Dornase Alfa: A New Option in the Management of Cystic Fibrosis

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Recombinant human DNase I, or dornase alfa, is the first new therapy developed specifically for cystic fibrosis in almost 30 years. It selectively digests extracellular DNA and reduces the viscosity of purulent sputum. In clinical trials dornase alfa modestly improved pulmonary function, slightly decreasing the number of respiratory exacerbations requiring parenteral antibiotics compared with placebo. Phase III studies suggest that patients receiving dornase alfa also spend slightly fewer days in the hospital than those treated with placebo. The aerosolized preparation is safe and generally well tolerated. Voice alteration and sore throat are the most commonly reported adverse effects. Further research is necessary to determine the optimum time to initiate therapy and to evaluate the agent's pharmacoeconomic impact on the treatment of cystic fibrosis. Aerosolized dornase alfa should always be given in conjunction with standard cystic fibrosis therapies including antibiotics, chest physiotherapy, and pancreatic enzyme supplementation.
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OUTLINE

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Conclusion

Cystic fibrosis (CF) is a recessive genetic disorder involving several organ systems, including the pancreas, lungs, and gastrointestinal tract.[1] The primary defect in CF is a disturbance of transluminal chloride transport across the secretory epithelia of the gut, pancreas, lung, and biliary ducts.[1] This defect produces sticky mucus in the lung, pancreas, and liver, leading to mechanical obstruction and chronic inflammation in these organs, and forms the basis for resistant infection, especially in the lungs. Pancreatic insufficiency is present in 85% of patients due to obstruction of the pancreatic ducts.[1]

Thirty years ago, an aggressive treatment approach was developed that emphasized combating pulmonary infection, improving bronchial drainage, and attending to nutrition, including pancreatic enzyme supplementation. This approach improved median survival age from 3 to 30 years and dramatically enhanced the quality of life of these patients.[2]

Dornase alfa (Pulmozyme; Genentech, Inc.,

San Francisco), a mucolytic, is the first new treatment developed specifically for CF in almost 30 years.[3] It was approved by the Food and Drug Administration (FDA) on December 30, 1993, for use in conjunction with standard therapies in selected patients. In combination with other recent advances in the understanding of CF, such as the discovery of the chromosomal defect responsible for the expression of the CF gene and illumination of the basic defect in epithelial chloride transport, new treatments such as dornase alfa, leucoprotease inhibitors, and gene therapy offer hope for decreased morbidity and mortality in these patients.[4]

Chemistry

Dornase alfa, a product of biotechnology, is a purified solution of recombinant human deoxyribonuclease I (rhDNase). In the literature rhDNase has also been referred to as DNase I, pancreatic DNase, human DNase, and thymonuclease.[5] It is a 37,000-D glycosylated enzyme cloned in Chinese hamster ovary cells transfected with a plasmid containing a human DNase complementary DNA (cDNA).[6] The purified glycoprotein contains 260 amino acids, the primary sequence of which is identical to that of the native human enzyme.[7]

Bovine DNase was initially tested in the 1950s to promote drainage of viscous, purulent lung secretions. However, the formulation was suspected of being contaminated with proteases (trypsin, chymotrypsin), and it was removed from clinical use in the 1970s due to allergic reactions and bronchial irritation.[2, 8] A source of potentially nonallergenic DNase was discovered when human DNase I was partially purified from the human pancreas, duodenal juice, serum, and urine.[6]

Human DNase I was recently cloned by screening a human pancreatic cDNA library using two long oligonucleotide probes based on the amino acid sequence of bovine pancreatic DNase I.[6] The expression and purification of this cloned enzyme produced a reliable source of rhDNase (dornase alfa), enabling clinical trials to take place.

