Published in final edited form as:

Int Forum Allergy Rhinol. 2015 February ; 5(2): 178–181. doi:10.1002/alr.21440.

Medical reversal of chronic rhinosinusitis in a cystic fibrosis patient with ivacaftor

Eugene H. Chang, M.D.¹, Xiao Xiao Tang, Ph.D.^{2,3}, Viral S. Shah, B.A.², Janice L. Launspach, R.N., CCRC², Sarah E. Ernst, B.S.^{2,3}, Brianna Hilkin, B.S.¹, Philip H. Karp, B.S.^{2,3}, Mahmoud H. Abou Alaiwa, M.D.², Scott M. Graham, M.D.¹, Douglas B. Hornick, M.D.², Michael J. Welsh, M.D.^{2,3}, David A. Stoltz, M.D., Ph.D.², and Joseph Zabner, M.D.²

¹Department of Otolaryngology-Head and Neck Surgery, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA

²Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA

³Howard Hughes Medical Institute, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA

Abstract

Importance—Chronic sinusitis is universal in cystic fibrosis (CF) and our current treatments are ineffective in reversing sinus disease.

Objective—to determine if increasing CF transmembrane conductance regulator (CFTR) activity by ivacaftor could treat CF sinus disease and assess its effect on primary sinus epithelial cultures.

Methods—Case report of one patient with long-standing chronic sinus disease and a new diagnosis of CF with a mild mutation (P205S) and a severe mutation (G551D). We discuss clinical changes in symptoms, radiographic findings, nasal potential difference testing, and nasal pH values before and after treatment with ivacaftor. We then developed primary sinonasal epithelial cell cultures from a biopsy of the patient to determine changes in airway surface liquid (ASL) pH and ASL viscosity after ivacaftor treatment.

Results—Ivacaftor treatment reversed CT findings of CF sinus disease, increased nasal voltage and pH and resolved sinus symptoms after ten months of therapy. Ivacaftor significantly increased ASL pH and decreased ASL viscosity in primary airway cultures.

Conclusion—This report documents the reversal of CF sinus disease. Based on our *in vivo* and *in vitro* results, we speculate that ivacaftor may reverse CF sinusitis by increasing ASL pH and decreasing ASL viscosity. These studies suggest that CFTR modulation may be effective in treating CF and perhaps non-CF sinusitis.

Corresponding author: Eugene H Chang, MD, Department of Otolaryngology-Head and Neck Surgery, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, 21200 PFP, Iowa City, Iowa 52242; Tel: 319-384-6865, Fax: 319-356-4547; Eugene-Chang@uiowa.edu.

There is no conflict of interest to disclose.

Chronic sinusitis is universal in cystic fibrosis (CF). Although not all people with CF will report sinus symptoms, nearly 100 percent will develop sinus opacification and mucosal thickening on computed tomography (CT).¹ In CF, the paranasal sinus is commonly infected with opportunistic pathogens such as *Pseudomonas aeruginosa*, the mucosa is inflamed, and the sinonasal cavity is occluded with thick viscous mucus. Furthermore, sinus disease may contribute to lower airway infections, which are the major cause of morbidity and mortality in CF.²

To date, no treatment has been shown to reverse the CT findings of CF sinusitis. McMurphy *et al.* investigated CT findings in 134 CF patients and did not find any significant differences before or after medical or surgical therapy.³ Other studies have shown significantly worse findings after treatment,⁴ which likely represents the inevitable progression of disease.

Ivacaftor, also known as VX-770 or Kalydeco, is the first FDA-approved therapy to target the molecular defect in CF. CF is caused by mutations in the *CF transmembrane conductance regulator (CFTR)* gene,⁵ which encodes a cell membrane anion channel that transports chloride and bicarbonate.⁶ Ivacaftor is a CFTR potentiator that targets the *G551D-CFTR* mutation and restores channel activity to mutant CFTR.⁷ In clinical trials, ivacaftor improved assays of CFTR function (nasal potential difference and sweat chloride levels) and it improved lung function in people with CF who had a *G551D-CFTR* mutation on at least one allele.⁸

We report a patient with a long history of chronic sinus disease refractory to medical and surgical treatment, who was diagnosed at the age of 23 with a *G551D-CFTR* mutation. She began ivacaftor therapy and had a remarkable response with resolution of her CF sinus symptoms and reversal of CT findings of chronic sinusitis. In order to better understand how ivacaftor therapy improved CF sinus disease, we developed primary airway epithelial cultures from biopsies of her sinonasal tissue and tested ion transport, airway surface liquid (ASL) pH, and ASL viscosity.

