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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S<sup>®</sup>

# Treatment of Idiopathic Bronchiectasis With Aerosolized Recombinant Human DNase I\*

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**Study objective:** To study the safety and efficacy of aerosolized recombinant human DNase I in the treatment of idiopathic bronchiectasis.

**Design:** Double-blind, randomized, placebo-controlled, multicenter study.

**Populations:** Three hundred forty-nine adult outpatients in stable condition with idiopathic bronchiectasis from 23 centers in North America, Great Britain, and Ireland.

**Interventions and measurements:** Study patients received aerosolized rhDNase or placebo twice daily for 24 weeks. Primary end points were incidence of pulmonary exacerbations and mean percent change in FEV<sub>1</sub> from baseline over the treatment period.

**Results:** Pulmonary exacerbations were more frequent and FEV<sub>1</sub> decline was greater in patients who received rhDNase compared with placebo during this 24-week trial.

**Conclusions:** rhDNase was ineffective and potentially harmful in this group of adult outpatients in stable condition with idiopathic bronchiectasis. This contrasts with previously published results that demonstrated efficacy of rhDNase in patients with cystic fibrosis bronchiectasis.

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**Key words:** bronchiectasis, therapy; COPD; expectorants

**Abbreviations:** CF=cystic fibrosis; CI=confidence interval; NPDE=nonprotocol-defined exacerbation; PDE=protocol-defined exacerbation; rhDNase=recombinant human DNase I

The accumulation of viscous purulent secretions in the airways causes acute and chronic complications in lung diseases that are characterized by persistent airway infection such as cystic fibrosis (CF) and bronchiectasis. Purulent airway secretions contain mucus glycoproteins and abundant amounts of DNA.<sup>1,2</sup> DNA is an extremely viscous polymerized polyanion and a major cause of the increased viscosity of purulent airway secretions.<sup>3,4</sup>

Recombinant human DNase I (rhDNase, Pul-

mozyme, dornase alfa) has been approved for the management of CF. rhDNase is produced by genetically engineered Chinese hamster ovary cells containing DNA encoded for the native human protein, deoxyribonuclease I (DNase). The primary amino acid sequence is identical to that of the native human enzyme. Daily administration of rhDNase in conjunction with standard therapies is effective in the treatment of CF patients, reducing the frequency of respiratory tract infections requiring parenteral antibiotics and improving pulmonary function.<sup>5-7</sup> Small, uncontrolled studies have reported the efficacy of rhDNase in the management of lobar atelectasis due to retained secretions.<sup>8-10</sup>

Patients with idiopathic bronchiectasis (that is, not related to CF) commonly expectorate viscous, mucopurulent, infected sputum.<sup>11,12</sup> If the condition is not effectively treated, chronic respiratory infections result in cellular necrosis and airway lesions that contribute significantly to morbidity.<sup>13</sup> It has been shown that normal mucus clearance is delayed in the lungs of patients with bronchiectasis, and that intra-bronchial mucus is the major site of microbial colo-

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<sup>†</sup>A list of participants of the rhDNase Study Group is located in the Appendix.

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nization in these patients.<sup>14,15</sup> Consequently, the disease is progressive and is marked by delayed mucus clearance, which permits microbial colonization. There is stimulation of a chronic host inflammatory response such that pathogen does not clear and ultimately damages the lung epithelium.<sup>16</sup>

Since rhDNase was effective in patients with CF bronchiectasis and atelectasis,<sup>5-10</sup> we postulated that rhDNase would be a useful therapeutic agent in adults with idiopathic bronchiectasis. This randomized, double-blind, placebo-controlled, multicenter clinical trial was designed to investigate whether the aerosol administration of rhDNase for up to 168 consecutive days would decrease exacerbations, decrease antibiotic use, and improve spirometry and quality of life in patients with idiopathic bronchiectasis.