Dornase alfa depends on divalent cations for optimum enzymatic activity. In vitro DNA hydrolysis is reduced 10-fold by the absence of Ca^{2+} and Mg^{2+}. In addition, like bovine DNase I, it is inactivated by heat (100°C for 10 min). Optimum enzyme activity occurs at a neutral pH of 5.5–7.5. Both the reported concentration of Ca^{2+} and Mg^{2+} in sputum and the pH of sputum are sufficient to support the activity of dornase alfa.[6]

Pharmacokinetics and Pharmacodynamics

Absorption

The agent has minimal systemic absorption after administration by inhalation. A phase I study used dose escalation to evaluate the safety of aerosolized dornase alfa 2, 6, or 10 mg 3 times/day.[9] Systemic absorption was determined by drawing venous blood samples at 0, 1, 2, 4, 8, 12, 16, and 24 hours after the first dose on days 1 and 12. Small increases in serum DNase levels were observed in patients with CF. The concentrations increased from 1 ± 2 ng/ml (mean ± SD) before dornase alfa administration to 3 ± 3 ng/ml 6 hours after the final dose on day 12. Examination of serum DNase levels at frequent intervals after inhalation of DNase on both days 1 and 12 indicated no appreciable increases in concentration and no evidence of accumulation.

Therapeutic Drug Levels

Quantification of serum dornase alfa is not clinically useful, as only slight elevations in serum concentrations occur.[9, 10] Sputum DNase levels and mucolytic activity, as measured by cleaved DNA, were significantly increased in parallel fashion in posttherapy samples.[10]

Onset of Action

Significant improvement in lung function, as measured by increases in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), was seen within 3 days of twice/day administration of dornase alfa 0.6, 2.5, or 10 mg compared with placebo.[8] The onset of efficacy did not appear to be dose dependent.

Duration

In clinical trials, FEV_1 and FVC returned to baseline measurements within 2–3 weeks after withdrawal of the drug.[8, 9, 11] Selected patients experienced residual improvements in lung function as long as 32 days after discontinuing dornase alfa.[8]

Clinical Pharmacology

The most important cause of morbidity and mortality in CF is chronic progressive lung

disease, which is manifested as chronic obstructive pulmonary disease and pneumonia.[1, 10] Patients' airway secretions are thick, viscous, difficult to expectorate, and persistently infected with bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenzae* despite aggressive antibiotic therapy.[6, 10, 11] An underlying defect in secretory epithelial cell ion transport is initially responsible for the thick, dehydrated mucus, and it is hypothesized that high concentrations of DNA (3–14 mg/ml) present in purulent lung secretions may further contribute to their viscous properties.[4, 6]

This hypothesis is based on the observation that airway secretions are composed of complex, nonhomogeneous materials that form a hydrophilic gel. The viscosity of this gel may be determined in part by the aggregation of mucus glycoproteins that yield an entangled web of fibers. In purulent secretions such as those in the airways of patients with CF, the large amounts of DNA released from the nuclei of disintegrating polymorphonuclear neutrophils may contribute substantially to this tangled web, thereby increasing sputum viscosity.[6]

Native human DNase I is an enzyme that selectively digests extracellular DNA. In vitro studies demonstrated that dornase alfa hydrolyzes extracellular DNA in purulent sputum from patients with CF and reduces sputum viscoelasticity.[6] By decreasing the viscosity of airway secretions, the agent may facilitate the clearance of purulent sputum from sites important for lung function, including areas where impaired mucociliary mechanisms are not able to free thick, entrapped, purulent mucus.[10] Based on this mechanism of activity, dornase alfa is unlikely to be of benefit in patients with nonpurulent sputum.[10] Alternatively, it was hypothesized that agents that affect the kinetics of mucus, such as dornase alfa, could potentially alter the clearance of secretions by reducing their adhesion to the respiratory epithelium regardless of their effects on viscoelasticity.[12]

Clinical Trials

Safety

Aerosolized dornase alfa 0.1–40 mg/day was administered to 16 inpatients (mean age 27 ± 8 yrs) with CF for up to 1 week.[10] Various measurements of safety, including physical examination, serum chemistry, hematologic tests, urinalysis, arterial blood gases, spirometry, and chest radiography, were assessed before and after administration. The results revealed no significant adverse effects attributable to the drug. Compared with baseline for all doses studied, there was a mean increase in FEV_1 of 0.26 ± 0.07 L and in FVC of 0.35 ± 0.10 L at day 5 of therapy ($p<0.01$ and $p<0.01$, respectively). No significant differences were seen among the three doses in their effects on lung function.

This preliminary uncontrolled, dose-ranging study demonstrated the short-term safety of dornase alfa in hospitalized patients with CF. Doses exceeding the current recommendation of 2.5 mg/day were administered without apparent adverse events. No information regarding baseline pulmonary function was provided, making the reported improvements in FEV_1 and FVC difficult to interpret.

