Pseudomonas aeruginosa in Cystic Fibrosis Patients With G551D-CFTR Treated With Ivacaftor

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Background. Ivacaftor improves outcomes in cystic fibrosis (CF) patients with the G551D mutation; however, effects on respiratory microbiology are largely unknown. This study examines changes in CF respiratory pathogens with ivacaftor and correlates them with baseline characteristics and clinical response.

Methods. The G551D Observational Study enrolled a longitudinal observational cohort of US patients with CF aged 6 years and older with at least 1 copy of the G551D mutation. Results were linked with retrospective and prospective culture data in the US Cystic Fibrosis Foundation’s National Patient Registry. Pseudomonas aeruginosa infection category in the year before and year after ivacaftor was compared and correlated with clinical findings.

Results. Among 151 participants prescribed ivacaftor, 29% (26/89) who were culture positive for P. aeruginosa the year prior to ivacaftor use were culture negative the year following treatment; 88% (52/59) of those P. aeruginosa free remained uninfected. The odds of P. aeruginosa positivity in the year after ivacaftor compared with the year prior were reduced by 35% (odds ratio [OR], 0.65; P < .001). Ivacaftor was also associated with reduced odds of mucoid P. aeruginosa (OR, 0.77; P = .013) and Aspergillus (OR, 0.47; P = .039), but not Staphylococcus aureus or other common CF pathogens. Patients with intermittent culture positivity and higher forced expiratory volume in 1 second (FEV1) were most likely to turn culture negative. Reduction in P. aeruginosa was not associated with change in FEV1, body mass index, or hospitalizations.

Conclusions. Pseudomonas aeruginosa culture positivity was significantly reduced following ivacaftor treatment. Efficacious CFTR modulation may contribute to lower frequency of culture positivity for P. aeruginosa and other respiratory pathogens, particularly in patients with less established disease.

Keywords. cystic fibrosis; CFTR modulator; ivacaftor; P. aeruginosa.

Cystic fibrosis (CF) is an ion transport disorder resulting from heritable mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The disease is characterized by inadequate mucociliary clearance of the lung, chronic infection, inflammation, and structural damage of the airways; most CF patients eventually experience lung function decline and premature death [1]. The CFTR potentiator ivacaftor treats the protein defect in CF patients with a G551D or other gating mutation by improving CFTR function, augmenting anion transport and reducing sweat chloride concentrations—a diagnostic criterion for CF [2, 3]. Clinical trials evaluating ivacaftor in CF patients with the G551D CFTR mutation showed significant improvements in lung function, exacerbation rate, weight gain, and CF-specific quality-of-life measures [2, 4], leading to drug approval and widespread use in the US population.

Pseudomonas aeruginosa is one of the hallmark pathogens in the CF lung and is strongly associated with
increased morbidity [5–7] and mortality [8]. Preliminary findings from an observational study of ivacaftor in CF patients with at least 1 copy of the G551D mutation (the G551D Observational [GOAL] study) indicated a marked decrease in *P. aeruginosa* culture positivity after initiation of ivacaftor [9]. The objectives of this analysis were to (1) comprehensively describe microbiologic changes in common CF pathogens, including *P. aeruginosa*, in G551D participants after starting ivacaftor; (2) determine baseline clinical characteristics associated with reduced frequency of *P. aeruginosa* culture positivity after initiation of ivacaftor; and (3) examine whether changes in *P. aeruginosa* positivity were associated with clinical outcomes following initiation of ivacaftor. We hypothesized that ivacaftor treatment would be associated with a significant reduction in *P. aeruginosa* culture positivity.

**METHODS**

**Study Design**

A longitudinal observational cohort study was initiated in 2012 at 28 US Cystic Fibrosis Therapeutic Development Network–accredited sites to follow CF patients aged ≥6 years with at least 1 copy of the G551D mutation [9]. Each participant/guardian gave written informed consent, and site institutional review boards approved the study. All enrolled participants had no prior exposure to ivacaftor. Upon the decision to prescribe ivacaftor, clinical assessments included spirometry, weight, height, and sweat chloride analysis at baseline and at 1, 3, and 6 months after ivacaftor initiation. Study data were augmented by linked microbiology, hospitalization, and CF medication data collected in the Cystic Fibrosis Foundation’s National Patient Registry (CFFNPR) [10]. Investigators were encouraged to follow CF treatment guidelines [11, 12] including surveillance respiratory cultures every 3 months or with change in clinical status.

