, especially with bronchiectasis — a condition where the airways are permanently damaged and widened.

This overlap creates severe syndromes (asthma–bronchiectasis overlap (ABO) and bronchiectasis–COPD overlap syndrome (BCOS)) that are characterized by:

- More frequent and severe flare-ups (exacerbations).
- Faster decline in lung function.
- Higher risk of death.

The main reason these patients get so sick is a problem shared by all three conditions: uncontrolled inflammation driven by white blood cells called neutrophils.

The core problem: the 'vicious vortex'

When the lungs try to fight off infections (which are common in these diseases), the immune system sends in huge numbers of neutrophils. These cells carry a toxic payload of enzymes, primarily neutrophil elastase (NE). While NE is meant to kill bacteria, it also acts like 'acid' on the patient's own lung tissue.

This damage creates a 'vicious vortex':

1. NE destroys the airway structure, leading to the permanent damage of bronchiectasis.
2. NE makes the lungs produce excessive mucus, which traps more bacteria.
3. More bacteria lead to more neutrophil influx, which releases more NE, starting the destructive cycle all over again.

Traditional treatments, like standard inhalers and even some modern biologic drugs used for asthma, do not effectively stop this neutrophil-driven destruction, leaving this high-risk patient group with few options.

The solution: disarming the neutrophils

Brensocatib represents a new way to treat these diseases by targeting the root cause of the damage not just the symptoms. It is a medicine that works upstream in the body, specifically in the bone marrow where neutrophils are made.

- How it works: brensocatib stops an enzyme called dipeptidyl peptidase 1 (DPP1). This enzyme is the 'master switch' that activates the destructive NE inside the neutrophils before they leave the bone marrow.
- The result: neutrophils are still made, and they still travel to the lungs to fight infection (so the immune system remains largely intact). However, they are now 'disarmed' because they carry almost no active NE.

The evidence: stopping disease progression

A large study (the phase III ASPEN trial) proved this strategy works in patients with bronchiectasis:

- Fewer exacerbations: patients taking brensocatib had a significant reduction in the rate of pulmonary exacerbations.
- Protecting the lungs: most importantly, the 25 mg dose significantly slowed the decline in lung function (forced expiratory volume in 1 second (FEV_1)). This is a game-changer because it suggests the drug is not just treating symptoms but actually modifying the course of this progressive, destructive disease.

Because the drug works by stopping the damage shared by COPD, asthma and bronchiectasis overlap, it is now seen as a promising new therapy for the sickest patients with these neutrophilic endotypes, offering hope for long-term lung preservation.