CORRESPONDENCE

Ivacaftor-treated Patients with Cystic Fibrosis Derive Long-Term Benefit Despite No Short-Term Clinical Improvement

To the Editor:

Ivacaftor was the first cystic fibrosis transmembrane conductance regulator (CFTR) modulator approved by the U.S. Food and Drug Administration, and has been shown to rapidly improve FEV_1, body mass index (BMI), and symptoms in patients with cystic fibrosis (CF) with the G551D-CFTR (1, 2) and other gating mutations (3). It has also been shown to improve the rate of FEV_1 decline (4). However, some ivacaftor-treated patients fail to show an immediate benefit, and it is unknown whether the absence of a short-term response is predictive of subsequent FEV_1 rate of decline, pulmonary exacerbation rate, or BMI. We hypothesized that patients without short-term improvements would still experience long-term benefit.

One-month changes in FEV_1 and BMI in ivacaftor-treated participants aged 6 years and older in the GOAL (G551D Observational) study cohort (2) were combined with spirometry, BMI, and hospitalization data from the U.S. Cystic Fibrosis Foundation's Patient Registry (5). For each participant with at least one G551D-CFTR allele, estimates of FEV_1 change per year (based on Global Lung Function Initiative percentage predicted [PP] equations [6]), BMI (kg/m^2/yr), and pulmonary exacerbation (PEx) rate requiring hospitalization were calculated for the 2-year periods before and after starting ivacaftor to determine whether short-term response to ivacaftor was associated with change in the trajectory of key clinical measures of CF. Written informed consent was obtained, and the study was approved by site institutional review boards.

The GOAL cohort is described elsewhere (2, 7). Briefly, the participants were 46% female, with a mean age of 21.1 years at enrollment (46% were 6–17 yr of age); 87% of the non–G551D-CFTR mutations were minimally functional (8); mean baseline FEV_1 PP was 81%, and 52% were *Pseudomonas aeruginosa*–positive. Overall, FEV_1 increased by 7 PP (95% confidence interval [CI], 5–8) at 1 month postivacaftor; however, 22% (32/144) had no change or a decrease in FEV_1 PP 1 month after starting ivacaftor (nonresponder). BMI increased 0.3 kg/m^2 at 1 month, but 28% had no change or a decrease in BMI (nonresponder). Characteristics of ivacaftor-treated responders and nonresponders with respect to FEV_1 and BMI are shown in Table 1.

Responder and Nonresponder Outcomes at 2 Years and Changes in Clinical Trajectory

To examine differences in 2-year outcomes between short-term ivacaftor responders and nonresponders, we assessed the annual rate of PEx, changes in BMI, and FEV_1 decline, all compared with the 2-year window before ivacaftor initiation. Overall, there was a significant reduction in PEx after initiation of ivacaftor from 0.71 to 0.38 PEx/yr (rate ratio [RR], 0.53; 95% CI, 0.38–0.75; $P < 0.001$). PEx reduction was from 0.70 PEx/yr (95% CI, 0.52–0.94) to 0.38 PEx/yr (95% CI, 0.26–0.57; RR, 0.55 [95% CI, 0.38–0.80; $P = 0.002$]) and from 0.76 PEx/yr (95% CI, 0.46–1.27) to 0.37 PEx/yr (95% CI, 0.16–0.86; RR, 0.49 [95% CI, 0.21–1.11;

Table 1. Characteristics and Outcomes of the G551D Observational Cohort by 1 Month FEV_1 and BMI Responder Status

