Dornase Alfa as Postoperative Therapy in Cystic Fibrosis Sinonasal Disease

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Objective: To determine the benefit of nasally inhaled dornase alfa in patients with cystic fibrosis and nasal symptoms.

Design: Double-blind placebo-controlled trial.

Setting: Cystic Fibrosis Regional Center of Campania at the University of Naples “Federico II.”

Patients: A total of 24 patients with cystic fibrosis and chronic sinusitis.

Interventions: Patients underwent sinonasal surgery during a 3-year period and received once-daily doses of either dornase alfa (2.5 mg) or hypotonic saline solution (5 mL) beginning 1 month after surgery and for a 12-month period.

Main Outcome Measures: Primary outcomes were nasal-related symptoms and nasal endoscopic appearance; secondary outcomes were forced expiratory volume in 1 second, nasal computed tomography findings, and saccharine clearance test results. Patients were evaluated before and after treatment.

Results: After surgery, all outcomes were significantly improved for each treatment at 1 month ($P<.05$); primary outcomes were improved at 24 and 48 weeks in the group receiving dornase alfa ($P<.05$), and at 12 weeks in the group receiving placebo. Secondary outcomes were better in the dornase alfa group ($P<.01$) than in the placebo group at 12 months except for the saccharine clearance test results. In particular, median relative difference in forced expiratory volume in 1 second between dornase alfa and placebo was significantly improved in the dornase alfa group ($P<.01$).

Conclusions: Nasally inhaled dornase alfa can be effective in patients with cystic fibrosis and sinonasal disease who do not respond to conventional therapy after surgical treatment. Further studies should be carried out to determine the long-term effect on sinus disease, recurrence of polyps, and quality of life.


Cystic fibrosis (CF) is the most common lethal recessive disorder in white populations and is caused by a defective cystic fibrosis transmembrane conductance regulator, a chloride channel protein, leading to improper salt balance and thick tenacious secretions. Chronic bacterial infection and a vigorous host inflammatory response damage lungs and cause loss of pulmonary function. Large amounts of DNA coming from the degeneration of neutrophils lead to high viscosity of airway secretions in the sputum of patients with CF. It has been proposed that dornase alfa (recombinant human deoxyribonuclease) should cleave extracellular DNA in airway secretions and thus reduce in vivo sputum viscosity. Clinical trials and observational studies on the efficacy of dornase alfa inhalatory therapy have shown improvement in lung function (from 4.3% to 16% of median forced expiratory volume in 1 second [FEV$_1$] increase) and a decrease of respiratory exacerbations in patients with CF and moderate lung disease.

Sinonasal disease with or without nasal polyps is a common feature in patients with CF. Little information about its possible adverse effect on pulmonary function is currently available. It is suggested that mucus viscosity can lead to mechanical obstruction of sinus ostia, and impaired mucociliary clearance causes widespread inflammatory paranasal sinus disease and recurrent infections. The reestablishment of ventilation and drainage of sinonasal pathways are the goals of conventional treatment of CF. Nasal irrigation is used to clear secretions, de-
Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dornase Alfa</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age, y</td>
<td>10.6 ± 2.7</td>
<td>10.0 ± 2.6</td>
</tr>
<tr>
<td>Sex, M/F</td>
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<td>5/7</td>
</tr>
<tr>
<td>Sweat chloride, mEq/L</td>
<td>102.0 ± 13.5</td>
<td>103.5 ± 12.8</td>
</tr>
<tr>
<td>Genetic analysis</td>
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<tr>
<td>Homozygous delta F508</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Heterozygous delta F508</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Other genotypes</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Chronic infection by Pseudomonas aeruginosa</td>
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<td>5</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Surgery score†</td>
<td>7.0 ± 2.4</td>
<td>6.6 ± 2.3</td>
</tr>
</tbody>
</table>

*Data are reported as number of patients or mean ± SD.
†See the “Procedures” subsection of the “Methods” section for detailed information on surgery scoring.

