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JOURNAL CLUB

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ARTICLE

Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med. 2020;383:2127-2137. https://www.nejm.org/doi/full/10.1056/nejmoa2021713.

CLINICAL QUESTION

In patients with non-cystic fibrosis bronchiectasis, does treatment with brensocatib affect time to first exacerbation or frequency of exacerbations?

SUMMARY

Patients with bronchiectasis have frequent exacerbations that are thought to be related to neutrophilic inflammation. The activity and quantity of neutrophil serine proteases, including neutrophil elastase, are increased in the sputum of patients with bronchiectasis at baseline and increase further during exacerbations. Brensocatib (INS1007) is an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), an enzyme responsible for the activation of neutrophil serine proteases.

In a phase 2, randomized, double-blind, placebo-controlled trial, patients with bronchiectasis who had at least two exacerbations in the previous year were randomly assigned, in a 1:1:1 ratio, to receive placebo, 10 mg of brensocatib, or 25 mg of brensocatib once daily for 24 weeks. The primary endpoint was the time to the first exacerbation during the 24-week treatment period. Secondary endpoints included the rate of exacerbations (number of events per patient-year), the change from screening in the percent predicted FEV1 after bronchodilator use, the change from baseline in the Respiratory Symptoms score on the Quality of Life Bronchiectasis Questionnaire, and the change in the concentration of active neutrophil elastase in sputum from baseline. The trial was conducted at 116 sites across 14 countries.

Key inclusion criteria included: ages 18 to 85 years, clinical history consistent with bronchiectasis and confirmed on chest CT. Patients had to have at least two documented exacerbations in the previous 12 months, a history of chronic sputum expectoration, sputum color at screening that was rated as mucopurulent or purulent and the ability to provide a sputum sample during screening.

Key exclusion criteria included: cystic fibrosis, hypogammaglobulinemia, common variable immunodeficiency, alpha-one-antitrypsin deficiency, primary diagnosis of COPD. Because of potential dental side effects with brensocatib, those with severe periodontitis were excluded. Importantly, patients receiving treatment for NTM-LD were excluded.

Overall, 416 patients were screened and 256 were randomized of whom 87 were assigned to receive placebo, 82 to receive 10 mg of brensocatib, and 87 to receive 25 mg of brensocatib. The 25th percentile of the time to the first exacerbation was 67 days in the placebo group, 134 days in the 10-mg brensocatib group, and 96 days in the 25-mg brensocatib group. Brensocatib treatment prolonged the time to the first exacerbation as compared with placebo (P = 0.03 for 10-mg brensocatib vs. placebo; P = 0.04 for 25-mg brensocatib vs. placebo).

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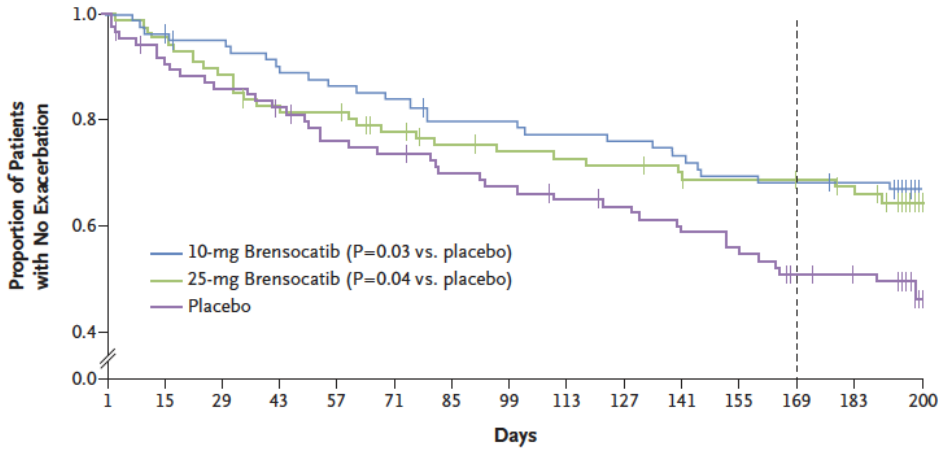

Cumulative No. of Events/ No. at Risk															
10-mg Brensocatib	0/82	3/79	4/76	9/72	11/69	13/66	16/62	16/62	18/60	19/59	21/57	24/54	25/53	25/52	26/4
25-mg Brensocatib	0/87	4/83	10/77	16/71	16/70	19/64	21/60	22/58	23/57	24/56	26/54	26/52	26/52	28/49	29/10
Placebo	0/87	8/78	12/73	15/69	20/63	22/61	25/57	27/55	29/52	30/50	34/47	37/44	40/38	40/37	42/5

The adjusted hazard ratio for exacerbation in the comparison of brensocatib with placebo was 0.58 (95% confidence interval [CI], 0.35 to 0.95) in the 10-mg group (P = 0.03) and 0.62 (95% CI, 0.38 to 0.99) in the 25-mg group (P = 0.046). The incidence-rate ratio was 0.64 (95% CI, 0.42 to 0.98) in the 10-mg group, as compared with placebo (P = 0.04), and 0.75 (95% CI, 0.50 to 1.13) in the 25-mg group, as compared with placebo (P = 0.17).

With both brensocatib doses, sputum neutrophil elastase activity was reduced from baseline over the 24-week treatment period.

The incidence of dental and skin adverse events of special interest was higher with the 10-mg and 25-mg brensocatib doses, respectively, than with placebo.

GROUP OPINION

Reduction of neutrophil serine protease activity with brensocatib in patients with bronchiectasis was associated with improvements in bronchiectasis clinical outcomes. Brensocatib prolonged time to first exacerbation and led to a lower frequency of exacerbations than placebo in patients with bronchiectasis who were considered frequent exacerbators. Decreasing neutrophilic inflammation was associated with potential clinical benefits without causing significant adverse reactions although larger populations will need to be studied in order to better determine the risks of adverse reactions. Patients who were being treated for NTM-LD were excluded so this group will require further investigation in the future. In this Phase 2 randomized placebo-controlled trial, brensocatib appears to be a promising candidate for treatment of bronchiectasis patients who have had at least 2 exacerbations in the previous 12 months. A Phase 3 trial (ASPEN) of brensocatib is now enrolling patients.

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