**Outcomes and Analysis Variables**

CFFNPR data from the year before and the year after ivacaftor initiation were used to ascertain number of respiratory cultures, specimen type (sputum or oropharyngeal [OP] swab), number of culture positives for CF pathogens (*P. aeruginosa*, mucoid *P. aeruginosa*, methicillin-susceptible *Staphylococcus aureus* [MSSA], methicillin-resistant *Staphylococcus aureus* [MRSA], *Stenotrophomonas maltophilia*, *Haemophilus influenzae*, *Burkholderia cepacia* complex, and *Aspergillus* species), number of hospitalizations (for any reason), number of pulmonary exacerbations (treated in hospital or via home intravenous antibiotics), and use of maintenance CF therapies. Respiratory culture data from 2 years before ivacaftor were also obtained to serve as a control comparator.

Participants’ *P. aeruginosa* infection categories were defined within each year interval according to modified Leed criteria as infection free (no positive cultures), intermittent infection (≤50% culture positive), or persistent infection (>50% culture positive) [13]. Because these criteria are dependent on the number of cultures performed, a sensitivity analysis was done on the subset of participants with ≥3 cultures in each year. For associations with clinical outcomes, each participant was categorized as either experiencing a reduction in *P. aeruginosa* after initiation of ivacaftor (eg, shift of *P. aeruginosa* infection category from persistent to intermittent or free, or intermittent to free) or as experiencing no change or increased frequency of positive cultures.

The change in forced expiratory volume in 1 second (FEV1) percentage predicted [14, 15] and body mass index (BMI) were calculated from baseline through 12 months after starting ivacaftor, whereas change in sweat chloride was calculated from baseline through 6 months. Hospitalization rate (for any reason) for each participant each year (pre- and postivacaftor) accounted for observed follow-up time, as did pulmonary exacerbation rate (treated in hospital or at home with intravenous antibiotics).

**Statistical Analysis**

Summary statistics (eg, mean, standard deviation [SD], proportion) were used to describe the cohort. Analysis of variance, *t* test, and Fisher exact test were used to compare groups, and McNemar test for paired data was used to compare pre-ivacaftor to post-ivacaftor microbiologic findings, including shift in *P. aeruginosa* infection category, which tests the null hypothesis of no distributional change in category by time period. Repeated measures logistic regression with a compound symmetric error structure for each individual estimated the odds of culture positivity, accounting for number of and type of respiratory culture specimens, and use of concomitant chronic CF therapies.

Sensitivity analyses were performed that assumed those participants with missing respiratory cultures or with <3 cultures in the year post-ivacaftor had positive cultures for *P. aeruginosa* at the missing time points. Multivariable regression was used to determine the association of change in *P. aeruginosa* (infection category and continuous reduction) after ivacaftor with changes in FEV1, BMI, and hospitalization rate—adjusting for sex, age, *P. aeruginosa* in year prior, baseline FEV1, and baseline sweat chloride. All covariates were selected a priori as known potential predictors of clinical response. *P* values and confidence intervals (CIs) are 2-sided, with .05 significance level; analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

**RESULTS**

**Cohort Description**

There were 153 participants in the GOAL study; 2 did not receive ivacaftor and were not analyzed further; thus, 151 were
prescribed and initiated ivacaftor from February through September 2012. The cohort was 46% female and 54% aged ≥18 years. Lung function distribution showed that 30% had baseline FEV₁ <70% predicted, 26% were 70%–89% and 90% or higher predicted, and 44% had a baseline FEV₁ 90% or higher predicted; more detailed characteristics are reported elsewhere [9]. Median follow-up in the CFFNPR at the time of analysis was 12.5 months after initiation of ivacaftor. Seventy-six percent (n = 115) had ≥10 months’ follow-up in the year after ivacaftor initiation. Baseline characteristics presented by *P. aeruginosa* infection category in the year before ivacaftor are presented in Table 1. Among the 148 of 151 participants (98%) with respiratory cultures in the year prior to ivacaftor, 40% (59/148) had persistent infection (>50% of cultures in the year *P. aeruginosa* positive), 20% (30/148) intermittent infection (1%–50% of cultures *P. aeruginosa* positive), and 40% (59/148) were infection free. Participants with persistent infection were older, had lower FEV₁, and higher hospitalization rates at baseline (Table 1).