Twenty-nine (11%) of 236 patients with CF who were surgically treated for chronic sinusitis with or without nasal polyposis were consecutively enrolled during a 3-year period. Cystic fibrosis was diagnosed during regular follow-up at the CF Regional Center of Campania by the presence of typical clinical symptoms and repeatedly positive findings from the sweat test, according to guidelines.5 Five of 29 subjects withdrew from the study immediately before randomization without starting any treatment owing to a prolonged illness after surgery. Twenty-four patients with sinonasal disease (13 girls and 11 boys; mean ± SD age, 10.6 ± 2.7 years; age range, 7-15 years) were considered eligible for the study when they were clinically stable.

Disease severity was assessed by the clinical Shwachman-Kulczycki (SK) score based on general activity, physical examination, nutrition, and conventional chest radiographic findings. In general, SK scores rate the patient’s condition as excellent (86-100), good (71-85), fair (56-70), moderate (41-55), or severe (≤40).11 The mean SK score was 70 (range 55-80) in enrolled patients. At enrollment, lung function was assessed by standard spirometry with a compact spirometer: FEV1, ranging from about 57% to about 70% of predicted values.

Ten patients were considered to have chronic Pseudomonas aeruginosa (PA) infection on the basis of persistent isolation of PA from respiratory samples for at least 6 consecutive months. Ten (42%) of 24 patients had allergic rhinitis (determined by skin prick test) and did not respond to conventional topical therapy for allergy. The mean number of pulmonary exacerbations per year was 0.9 (range, 0-2) for patients with CF enrolled during the study.

Baseline characteristics of enrolled patients are summarized in Table 1. Ethics approval for this trial was obtained from the center, and written informed consent was obtained from the guardian of each child (and the patient when appropriate).

PROCEDURES

This prospective, randomized, double-blind trial was performed primarily to evaluate the beneficial therapeutic effect of aerosolized dornase alfa vs placebo in the postsurgical treatment of chronic sinusitis related to CF. Indications for sinus surgery included chronic nasal obstruction with mouth breathing, chronic purulent draining unresponsive to medical treatment for at least 6 consecutive months, and persistent headaches. No participants had received any investigational drug therapy within 4 months prior to nasal surgery.

Endoscopic sinus surgery consisted of nasal polypectomy, anterior and/or posterior ethmoidectomy, frontal recess surgery, middle meatal antrostomy, reduction of inferior and middle turbinate, sphenoïdotomy, and uncinctomy.12 To ensure a clinically stable status prior to randomization, all patients received nasal lavages with 7% hypertonic saline solution for 2 weeks after surgery.

One month after surgery, patients were randomly assigned to receive for 1 year either dornase alfa or placebo. The first group of 12 patients underwent 4 consecutive treatment cycles, each cycle consisting of 8 weeks of therapy with once-daily 2.5-mg doses of dornase alfa (in 2.5 mL of vehicle; Genentech, San Francisco, Calif) separated by 4-week washout periods. The second group followed the same dosing schedule with once-daily placebo inhalation (21.9 mg of sodium chloride and 0.38 mg of calcium chloride in 2.5 mL of water for inhalation) (Genentech). Both therapies were iso-osmolar and administered into both nostrils in the morning via a Sidestream nebulizer and Portaneb compressor (Medic-Aid Ltd, West Sussex, England), with a mean daily inhalation time of 11 minutes.

No patient discontinued treatment. Vials were assigned by an operator not participating in the study, returned, and counted at the end of each treatment course as a measure of compliance. The patients, investigators, and all study participants remained blinded to the treatment assignment until the study was completed. The follow-up visits were performed before surgery and 4, 12, 24, and 48 weeks after surgery for both groups of patients. Routine medication and physiotherapy were continued throughout the study.