## MATERIALS AND METHODS

### Study Population

Patients with idiopathic bronchiectasis, defined by clinical and radiographic criteria (Table 1; 1,2,3), were recruited from 23 centers in North America, Great Britain, and Ireland. All patients were  $\geq 18$  years and met the four study inclusion requirements listed in Table 1.<sup>17,18</sup>

Patients were excluded if they had any deterioration in pulmonary status that caused a change in antibiotic, corticosteroid, or bronchodilator regimen or any hospitalization within 14 days prior to randomization. Other exclusion criteria included a history of major hemoptysis requiring interventional therapy or transfusion within 180 days of randomization, active allergic bronchopulmonary aspergillosis, active *Mycobacterium tuberculosis*, or atypical mycobacteria infection. Patients were screened to exclude those with CF, tracheostomy, and nondermal malignancy within the past 2 years. Pregnant or lactating women were not enrolled. Study patients could not have used any investigational drug within 28 days of randomization.

**Table 1—Enrollment Criteria**

Criteria
1. Radiographic
One of the following four criteria:
(a) Standard chest radiograph compatible with bronchiectasis, eg, fusiform infiltrates of mucoid impaction, "signet ring" or "tram tracks"
(b) Chest CT showing ectasia of peripheral bronchi, fluid-filled airways, or thickening of the mucosa <sup>17,18</sup>
(c) Contrast bronchography compatible with bronchiectasis
(d) Bacterial pneumonia localized to the same lobe or segment, twice or more within the past 12 months
2. Daily purulent sputum production $>15$ mL for the majority of days in the 3 months prior to enrollment
3. Sweat chloride level $<60$ mEq/L
4. Reproducible spirometry demonstrating FEV <sub>1</sub> $>30\%$ and $<80\%$ predicted for age, sex, and height

### DNase

The rhDNase used in the study was provided by the manufacturer (Genentech; South San Francisco) as a solution (1.0 mg/mL rhDNase in 2.5 mL of excipient [150 mM NaCl, 1.5 mM calcium chloride, pH 6.0]). The placebo used in the study was excipient alone. Active drug or placebo solution, 2.5 mL, was delivered by a nebulizer (Marquest Acorn II Nebulizer; Marquest; Inglewood, Colo) powered by a compressor (DeVilbiss Pulmo-Aide; DeVilbiss; Somerset, Pa).

### Spirometry

Spirometry included measurements of FEV<sub>1</sub>, FVC, and slow vital capacity. Each center was instructed to use the same testing equipment for each patient throughout the study. The equipment was calibrated daily and patients were tested during the same 3- to 4-hour period.<sup>19</sup>

### Quality-of-Life Questionnaire

Quality of life was assessed using a questionnaire<sup>5</sup> that included seven domains of well-being: cough and congestion, dyspnea, activity limitations, emotional well-being, fatigue, disability days, and overall health.

### Study Design

This was a double-blind, randomized, placebo-controlled, multicenter study. Patients received 2.5 mg of aerosolized rhDNase or placebo twice daily for 24 consecutive weeks, a dosage based on previous studies.<sup>5,20</sup> A 24-week study was required to identify a significant reduction in respiratory exacerbations, which an earlier short-term trial of 14 days did not capture.<sup>20</sup> The initial study drug administration was attended by a study coordinator and the remainder of the treatments were self-administered. All the patients continued to receive their usual care with personal physicians.

The patients were evaluated on three occasions within 8 days prior to first administration of study drug at which time symptoms, medication use, and spirometry were recorded. Patients were contacted by telephone 3 days after study initiation to review the protocol and answer questions. There were five visits during the study and at each, the following data were obtained: vital signs, spirometry, self-administered quality-of-life questionnaire, dyspnea score,<sup>21</sup> and review of patient log and any adverse events. A 24-h sputum sample was collected at baseline and on 3 subsequent study days, including the completion day. At baseline and on 2 study days, patients had a limited physician examination, CBC count, serum chemistries, and measurement of antibodies to rhDNase. These antibodies were determined by a radio immunoprecipitation assay that detected immunoglobulins of the IgG, IgM, and IgE classes.<sup>22</sup> Patients had posteroanterior and lateral chest radiographs and CT of the chest at baseline and at the time of completion of the study. CT scans were analyzed separately and graded by two radiologists outside the study with a five-point semiquantitative system.<sup>23</sup>