**Changes in the Prevalence of CF Pathogens Before and After Ivacaftor Use**

The prevalence of common CF pathogens among respiratory cultures obtained in the 2 years before and the year after ivacaftor use are shown in Figure 1. The prevalence of *P. aeruginosa*, mucoid *P. aeruginosa*, and *Aspergillus* species decreased significantly with ivacaftor use, whereas there was no significant change in MSSA, MRSA, *H. influenzae*, or *S. maltophilia*. Paired comparisons among the 134 with respiratory results in both years yield identical findings; notably, 27% (15/55) of those with mucoid *P. aeruginosa* prior to ivacaftor did not have mucoid *P. aeruginosa* in the year after (P < .01). There were no differences in prevalence between 2 years and 1 year pre-ivacaftor.

Because there were more respiratory cultures overall (mean, 3.7 [SD, 1.8] vs 3.0 [SD, 1.7]; P < .001) and more sputum cultures (mean, 2.4 [SD, 1.9] vs 1.9 [SD, 1.8]; P = .01) in the years prior to ivacaftor use vs after, multivariable logistic regression was performed to estimate the odds of respiratory culture positivity after ivacaftor, adjusting for number and type of respiratory culture (Table 2). Ivacaftor reduced the odds of *P. aeruginosa* culture positivity by 35% (odds ratio [OR], 0.65; P < .001), adjusting for sputum (vs OP swabs) and number of cultures performed in each year treatment interval. Similarly, ivacaftor significantly reduced the odds of culture positivity for mucoid *P. aeruginosa* (23% reduction), and *Aspergillus* (53% reduction) but not MSSA, MRSA, or *S. maltophilia* (Table 2). In contrast, there was a significant increase in *H. influenzae* following ivacaftor therapy (OR, 2.13; 95% CI, 1.15–3.96; P = .017). Chronic CF therapies were not significantly altered after ivacaftor (Supplementary Table 1), and adjustment for inhaled tobramycin, macrolide, oral antibiotic, dornase alfa, and hypertonic saline use produced similar results (data not shown).

**Table 1. Characteristics of Study Participants Prior to Ivacaftor Initiation, by Pseudomonas aeruginosa Infection Category**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Free (n = 59)</th>
<th>Intermittent (n = 30)</th>
<th>Persistent (n = 59)</th>
<th>NA (n = 3)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>26 (44.1)</td>
<td>17 (56.7)</td>
<td>27 (45.8)</td>
<td>0 (0.0)</td>
<td>.26</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>18.3 (11.5)</td>
<td>17.6 (11.3)</td>
<td>25.6 (10.1)</td>
<td>23.0 (3.3)</td>
<td>.001</td>
</tr>
<tr>
<td>6–11 y</td>
<td>22 (37.3)</td>
<td>10 (33.3)</td>
<td>6 (10.2)</td>
<td>0 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12–17 y</td>
<td>16 (27.1)</td>
<td>8 (26.7)</td>
<td>8 (13.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>≥18 y</td>
<td>21 (35.6)</td>
<td>12 (40.0)</td>
<td>45 (76.3)</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>FEV₁ % predicted at baseline, mean (SD)</td>
<td>88.4 (24.3)</td>
<td>93.6 (23.2)</td>
<td>72.6 (24.1)</td>
<td>57.5 (28.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FEV₁ predicted at baseline &lt;90%</td>
<td>28 (47.5%)</td>
<td>10 (33.3)</td>
<td>43 (72.9)</td>
<td>3 (100)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Genotype class of other allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>45 (76.3)</td>
<td>25 (83.3)</td>
<td>51 (86.4)</td>
<td>3 (100)</td>
<td>.77</td>
</tr>
<tr>
<td>III–V</td>
<td>8 (13.6)</td>
<td>2 (6.7)</td>
<td>4 (6.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (10.2)</td>
<td>3 (10.0)</td>
<td>4 (6.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>21.1 (5.9)</td>
<td>20.1 (3.2)</td>
<td>22.1 (3.4)</td>
<td>21.4 (2.7)</td>
<td>.28</td>
</tr>
<tr>
<td>BMI z scoreb, No., mean (SD)</td>
<td>41, 0.08 (0.99)</td>
<td>22, 0.18 (0.99)</td>
<td>19, 0.20 (0.69)</td>
<td>0, NA</td>
<td>.87</td>
</tr>
<tr>
<td>Hospitalization rate, count/person/year, mean (SD)</td>
<td>0.42 (0.70)</td>
<td>0.60 (0.81)</td>
<td>1.0 (1.5)</td>
<td>0 (0)</td>
<td>.01</td>
</tr>
<tr>
<td>Pulmonary exacerbation rate, count/person/year, mean (SD)</td>
<td>0.53 (0.97)</td>
<td>0.60 (0.86)</td>
<td>1.26 (1.88)</td>
<td>0 (0)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; NA, not available; Pa, *Pseudomonas aeruginosa*; SD, standard deviation.