Demographics and Baseline Characteristics	FEV_1 1-Month Response to Ivacaftor		BMI 1-Month Response to Ivacaftor	
	Non-responders (≤0 ↑ FEV_1 PP) (n = 32)	Responders (>0 ↑ FEV_1 PP) (n = 112)	Nonresponders (≤0 ↑ kg/m^2) (n = 40)	Responders (>0 ↑ kg/m^2) (n = 104)
Female, n (%)	18 (56%)	49 (44%)	22 (55%)	45 (43%)
Age, mean (SD)	16.0 (9.9)	22.6 (11.7)	23.7 (13.4)	20.1 (10.8)
Other CFTR allele, n (%)				
Not active	26 (81%)	100 (89%)	35 (88%)	91 (88%)
Partially active	3 (9%)	4 (4%)	3 (8%)	4 (4%)
Unknown	3 (9%)	8 (7%)	2 (5%)	9 (9%)
Baseline FEV_1 PP, mean (SD)	91.7 (25.5)	78.1 (24.3)	83.0 (27.1)	80.4 (24.4)
Baseline sweat chloride mEq/L, mean (SD)	101.5 (12.5)	103.1 (14.5)	100.7 (21.6)	103.4 (10.0)
Baseline BMI, kg/m^2, mean (SD)	19.2 (3.9)	21.6 (4.3)	22.1 (5.2)	20.7 (3.8)
CF-related diabetes, n (%)	7 (22%)	35 (31%)	14 (35%)	28 (27%)
Pa on respiratory culture, n (%)	19 (59%)	79 (71%)	31 (78%)	67 (64%)

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductace regulator; *Pa* = *Pseudomonas aeruginosa*; PP = percentage predicted via Global Lung Function Initiative equations.

Table 2. Two Year Pre- and Postivacaftor Pulmonary Exacerbations, BMI, and FEV₁ by 1 Month FEV₁ and BMI Responder Status

2-Year Outcomes	FEV₁ 1-Month Response to Ivacaftor			BMI 1-Month Response to Ivacaftor		
	Nonresponders (≤0 ↑ FEV₁PP)	Responders (>0 ↑ FEV₁ PP)	Difference (Responder − Nonresponder)	Nonresponders (≤0 ↑ kg/m²)	Responders (>0 ↑ kg/m²)	Difference (Responder − Nonresponder)
PEx rate/yr preivacaftor, mean (95% CI)	0.76 (0.46 to 1.27)	0.70 (0.52 to 0.94)	0.92 (0.51 to 1.65)	0.78 (0.53 to 1.16)	0.69 (0.50 to 0.95)	0.88 (0.53 to 1.47)
PEx rate/yr postivacaftor, mean (95% CI)	0.37 (0.16 to 0.86)	0.38 (0.26 to 0.57)	1.03 (0.41 to 2.61)	0.42 (0.22 to 0.80)	0.37 (0.24 to 0.56)	0.86 (0.40 to 1.86)
PEx rate ratio (postivacaftor: preivacaftor) (95% CI)	0.49 (0.21 to 1.11)	**0.55 (0.38 to 0.80)**	1.13 (0.46 to 2.79)	**0.54 (0.33 to 0.89)**	**0.53 (0.34 to 0.82)**	0.98 (0.50 to 1.90)
BMI/yr preivacaftor, mean (95% CI)	0.57 (0.21 to 0.92)	0.18 (−0.01 to 0.37)	−0.39 (−0.79 to 0.01)	0.59 (0.28 to 0.90)	0.14 (−0.05 to 0.34)	**−0.44 (−0.81 to −0.08)**
BMI/yr postivacaftor, mean (95% CI)	0.38 (0.03 to 0.73)	0.36 (0.18 to 0.55)	−0.02 (−0.41 to 0.37)	0.21 (−0.09 to 0.52)	0.42 (0.23 to 0.61)	0.21 (−0.15 to 0.56)
BMI difference (postivacaftor: preivacaftor) (95% CI)	−0.19 (−0.42 to 0.05)	**0.18 (0.05 to 0.31)**	0.37 (0.10 to 0.64)	**−0.37 (−0.59 to −0.16)**	**0.28 (0.15 to 0.41)**	**0.65 (0.40 to 0.90)**
FEV₁ PP/yr preivacaftor, mean (95% CI)	−2.27 (−4.44 to −0.10)	−1.92 (−3.08 to −0.77)	0.35 (−2.11 to 2.81)	0.20 (−1.75 to 2.15)	−2.87 (−4.08 to −1.66)	**−3.07 (−5.36 to −0.77)**
FEV₁ PP/yr postivacaftor, mean (95% CI)	−0.57 (−2.63 to 1.50)	−1.58 (−2.67 to −0.49)	−1.01 (−3.35 to 1.32)	−0.94 (−2.82 to 0.93)	**−1.52 (−2.65 to −0.38)**	**−0.57 (−2.76 to 1.62)**
FEV₁ difference (postivacaftor: preivacaftor) (95% CI)	1.71 (−0.52 to 3.93)	0.34 (−0.84 to 1.53)	−1.36 (−3.88 to 1.16)	−1.15 (−3.17 to 0.88)	1.35 (0.13 to 2.58)	2.50 (0.13 to 4.87)

