Normalization of Sweat Chloride Concentration and Clinical Improvement With Ivacaftor in a Patient With Cystic Fibrosis With Mutation S549N

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The cystic fibrosis (CF) protein forms an anion channel in epithelial cells, and the absence or defective function of this channel results in the clinical manifestations of CF. CF is an autosomal recessive disorder, and its many disease-causing mutations divide into five or six classes. There are 10 known class 3 gating mutations, the most common of which is G551D. Ivacaftor is a drug that in vitro increases open time and trans-epithelial chloride transport in all 10 gating mutations, but it is approved for use only in patients with the G551D mutation. We report complete normalization of sweat chloride concentration and rapid clinical improvement over 6 weeks of treatment with ivacaftor in a patient with CF with the gating mutation S549N. The findings suggest that ivacaftor should be considered for use in patients with any of the known gating mutations. *CHEST* 2013; 144(4):1376–1378

Abbreviations: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator

Ten known cystic fibrosis (CF) mutations result in a gating (class 3) defect in CF channel function.¹ In affected cells, the channel is present and has normal conductivity but does not open. Ivacaftor increases open time, which increases transepithelial chloride transport. G551D is the most common CF gating mutation, occurring in 4% of patients. The remaining nine gating mutations affect 1% of patients. All gating mutations are associated with a severe phenotype. Ivacaftor is approved only for patients with the G551D mutation, but in vitro, it potentiates the function

of all 10 gating mutations.¹ We report our experience with ivacaftor in a patient with CF with the S549N gating mutation.

CASE REPORT

The patient is a 12-year-old girl with rapidly advancing CF lung disease who has the gating mutation S549N. Her second mutation, 1811 + 1.6kbA>G, is a severe class 1 mutation that results in no CF transmembrane conductance regulator (CFTR) protein production.² Since diagnosis, she has been hospitalized 19 times for pulmonary exacerbations, including eight admissions (117 days) over the past 2 years. Her lung function deteriorated in spite of aggressive CF treatment (Fig 1), and in October 2012 we prescribed ivacaftor 150 mg bid. Because it was covered by public insurance, the prescription was approved and dispensed for off-label use without questions or delay.

Prior to ivacaftor, the patient's sweat chloride level was 95 mmol. After 2 and 4 weeks of treatment, it was 19 and 20 mmol, respectively. Her productive cough cleared completely in 3 weeks. Previously unable to walk 1 block, the patient was able to engage in normal school exercise classes by 4 weeks. She changed her high-calorie, high-fat diet to a normal diet because of rapid weight gain (Table 1). Her

FIGURE 1. Deteriorating lung function on standard CF treatment (◆) reversed by adding ivacaftor 150 mg bid (■). Data are presented as mean ± SE for FEV₁ % predicted over time. Means are calculated by data clustered around treatment courses for pulmonary exacerbations. In years prior to treatment with ivacaftor, the patient's FEV₁ % predicted decreased an average of 6.7 per year ($R^2 = 0.86$). Outpatient treatment did not change for months prior to initiation of ivacaftor and included high-frequency vest treatments two to three times daily and inhaled treatments of 7% saline bid, deoxyribonuclease daily, and albuterol 180 µg bid. For the long term, she also was taking azithromycin 500 mg three times weekly, cotrimoxazole one double-strength tablet bid, pancreatic enzymes, and a proton pump inhibitor.

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Table 1—Lung Function Improvement and Weight Gain During a 6-wk Course of Ivacaftor 150 mg Twice Daily

Function	Day 0	Day 14	Day 28	Day 42
FVC, L (%)	1.52 (58)	1.86 (74)	1.90 (75)	2.12 (82)
FEV ₁ , L (%)	0.70 (33)	1.17 (52)	1.11 (49)	1.31 (57)
FEV ₁ /FVC	0.50	0.63	0.58	0.62
FEF _{25%-75%} , L/s (%)	0.34 (12)	0.71 (23)	0.61 (22)	0.70 (25)
Weight, kg	42.9	44.7	47.5	48.7
BMI, kg/m ²	19.2	20.3	21.4	21.7

There was no change in any other medication or treatment during the course. FEF_{25%-75%} = forced expiratory flow, midexpiratory phase.

chest radiograph and lung function improved significantly (Fig 2, Table 1). The 39% increase in FVC and 87% in FEV₁ resulted in her best lung function in > 3 years.

DISCUSSION

CF is an autosomal recessive disorder that results in the absence or dysfunction of the CF anion channel in respiratory epithelia, causing abnormal transport of salt and water and leading to the respiratory problems typical of CF.³ There are five or six functional classes of mutations. Class 1 mutations result in no protein production. Class 3 mutation channels transport little chloride because the channels remain closed most of the time. The patient has severe CF, which is typical of heterozygous patients with class 1 and 3 mutations.