a Free: 0% of respiratory cultures *Pa* positive; intermittent: 1%–50% *Pa* positive; persistent: >50% *Pa* positive.

b Three participants did not have recorded respiratory culture results in year prior to ivacaftor.

c BMI z scores for those aged <20 years at baseline using US Centers for Disease Control and Prevention growth charts.
Change in *P. aeruginosa* Infection Category

In the year after ivacaftor, there was a significant shift in the distribution of *P. aeruginosa* infection categories (Table 3; \(P < .001\)): 27% (36/134) had less frequent isolation of *P. aeruginosa* (ie, reduction of infection category), 5% (7/134) had more frequent isolation, and 68% (91/134) did not change (Figure 2). Seventy percent (21/30) of those with intermittent infection were *P. aeruginosa* infection free after initiation of ivacaftor, compared with only 10% (5/48) of those with persistent infection (\(P < .001\)). Findings remained significant with a sensitivity analysis that assumed everyone without respiratory cultures in a year had *P. aeruginosa* culture positivity. In contrast to the change observed with ivacaftor, *P. aeruginosa* infection category shift between the 2 years before ivacaftor are shown in Supplementary Table 2; there was no significant change in the distribution of *P. aeruginosa* frequency (\(P = .95\)) in the absence of ivacaftor: 15% (21/139) had less frequent *P. aeruginosa*, 14% (20/139) had more frequent isolation, and 71% (98/139) did not change.

To further evaluate the robustness of these findings, we limited the analysis to those participants with \(\geq 3\) respiratory cultures in the year prior to ivacaftor initiation. Seventy-eight percent (118/151) of participants met this criteria and had a similar distribution of change in *P. aeruginosa* status (Supplementary Table 3). Among participants with \(\geq 3\) cultures in both years, there was a significant reduction in the distribution of *P. aeruginosa* isolation frequency category (\(P = .014\); Figure 2). Again, among those with \(\geq 3\) cultures in both years, participants with intermittent infection were more likely to be infection free after ivacaftor than the participants with persistent infection (70% [14/20] vs 7% [2/27], respectively; \(P < .001\)). A sensitivity analysis assuming that participants with \(< 3\) respiratory cultures in a year were persistently infected also showed a significant (\(P = .017\)) reduction in *P. aeruginosa* status, driven by the high proportion of intermittent participants who were *P. aeruginosa* free in the year following ivacaftor.

*Pseudomonas aeruginosa* infection category and other clinical characteristics are presented by their change in infection...
status to assess possible associations (Table 4). Higher FEV$_1$ at baseline was the only other baseline clinical characteristic shown to be associated with reduction in *P. aeruginosa* frequency after ivacaftor initiation (92.5 vs 81.3%; *P* = .024).

**Associations With Clinical Outcomes**

Overall for the entire cohort, there were significant improvements in FEV$_1$ percentage predicted (mean change, 5.7% [95% CI, 3.8%–7.5%]; *P* < .001), BMI (1.0 kg/m$^2$ [95% CI, .76–1.24 kg/m$^2$]; *P* < .001), hospitalization rate (−0.45 [95% CI, −0.60 to −0.30]) admissions/participant/year; *P* < .001), and pulmonary exacerbations/participant/year (−0.57 [95% CI, −0.78 to −0.36]; *P* < .001) 1 year after ivacaftor initiation. Although there were differences in age, baseline FEV$_1$, and hospitalization rate with *P. aeruginosa* infection category in the year before ivacaftor (Table 1), reduction in *P. aeruginosa* frequency with ivacaftor was not significantly associated with improvement in FEV$_1$, BMI, hospitalization, or exacerbation rate alone (Table 4), or after adjustment for year-prior *P. aeruginosa* infection category, sex, age, baseline FEV$_1$, or sweat chloride.
(Supplementary Table 4). However, when \textit{P. aeruginosa} culture positivity was analyzed as a continuous variable based on the proportion of positive cultures, we detected a weak but statistically significant association with FEV\(_1\) improvement: a 10% reduction in \textit{P. aeruginosa} positivity corresponds with a 0.765% increase in FEV\(_1\) percentage predicted (95% CI, 0.04%–1.5%; \(P = .030\); Supplementary Table 5).