The protocol-defined primary outcome was the assessment of nasal-related symptoms and nasal endoscopic appearance. Secondary outcome measures were results of nasal radiologic examination, saccharine clearance test,13 and FEV1. At each visit, the severity of 6 symptoms was evaluated on a well-established scale13 of 0 to 10, with 10 being the most severe: (1) facial pain or pressure, (2) headache, (3) nasal blockage and congestion, (4) nasal discharge, (5) olfactory disturbance, and (6) overall discomfort.

Endoscopic investigations were performed with the patient in a sitting position by a 2.7-mm flexible endoscope. No decongestant or local anesthesia was used. Nasal endoscopic appearance was scored by 2 otorhinolaryngologists using the postoperative criteria described by Lund and Kennedy.14 In particular, the presence of residual polyps, edema, discharge, scarring, and crusting of both nasal cavities was scored as follows: absence of polyps, 0; presence of polyps confined to the middle meatus, 1; presence of polyps beyond the middle meatus, 2; no discharge, 0; clear and thin discharge, 1; thick and purulent discharge, 2; the absence and presence of edema, scarring, and crusting were scored at 0 and 1, respectively.14

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Mucociliary clearance was assessed at each visit by performing a saccharine test. A fragment of saccharin tablet was placed 1 cm behind the anterior margin of the inferior turbinate, and the patient was instructed to sit with his head inclined forward by 10 degrees. During the test, the patient had to frequently swallow (every 30 seconds) and avoid blowing the nose. Mucociliary transport time under endoscopic control was investigated.

Axial and coronal computed tomographic (CT) scans of the nose and paranasal sinuses were performed, mostly using the limited-slice CT method before surgery and at weeks 24 and 48 after surgery. The CT findings were scored by 2 otorhinolaryngologists according to well-defined radiologic staging standards. Each sinus (maxillary sinus, anterior ethmoid, posterior ethmoid, sphenoid sinus, and frontal sinus) was graded as 0 (no abnormality), 1 (partial opacification), or 2 (total opacification). The osteomeatal complex was scored only as 0 (not occluded) or 2 (occluded). Before surgery and at the end of the trial, spiromgrams were assessed by a compact spirometer (Vitalograph, Buckingham, England). Forced vital capacity (FVC), FEV1, FEV1/FVC ratio, and the forced expiratory flow during the middle half of the FVC (FEF25%-75%) were recorded and expressed as a percentage of predicted values based on sex, height, and age according to American Thoracic Society standards. A standard costing method was not used to assess the total health care cost for therapy.

STATISTICAL ANALYSIS

Data analysis of the 2 groups in the clinical trial are presented as mean ± SD and percentages. Findings for each parameter were compared within the groups by 1-way analysis of variance for repeated measures. The null hypothesis tested for each outcome measure was that the mean values were equal at all time points. If a significant difference was found either after surgery or during therapy, pairwise comparisons were performed using the Newman-Keuls method.

To determine the effect of sinus surgery and drug therapy on pulmonary function, FEV1 was compared by the t test for paired data. Comparisons between treatment groups were analyzed by unpaired t tests. In keeping with the aim of the study, multiple regression was used to account for potential confounding factors that might have introduced bias (number of operations, the child's age at first operation, presence of allergic rhinitis, and extrinsic factors). The osteomeatal complex was scored only as 0 (not occluded) or 2 (occluded). Before surgery and at the end of the trial, CT scans were scored by 2 radiologists according to well-defined radiologic staging standards. A standard costing method was not used to assess the total health care cost for therapy.

RESULTS

Twelve patients were randomized to receive dornase alfa, and 12 placebo. None of the enrolled patients without chronic colonization acquired PA during the study. On the basis of returned treatment packs, the estimated adherence (average proportion of medication taken) was 94% for placebo and 98% for dornase alfa. At baseline, there were no significant differences between the treatment groups and no order of randomization effect on either primary outcomes (symptom score, P = .93; endoscopic appearance score, P = .28) or secondary outcomes (surgery score, P = .75; radiologic score, P = .72; saccharine clearance test, P = .78).