Case report

Our patient was a Caucasian female of European origin, with chronic sinus symptoms of nasal congestion, facial fullness, and thick postnasal drainage since the age of nine. Despite a history of two sinus surgeries and multiple rounds of antibiotics, her symptoms persisted and her sinus CT scan showed complete opacification of the ethmoid, frontal, and sphenoid sinuses, as well as extensive mucosal thickening of both maxillary sinuses (Fig. 1A and B).

At the age of 23, the patient complained of several months of chronic cough and dyspnea after exercise. Spirometry showed mild obstructive physiology with a forced expiratory volume in 1 second (FEV1), 72% of predicted, and chest CT showed diffuse cylindrical bronchiectasis. Quantitative culture from bronchoalveolar lavage fluid grew mucoid *Pseudomonas aeruginosa*, and methicillin resistant *Staphylococcus aureus*. The patient was diagnosed with CF based on several criteria: a sweat chloride test of 89 mmol/L (levels greater than 60 mmol/L diagnostic of CF), no nasal voltage response to isoproterenol (0 mV), and genotyping identifying mutations in both *CFTR* alleles (*G551D* and *P205S*).⁹

The patient began ivacaftor (150 mg PO bid) and her sinus symptoms resolved within one month. She then briefly stopped therapy for three days and her sinus symptoms recurred. After resuming ivacaftor, her nasal congestion and postnasal drainage symptoms abated, but she continued to have persistent headaches. A sinus CT scan performed 10 months after initiating ivacaftor revealed that her maxillary and frontal sinuses were clear, and that her ethmoid sinuses were aerated except for two small posterior ethmoid mucocoeles (Fig. 1C and D). These headaches resolved after endoscopic surgery to address her mucocoeles. Her pulmonary symptoms also improved within three months of initiation of treatment with resolution of her cough, increase in FEV1 to 90% of predicted, and improvement in bronchial mucosal thickening on chest CT.

Methods

Clinical specimens

The study was approved by our institutional review board, and the patient provided written informed consent. Nasal potential difference testing¹⁰ and pH measurements¹¹ were performed as previously described. CFTR gene sequence analysis was performed on a DNA sample of peripheral blood.

In vitro studies of G551D/P205S primary sinonasal airway cultures

A small biopsy of nasal tissue from the inferior turbinate was excised during surgery to marsupialize the ethmoid mucocoeles and differentiated primary epithelial cell cultures were grown at the air-liquid interface as previously described.¹² Ion transport measurements of primary cultures were performed in Ussing chambers as previously described.¹³ ASL pH of cultures was measured using a ratiometric method with fluorescent pH indicators,¹⁴ and ASL viscosity was assayed using fluorescence recovery after photobleaching as previously described.¹⁵

Statistical analysis

Data are presented as mean $\pm$ SE. Paired *t*-test was performed using GraphPad Prism version 5.0 (Graphpad Software, San Diego, CA). Differences were considered statistically significant at $P < 0.05$.

Results

Physiological response to ivacaftor *in vivo*

One year after ivacaftor treatment was initiated, the nasal voltage response to isoproterenol had increased from 0 mV to -4 mV, consistent with the response seen in G551D CF humans in the ivacaftor clinical trial.⁸ Nasal pH *in vivo* increased from 5.0 to 6.9.

Physiological response to ivacaftor *in vitro*

The sinonasal biopsy from our patient was used to develop *in vitro* primary epithelial cell cultures at the air-liquid interface that recapitulate the ciliated, pseudostratified human sinonasal airway epithelia (Fig. 2A).

To assess the effect of ivacaftor on ion transport, we studied epithelia in Ussing chambers. The *G551D-CFTR* mutation reduces the open probability of the CFTR channel, and thus decreases transepithelial current.¹⁶ After adding forskolin to increase cellular levels of cAMP and phosphorylate the channel, we found that ivacaftor (Selleckchem) potentiated CFTR-mediated ion transport (Fig. 2B). These results are consistent with previous findings in human bronchial epithelial cell cultures.¹³

Loss of CFTR decreases bicarbonate secretion¹⁷ and reduces ASL pH¹⁸, which impairs bacterial killing.¹⁴ Therefore, we tested primary airway epithelial cell cultures using a fluorescent pH indicator. We found that ivacaftor increased ASL pH (Fig. 2C).

Thick viscous mucus lines the sinonasal airway and occludes the sinus ostia in CF humans¹ and in transgenic *CFTR* null pigs.¹⁹ Therefore, we tested the effect of ivacaftor on ASL viscosity. Ivacaftor decreased ASL viscosity measured by fluorescence recovery after photobleaching (Fig. 2D).

Discussion

These data report reversal of CF sinus disease in a patient after ivacaftor. The patient received mutation specific therapy directed at the molecular defect of *G551D-CFTR* and had a dramatic clinical response. These findings may have several additional implications.