Patients were instructed to contact the study coordinator or investigator if they were having an exacerbation of their underlying lung disease. A protocol-defined exacerbation (PDE) was prospectively defined as abnormalities in four of the following nine symptoms, signs, or laboratory findings: (1) change in sputum production (consistency, color, volume, or hemoptysis); (2) increased dyspnea (chest congestion or shortness of breath); (3) increased cough; (4) fever (38°C); (5) increased wheezing; (6) decreased exercise tolerance, malaise, fatigue, or lethargy; (7)

FEV<sub>1</sub> or FVC decreased 10% from a previously recorded value; (8) radiographic changes indicative of a new pulmonary process; or (9) changes in chest sounds. A non-PDE (NPDE) was noted when a patient had fewer than four of the above abnormalities.

If a patient was found to have an exacerbation, the investigator decided the type of therapy. If the patient required hospitalization and was to remain in the study, the patient was hospitalized at an institution with institutional review board approval of this protocol. Administration of rhDNase or placebo continued while the patient was hospitalized and/or intubated. The study coordinator recorded the exacerbation, the associated signs and symptoms, the dates of initiation, and conclusion of the exacerbation.

#### Safety and Adverse Events

At each study visit, clinical adverse experiences were recorded. An adverse event was defined as any unintended change in the physical examination or laboratory sign or symptom, whether or not it was considered drug related. Adverse events included any side effect, injury, toxic reaction, or sensitivity reaction. A serious adverse event included any experience that was fatal or life threatening, was permanently disabling, required inpatient hospitalization, or prolonged existing hospitalization. The patients were questioned in a general manner without suggesting specific adverse symptoms.

#### Statistical Analysis

All patients randomized to either rhDNase or placebo treatment who satisfied the on-study eligibility criteria were included in the analysis regardless of early failures, treatment withdrawal, or treatment compliance ("intent-to-treat" analysis). Generalized linear models were used to estimate PDE rates and associated relative risk, 95% confidence intervals (CIs), and p values for the two treatment groups.<sup>24</sup> Results are presented as number of exacerbations per patient per 168 days. These models were developed assuming a log link and proportionality of the mean and variance. An offset was used to take into account differing lengths of observation.

The mean percentage change in FEV<sub>1</sub> from baseline over the treatment period was compared between the two treatment groups using analysis of variance. The measure of analysis was the mean FEV<sub>1</sub> while receiving treatment minus the mean FEV<sub>1</sub> at baseline divided by the mean FEV<sub>1</sub> at baseline:

$$\frac{(\text{Mean treatment FEV}_1 - \text{mean base FEV}_1)}{\text{mean baseline FEV}_1}$$

The mean baseline FEV<sub>1</sub> of a patient was defined as the average of FEV<sub>1</sub> values performed at the three visits before study drug initiation. Mean treatment FEV<sub>1</sub> was defined as the mean of all FEV<sub>1</sub> measurements taken while receiving treatment. If on-treatment measurements were missing, then the mean of the remaining FEV<sub>1</sub> values was used. Also, the mean percentage change of FEV<sub>1</sub> at each visit was plotted over time to depict the onset and duration of the treatment effect.

Analyses of secondary end points were compared using analysis of variance. Secondary end points included scores on quality-of-life domains, dyspnea index, time to resolution of pulmonary exacerbations, and antimicrobial use (number of agents, course, and total days of use) between baseline values and final treatment day values. The two treatment groups were compared at each timepoint using the Wilcoxon rank-sum test.

The sample size was based on the results from a trial of chronic bronchitis exacerbations in which the proportion of patients with annual exacerbation of chronic bronchitis was 54% in the ambr-oxol-treated group and 85% in placebo-treated patients.<sup>25</sup> Since

this study allows the use of standard therapies, the sample size calculation is based on the assumption that the cumulative exacerbation rate for the placebo group is about 50%. With a study size of 300 patients (150 in each group), there was an 80% power to detect a 34% reduction in the exacerbation rate from 50% in the placebo group to 33% in the rhDNase group.

#### Ethical Considerations

The study design was approved by the institutional review board at each center, and informed consent was obtained from each patient. The study was monitored by a safety advisor at Genentech.

