A Pilot Study of the Safety and Efficacy of Tobramycin Solution for Inhalation in Patients With Severe Bronchiectasis*

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Study objective: **To evaluate the efficacy and safety of tobramycin solution for inhalation (TSI) in patients with severe bronchiectasis.**
Design: **Open-label clinical trial consisting of three treatment cycles (14 days of drug therapy, and 14 days off drug) and an additional 40-week follow-up by chart review.**
Setting: **Nine clinical sites throughout the United States.**
Subjects: **Forty-one adult patients (≥ 18 years old) with diffuse bronchiectasis affecting two or more lung segments and a history of *Pseudomonas aeruginosa* infection.**
Interventions: **TSI, 300 mg tobramycin per dose bid.**
Measurements and results: **During the 12-week treatment period, significant improvements (reduction of 1.5 U [$p = 0.006$]) occurred in mean pulmonary total symptom severity score, a composite score that assesses the severity of cough, shortness of breath, sputum production, fatigue, and wheezing. Significant improvements (reduction of 9.8 U [$p < 0.001$]) were also observed in St. George Respiratory Questionnaire scores, which measure health-related quality of life. Eradication or presumed eradication of *P aeruginosa* occurred in 6 of 27 evaluable subjects (22.2%). Tobramycin-resistant *P aeruginosa* developed in two subjects (minimal inhibitory concentration ≥ 16 μg/mL). Ten subjects withdrew from the study due to adverse events; in nine of these subjects, adverse events were considered probably or possibly related to treatment. The most common adverse events were cough, wheezing, and dyspnea.**
Conclusions: **TSI therapy resulted in significant improvements in respiratory symptoms and health-related quality of life in subjects with severe bronchiectasis, but some subjects did not tolerate TSI therapy. Bronchiectasis patients receiving this therapy should be monitored for signs of intolerance.** ***(CHEST 2005; 127:1420–1426)***

Key words: bronchiectasis; chronic pulmonary disease; clinical trial; *Pseudomonas aeruginosa*; St. George Respiratory Questionnaire; tobramycin solution for inhalation; treatment

Abbreviations: ITT = intention to treat; LRCF = last result carried forward; SGRQ = St. George Respiratory Questionnaire; TSI = tobramycin solution for inhalation

Bronchiectasis, the abnormal and permanent dilation of the bronchi, is a chronic lung condition that can be difficult to manage. In most patients with bronchiectasis, airway damage is related to a combination of infection and the associated release of inflammatory mediators.[1] Accordingly, antibiotic therapy is frequently required to reduce infection and inflammation and to ease symptoms. Several different bacteria are commonly isolated from the sputum of patients with bronchiectasis, including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. Of these, *P aeruginosa* infection is one of the most frequently observed[2,3] and, by releasing proinflammatory cytokines, pseudomonal colonization is associated with more

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severe disease, as indicated by lung function tests, quality-of-life measures, number of hospital admissions, and CT imaging.[4–6]

Management of chronic infections in bronchiectasis patients is variable, and based both on the infecting species and individual clinician experience. Tobramycin solution for inhalation (TSI) has been

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shown to be an effective outpatient therapy for long-term treatment of pseudomonal infections in patients with cystic fibrosis.[7,8] A placebo-controlled, double-blind, randomized study[9,10] of 4 weeks of treatment with TSI in subjects with bronchiectasis and *P aeruginosa* infection found that TSI-treated subjects showed significantly greater clinical improvement and a significantly higher rate of Pseudomonas eradication than subjects receiving placebo. However, subjects in the TSI group experienced higher incidences of cough, dyspnea, and wheezing than placebo subjects, and a slightly higher rate of development of tobramycin-resistant Pseudomonas strains (11% vs 3% for placebo).

We sought to further characterize the efficacy and safety profile of TSI in patients with severe bronchiectasis in an open-label, multicenter, clinical trial. Our data suggest that TSI may be a useful treatment option in some patients with bronchiectasis.

Materials and Methods

This open-label study was conducted between June 2000 and January 2002 at nine sites in the United States. The institutional review board at each site approved the study protocol and informed consent document. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to International Conference on Harmonisation guidelines. All subjects gave informed consent.