First, the clinical presentation of CF in our patient was unusual in two respects. A mild mutation (*P205S*)²⁰ was paired with a severe mutation (*G551D*) that was amenable to treatment with ivacaftor. Moreover, the patient had a mild CF phenotype, with normal sinus anatomy, late-onset pulmonary disease, and a CF diagnosis at age 23. Nevertheless, she also had long-standing sinus symptoms and severe changes on sinus CT that were reversed with ivacaftor. Thus, it will be important to investigate if similar improvements occur with more severe combinations of mutations, such as *G551D/ F508*. As better CFTR correctors are developed for *F508-CFTR*, sinus CT could be used as a surrogate end point for clinical efficacy.

Second, people who are heterozygotes for CFTR mutations have 50% of normal CFTR function and do not develop CF lung disease. However, they have an increased incidence of chronic sinusitis.²¹ Similarly, cigarette smoking increases the prevalence of sinusitis²² and decreases CFTR function.²³ Since ivacaftor also increases wild-type CFTR activity,⁷ it may have therapeutic effects on these populations.

Finally, chronic sinusitis is estimated to affect 13–17% of the population,²⁴ yet the pathophysiology of disease is not well understood. Non-CF chronic sinusitis shares many clinical features with CF: chronic infection and inflammation of the sinus, mucosal thickening on sinus CT, and thick viscous mucus. Investigating the effect of CFTR potentiators on pH modulation^{14,25} may shed light on the pathophysiology of non-CF sinusitis and improve the options for treatment.

Conclusion

Based on our *in vivo* and *in vitro* results, we speculate that ivacaftor may reverse CF sinusitis by increasing ASL pH and decreasing ASL viscosity. These studies suggest that CFTR modulation may be effective in treating CF and perhaps help us understand the pathophysiology of chronic sinusitis.

Acknowledgements

We are especially indebted to the patient with CF who volunteered for these studies. We also thank Drs. Thomas Gross, Paul McCray, and Richard Smith for their helpful comments and discussion. This work was funded by the NIH (DE021413-01A1, HL51670, HL091842) and a grant from the Cystic Fibrosis Foundation (CHANG13IO). DAS was supported by the Gilead Sciences Research Scholars Program in CF. MJW is an investigator of the Howard Hughes Medical Institute.

Bibliography

1. King VV. Upper respiratory disease, sinusitis, and polyposis. *Clin Rev Allergy*. 1991; 9:143–157. [PubMed: 1884322]
2. Mainz JG, Naehrlich L, Schien M, et al. Concordant genotype of upper and lower airways *P aeruginosa* and *S aureus* isolates in cystic fibrosis. *Thorax*. 2009; 64:535–540. [PubMed: 19282318]
3. McMurphy AB, Morriss C, Roberts DB, Friedman EM. The usefulness of computed tomography scans in cystic fibrosis patients with chronic sinusitis. *Am J Rhinol*. 2007; 21:706–710. [PubMed: 18201451]
4. Eggesbo HB, Sovik S, Dolvik S, Kolmannskog F. CT characterization of inflammatory paranasal sinus disease in cystic fibrosis. *Acta Radiol*. 2002; 43:21–28. [PubMed: 11972457]
5. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science*. 1989; 245:1066–1073. [PubMed: 2475911]
6. Welsh, MJ.; Ramsey, BW.; Accurso, F.; Cutting, GR. Cystic Fibrosis. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D.; Childs, B.; Vogelstein, B., editors. *The Metabolic and Molecular Basis of Inherited Disease*. New York: McGraw-Hill; 2001.
7. Jih KY, Hwang TC. Vx-770 potentiates CFTR function by promoting decoupling between the gating cycle and ATP hydrolysis cycle. *Proc Natl Acad Sci U S A*. 2013; 110:4404–4409. [PubMed: 23440202]
8. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med*. 2010; 363:1991–2003. [PubMed: 21083385]
9. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008; 153:S4–S14. [PubMed: 18639722]
10. Standaert TA, Boitano L, Emerson J, et al. Standardized procedure for measurement of nasal potential difference: an outcome measure in multicenter cystic fibrosis clinical trials. *Pediatr Pulmonol*. 2004; 37:385–392. [PubMed: 15095320]
11. Abou Alaiwa MH, Beer AM, Pezzulo AA, et al. Neonates with cystic fibrosis have a reduced nasal liquid pH; A small pilot study. *J Cyst Fibros*. 2014
12. Karp PH, Moninger TO, Weber SP, et al. An *in vitro* model of differentiated human airway epithelia. *Methods for establishing primary cultures*. *Methods in molecular biology*. 2002; 188:115–137. [PubMed: 11987537]
13. Van Goor F, Hadida S, Grootenhuys PD, et al. Rescue of CF airway epithelial cell function *in vitro* by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A*. 2009; 106:18825–18830. [PubMed: 19846789]
14. Pezzulo AA, Tang XX, Hoegger MJ, et al. Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. *Nature*. 2012; 487:109–113. [PubMed: 22763554]