## RESULTS

### Demographics

A total of 349 patients were randomized. The treatment groups were clinically comparable at the time of enrollment (Table 2). Two placebo-treated patients (one patient with self-limited hemoptysis and one patient with sinus symptoms) and one rhDNase-treated patient with increased sputum production withdrew from the study.

### Primary Efficacy End Points

*Protocol-Defined and Nonprotocol-Defined Exacerbations:* The rhDNase group had a higher PDE

**Table 2—Baseline Demographics of Study Patients**

	Placebo (n=176)	rhDNase (n=173)
No.		
Female/male	104/72	113/60
Mean age, yr	60	60
Ever smoked		
No	87	100
Yes	89	73
Sputum volume, mL/d		
n	173	173
Mean	34.73	33.25
Sputum appearance		
n	175	173
Mucoid	8	3
Mucopurulent	67	74
Purulent	100	96
Sputum DNA, mg/mL		
n	167	168
Mean	1.73	1.5
Minimum-maximum	0.07-7.56	0.07-8.68
FEV <sub>1</sub> , L		
Mean	1.43	1.34
% predicted	52.05	50.76
FVC, L		
Mean	2.4	2.3
% predicted	70.35	69.51
Pseudomonas in sputum		
n	173	173
% with Pseudomonas	19.08	30.06
Bronchiectasis score <sup>23</sup>		
n	148	146
Mean	28.07	31.82

rate, 0.66 exacerbations per patient per 168 days, compared with a rate of 0.56 exacerbations per patient in the placebo group (Table 3). The relative risk was 1.17 and the 95% CI contains the number 1 so the observed difference cannot be attributed to treatment. NPDE rate for the rhDNase group was significantly greater than the placebo group (relative risk=2.01). When PDEs and NPDEs were combined for analysis, there was still a significant increase in the occurrence of these events in the rhDNase group (relative risk=1.35) compared with the placebo rate.

*Mean Percent Change in FEV<sub>1</sub> From Baseline Over Treatment Period:* Mean percent decline in FEV<sub>1</sub> was -1.7% in the placebo group (n=176) and -3.6% in the rhDNase group (n=172, p≤0.05). rhDNase had a statistically significant negative effect on FEV<sub>1</sub> in this population, although the clinical relevance of such small changes is minimal.

### Secondary Efficacy End Points

The mean percent change in FVC was 0.3% in the placebo group and -3.4% in the rhDNase group (p≤0.01). No significant differences were seen in any of seven quality-of-life domains. Placebo-treated patients used antibiotics less than rhDNase-treated patients (44.1 vs 56.9 days; p≤0.05) and also used steroids less than rhDNase-treated patients (23.4 vs 29.4 days; p≤0.05). Difference in bronchodilator use was not statistically significant between the groups.

Hospitalization rates (number of hospitalizations per patient per 168 days) were 0.21 and 0.39 in the placebo and rhDNase groups, respectively. The relative risk (95% CI) was 1.85.

### Subgroup Analysis

Subgroups analyzed included subjects with FEV<sub>1</sub> >50% predicted or <50% predicted, subjects who expectorated >30 mL or <30 mL of sputum per day, and sputum quality subgroups. No statistically significant differences were seen in PDEs between placebo-treated and rhDNase-treated patients in these subgroups.

## SAFETY RESULTS

Four of the 349 patients (1.1%) died during the 168-day study; 1 patient received placebo and 3

**Table 3—Pulmonary Exacerbations: Rates and Risk**

	Placebo Rate	rhDNase Rate	Relative Risk	95% CI
PDEs	0.56	0.66	1.17	0.85, 1.65
NPDEs	0.14	0.29	2.01	1.15, 3.50
PDEs and NPDEs	0.71	0.95	1.35	1.01, 1.79

received rhDNase. Death was due to pneumonia in the placebo-treated patient; cardiomyopathy, small cell carcinoma, and cardiac arrest caused the three deaths in the study group patients. No death was considered by the investigator to be related to rhDNase.

The most common serious adverse event was nonspecific respiratory disorder (10.2% in the placebo group and 15% in the rhDNase group). There was no significant difference in the incidence of adverse events between control and study groups.