Aerosolized dornase alfa was administered 3 times/day, Monday through Friday, on two consecutive weeks (the dosage was increased in the first week and remained constant in the second week) to 12 healthy subjects (mean age 34 ± 11 yrs) and 14 adults (mean age 26 ± 8 yrs) with CF in an inpatient setting.[9] Constant dosages ranged from 6–30 mg/day, and all subjects were rechallenged with a single dose 21 days after the last dose. Safety was evaluated based on prestudy and poststudy differences in physical examination, chest radiograph, blood tests (coagulation, chemical analyses, hematologic profiles), and pulmonary function tests. All healthy subjects tolerated the agent up to the highest dosage. They experienced no adverse reactions and no significant changes in pulmonary function at any time during the study. All patients with CF also tolerated inhaled dornase alfa up to the highest dosage. Two withdrew from the study for reasons unrelated to the drug.

Minor adverse reactions included small amounts of hemoptysis and transient decreases in pulmonary function, and they were thought to be consistent with the natural course of CF. Mean morning predose FEV_1 and FVC improved significantly ($p=0.01$ and $p=0.01$, respectively), and returned to baseline by the end of the study. Rechallenge at study completion was uneventful in all subjects, and no subject developed detectable serum antibodies directed against dornase alfa.

This phase I study provides additional evidence of the agent's short-term safety in inpatients with CF, although small decreases in lung function occurred during the treatment period in some patients. Three patients experienced a greater

than 10% decrease in FEV_1 compared with baseline. Such changes in pulmonary function would not be expected over a short-term study, making it difficult to accept the authors' contention that they were consistent with the natural history of CF. Alternatively, the reductions in spirometry may simply reflect the difficulty of obtaining reproducible pulmonary function test results in patients with CF.[2]

Efficacy

Preliminary efficacy data were reported in a single-blinded, placebo-controlled, crossover study involving 16 inpatients age 27 ± 3.3 years, 11 of whom completed the trial.[10] These 11 had a mean (± SD) FVC of 53 ± 13% of predicted, daily production of sputum, no change in antibiotics, corticosteroids, or bronchodilators in the 3 weeks before study initiation, and no hospitalizations for respiratory infection within the previous 6 weeks. Either dornase alfa 10 mg twice/day or placebo was administered for 6 days, with crossover after 2–3 weeks. Pulmonary function was assessed twice each day before, during, and 1 week after drug administration. After 3 months, all tests of clinical safety and lung function were repeated.

Of the five patients who did not complete both arms of the study, four dropped out for personal reasons not related to therapy and one did so because of respiratory infection. Dornase alfa was associated with significant increases in both FEV_1 and FVC in the morning and early evening ($p<0.01$ for all comparisons of the mean of days 1–6 with baseline). None of the changes in lung function associated with placebo reached statistical significance compared with baseline. The morning and early evening FEV_1 and FVC values were significantly improved during dornase alfa therapy compared with placebo ($p<0.01$ for days 1–6). Evaluation at 3 months detected no adverse events related to the drug and no rhDNase antibodies.

This study was published in conjunction with the safety data described earlier.[10] The results provide preliminary evidence regarding the ability of dornase alfa to improve lung function during short-term administration in hospitalized patients with CF with stable lung disease. The authors compared improvements obtained with dornase alfa with those after systemic antibiotic therapy for exacerbations of respiratory infections in patients with CF. However, caution should be exercised when making comparisons between different study populations, as the baseline severity of disease can differ, and patients in this study were not experiencing respiratory exacerbations. The results of subsequent studies raised concerns that the washout interval in this trial may not have been adequate, and the potential for carryover effect led others to question the results of this study.[8]

A double-blind, randomized, parallel trial compared the efficacy of three doses of dornase alfa with that of placebo in 181 patients with CF age 8–65 years.[8] Exclusion criteria were mean FVC below 40% of predicted, unstable pulmonary status, and current therapy with aerosolized antibiotics, mucolytic agents, or narcotics, and previous exposure to DNase. Patients inhaled 0.6, 2.5, 10 mg of dornase alfa or placebo twice/day for 10 days at home. Randomization was stratified based on illness severity (FVC ≤ 70% and > 70%). Routine chest physiotherapy and other drugs were continued throughout the study. The four groups were compared on the basis of pulmonary function, quality of life, and safety.

