Effect of N-acetylcysteine on Exacerbations of Bronchiectasis (BENE): a randomized controlled trial

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MATERIALS AND METHODS

Study subjects

Bronchiectasis was diagnosed based on the clinical manifestations and high-resolution computed tomography scans. Patients were screened for potential eligibility at five general hospitals in Shandong Province of China from April 1, 2014 to December 31, 2016. The inclusion criteria were as follows: 1) subjects were aged 18–80 years old; 2) a diagnosis of idiopathic or post-infective bronchiectasis was made; and 3) patients had at least two exacerbations in the past year and were in a stable state for at least 4 weeks prior to the primary enrollment. Patients were excluded if they fulfilled any of the following criteria: current smokers; cigarette smoking within 6 months; cystic fibrosis or other etiologies (such as immunodeficiency, allergic bronchopulmonary aspergillosis, traction bronchiectasis caused by emphysema, advanced pulmonary fibrosis, etc.); pulmonary function test results showing a forced expiratory volume in 1 s (FEV_1) ≤ 30% of the predicted value; a history of severe cardiovascular or neurological disease; comorbidity with liver disease, kidney disease, malignant tumor, gastric ulcer, or intestinal malabsorption; a known allergy to N-acetylcysteine; pregnancy or lactation (for women); a history of prior macrolide use of more than 1 week; and poor compliance. This study was registered at *ClinicalTrials.gov* (NCT02088216) and was approved by the ethics committees of the five participating hospitals. Informed consents were obtained from all patients.

Study design

The Effect of N-acetylcysteine on Exacerbations of Bronchiectasis (BENE) study was a prospective, randomized, controlled, multicenter clinical trial. The main study objective was to assess whether the long-term use of oral N-acetylcysteine (600 mg, twice daily, 12 months) might reduce the incidence of exacerbations and improve the quality of life in patients with bronchiectasis. According to previous clinical data on exacerbations of bronchiectasis and the inclusion criteria that a subpopulation of bronchiectasis patients with at least two exacerbations in the past year were included in our study, we hypothesized that the baseline frequency of exacerbations was 3. Due

to the lack of clinical data on the efficiency of N-acetylcysteine in the treatment of bronchiectasis, we assumed that approximately 154 patients would need to be enrolled in this study to have 80% power to detect a reduction of at least 33% in the yearly exacerbation incidence, assuming a two-sided α level of 0.05 and 20% attrition.

Methods

The sequence was generated by a computer, and the patients who met the criteria were allocated in a 1:1 ratio to receive either oral N-acetylcysteine (600 mg, twice daily) or control (receive as-needed therapy) for 12 months. All the participants were followed for up to 12 months. Outpatient and/or telephone visits were obtained for the primary and secondary outcomes at 1, 3, 6, 9, and 12 months. Moreover, compliance and adverse reactions were also documented. The treatment strategy based on current guidelines was instituted for patients with exacerbations. Meanwhile, patients in the N-acetylcysteine group were also required to receive oral N-acetylcysteine (600 mg, twice daily) during the study period. For the control group, interventions would be discontinued once the patient recovered from the exacerbation. Maintenance therapies that had already started in patients with pulmonary ventilation dysfunction prior to enrollment, such as short-acting bronchodilators, long-acting bronchodilators, inhaled glucocorticoids, or theophylline, were continued during the study. However, the use of other mucolytics or expectorants, antioxidant agents, or vitamins with antioxidant properties was not recommended.

Study end-points

The primary end-point was the incidence of exacerbations in a year, defined as the number of all exacerbations associated with bronchiectasis within one year. An exacerbation of bronchiectasis is defined by the British Thoracic Society guidelines for bronchiectasis. Details regarding symptoms of an exacerbation such as dyspnea, sputum volume (collected over 24 h), sputum properties, fever, and persistent upper respiratory tract infection were also documented by site investigators from all centers.

Secondary end-points included the time to the first exacerbation, 24-h sputum volume, lung function, inflammation indices, quality of life (assessed by COPD assessment test score, CAT score), and adverse events. The volume of 24-h sputum

was measured by a graduated cylinder marked in milliliters. Eligible sputum samples were used for testing sputum microbiological culture and antibiotic resistance. Pulmonary function was assessed three times before recruitment, and the maximum value was used for analysis. Following treatment, pulmonary function was reassessed for forced vital capacity (FVC), FEV_1, percentage of predicted FEV1, FEV_1/FVC ratio (FEV_1/FVC), and inspiratory capacity, etc. Inflammatory markers including serum C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were tested at each visit. The severity of bronchiectasis was quantified by high-resolution computed tomography (HRCT), and the number of lobes involved was counted according to the modified Reiff grade. Furthermore, the degree of dyspnea was assessed by the modified Medical Research Council (mMRC) scale.