Subjects

Subjects were required to be at least 18 years of age and to have a diagnosis of diffuse bronchiectasis affecting two or more lung segments by conventional CT or high-resolution CT scan of the chest. In addition, subjects were required to have purulent sputum production, a history of *P aeruginosa* in sputum, and four or more courses of antibiotics for respiratory symptoms in the past 12 months, including either one course of IV antibiotics or one course of failed oral antibiotics requiring additional antibiotic therapy for relief of symptoms. Subjects who had used TSI or smoked tobacco within 6 months of the baseline visit, used any antibiotics within 2 weeks of the baseline visit, or used any investigational agents within 4 weeks of the baseline visit were excluded from the study. Other key exclusion criteria included a diagnosis of cystic fibrosis or allergic bronchopulmonary aspergillosis at entry, known hypersensitivity to aminoglycosides, unexpected chest radiograph findings, and history of renal disease or cancer.

Study Design

Subjects enrolled in this study received three treatment cycles with TSI (300 mg/5 mL tobramycin per dose) using a reusable air jet nebulizer (PARI LC Plus; PARI Respiratory Equipment; Richmond, VA) with a compressor (Pulmo-Aide; DeVilbiss; Somerset, PA). Each treatment cycle consisted of twice-daily dosing for 14 days, followed by 14 days off treatment (Fig 1). Following the third cycle, the subjects were followed up for an additional 40 weeks by chart review. The total duration of the study was 52 weeks. Treatment administration began on day 0 (baseline visit).

Subjects were given nose clips and trained in self-administration of study medication, use and cleaning of the nebulizer, and use of the compressor. The first dose was administered in the hospital in the presence of the research coordinator or investigator. Subjects were instructed to self-administer the rest of the study treatments at home two times per day, approximately 12-h apart, and not < 6-h apart. No restrictions for dosing were made regarding the time of day or relationship to meals. Those subjects receiving concomitant bronchodilators were asked to administer their bronchodilator 15 to 30 min before TSI treatment. Subjects were not allowed to use aerosolized/inhaled antibiotics other than study drug throughout the trial. Other antibiotics could be administered at the discretion of the investigator after study initiation. The use of investigational agents was not allowed at any time during the trial. Subjects were not allowed to use > 80 mg/d of furosemide at baseline or during the study, or to initiate or discontinue antidepressant therapy during the study. Other concomitant medications and therapies were permitted during this trial.

Baseline assessments were performed either during screening or before the first dose of study treatment on day 0 of the study. Efficacy assessments were performed at 2-week intervals throughout the study. Microbiological samples were obtained at week 0 and week 12 (or withdrawal visit). Sputum was cultured for the presence of *P aeruginosa* and other typical respiratory pathogens. Tobramycin minimal inhibitory concentration values for *P aeruginosa* were determined at week 0 and week 12 (or withdrawal visit). Subjects were examined at week 0 for baseline symptoms, and questioned concerning new conditions or changes in existing conditions at weeks 2, 6, 10, and 12. Clinical laboratory variables (serum chemistry, hematology, estimated creatinine clearance, and urine dipstick tests for proteinuria) were assessed at week 0 and at week 10 (or withdrawal visit). Acute bronchoconstriction was evaluated by measuring FEV_1 before and 30 min after TSI dosing.

The change in the mean pulmonary total symptom severity score from week 0 to week 10 was assessed based on subject responses to the Patient Symptoms Questionnaire, which employs symptom frequency and severity scales described for the validated Memorial Symptoms Assessment Scale.[11] Symptom severity was scored on a scale of 0 (not applicable or symptom not present) to 4 (very severe) for each of five symptoms (cough, shortness of breath, sputum production [frequency and severity],

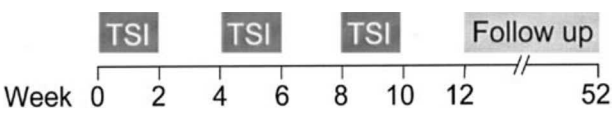

Figure 1. In this open-label trial, subjects received three cycles of TSI treatment (300 mg bid), with each cycle consisting of 14 days of drug therapy followed by 14 days off drug. Following the third cycle, subjects were followed up for an additional 40 weeks by chart review.