**DISCUSSION**

This is the first report on CF respiratory pathogens after clinical exposure to the CFTR modulator ivacaftor. Significant reductions in \textit{P. aeruginosa} culture positivity (both overall and mucoid isolates) were observed in CF patients with at least 1 copy of the G551D mutation who were prescribed ivacaftor as part of clinical care. Reductions were not observed in the same cohort over the preceding 2-year period in the absence of ivacaftor. Participants with intermittent infection in the year prior to ivacaftor as well as those with higher FEV\(_1\) at the time of ivacaftor initiation had greater likelihoods of experiencing reduced frequency of \textit{P. aeruginosa} culture positivity compared to those with persistent infection (>50% cultures positive). To address variation in clinical care among centers, a number of sensitivity analyses were performed to account for differential follow-up, specimen type, respiratory culture frequency, changes in concomitant chronic CF medications, and missing data. All of these substantiate the overall findings that there was a decrease in the frequency of \textit{P. aeruginosa}-positive cultures associated with ivacaftor among CF patients with G551D.

The underlying mechanisms responsible for the susceptibility of the CF lung to \textit{P. aeruginosa} infection are challenging to define and cannot be answered by this observational study [16]. However, several hypotheses relate directly to CFTR function, including \textit{P. aeruginosa} adherence to airway epithelial cells [17], CFTR as a receptor of \textit{P. aeruginosa} lipopolysaccharide [18], and alteration of CFTR expression by \textit{P. aeruginosa} cytotoxins [19]. Changes in CF-specific pathogens may be attributed to increased mucociliary clearance [9]; sloughing of bacteria-laden epithelial cells [20] and biofilms due to improved chloride transport could also contribute. CFTR modulation can also lead to increased bicarbonate secretion, elevating pH, which may produce an antagonistic airway environment for \textit{P. aeruginosa} by augmenting defense-related bacterial killing [21]. There is evidence that ivacaftor raises the pH in the gastrointestinal tract in CF [9]; however, its effects on airway pH are not yet known. Although in vitro data have shown that ivacaftor may have quinolone-like anti-infective properties against \textit{S. aureus},

<table>
<thead>
<tr>
<th>Pa Infection Category in Year Prior to Ivacaftor</th>
<th>No. (%) of Participants (N = 151)</th>
<th>Pa Infection Category in Year After Ivacaftora</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Free</td>
<td>Intermittent</td>
</tr>
<tr>
<td>Free</td>
<td>59 (39.1)</td>
<td>52 (88.1)</td>
</tr>
<tr>
<td>Intermittent</td>
<td>30 (19.9)</td>
<td>21 (70.0)</td>
</tr>
<tr>
<td>Persistent</td>
<td>59 (39.1)</td>
<td>5 (8.5)</td>
</tr>
<tr>
<td>No cultures</td>
<td>3 (2.0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Abbreviation: Pa, \textit{Pseudomonas aeruginosa}.

\(\text{a Free: 0\% of respiratory cultures Pa positive; intermittent: 1\%–50\% Pa positive; persistent: >50\% Pa positive.}\)