Antibodies to rhDNase were measurable in 24 rhDNase-treated patients (7.2%) and 1 placebo-treated patient (0.6%) during the study. The frequency of abnormal hematologic values or serum chemistry profiles was comparable among the two groups.

## DISCUSSION

rhDNase was not effective in the treatment of patients with stable idiopathic bronchiectasis. Overall pulmonary exacerbation rate (PDE and NPDE), one primary study end point, was higher in the rhDNase group than in the placebo group, although it did not achieve statistical significance. With regard to the second primary end point, mean percentage change in FEV<sub>1</sub>, there was statistically significant deterioration in the patients who received rhDNase compared with placebo. Among secondary end points, increased hospitalization rates, increased use of antibiotics, and FVC decline were noted in patients who received rhDNase. Therefore, the long-term use of rhDNase in patients with idiopathic bronchiectasis cannot be recommended; in fact, it may be harmful in this population.

These results contrast with the successful studies of rhDNase in bronchiectasis secondary to CF, which demonstrated efficacy in improving pulmonary function and reducing respiratory tract infections.<sup>5-7</sup> However, the current results are consistent with results seen in a small short-term study of adults with idiopathic bronchiectasis.<sup>20</sup> Wills and his associates<sup>20</sup> showed that rhDNase did not improve ciliary transportability of sputum *in vivo* and had a detrimental effect on sputum transportability *in vitro*.<sup>20</sup> They postulated that upper lobe predominance of CF bronchiectasis may make rhDNase more effective, since gravitational drainage of the thinned mucus may be easier from the upper lobes. Most patients with idiopathic bronchiectasis have diffuse or lower lobe predominant disease that may be more difficult to drain. Wills et al<sup>20</sup> also speculated that idiopathic bronchiectatic patients may be less likely to use chest physiotherapy than CF patients and that

chest physical therapy may be needed to render rhDNase most effective. Finally, CF patients have higher concentrations of DNA in their sputum compared with idiopathic bronchiectatic patients,<sup>26,27</sup> but there is no known direct correlation between DNA content and efficacy of rhDNase.

Another consideration is that patients with idiopathic bronchiectasis are substantially older than patients with CF.<sup>28</sup> Perhaps some aspect of aging (*ie*, deleterious changes in muscle strength, changes in the immune system or mucociliary clearance, changes in elastic recoil affecting ability to cough) might influence the older patients' ability to tolerate less viscous secretions. These changes, which may result in pooling of purulent secretions, airway obstruction, and subsequent infectious exacerbations, could potentially make rhDNase less effective. It is also possible that the rhDNase was effective in reducing viscid secretions, yet the thinned secretions then went more distally into the airways and lung parenchyma rather than being expectorated.

Lastly, there could be a flaw in randomization that led to disparity between control patients and those randomized to receive rhDNase. However, baseline demographics showed that the two groups were well matched with regard to age, pulmonary function, and sputum volume and bacteriology. Subgroup analysis mirrored the findings of the entire group. Additionally, the diagnosis of bronchiectasis seemed firm in all enrolled patients and independent radiographic confirmation of bronchiectasis was performed in all patients.

This study was the largest, prospective, long-term study of idiopathic bronchiectasis to date (and to our knowledge). Several observations from the placebo arm of the study are worthy of comment. A pulmonary exacerbation occurred at a rate of 0.71 (in units of exacerbations per patient per 168 days) or about once every 8 months. Mean percent change in FEV<sub>1</sub> was -1.7% in the placebo group, corresponding to a change in FEV<sub>1</sub> of 3.7%/yr, or approximately 53 mL/yr. This compares with a loss in FEV<sub>1</sub> of 70 to 87 mL/yr in a group of patients with COPD.<sup>29,30</sup>

## CONCLUSIONS

Bronchiectasis unrelated to CF is a relatively common cause of viscous pulmonary secretions. There was a strong rationale to study rhDNase in this patient population, but this large clinical trial shows that it is not effective and may be harmful. Based on the findings of this study, rhDNase should not be used in the treatment of stable, adult bronchiectasis unrelated to CF.

## APPENDIX

### List of Investigators and Study Sites

Name	Study Site
Alan Barker, MD	Oregon Health Sciences University Portland, OR 97201
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