CHEST

Original Research

BRONCHIECTASIS

Addition of Inhaled Tobramycin to Ciprofloxacin for Acute Exacerbations of *Pseudomonas aeruginosa* Infection in Adult Bronchiectasis*

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Rationale: **_Pseudomonas aeruginosa_ lung infection in patients with bronchiectasis, a chronic airway disease that is characterized by episodes of exacerbation, is associated with more severe disease and a higher utilization of health-care resources. Inhaled tobramycin solution reduces the number of acute exacerbations in patients with cystic fibrosis (CF)-related bronchiectasis with _P aeruginosa_ infection but remains untested in the treatment of exacerbations in patients with non-CF bronchiectasis.**

Objectives: **This study tested the effect of adding inhaled tobramycin solution to oral ciprofloxacin (Cip) for the treatment of acute exacerbations of non-CF bronchiectasis in patients with _P aeruginosa_ infection.**

Methods: **A double-blind, randomized, active comparator, parallel-design study conducted at 17 study centers (5 in the United Kingdom, and 12 in the United States) compared 2 weeks of therapy with Cip with either an inhaled tobramycin solution or placebo in 53 adults with known _P aeruginosa_ infection who were having acute exacerbations of bronchiectasis.**

Measurements: **Clinical symptoms, pulmonary function, clinical efficacy, and sputum microbiology were investigated prospectively.**

Main results: **An inhaled solution of Cip with tobramycin, compared to placebo, achieved greater microbiological response but no statistically significant difference in clinical efficacy at days 14 or 21. Clinical and microbiological outcomes at the test of cure (_ie_, the clinical outcome assessment at day 21) were concordant when an inhaled tobramycin solution was added to therapy with Cip and compared to placebo ($p = 0.01$). Both subject groups had similar overall adverse event rates, but subjects receiving therapy with an inhaled tobramycin solution reported an increased frequency of wheeze (50%; placebo group, 15%).**

Conclusions: **The addition of an inhaled tobramycin solution to therapy with oral Cip for the treatment of acute exacerbations of bronchiectasis due to _P aeruginosa_ improved microbiological outcome and was concordant with clinical outcome; the inability to demonstrate an additional clinical benefit may have been due to emergent wheeze resulting from treatment.**

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Key words: acute disease; bronchiectasis; *Pseudomonas aeruginosa*; tobramycin

Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; CF = cystic fibrosis; Cip = ciprofloxacin; MIC = minimum inhibitory concentration; TIS = tobramycin inhalation solution

Bronchiectasis, which is a permanent dilation of the bronchial walls, often presents with chronic productive cough and chronic bacterial infection. Cycles of recurrent infection, local inflammation, and bronchial wall damage cause and perpetuate bronchiectasis. The initial insult to the lungs is linked to a variety of diseases including immunodeficiencies and local structural damage to the airway.[1,2] Effective management of bronchiectasis requires treatment of the underlying cause (when known) and control of recurrent infection. The current management paradigm includes the promotion of bronchial

hygiene, the reduction of bronchial inflammation, and administration of courses of directed antibiotic treatment aimed at pathogen reduction rather than eradication. These measures can improve patient quality of life,[2,3] but neither can reverse bronchial dilation or cure the underlying pathology.

Bronchiectatic patients can be infected with a variety of bacterial species, including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. Chronic infection with *P aeruginosa* is observed in 24 to 33% of patients with bronchiectasis,[1,4] and is associated with poorer lung function, decreased quality of life, and more frequent hospitalization.[5,6]

It is estimated that 110,000 people in the United States may be receiving treatment for symptoms of bronchiectasis. Twenty percent of these patients account for nearly 80% of the total resources devoted to bronchiectasis management (approximately $600 million annually).[7] These costs can be attributed in part to hospital admission for the treatment of acute exacerbations of bacterial infection that cannot be effectively managed in an outpatient setting. This is a particular problem for persons chronically infected with *P aeruginosa* who have become refractory to management with oral antipseudomonal antibiotics such as ciprofloxacin (Cip) and levofloxacin.

Previously, a single 28-day course of tobramycin inhalation solution (TIS) [TOBI; Chiron Corporation; Emeryville, CA] had been shown[8,9] to dramatically reduce sputum bacterial load and lead to clinical improvement in stable subjects with *P aeruginosa*-infected non-cystic fibrosis (CF) bronchiectasis. Also, successive 14-day cycles of twice-daily therapy with TIS followed by 14-day rest periods had been shown to improve pulmonary symptom scores and quality of life in stable subjects.[3] In previous studies,[3,8] approximately 20 to 30% of subjects experienced reversible respiratory adverse events (AEs) that were associated with the inhalation of TIS. In this blinded, active-controlled study, we attempted to determine the effect of adding twice-daily TIS treatment to a 14-day outpatient regimen of oral Cip for the treatment of acute exacerbations of bronchiectasis in subjects chronically infected with *P aeruginosa*.

Materials and Methods

Design

A double-blind, randomized, active comparator, parallel-design study was conducted in 17 study centers (12 in the United States and 5 in the United Kingdom). Each center received Institutional Review Board or Ethics Committee approval prior to initiation. All subjects provided written informed consent before enrollment; confirmation of consent was obtained at the time of the exacerbation.

Population

Men and women between 18 and 80 years of age with bronchiectasis confirmed by the results of a central reading of a high-resolution CT scan of the chest were considered for this study. Patients with CF, allergic bronchopulmonary aspergillosis, active tuberculosis, glucose-6-phosphate dehydrogenase deficiency, significant renal disease, or a change in steroid therapy within 2 weeks of the acute exacerbation were excluded from the study. A history of chronic *P aeruginosa* lung infection, confirmed by a sputum culture that was positive for *P aeruginosa* both within the 12 months before screening and at the time of screening, was required for eligibility. In addition, the *P aeruginosa* isolate had to show Cip sensitivity (minimum inhibitory concentration [MIC], ≤ 4 μg/mL) at the time of study enrollment.

Subjects were not allowed to use TIS within the 28 days before screening, or at anytime between their screening visit and the time of the exacerbation. Maintenance therapy with antibiotics, including aerosolized antibiotics other than TIS, were allowed up until the time of the exacerbation; however, changes were not permitted within the 14 days before the exacerbation and were not permitted during the study.

Procedures

Data were collected on subjects' baseline disease status during a period of stable respiratory health. Subjects were asked to return at the time of an acute exacerbation. Acute exacerbations were defined using the criteria in Table 1. Subjects who did not experience an acute exacerbation within 2 months of the screening visit were rescreened for study eligibility.

The following three medications were used: (1) 750 mg of oral Cip; (2) 300 mg per 5 mL of TIS aerosolized with a jet nebulizer (PARI LC PLUS; Pari; Starnberg, Germany); and (3) 1.25 mg of quinine sulfate per 5 mL of inhalation solution (*ie*, the placebo) aerosolized a jet nebulizer (PARI LC PLUS; Pari). At the time of exacerbation, subjects were randomized to one of the following two active treatment arms: (1) therapy twice daily with TIS and

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