Definition of abbreviations: BMI = body mass index; CI = confidence interval; PEx = pulmonary exacerbation; PP = percentage predicted via Global Lung Function Initiative equations.
Bold text indicates P value < 0.05.
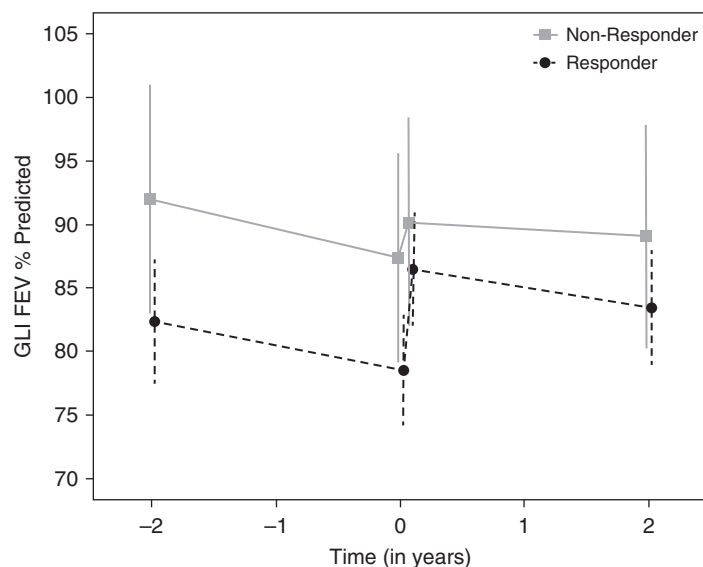
Figure 1. FEV$_1$ percentage predicted (PP) rate of decline 2 years pre- and postivacaftor by 1-month FEV$_1$ response categories (responders had >0 PP change at 1 month postivacaftor [gray solid line]; nonresponders had ≤0 PP change [black dashed line]). Means and 95% confidence intervals. GLI = Global Lung Function Initiative equations (6).

$P = 0.087$]) in FEV$_1$ responders and nonresponders, respectively (Table 2). Similarly, the PEx reduction from pre- to postivacaftor was nearly identical between 1-month BMI responders and nonresponders (RR, 0.53 [95% CI, 0.34–0.82; $P = 0.005$] and RR, 0.54 [95% CI, 0.33–0.89; $P = 0.016$], respectively).

Overall BMI changed from an increase of 0.27 kg/m^2/yr (95% CI, 0.10–0.43) before ivacaftor to 0.37 kg/m^2/yr (95% CI, 0.21–0.53) after ivacaftor (0.10 kg/m^2/yr improvement; 95% CI, −0.01 to 0.22; $P = 0.073$). Both FEV$_1$ and BMI responders had statistically significant improvements in BMI/yr from pre- to postivacaftor (0.18 kg/m^2/yr [95% CI, 0.05–0.31; $P = .005$] and 0.28 kg/m^2/yr [95% CI, 0.15–0.41; $P < 0.0001$]) compared with nonresponders, whose BMI gains slowed postivacaftor. This may be in part because nonresponders were rapidly increasing their BMI before ivacaftor (significantly faster than BMI responders: 0.44 kg/m^2/yr; $P = 0.017$).

Finally, overall FEV$_1$ decline was −1.34 PP/yr (95% CI, −2.31 to −0.37) postivacaftor compared with −2.02 PP/yr (95% CI, −3.05 to −1.00) before ivacaftor (difference, 0.68 PP/yr; 95% CI, −0.37 to 1.73; $P = 0.20$). In FEV$_1$ nonresponders, decline was −2.27 PP/yr (95% CI, −4.44 to −0.10) preivacaftor and −0.57 PP/yr (95% CI, −2.63 to 1.50) postivacaftor (Figure 1). FEV$_1$ responders showed a smaller attenuation in lung function decline, from −1.92 PP/yr (95% CI, −3.08 to −0.77) to −1.58 PP/yr (95% CI, −2.67 to −0.49), but neither group demonstrated statistically significant changes from preivacaftor decline rates. Stratified by BMI response, the BMI nonresponders had no decrease in FEV$_1$ in the 2 years before ivacaftor initiation and did not show an attenuation in FEV$_1$ decline, whereas the BMI responders changed from −2.87 PP/yr (95% CI, −4.08 to −1.66) to −1.52 PP/yr (95% CI, −2.65 to −0.38; $P = 0.03$).