The mean percentage changes in FEV_1 from baseline to day 10 were significantly greater in each dornase alfa group than in the placebo group: 9.9 ± 13.4%, 13.8 ± 13.3%, and 14.5 ± 13.9% for 0.6, 2.5, and 10 mg, respectively. Only the group receiving dornase alfa 2.5 mg was significantly improved when FVC (11.8 ± 12.6%) was compared with the placebo group at day 10. Patients with more severe pulmonary disease (FVC ≤ 70% predicted) had 2- to 3-fold greater improvements in spirometry than those with less severe pulmonary disease (FVC > 70%). Patients using bronchodilators were also more likely to experience greater improvements. There was a significant association between disease severity and the likelihood of receiving bronchodilators ($p=0.002$).

Of the nine quality of life assessments, only two were significantly improved relative to placebo at day 10. General well-being was improved ($p=0.04$) and cough frequency was decreased ($p=0.03$). Dyspnea score was significantly improved only in the group receiving 2.5 mg compared with placebo. No significant difference was seen in the distribution of respiratory events requiring hospitalization or the number of patients receiving a new prescription for parenteral antibiotic therapy among the four groups. Reports of voice alteration and sore throat during treatment were most frequent among patients receiving active

drug. No patients developed detectable anti-rhDNase antibodies during the 42-day observation period.

In this phase II study, short-term administration of dornase alfa in an ambulatory setting slightly improved lung function in patients with CF with stable pulmonary disease. Improvements in spirometry were widely variable across all doses. This is likely due to the inherent variability in the results of spirometric testing in patients with CF, but could also indicate that certain patients have greater responses to dornase alfa than others. Patients with more severe lung disease (FVC 40–70% predicted or using bronchodilators) received greatest benefit from dornase alfa. No information was given regarding the percentage improvement in spirometry for specific levels of baseline pulmonary function.

The length of the study was not sufficient to determine if the nominal improvements in pulmonary function translated into fewer courses of parenteral antibiotics and days in the hospital. The trends were toward improvements in quality of life assessments, but many of these improvements failed to reach statistical significance. This may have been due in part to the short observation period (10 days) or flaws in statistical methods (ordinal scale data were treated as continuous variables).

The efficacy of dornase alfa 2.5 mg inhaled twice/day for 10 days was compared with that of placebo in a similar randomized, double-blind, parallel trial.[11] Subjects were 71 patients with CF, age 16–55 years, with stable lung function and FVCs 40% or greater of predicted. The mean change for FEV_1 from baseline was 13.3% for dornase alfa and -0.2% for placebo (difference 13.5%, 95% CI 7.6–19.4%, $p<0.001$). Changes in FVC were smaller (7.2% dornase alfa, 2.3% placebo) and failed to reach statistical significance. Significant improvements were noted for three of five questions on a quality of life questionnaire, namely, general well-being, cough frequency, and chest congestion (probability not reported). Dyspnea scores were not significantly different between the two treatment groups, nor were the numbers of patients requiring antibiotics or hospital admission. There were no differences in reported adverse events between the groups.

Again, certain patients had greater responses than others; 10 had a 20% or greater improvement in FEV_1 after dornase alfa. The severity of lung disease in these patients was not stated. This and the previous study both reported that improvements in lung function returned to baseline after the drug was discontinued, underscoring the need for continuous administration to maintain benefit.

A phase III multicenter clinical trial tested the hypothesis that daily dornase alfa administration would maintain improvement in pulmonary function (FEV_1) and reduce the risk of exacerbations of respiratory symptoms requiring parenteral antibiotics.[13] This was a parallel-design, randomized, placebo-controlled, three-arm, double-blind study lasting 24 weeks. The three arms were dornase alfa 2.5 mg once/day, 2.5 mg twice/day, and placebo. Entry criteria included clinically stable lung function defined as receiving a consistent regimen of antibiotics, or no antibiotics, during the 14 days before randomization, FVC above 40% of predicted, and age greater than 5 years. A total of 968 outpatients with CF satisfied these requirements. A standard definition of exacerbation of respiratory symptoms, specified in the clinical protocol, was the need for treatment with parenteral antibiotics for at least 4 of 12 signs or symptoms, including change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10% or more from a previously recorded value; or radiographic changes indicative of pulmonary infection. Dornase alfa was given in conjunction with other forms of therapy for CF including nutrition, pancreatic enzyme replacement, antibiotics, bronchodilators, and chest physiotherapy.

