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# Improved Clinical and Radiographic Outcomes After Treatment With Ivacaftor in a Young Adult With Cystic Fibrosis With the *P67L* CFTR Mutation

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The underlying cause of cystic fibrosis (CF) is the loss of epithelial chloride and bicarbonate transport due to mutations in the CF transmembrane conductance regulator (CFTR) gene encoding the CFTR protein. Ivacaftor is a gene-specific CFTR potentiator that augments in vivo chloride transport in CFTR mutations affecting channel gating. Originally approved for the *G511D* CFTR mutation, ivacaftor is now approved for eight additional alleles exhibiting gating defects and has also been tested in *R117H*, a CFTR mutation with residual function that exhibits abnormal gating. *P67L* is a class 4 conductance (nongating) mutation exhibiting residual CFTR function. We report marked clinical improvement, normalization of spirometry, and dramatic reduction in radiographic structural airway changes after >1 year of treatment with ivacaftor in a young adult with the compound heterozygous genotype *P67L/F508del* CFTR. The case suggests that ivacaftor may have a potential benefit for patients with CF with nongating mutations.

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**ABBREVIATIONS:** CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator

Despite major advances in management, cystic fibrosis (CF) remains an illness with high morbidity and mortality.[1,2] The underlying cause of CF is the loss of epithelial chloride and bicarbonate transport due to mutations in the CF transmembrane conductance regulator (CFTR) gene encoding the CFTR protein.[3] A new therapeutic approach involves improving the function of mutant CFTR.[4] Ivacaftor (formerly VX-770) is a gene-specific CFTR potentiator that augments in vivo chloride transport in CFTR mutations affecting channel gating, such as *G551D*.[5] Although marked improvements in spirometry, clinical outcome, and sweat chloride were observed in patients with *G551D*-CF treated with ivacaftor,[4,6] its effect on structural lung disease has not been studied. Moreover, although ivacaftor alone has minimal effect on *F508del* homozygous individuals,[7] it has demonstrated in vitro efficacy for conductance mutations other than *G551D* by augmenting gating to supernormal levels[8] but has not yet been

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studied clinically. This includes *P67L*, a class 4 conductance mutation that exhibits residual CFTR function and relatively preserved CFTR expression, has a worldwide prevalence of 0.2%, and is the sixth most common mutation in Scotland.[9] We report a case of a patient with CF who is a complex heterozygote for *P67L/F508del* with severe CF lung disease who improved significantly shortly after starting treatment with ivacaftor, including evidence of resolving structural lung disease.

## Case Report

The patient is an 18-year-old woman of Scottish descent with genotype *F508del/P67L*. Newborn screening for CF revealed an elevated immunoreactive trypsinogen and abnormal genotype. Until adolescence, multiple sweat tests revealed intermediate results (40-60 mmol/L), and she was managed for asthma, with occasional systemic antibiotics for sinopulmonary infections. Repeat sweat test at age 11 years demonstrated a sweat chloride level of 51 mmol/L. Chest and sinus CT scans revealed bronchiectasis and pansinusitis, respectively. At age 18 years, $FEV_1$ and forced expiratory flow midexpiratory phase were 88% and 75% predicted, respectively. Sputum cultures demonstrated chronic mucoid *Pseudomonas aeruginosa* infection. Despite the use of dornase alfa, inhaled antibiotics, azithromycin, and IV antibiotics for pulmonary exacerbations, she experienced several incidents of pulmonary exacerbations associated with $FEV_1$ decline (Fig 1) accompanied by worsening bronchiectasis (Fig 2) and increasing pulmonary exacerbations (three to four episodes per year). She also developed pancreatic insufficiency requiring pancreatic replacement therapy.

Given her clinical trajectory, a trial of ivacaftor 150 mg bid was initiated at age 19 years after a successful physician appeal to her prescription drug provider, which was based on in vitro data and clinical experience. Following initiation of ivacaftor, she experienced improved spirometry, reaching 100% predicted at peak benefit and a mean improvement rate of 8.1 $FEV_1$% predicted per year ($P = .06$ vs rate of change in $FEV_1$% predicted prior to ivacaftor) (Fig 1), a reduction of sweat chloride level from 51 mmol/L to 25 mmol/L (obtained 1 month after initiating ivacaftor therapy), reduced frequency of exacerbations (one over a 1-year follow-up period), and improved pulmonary symptoms. She also gained > 4 kg body weight (a 10% improvement in BMI from pre-ivacaftor baseline). Sputum microbiology significantly improved, in that a culture of *Mycobacterium abscessus* resolved without treatment (confirmed by two serial assessments); *P aeruginosa* mucoidy also resolved as determined by five sequential sputum cultures, which demonstrated nonmucoid *P aeruginosa* in two cultures and no *Pseudomonas* in the other three culture samples). Additionally, the C-reactive protein levels declined from 47.1 mg/L based on historical data to 2.52 mg/L posttherapy. Serial CT scans revealed marked improvement in air trapping and mucous plugging. Multiple ectatic airways decreased in size between the two studies (Fig 2). The Brody score, assessed by a radiologist blinded to CT scan date and treatment data, improved from 58.5 to 42, with improvement in the bronchiectasis component from 24.5 to 21.5, and the air trapping component improved from 16 to 4.5. A marked decrease in large and small airway mucous plugging was seen, with a decrease in the mucous plugging component of the score from 13 to 11.

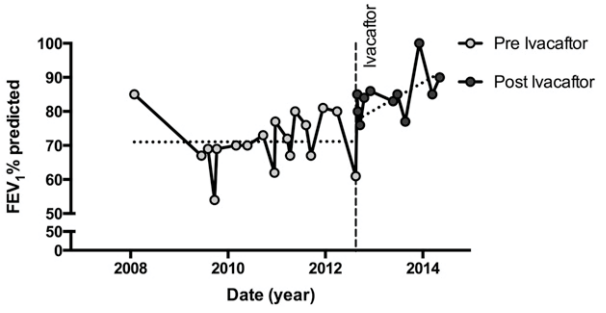


Figure 1 – *Comparison of the average $FEV_1$ of all available measurements obtained during the years prior to ivacaftor and after the start of ivacaftor treatment. Following initiation of ivacaftor, improved spirometry reaching 100% predicted at peak benefit was noted, with a mean improvement rate of 8.1 $FEV_1$% predicted per y (P = .06 vs rate of change in $FEV_1$% predicted prior to ivacaftor).*

## Discussion

This case expands our knowledge about potential benefits of ivacaftor for nongating CFTR mutations. In vitro, ivacaftor has been shown to potentiate the function of 10 gating mutations,[8] with recent reports of clinical[10] and radiographic improvement[11] in such patients. *P67L* is generally considered a CFTR mutation with reduced conductance.[12] Furthermore, Sosnay and colleagues[13] reported lower levels of mature glycosylated protein compared with wild-type CFTR (low band C/B ratio), suggesting an additional abnormality caused by ineffective maturation of *P67L*. Van Goor et al[12] studied the in vitro effect of ivacaftor on multiple mutant CFTR forms due to missense mutations, including mutations that cause abnormal protein processing and reduced CFTR activity at the plasma membrane, such as *P67L*. In vitro, ivacaftor caused a significant increase in chloride current in epithelial cells expressing these mutations.[12] Combined with data illustrated by this case, results strongly indicate that *P67L* is among the mutations that can