Brensocatib: An Anti-neutrophil Elastase Drug With Potential in the Management of Bronchiectasis

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Bronchiectasis is a reversible inhibitor of dipeptidyl peptidase 1, the enzyme that activates neutrophil serine proteases. In a phase II study in patients with bronchiectasis with frequent exacerbations, brensocatib was shown to reduce sputum elastase levels compared with placebo and, importantly, to reduce the number of pulmonary exacerbations and prolong the time to exacerbation without increasing infections or with significant side effects. A larger phase III study is underway and, if it confirms these findings, may pave the way for a novel treatment for bronchiectasis.

Keywords
Bronchiectasis, dipeptidyl peptidase I, Haemophilus influenzae, neutrophil extracellular traps, Pseudomonas, serine protease inhibitors

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Brensocatib:

Brensocatib is a small-molecule, reversible inhibitor of the lysosomal cysteine proteinase dipeptidyl peptidase 1 (DPP1, also known as cathepsin C). DPP1 activates neutrophil serine proteases, and its inhibition within the bone marrow reduces the levels of what may be excessive neutrophil and airway serious proteases, including neutrophil elastase. Studies in human neutrophils have shown that brensocatib significantly inhibits the activation of neutrophil serine proteases, resulting in a decreased elastolytic ability of the cells in vitro. Furthermore, brensocatib has been shown to produce concentration-dependent reductions in both the percentage of neutrophils with membrane-bound PR3 and the overall surface expression of PR3 in vitro.

Brensocatib was found to be a safe and side-effect-free agent in animal studies and in short-term studies with healthy human volunteers. As such, it was further investigated in the WILLOW trial, a multicentre, international, phase IIa study in patients with bronchiectasis and at least two exacerbations in the previous year.

The WILLOW trial randomized 256 patients in a 1:1:1 ratio to receive 10 mg brensocatib, 25 mg brensocatib or placebo once daily for 24 weeks, with time to the first exacerbation as the primary outcome. Brensocatib resulted in a significantly prolonged time to exacerbation: the 25th percentile of the time to the first exacerbation was 67 days in the placebo group compared with 134 days in the 10 mg brensocatib group (p=0.03 versus placebo) and 96 days with 25 mg brensocatib group (p=0.04). However, the absolute rate of exacerbations was significantly reduced only for the 10 mg dose, and brensocatib had no effect on forced expiratory volume in 1 second. Brensocatib reduced sputum neutrophil elastase activity but did not improve quality of life.

If the benefits seen in the WILLOW trial are replicated in ASPEN, and if regulatory approval is then granted, brensocatib, as a simple, single, daily tablet with (as yet) few side effects, will be a major addition to the treatment options available for patients with bronchiectasis.

To what extent other direct inhibitors of airway serine proteases and perhaps other modulators of inflammation will be important remains to be seen. Whatever happens, someone born today is unlikely to suffer the same complications that Judith Durham endured for more than 75 years.