Administration of dornase alfa once/day reduced the risk of an exacerbation of respiratory symptoms requiring parenteral antibiotics relative to placebo by 22% ($p=0.11$), and twice-daily administration reduced the use of parenteral antibiotics by 34% ($p=0.012$). When a covariate adjustment for imbalances in age between groups was included in the analysis, once-daily dornase alfa reduced the risk of a respiratory exacerbation requiring parenteral antibiotics by 28% ($p=0.04$) and twice-daily dosing resulted in a 37% reduction ($p<0.01$). Administration of the drug once a day reduced the age-adjusted risk of all exacerbations requiring parenteral antibiotics, including those not meeting the protocol criteria, by 31%

($p<0.01$) and twice-daily dosing resulted in a 32% reduction ($p<0.01$) compared with placebo.

Once-daily administration improved FEV_1 5.8 ± 12.6% ($p<0.01$), and twice-daily dosing resulted in a 5.6 ± 12.5% improvement ($p<0.01$). Dornase alfa improved patients' perception of dyspnea, overall well-being, and CF-related symptoms, with the once-daily administration group having significant improvements compared with the placebo group. Patients receiving once-daily dornase alfa spent 1.3 fewer days in the hospital than placebo-treated patients ($p=0.06$), and those who received twice-daily dosing spent 1.0 fewer days in the hospital ($p<0.05$). Antibodies to the agent developed in less than 5% of treated patients, and the drug did not cause allergy or anaphylaxis.

Adverse reactions were minor and infrequent. Voice alteration described as hoarseness was significantly increased in frequency compared with placebo (7% placebo, 12% once/day, 16% twice/day). It was self-limited, rarely severe, and in most cases resolved within 21 days of onset. Laryngitis and rash were also reported.

In this large multicenter study, daily dornase alfa administration over 24 weeks modestly reduced the number of exacerbations of respiratory symptoms requiring parenteral antibiotics in CF patients with stable pulmonary disease. In addition, small improvements in lung function were maintained over 6 months. However, the greatest improvement in FEV_1 occurred in the first 2 weeks of treatment and declined over the 24 weeks, prompting concerns by an FDA advisory committee regarding the drug's effect for periods greater than 6 months.[14]

This observation is consistent with results reported during a 5-month study in which improvements in FEV_1 and FVC declined 7.3% and 6.4%, respectively, after reaching 12.3% and 13.6% during the first month.[15] The manufacturer subsequently committed to open label clinical study extensions as part of approval discussions with the FDA.[14] Preliminary data from this extension indicated that dornase alfa appeared to be well tolerated and associated with continuing clinical efficacy over a 2-year period.[14]

An editorial accompanying the phase III study observed that, based on earlier data, an increase in FEV_1 of 13% is required to document significant improvement in a given patient with CF. Fewer than 30% of patients receiving dornase alfa in this study satisfied this criterion.[2] Although changes in the perception of dyspnea and overall well-being reached statistical significance, the improvements were small and probably not clinically important.[2]

Adverse Reactions

Adverse events associated with aerosolized dornase alfa are generally mild and transient, and rarely require changes in dosing. Dose-ranging studies employing daily doses as high as 40 mg revealed no significant adverse effects.[10]

It is unclear whether the adverse reactions associated with bovine DNase were secondary to nonspecific bronchial irritation or to the development of allergic sensitivity to the protein.[11] Consequently, it was necessary to evaluate whether dornase alfa would induce nonspecific bronchial irritation or immunologic sensitivity. Although a very small percentage (average 2–4%) of patients exposed to the drug during clinical trials developed serum antibodies to rhDNase, no anaphylaxis or severe allergic reactions have been reported to date.[7] The clinical relevance of rhDNase antibodies is unknown at the present time. No immunoglobulin E antibodies have been detected.[16]

The frequency of adverse events (n=643) summarized by the manufacturer demonstrates the drug's excellent clinical tolerability and safety profile. The only consistent adverse effects have been voice alteration (hoarseness) (7% placebo, 12–16% dornase alfa) and pharyngitis (33%, 36–40%).[7, 8, 13] They appear to be dose related.[8] Most adverse events occurred at a similar rate in placebo-treated patients and in some instances (e.g., hemoptysis, apnea, bronchiectasis, change in sputum, cough increase, dyspnea) were consistent with the underlying lung disease. Drop-out rates during phase III trials were similar for dornase alfa (3%) and placebo (2%).[13] Safety data with long-term use (>24 mo) and in patients less than 5 years of age are lacking.