15. Derichs N, Jin BJ, Song Y, Finkbeiner WE, Verkman AS. Hyperviscous airway periciliary and mucous liquid layers in cystic fibrosis measured by confocal fluorescence photobleaching. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2011; 25:2325–2332. [PubMed: 21427214]
16. Illek B, Zhang L, Lewis NC, Moss RB, Dong JY, Fischer H. Defective function of the cystic fibrosis-causing missense mutation G551D is recovered by genistein. *Am J Physiol*. 1999; 277:C833–C839. [PubMed: 10516113]
17. Smith JJ, Welsh MJ. cAMP stimulates bicarbonate secretion across normal, but not cystic fibrosis airway epithelia. *J Clin Invest*. 1992; 89:1148–1153. [PubMed: 1313448]
18. Coakley RD, Grubb BR, Paradiso AM, et al. Abnormal surface liquid pH regulation by cultured cystic fibrosis bronchial epithelium. *Proc Natl Acad Sci U S A*. 2003; 100:16083–16088. [PubMed: 14668433]
19. Chang EH, Pezzulo AA, Meyerholz DK, et al. Sinus hypoplasia precedes sinus infection in a porcine model of cystic fibrosis. *Laryngoscope*. 2012; 122:1898–1905. [PubMed: 22711071]
20. Chillón M, Casals T, Nunes V, Gimenez J, Perez Ruiz E, Estivill X. Identification of a new missense mutation (P205S) in the first transmembrane domain of the CFTR gene associated with a mild cystic fibrosis phenotype. *Hum Mol Genet*. 1993; 2:1741–1742. [PubMed: 7505694]
21. Wang X, Moylan B, Leopold DA, et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. *JAMA : the journal of the American Medical Association*. 2000; 284:1814–1819.
22. Lieu JE, Feinstein AR. Confirmations and surprises in the association of tobacco use with sinusitis. *Arch Otolaryngol Head Neck Surg*. 2000; 126:940–946. [PubMed: 10922224]
23. Cantin AM, Hanrahan JW, Bilodeau G, et al. Cystic fibrosis transmembrane conductance regulator function is suppressed in cigarette smokers. *Am J Respir Crit Care Med*. 2006; 173:1139–1144. [PubMed: 16497995]
24. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat*. 2009; 10:1–157.
25. Gustafsson JK, Ermund A, Ambort D, et al. Bicarbonate and functional CFTR channel are required for proper mucin secretion and link cystic fibrosis with its mucus phenotype. *The Journal of experimental medicine*. 2012; 209:1263–1272. [PubMed: 22711878]

Figure 1. Ivacaftor reverses CT findings of CF sinus disease

Sinus CT scans before (A,B) and 10 months after initiating ivacaftor (C,D). Pre-treatment CT scans show bilateral opacified frontal sinuses (black arrow) and maxillary sinus mucosal thickening (white arrow). Ten months after beginning ivacaftor, the frontal sinuses have cleared and the mucosal thickening resolved.

Figure 2. Ivacaftor increased ion transport and ASL pH, and decreased ASL viscosity in primary cultures of sinonasal epithelia

(A) Histology of the cultures revealed pseudostratified, ciliated epithelia. (Scale bar = 10 μm). (B) Effect of ivacaftor on current. Cultures were mounted in Ussing chambers in the presence of a basolateral to apical chloride gradient and current measured under voltage clamp mode using the following protocol: 10 μM forskolin (FSK), 10 μM ivacaftor, and 10 μM CFTR_{inh-172}. 60 μM amiloride was present throughout. (C) Effect of 10 μM ivacaftor on ASL pH. Cultures were exposed to either ivacaftor or DMSO control to the basolateral surface for 2 hours after stimulating phosphorylation with 10 μM forskolin (FSK). ASL pH was measured using a fluorescent pH indicator (SNARF-dextran). Hepes lacking HCO_3^- (pH 7.4) was then applied to the basolateral compartment to reverse the effect. $n = 4$ cultures per group; $*P=0.03$. (D) Effect of 10 μM ivacaftor on ASL viscosity. Cultures were exposed to either ivacaftor or DMSO control to the basolateral surface for 2 hours after stimulating

phosphorylation with 10 μ M forskolin (FSK). ASL viscosity was measured by fluorescence recovery after photobleaching of FITC-dextran. Data are expressed as ASL viscosity of cultures relative to saline (with viscosity of saline=1). $n = 5$ cultures per group; $*P=0.0002$.