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Original Research

BRONCHIECTASIS

Phase 3 Randomized Study of the Efficacy and Safety of Inhaled Dry Powder Mannitol for the Symptomatic Treatment of Non-Cystic Fibrosis Bronchiectasis

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Background: **Inhaled dry powder mannitol enhanced mucus clearance and improved quality of life over 2 weeks in non-cystic fibrosis bronchiectasis. This study's objective was to investigate the efficacy and safety of dry powder mannitol over 12 weeks.**

Methods: **Patients with bronchiectasis confirmed by high-resolution CT (HRCT) scan, aged 15 to 80 years, with $FEV_1 \geq 50\%$ predicted and ≥ 1 L participated in a randomized, placebo-controlled, double-blind study. Patients with a negative mannitol provocation test were randomized to inhale 320 mg mannitol (n = 231) or placebo (n = 112) bid for 12 weeks. To further assess safety, the same mannitol dose/frequency was administered to a patient subset in an open-label extension over 52 weeks. Primary end points were changes from baseline at 12 weeks in 24-h sputum weight and St. George's Respiratory Questionnaire (SGRQ) score.**

Results: **There was a significant difference of 4.3 g in terms of change in sputum weight over 12 weeks (95% CI, 1.64-7.00; *P* = .002) between mannitol and placebo; however, this was largely driven by a decrease in sputum weight in the placebo group. This was associated, in turn, with more antibiotic use in the placebo group (50 of 112 [45%]) than in the inhaled mannitol group (85 of 231 [37%]). There was no statistical difference between the groups (*P* = .304) in total SGRQ score (mannitol, −3.4 points [95% CI, −4.81 to −1.94] vs placebo, −2.1 points [95% CI, −4.12 to −0.09]). In a subgroup study (n = 82), patients receiving mannitol showed less small airway mucus plugging on HRCT scan at 12 weeks compared with patients receiving placebo (*P* = .048). Compliance rates were high, and mannitol was well tolerated with adverse events similar to those of placebo.**

Conclusion: **Because the difference in sputum weights appears to be associated with increased antibiotic use in the placebo group, a larger controlled study is now required to investigate the long-term mannitol effect on pulmonary exacerbations and antibiotic use.**

Trial registry: **ClinicalTrials.gov; No.: NCT0027753; URL: www.clinicaltrials.gov**

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Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; BSQ = Bronchiectasis Symptoms Questionnaire; CF = cystic fibrosis; HRCT = high-resolution CT; ITT = intention-to-treat; LCQ = Leicester Cough Questionnaire; OLE = open-label extension; SGRQ = St. George's Respiratory Questionnaire

Bronchiectasis is a chronic lung condition in which damage to the airways causes abnormal dilatation of the bronchi and impaired mucociliary clearance.[1] The increase in mucus accumulation is accompanied by chronic cough and recurrent infections,[1] often resulting in significant morbidity and mortality.[2] The incidence of non-cystic fibrosis (CF) bronchiectasis varies from approximately 3.7 in 100,000[3,4] to up to 1,470 in 100,000 per year in remote and less-affluent populations.[5] However, because of the coexistence of other chronic respiratory diseases, it is likely that many people with non-CF bronchiectasis remain undiagnosed and undertreated.[1,6]

Airway clearance techniques are strongly recommended to help clear secretions.[7,8] Pharmacologic agents such as mucolytics, osmotic agents, bronchodilators,

and antibiotics may also be employed. However, few well-controlled clinical studies have investigated the efficacy and safety of these agents.[7] Recent focus has been on the osmotic agents (hypertonic saline and mannitol) that increase airway hydration.[9-15]

Mannitol is a naturally occurring sugar alcohol.[9] It improves mucus clearance both acutely[16,17] and over 24 h in non-CF bronchiectasis[18] and improves mucus clearance and FEV_1 in patients with CF.[10,11,19] The mechanism by which mannitol increases mucus clearance is unclear. It is likely that water drawn into the airway lumen in response to the osmotic gradient favorably changes the physical properties of the mucus.[9,17,20] Improvement in hydration and a reduction in the surface and rheologic properties of mucus are postulated to increase mucociliary and cough clearance.[9,17,20]