In this letter, we report that 1) ivacaftor-treated G551D patients demonstrate benefit 2 years after initiation; 2) patients without short-term benefit may still demonstrate long-term efficacy; and 3) there was no statistically significant attenuation in rate of FEV$_1$ decline in the 2 years after initiating ivacaftor compared with the 2 years immediately before. Notably, there was no statistically significant difference between the responders and nonresponders (by either definition) when comparing postivacaftor PEx rates, BMI change/yr, or FEV$_1$ decline/yr. These data mirror an open-label extension study of ivacaftor-treated G551D patients, showing increased FEV$_1$ and BMI as well as reduced PEx frequency at 144 weeks (9), and other observational studies in this group (10).

Our analysis suggests that approximately 25% of G551D patients may fail to show an increase in FEV$_1$ or BMI but will nonetheless derive measurable benefit at 2 years. This finding has important implications on long-term treatment decisions, as the absence of acute response should not be used to rule out the possibility of tangible and important long-term benefit. It should be noted that we used a conservative threshold of nonresponders: no change or decrease in FEV$_1$ or BMI at 1 month.

The reduction in PEx was arguably the most robust clinical improvement observed, irrespective of acute response, as both responders and nonresponders had a 50% reduced risk compared with pretreatment. Although correlated as outcomes in CF trials, these data suggest factors that affect short-term FEV$_1$ and PEx are related but distinct, and change in FEV$_1$ may not predict PEx frequency. In contrast to a previous study that reported a 47% annualized reduction in FEV$_1$ decline attributable to ivacaftor when compared with a propensity matched F508del homozygous registry cohort (4), the FEV$_1$ attenuation in this cohort was 33% and was not statistically significant, perhaps because of the much smaller sample or the variability in FEV$_1$ decline across and within patients (11). Thus, the question of whether ivacaftor attenuates FEV$_1$ decline remains to be fully answered and will require longer, larger studies. ■

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Mortality in Patients Treated with Continuous Positive Airway Pressure at the Population Level

To the Editor:

Obstructive sleep apnea (OSA) has been associated with increased morbidity and mortality because of its association with hypertension, cancer, and metabolic, cardiovascular, and cerebrovascular diseases (1). In patients with OSA, the application of nocturnal continuous positive airway pressure (CPAP) improves quality of life and moderately decreases arterial blood pressure, mainly in patients with resistant hypertension (2). However, the results of the SAVE (Sleep Apnea Cardiovascular Endpoints) study (3) and recent meta-analyses (4) do not support a role for CPAP in preventing major cardiovascular events or OSA-related mortality. Whether CPAP treatment could reduce mortality at the population level remains unclear, especially when considering the broad range of potential comorbidities generally associated with OSA.

In Catalonia, Spain, approximately 1% of the general population is currently estimated to be using CPAP. Data from all patients treated with CPAP attending the Catalan Health System (CatSalut) during 2012 to 2013, as well as matched control subjects, were gathered to assess the relationship between CPAP treatment and mortality at the population level.

A total of 70,469 patients treated with CPAP and 184,112 control subjects matched (1:3) on 5-year age group, sex, and health region attending CatSalut during 2012 to 2013 were included. Data on age, sex, health region, duration of CPAP treatment, associated comorbidities (*International Classification of Diseases*, ninth revision), and dead or alive status at the end of 2015 were collected. This study used anonymized data provided by the Catalan Health Quality and Assessment Agency (Public Data Analytical Program for Health Research and Innovation [PADRIS Program]). The ethics committee of Hospital Arnau de Vilanova approved the study (CEIC-1430). Patient informed consent was not required.

Mortality was estimated by fitting multivariable logistic regression models for men and women to measure the statistical contribution of CPAP treatment after adjusting for age and comorbidities with statistically significant contribution according to a likelihood ratio test. Interaction effects between CPAP treatment and comorbidities were tested and included in the models with the same