Surgical treatment followed by medical therapy with either dornase alfa or placebo produced a significant improvement in all the parameters within both groups (P < .01), and it appeared to be the most effective therapy after 4 weeks. The Figure shows individual patient responses to medical therapy and sinus surgery. An improvement of at least 30% in nasal symptoms was judged clinically significant. Each point on the graph represents 1 patient.

In the treatment group, all outcomes (ie, nasal symptoms score, endoscopic appearance score, radiologic score, and saccharine clearance test score) improved at each visit. The greatest improvement was observed 24 weeks after surgery for primary outcomes, as confirmed by the analysis of comparison between each treatment period (Table 2). In the placebo group, the greatest improvement in the primary outcomes was observed 12 weeks after surgery, with a mild worsening in the last 24 weeks of therapy, while the mucociliary transport appeared to improve at each measurement (Table 2). In particular, the placebo group showed a mean improvement in nasal symptoms score of 23.1% at 24 weeks after surgery and a worsening of 3% between weeks 24 and 48 after surgery. Conversely, the dornase alfa group showed a persistent improvement throughout the study in both nasal symptoms (up to a mean of 32.5%) and endoscopic appearance (43.5%) by 48 weeks after surgery. The overall increase in FEV1 was significant (8.9%; P < .05) for the dornase alfa group but not for the placebo group (3.03%; P = .08).

There were significant differences between the 2 groups for all the outcomes at the end of trial except for saccharine clearance test scores, which did not achieve a statistically significant difference. The efficacy of medical therapy, expressed as percentage differences of either symptoms score (adjusted R² = 0.87) or endoscopic appearance score (adjusted R² = 0.93) and adjusted for potential confounders with the multiple regression procedure, showed a very significant benefit in patients who received dornase alfa (P < .001). No patient treated with dornase alfa showed specific adverse events.
This randomized, prospective, double-blind trial compared the effects of placebo and dornase alfa in patients with CF surgically treated for chronic rhinosinusitis. In recent years, dornase alfa has been widely used in the treatment of patients with CF and moderate pulmonary disease, but there are still unclear issues associated with a wide variation in individual response. Recently, a preliminary report suggested the potential impact of nasally inhaled dornase alfa in controlling postoperative sinus surgery in controlling pulmonary exacerbations, although no improvement in lung function test was observed in this study, nor in that by Madonna et al.20 Nevertheless, surgery plays the most important role in the management of sinonasal disease. Nasal polyps occur at a rate ranging from 6% to 48% in CF and shows either a high recurrence rate after nasal polypectomy or frequent spontaneous resolution by late adolescence. In our study, surgery seems to result in the greatest improvement (Figure) and to enhance the efficacy of subsequent medical therapy. Nasal polypectomy with intranasal ethmoidectomy represents the procedure of choice, showing a lower recurrence rate than polypectomy alone. Dornase alfa could be considered a tool for reducing nasal complaints and extending the effects of surgery.

However, a longer follow-up period is needed to establish the role of dornase alfa in preventing recurrence of nasal polyps after sinus surgery and its cost-effectiveness (considering the high long-term cost of this daily therapy). Investigations should verify the effect of other medical therapies compared with dornase alfa either in improving rhinitis symptoms and nasal airway patency or in reducing both size and recurrence rates of polyps. Several studies have suggested a relationship between sinusitis and chronic pulmonary disease. In CF,
an association of sinus disease with lung worsening has not been clearly demonstrated; however, sinus disease could play a significant role in quality of life and morbidity. Furthermore, chronic mouth breathing and anosmia related to nasal obstruction and rhinorrhea, often complained of by patients with CF and sinus disease, may affect appetite. We have recorded (data not shown) a significant reversal of weight loss after 6 months of dornase alfa therapy in all patients.

The present study is a clinical pilot investigation. Longer-duration trials should be carried out to determine the effect of inhaled dornase alfa on recurrence rate of polyps after sinus surgery, on quality of life, and pulmonary function, and prospectively to assess dornase alfa as an alternative therapy to surgery.

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REFERENCES