A study quantifying the magnitude and duration of passive exposure to aerosol administration of dornase alfa indicated that the use of special filter systems is not necessary. The passive airborne concentration of the drug to which caregivers and family members could be exposed was well below the clinical dose during administration and nondetectable 15–45 minutes after treatment.[17]

Drug Interactions

Dornase alfa has been safely given in conjunction with established therapies for CF including oral, inhaled, and parenteral

antibiotics, bronchodilators, enzyme supplements, vitamins, oral and inhaled corticosteroids, and analgesics. The manufacturer recommends that it not be combined with other drugs in the nebulizer due to the potential for physicochemical or functional changes in either agent. Other nebulized drugs should be administered either before or after dornase alfa. No recommendations are currently available regarding the order in which concurrent CF therapies should be taken.[18] Formal drug interaction studies have not been conducted to date.[7]

Dosage and Administration

The initial dosage for all patients is 2.5 mg (2.5 ml) once/day by inhalation. Some patients may not obtain maximum therapeutic response at this dosage (e.g., those > 21 age yrs, FVC > 85% predicted) and may require 2.5 mg twice/day.[7] Experience with single doses greater than 10 mg and daily doses greater than 20 mg is limited.

Patients should initiate therapy under the direct supervision of a CF specialist to ensure proper administration. In addition, those with unstable lung function should be considered at risk for complications secondary to mobilization of copious airway secretions. Initiation in a hospital setting is recommended for these patients.[18]

Drug Formulation and Pharmaceutical Issues

Each 2.5-ml ampule contains 1.0 mg/ml (2500 U) dornase alfa formulated in 8.77 mg/ml sodium chloride, 0.15 mg/ml calcium chloride dihydrate, and sterile water for injection. The nominal pH of the solution is 6.3. The formulation contains no preservatives and is stable at room temperature for only 24 hours.

The 2.5-ml single-use polyethylene ampules for use with compressed air nebulizers have an 18-month expiration time when stored between 2 and 8°C (36–46°F). Ampules should be protected from light.[7]

Only nebulizer systems that can achieve approximately 25% respirable fraction delivery as a minimum standard should be used to administer dornase alfa.[18] Safety and efficacy have been demonstrated in clinical trials only with the following nebulizers and compressors:

Disposable jet nebulizers (intended for single use)
- Hudson T Updraft II
- Marquest Acorn II in conjunction with Pulmo-Aide compressor

Reusable jet nebulizer (can be used many times with proper care and cleaning)
- PARI LC Jet+ in conjunction with the PARI PRONEB compressor

Only these three systems, or systems that have similar in vitro characteristics, should be used to administer this drug. Battery-operated compressors are not recommended due to insufficient power. Ultrasonic nebulizers are also not recommended.[18]

Patient Instructions

Dornase alfa is administered primarily in the outpatient setting, and therefore patient consultation is important. Optimum delivery requires use of a recommended nebulizer system (see above), proper training of patients and caregivers regarding administration, and proper training for cleaning and maintenance of the equipment. Essential aspects of patient education are as follows:

- The package insert instructions for the assembly and care of the nebulizer should be reviewed with patients.
- Patients should wash their hands before assembling the equipment, and clean the surface where the nebulizer will be assembled. A specific location for drug administration should be maintained.
- The compressor of the nebulizer should be tested to be certain that it is functioning properly, and the filter should be checked weekly and replaced as necessary.
- Dornase alfa should not be combined with other drugs in the nebulizer. If other aerosol treatments are required, they must be given either before or after dornase alfa.
- The volume recommended for the nebulizer must not be exceeded. Patients should be instructed to inhale through the mouth with the nebulizer in an upright position; those who have difficulty breathing only from the mouth can use nose clips. Treatment lasts 10–15 minutes.
- The drug should be stored in the refrigerator; it should not be frozen or left at room temperature. Drug left at room temperature for greater than 24 hours should not be used. It must be refrigerated during transport.

