CASE REPORT

Long-term use of nebulized human recombinant DNase1 in two siblings with primary ciliary dyskinesia

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Summary
Primary ciliary dyskinesia (PCD) is characterized by ultra-structural defects of the cilia. In this report, we describe the long-term use of nebulized dornase alfa in two siblings with PCD. This is the first report of long-term use of dornase alfa in PCD.
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Introduction
Primary ciliary dyskinesia (PCD) is characterized by ultra-structural defects of the cilia.\textsuperscript{1} This leads to abnormal function of the cilia in different organs, including the lungs. PCD is an autosomal-recessive disease.\textsuperscript{2} Its prevalence is estimated to be 1:20,000.\textsuperscript{1} The main presentation of PCD includes chronic airway infection, inflammation, recurrent pneumonia, bronchiectasis and sinusitis. If untreated, it can lead to lung destruction.\textsuperscript{3}

PCD, similar to cystic fibrosis (CF), is associated with a neutrophil-dominant airway inflammation, which leads to increased extra-cellular DNA, although the clinical course is more benign than in CF.\textsuperscript{4} Similarities of the mucus properties of PCD and CF were recently published.\textsuperscript{5}

Recombinant human DNase1 [rhDNase, dornase alfa (Pulmozyme\textsuperscript{5}, Genentech, Inc)] has been shown to reduce sputum viscosity by degradation of extra-cellular DNA and liquefaction of the thick mucus, improve pulmonary function (PFT) and reduce the number of pulmonary exacerbations in CF.\textsuperscript{6,7}

An early diagnosis of PCD can lead to appropriate management, preservation of PFT and prevention of lung damage.\textsuperscript{8,9} Currently, PCD patients are treated with chest physiotherapy, antibiotics and bronchodilators.\textsuperscript{10} In this report, we describe the long-term use of dornase alfa in two siblings with PCD and worsening pulmonary symptoms and PFTs despite conventional treatment. To our knowledge,
Dornase alfa long-term use in PCD  

this is the first report showing the benefits of the long-term use of dornase alfa in PCD.

Case reports

Case 1

Patient was 13 years of age, born at 35 weeks gestation. He was diagnosed with situs inversus totalis, dextrocardia with double outlet right ventricle (DORV), tricuspid insufficiency and regurgitation as an infant. He underwent repair of DORV at 9 months of age and tricuspid valvuloplasty at age 9 years. He developed persistent cough and wheezing during the first year of life. An extensive workup revealed Kartagener’s (PCD) syndrome. That was confirmed by electron microscopy of a nasal mucosal biopsy, which revealed total absence of the dynein arms of the cilia. He was started on bronchodilators, chest physiotherapy, frequent antibiotics and diuretics (for his cardiac disease).

At 26 months of age, in view of worsening respiratory symptoms, a trial of nebulized dornase alfa (2.5 mg once daily) was initiated. Within few weeks, his respiratory symptoms improved which lead to improvement in quality of life.

On follow-up visits, he continued to do well with mild intermittent cough and wheezing. At 6 years of age, a PFT (Viasys Sensor Medics V6200 plethysmograph equipment [V6200]) was performed. Percent predicted forced expiratory volume (FEV$_1$) at 1 s was 92%. Dornase alfa was stopped twice due to poor adherence at age 7 and 9 years. In both occasions, the patient stated that he continued the rest of the treatment plan. FEV$_1$ decreased from 90% to 77% and from 80% to 59%, respectively, within 4 months. Both occasions were also associated with worsening respiratory symptoms. Once dornase alfa was resumed, respiratory symptoms improved and FEV$_1$ increased to 81% and 87%, respectively. The patient’s respiratory symptoms and FEV$_1$ (89%) continued to be stable at 13 years of age with continuation of dornase alfa.

Case 2

Patient was 17 years of age; he was born at full term. Before 6 years of age, he had chronic sinusitis and otitis media. He underwent functional endoscopic sinus surgery with several revisions, adenoidectomy and tympanostomy tube placement twice. He grew *Pseudomonas aeruginosa* from ear discharge and was treated with frequent oral and intravenous antibiotics. Immune deficiency and allergies were ruled out. He was diagnosed with PCD at age 6 years after his younger brother (case 1) was diagnosed. His ciliary structure was similar to case 1. At diagnosis, he had no respiratory symptoms, and FEV$_1$ was 87%. He did not have Kartagener’s syndrome or cardiac disease. He started to have respiratory symptoms 6 months after diagnosis, and his FEV$_1$ decreased to 69%. He was started on bronchodilators, chest physiotherapy and antibiotics. Dornase alfa was started 9 months later because of continuation of symptoms. At that time, FEV$_1$ was 78%. Respiratory symptoms gradually improved and FEV$_1$ increased to 89%, 7 months later. At 9 years of age, dornase alfa was stopped. That was followed by increase respiratory symptoms and decrease FEV$_1$ to 54%. After resumption of dornase alfa, his respiratory symptoms improved and FEV$_1$ increased to 83%.

He continued on his treatment plan including dornase alfa with stabilization of respiratory symptoms and PFT. At 16 years of age, he had increased coughing, wheezing, poor sleep pattern and shortness of breath. FEV$_1$ decreased to 58%. That was due to poor adherence to dornase alfa and depression. Attempts to improve adherence, including coaching and counseling have not been successful.

The institutional review board exempted the two case reports since they were retrospective in nature.

Discussion

It has been established that inhaled dornase alfa improves PFT and the well being of patients with CF. In two occasions when reported in CF literature. In two conditions, chronic inflammation leads to recruitment and necrosis of neutrophils. DNA and filamentous actin are released. They copolymerize to a rigid secondary network increasing both sputum viscosity and adhesiveness. Dornase alfa is both an effective mucolytic agent, reducing the viscosity of secretions and mucokinetic agent, improving cough clearance by reducing surface adhesiveness.

Two case reports documented the usefulness of the short term use of dornase alfa in treating PCD. The first report showed objective improvement in pulmonary function and marked improvements in both respiratory and gastrointestinal symptoms from the short-term use of nebulized dornase alfa. The patient was a 14-year-old girl with Kartagener’s syndrome, who had intractable symptoms and worsening PFT despite conventional treatment. The second report documented rapid improvement of oxygenation, lung function and symptoms in a 1-month-old infant, shortly after starting dornase alfa when treatment with antibiotics and physiotherapy had proven unsuccessful. Two more acute episodes over the next 7 months also showed rapid clearing of symptoms with dornase alfa and antibiotics.

This is the first report, to our knowledge, on the long-term use of nebulized dornase alfa. It is also the first report to demonstrate continued improvement with the use of this medication in PCD. Both siblings’ respiratory symptoms and PFT improved shortly after dornase alfa was started after conventional treatment was unsuccessful. The improvement continued for approximately 12 years. The long-term use of dornase alfa in these patients was safe and not associated with side effects. These findings are similar to those reported in CF literature. In two occasions when dornase alfa was stopped, significant deterioration of respiratory symptoms and PFT occurred and improvement resulted after the resumption of dornase alfa. This was similar to the experience with intermittent use of dornase alfa in CF.

In conclusion, the long-term use of dornase alfa is effective, well tolerated and safe in these patients with PCD. A larger study is warranted to confirm the role of dornase alfa in PCD management.
Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this work.

References