Ivacaftor⁴⁻⁶ is a first-of-its-kind drug approved by the Food and Drug Administration for patients with CF and at least one copy of the G551D mutation. Ivacaftor increases by sixfold the open time of the G551D CFTR protein. This increase in open time increases the movement of salt and water across the affected epithelium, which in patients with the G551D mutation results in an average decrease in sweat chloride concentration of 40 to 50 mmol.⁴⁻⁶ Ivacaftor treatment of patients with the G551D mutation also results

in an average increase in FEV₁ of 8.7%, a decrease in the frequency of pulmonary exacerbations and spontaneous weight gain.⁴⁻⁶ Improvement is sustained indefinitely, and ivacaftor accomplishes these beneficial changes without serious side effects.

Cells transfected with S549 respond to ivacaftor with a 99-fold increase in open probability that results in chloride transport equal to wild-type cells,¹ and in the present patient, the in vivo response to ivacaftor was rapid and remarkable, consistent with the in vitro response of S549N.¹ If the improvement in her clinical status is sustained, as it has been in patients with the G551D mutation,⁷ ivacaftor will have dramatically improved the course and quality of life of a 12-year-old girl with rapidly progressing and life-threatening CF lung disease.

Pharmacologic correction of mutant CFTR protein function currently offers the greatest promise for a major advance in the treatment of CF. Ivacaftor is a first-of-its-kind corrector currently available to patients with CF. Its effects in patients with the G551D mutation and now in the present patient with the S549N mutation strengthen the argument that correction of defective CFTR function is therapeutic, but the correlation of the magnitude of the sweat chloride decrease with clinical response in CF is uncertain.⁸

FIGURE 2. A, A chest radiograph taken just prior to the start of ivacaftor treatment showed changes of severe cystic fibrosis lung disease with bronchiectasis and diffuse patchy, hazy infiltrate. B, After 28 days of treatment with ivacaftor the hazy infiltrate cleared, leaving persistent changes of bronchiectasis. A surgical central line is seen in both radiographs.

However, accumulating experience, including this case report, suggests that clinicians should consider ivacaftor treatment of all patients with CF and a gating mutation. Whether all such patients will respond well to ivacaftor remains to be demonstrated, and significant barriers to off-label use of this costly new drug likely will arise.

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Periodic Breathing With No Heart Beat

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A protocol was originally designed to study breathing control during and following cardiac arrest in humans, taking advantage of the period of pulseless ventricular fibrillation (PVF) produced while testing a newly implanted cardioverter-defibrillator device. A patient aged in his 60s with New York Heart Association class III heart failure (HF) (left ventricular ejection fraction of 25%) who was originally part of this study displayed permanent periodic breathing (PB) and was

then excluded from the final data analysis; his response is presented in this report. The 8- to 9-s PVF was incidentally produced during the ascending phase of a PB cycle, followed by another 12-s recovery period of low BP. PVF and its recovery had no effect on PB characteristics (period or amplitude). This occurred despite a profound change in P_{aCO_2} , cerebral blood flow, and perfusion of the carotid bodies. It is concluded that PB in patients with HF could be produced by primary oscillations originating from the central pattern generator. *CHEST* 2013; 144(4):1378-1380

Abbreviations: CB = carotid body; HF = heart failure; ICD = implantable cardioverter-defibrillator device; PB = periodic breathing; PVF = pulseless ventricular fibrillation

The mechanisms believed to cause periodic breathing (PB) in patients with heart failure (HF) include enhanced gain of the carotid bodies (CBs),¹ increased circulatory time,² periodic variations in cerebral blood flow-induced brainstem changes in pH,³ or primary oscillating mechanisms within the central pattern generator for breathing.⁴ Although many of these mechanisms can be reproduced experimentally and can lead to breathing instability, there is still a vivid debate on the frame of reference to be used to understand PB in patients with HF.³

We had the opportunity to record the breathing pattern of a male patient aged in his 60s with New York Heart Association class III HF (left ventricular ejection fraction of 25%) who displayed long periods of PB (with cycles lasting from 40-50 s). This patient, who had no history of stroke or other neurologic deficit traditionally associated with PB, was originally part of an institutional review board-approved study on the control of breathing during cardiac arrest. This patient was excluded from that study because of the lack of stable baseline ventilation.

The procedure consisted of a subcutaneous placement of an implantable cardioverter-defibrillator device (ICD) (Intrinsic DR ICD generator; Medtronic, Inc) for standard clinical indications under IV conscious sedation with propofol (diisopropylphenol). Inspiratory and expiratory flows were measured via a low-dead-space face mask connected to a pneumotachograph (Fleisch Pneumotachograph #2; Phipps & Bird, Inc). Expired CO_2 was continuously measured, and end-tidal PCO_2 (P_{aCO_2}) was determined using a fast infrared CO_2 analyzer (VacuMed). The ventilatory variables were recorded (PowerLab; ADInstruments) along with BP (Finapres Medical Systems BV) and the ECG during

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