Patients who benefit from dornase alfa may notice improvements in dyspnea and other subjective measurements of disease severity within several days of initiating treatment.[8] Actual reductions in the number of pulmonary exacerbations requiring parenteral antibiotics may not be realized for several months.[13] The

need for daily administration should be emphasized, as well as the importance of continuing other CF therapies. The magnitude of clinical improvement in clinical trials was small, and health care providers should be careful not to create unrealistic expectations in patients receiving the agent.

Pharmacoeconomic Issues

Dornase alfa costs the pharmacist approximately $32.40 (average wholesale price) per 2.5-mg ampule, or $11,826 for a year's supply at the recommended dosage of 2.5 mg/day.[19] An unpublished analysis of phase III trials found a mean reduction in hospital and antibiotic costs of $3592 versus placebo, suggesting a net cost of therapy of approximately $6000.[20] The savings calculations do not include indirect medical or direct nonmedical costs. For certain patients the price of a delivery system, about $200 for a compressor and $17 for a reusable nebulizer, must be factored into the cost of therapy.[21]

Although the cost of therapy with dornase alfa appears to be offset partly by reduced costs of hospitalization and antibiotics, the agent's actual effect on the total long-term cost of care has not been adequately assessed at this time.[13] Genentech has set up a nonprofit organization, the Genentech Endowment for Cystic Fibrosis (1-800-297-5557), to provide assistance for patients based on finances, insurance coverage, and other preestablished criteria.

Other Uses

Dornase alfa may also be beneficial for treatment of acute chronic bronchitis. Although larger studies are necessary, a summary of an initial unpublished study showed a 61% decrease in the death rate for patients hospitalized with acute exacerbations of chronic bronchitis.[22] In this double-blind, phase II trial, 244 patients hospitalized for chronic bronchitis received standard therapy (antibiotics, steroids, bronchodilators) and either dornase alfa 2.5 mg twice/day for 14 days, or placebo. Six-month follow-up showed mortality at 5.6% for patients receiving the active treatment versus 14.4% for the placebo. Reductions in rehospitalizations and respiratory relapse were statistically significant. Length of hospitalization was decreased by 2 days, but was not significant.

A phase III trial in patients with acute exacerbations of chronic obstructive pulmonary disease was recently terminated on the recommendation of an independent data safety monitoring board.[23] An interim analysis of 3700 patients showed that 90-day mortality was 10.3% in dornase alfa-treated patients compared with 9.5% in those receiving placebo.

Conclusion

Clinical trials have demonstrated the drug's safety, and ability to improve lung function modestly and reduce the number of respiratory exacerbations requiring parenteral antibiotics in patients with CF. It should be used only as an adjunct to traditional management of CF and must be administered on a continuous daily basis to sustain its therapeutic effect. Long-term evaluations documenting the impact of dornase alfa on morbidity and mortality are required to define its role in the treatment of CF. An epidemiologic study assessing its impact on patient survival is presently under way.[16]

Further study is also required to determine the optimum time to institute therapy with dornase alfa as well as the drug's safety in patients less than 5 years of age. Certain patients experience greater improvements in pulmonary function with this agent than others. Studies aimed at prospectively identifying these patients may allow targeting of rhDNase therapy to those most likely to benefit. Until this information becomes available, the decision to initiate dornase alfa therapy should be based on the physician's clinical judgment that sufficient inflammation is present in the lower airways.[18] This determination is best made by clinicians who are familiar with the management of CF.

The high cost of this drug necessitates careful monitoring of clinical response to identify patients in whom continued therapy is warranted. Monitoring variables are dyspnea severity, cough frequency, sputum production, fatigue, appetite, sleeping patterns, exercise tolerance, ease of sputum expectoration, and sputum clearance. Spirometry may help identify patients who are responding to therapy.

Although objective lung function values may improve only slightly, patients may report substantial subjective improvements. In addition, phase III data indicate that the risk of infectious exacerbations was reduced by dornase alfa regardless of the observed initial effects on pulmonary function.[24] Therefore caution should be exercised in basing decisions to continue therapy solely on the results of pulmonary function tests.

Many clinicians believe that the high cost of dornase alfa will be more than offset by fewer respiratory exacerbations requiring hospitalizations and parenteral antibiotics.[3] However, available data indicate that drug costs are offset only partly by such decreases.[13, 20]

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