**Figure 2.** Change in \textit{Pseudomonas aeruginosa} frequency from year before to after ivacaftor initiation, stratified by number of respiratory cultures per year. Reduction includes transition from persistent infection (>50%) to intermittent infection (1%–50%) or infection free (0%), and intermittent infection to infection free. Increase includes transition from infection free to intermittent infection or persistent infection, and intermittent infection to persistent infection.
but not *P. aeruginosa* [22], no change in *S. aureus* (methicillin-sensitive or -resistant) was exhibited. Although less prevalent overall, there was a significant reduction of culture positivity for *Aspergillus* species, a pathogen associated with absent CFTR function [23] and worsened clinical outcomes, particularly when it is corresponds with allergic bronchopulmonary aspergillosis [24]. In contrast, we also observed an increase in *H. influenzae* culture positivity in this population. Interestingly, this is an organism generally seen early in the pathogenesis of CF [25, 26]. Complete PCR-based microbiome analysis in a subset of these GOAL participants found modest reductions in the relative abundance of CF pathogens and an increase in the anaerobe *Prevotella* [27], consistent with these findings that there may be a shift toward “normal” or less severe respiratory flora with efficacious CFTR modulation. Longer observation and more in-depth examination of the complex interaction between CF microbiota might elucidate these and other more subtle effects of ivacaftor.

**Table 4. Characteristics of Cohort by *Pseudomonas aeruginosa* Infection Category Change**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Change or Increase (n = 98)</th>
<th>Reduction* (n = 36)</th>
<th>NA** (n = 17)</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, No. (%)</td>
<td>43 (43.9)</td>
<td>19 (52.8)</td>
<td>8 (47.1)</td>
<td>.36</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>20.8 (11.4)</td>
<td>18.6 (11.4)</td>
<td>28.0 (8.5)</td>
<td>.32</td>
</tr>
<tr>
<td>6–11 y, No. (%)</td>
<td>25 (25.5)</td>
<td>13 (36.1)</td>
<td>0 (0)</td>
<td>.63</td>
</tr>
<tr>
<td>12–17 y, No. (%)</td>
<td>26 (26.5)</td>
<td>6 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>≥18 y, No. (%)</td>
<td>47 (48.0)</td>
<td>17 (47.2)</td>
<td>17 (100)</td>
<td></td>
</tr>
<tr>
<td>FEV1, % predicted at baseline</td>
<td>81.3 (25.7)</td>
<td>92.5 (22.6)</td>
<td>69.4 (25.0)</td>
<td>.024</td>
</tr>
<tr>
<td>FEV1 predicted at baseline &lt;90%, No. (%)</td>
<td>58 (59.2)</td>
<td>12 (33.3)</td>
<td>14 (82.4)</td>
<td>.008</td>
</tr>
<tr>
<td>Genotype class of other allele, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>79 (80.6)</td>
<td>32 (88.9)</td>
<td>13 (76.5)</td>
<td>.10</td>
</tr>
<tr>
<td>III–V</td>
<td>11 (11.2)</td>
<td>0 (0)</td>
<td>3 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (8.2)</td>
<td>4 (11.1)</td>
<td>1 (6.9)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.3 (5.0)</td>
<td>20.2 (3.3)</td>
<td>23.2 (3.1)</td>
<td>.14</td>
</tr>
<tr>
<td>Hospitalization rate, count/person/year</td>
<td>0.65 (1.1)</td>
<td>0.72 (1.0)</td>
<td>0.86 (1.4)</td>
<td>.75</td>
</tr>
<tr>
<td><em>Pa</em> infection category in year prior to ivacaftor, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free</td>
<td>56 (57.1)</td>
<td>. . .</td>
<td>3 (17.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intermittent</td>
<td>9 (9.2)</td>
<td>21 (58.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>33 (33.7)</td>
<td>15 (41.7)</td>
<td>11 (64.7)</td>
<td></td>
</tr>
<tr>
<td>No respiratory cultures</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Change after ivacaftor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 % predictedd</td>
<td>4.5 (11.4)</td>
<td>6.6 (9.6)</td>
<td>10.7 (13.0)</td>
<td>.31</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.1 (1.5)</td>
<td>0.9 (1.4)</td>
<td>0.7 (1.9)</td>
<td>.52</td>
</tr>
<tr>
<td>Hospitalization rate, count/person/year</td>
<td>−0.36 (0.92)</td>
<td>−0.58 (0.81)</td>
<td>−0.77 (1.3)</td>
<td>.20</td>
</tr>
<tr>
<td>Pulmonary exacerbation rate, count/person/year</td>
<td>−0.46 (1.18)</td>
<td>−0.64 (1.05)</td>
<td>−1.23 (2.24)</td>
<td>.43</td>
</tr>
<tr>
<td>Sweat chloride, mmol/L</td>
<td>−57.9 (19.7)</td>
<td>−64.1 (16.0)</td>
<td>−52.2 (17.4)</td>
<td>.12</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise indicated.