We have previously reported the results of two open-label pilot studies that demonstrated that mannitol, inhaled daily[9] or bid[12] for up to 2 weeks, reduced the surface tension of mucus,[9] improved small airways function (measured by impulse oscillometry),[21] and improved the health-related quality of life in a small group with bronchiectasis.[9,12] The aim of this randomized, placebo-controlled, double-blind study was to determine the impact of mannitol on mucus clearance and quality of life in patients with non-CF bronchiectasis. In addition, an open-label extension (OLE) study was designed to assess the long-term safety of mannitol administered over 52 weeks.

Materials and Methods

Subjects

Table 1 lists the inclusion and exclusion criteria for study patients recruited from 22 sites, approved by the relevant ethics committees in Australia, New Zealand, and the United Kingdom (e-Appendix 1).

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Treatment and Materials

Dry powder mannitol (Bronchitol; Pharmaxis) was supplied in 40-mg capsules. Placebo capsules (10 mg) (Roquette) consisted of nonrespirable (approximately 70 μm) United States Pharmacopeia/British Pharmacopoeia good manufacturing practice crystalline mannitol.

Mannitol and placebo were administered by a dry powder device (Plastiape). An Aridol diagnostic kit (Pharmaxis) was used to exclude patients with bronchial hyperresponsiveness to mannitol.[22] The Acapella device (DHD Healthcare) was used to obtain 24-h sputum samples.[23]

Study Design

The study was randomized, parallel, placebo-controlled, and double-blind, with a 12-week intervention phase (Table 2) and an OLE for up to 52 weeks of total treatment. The double-blind study phase included a screening visit and then baseline, week 6, and week 12 patient visits. At baseline, patients underwent mannitol provocation (e-Appendix 2)[22] and lung function testing[24,25] (e-Appendix 3). The 24-h sputum weight was recorded, and patients completed the St. George's Respiratory Questionnaire (SGRQ) (e-Appendix 3).[26] All staff, patients, and caregivers were blinded to treatment assignment.

At the end of the blinded phase, some participants in Australia and New Zealand were given the option to continue the OLE safety study and receive mannitol, 320 mg bid, for a total of 52 weeks, provided they exhibited no clinically significant deterioration in biochemistry/laboratory results during a subsequent 4-week run-in period. The OLE visits were at 4 weeks for the first open-label visit and thereafter every 9 weeks, with an additional 12-week period at the end prior to a washout for those who had originally been on placebo.

Study Evaluation

Primary End Points: Two primary efficacy measures, assessed during the double-blind phase, were absolute change in (1) wet sputum weight and (2) SGRQ score at week 12 from baseline. At each study visit, the 24-h sputum collected from the start of the prior day was weighed and recorded, and patients completed the SGRQ (e-Appendix 3).

Secondary End Points: Secondary end points (e-Appendix 3) to assess the impact of mannitol included the following:

1. Bronchiectasis symptoms using the Bronchiectasis Symptoms Questionnaire (BSQ) (a study-specific questionnaire)
2. Cough severity using the Leicester Cough Questionnaire (LCQ)[27]
3. Lung function testing (including spirometry, multibreath nitrogen washout, and carbon monoxide diffusing capacity)
4. Antibiotic use for flare of disease and pulmonary exacerbations (using a nonvalidated study-designed protocol definition based on the Fuchs definition)[28]
5. High-resolution CT (HRCT) scan[29,30] substudy at seven centers (n = 82) using both the modified Bhalla scoring system and quantitative image analysis
6. Microbiology and inflammatory markers on sputum samples
7. Exercise capacity using the shuttle walking test[31]
8. Safety (including adverse events [AEs], spirometry to assess potential bronchoconstriction, and emergence of new pathogens [qualitative microbiology])

Statistical Analysis

The sample size was based on the SGRQ, with an 80% power to detect a difference of six points (chosen based on previous studies)