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 second; NA, not available; *Pa*, *Pseudomonas aeruginosa*; SD, standard deviation.

* Reduction in *Pa* infection category with ivacaftor (eg, intermittent to free, or persistent to intermittent or free) vs no change or increase in *Pa* infection category.

* Seventeen participants did not have recorded respiratory culture results in year prior to and after ivacaftor.

* P value test of no change or increase vs reduction; NA not included.

* Change per subject from baseline through 12 months after initiation of ivacaftor (data from Cystic Fibrosis Foundation’s National Patient Registry).

* Maximal change per subject from baseline through 6 months after initiation of ivacaftor.
relationship between early indicators of CFTR recovery and clinical outcomes is complex, further evaluation of sweat chloride, mucociliary clearance, pH, inflammation, and CF respiratory pathogens as possible predictors of clinical response may reveal an important prognostic biomarker or panel of markers.

This observational study is subject to the potential biases one might expect from the epidemiologic collection of patient data [29]. There was differential follow-up between the year before and the year after ivacaftor initiation with regard to duration, and number and type of respiratory cultures. This observation may be due to improved patient health, reducing expectoration or opportunities to collect samples; chance; or another unobservable reason. Because of the potential sampling bias this might introduce [30], logistic regression was performed to adjust for number of cultures during each year and type of respiratory culture, which showed substantial reduction in culture positivity for both *P. aeruginosa* and mucoid *P. aeruginosa*.

Similarly, sensitivity analyses of only participants with at least 3 respiratory cultures and of a “worst case” where those missing data were treated as persistently infected produced results nearly identical to those using the primary data. The reported changes in microbiology are unlikely attributed to the unblinded nature of the study, as cultures are a relatively objective respiratory biologic measure. Although there is the possibility of confounding by concomitant medications or other latent exposures, significant reductions in respiratory bacterial burden were observed when adjusted for factors known to impact *P. aeruginosa* in CF. Less restrictive cohort studies are often more generalizable than data obtained in randomized controlled studies; nevertheless, the G551D CF patients who enrolled in this study may be unique in that some individuals may not have qualified or chose to enroll in concurrent clinical trials. Nevertheless, the clinical response in FEV₁ and BMI among the GOAL participants was consistent with that observed in controlled trials [2, 4, 9], indicating that these participants are likely representative. Further analyses of CFFNPR could be used to determine whether these microbiologic findings persist in all CF patients with G551D or over a longer observation period; however, we showed that these reductions were not observed in the same cohort 2 years prior to ivacaftor in the absence of CFTR modulation.

Reducing the burden of *P. aeruginosa* in CF patients is likely to be highly significant over the long term, and could alter the natural history of the disease [31]. There is reason to surmise that early eradication could positively impact pulmonary exacerbations, lung function, and even survival [5–8, 32]. The 25%–35% reduction in *P. aeruginosa* culture positivity observed within the GOAL cohort is greater than the 10%–20% reductions observed in ecologic studies spanning 1990 to 2005—a period associated with numerous therapeutic improvements, including the introduction of aerosolized antibiotics, early eradication routines, dornase alfa, and azithromycin [33, 34], and is more consistent with reductions seen due to eradication strategies [35, 36]. Although spontaneous clearance can occur [37, 38], aggressive antipseudomonal therapy may not only eradicate the organism, improving outcomes [39], but could also prolong time to chronic infection [40, 41] or development of mucoidy [31]. The mucoid phenotype is more resistant to antibiotics and immunologic defense [31] and is associated with poorer prognosis [8, 42]. Mucoid *P. aeruginosa* is thought to have limited treatment options [43, 44]; however, recent data indicate that eradication may be possible [45–47]. Ivacaftor or other CFTR modulators in development may be a surprisingly useful tool for early eradication or prevention of CF respiratory infections, even in those with mucoid *P. aeruginosa*, and warrants prospective evaluations. It is possible that CFTR modulators will supplement or augment certain anti-infectives’ activity as shown in vitro [22] without promoting antibiotic resistance, while also improving lung function and growth beyond what has been seen from antibiotic regimens alone. Further examination of the potential interaction between ivacaftor and other CF therapies such as mucolytics, antibiotics, or specific eradication regimens in vivo is warranted and may reveal long-term efficacy beyond the immediate improvements in weight, lung function, and exacerbation rate.

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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