Tobacco smoke exposure reduces the clinical efficacy of ivacaftor: Results from the G551D Observational Trial

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Background: Cigarette smoke causes acquired cystic fibrosis (CF) transmembrane conductance regulator (CFTR) dysfunction and may exacerbate CF lung disease by reducing protein expression and function. We used urinary biomarkers of second-hand smoke exposure to examine its effect on ivacaftor response in participants in the G551D Observational Trial (GOAL). We hypothesized that exposure to smoke would lessen the clinical efficacy of ivacaftor.

Methods: Smoke exposure was quantified using liquid chromatography with tandem mass spectrometry of urinary 4-(methylthiobutamino)-1-(3-pyridyl)-1-butanol (NNAL), a nicotine metabolite used in studies of second-hand smoke exposure, and 3-hydroxypropylmercapturic acid (3-HPMA), a metabolite of acrolein that affects CFTR channel gating. Smokers were categorized as exposed (NNAL ≥ 10 pg/mL or HPMA ≥ 75th percentile of the sample distribution), not exposed (NNAL<10 and 3-HPMA<50th percentile), or undetermined (NNAL<10 and 3-HPMA 50th–75th percentile). Primary outcome was change in sweat chloride from baseline (before ivacaftor) to 6 months after ivacaftor initiation. Secondary outcomes were change in FEV1pp and sweat chloride from baseline (before ivacaftor) to 6 months after ivacaftor initiation.

Results: One hundred forty-two individuals (mean age 20.8 ± 11.4, range 6–59) contributed urinary specimens. Forty-one (29%) were smoke exposed, 71 (50%) were unexposed, and 30 (21%) were undetermined. After 6 months of ivacaftor treatment, sweat chloride decreased by 44.0 mmol/L (95% CI, −53.0 to −35.0 mmol/L) in smoke-exposed subjects and 53.0 mmol/L in unexposed subjects (p < 0.01). At 6 months, mean absolute sweat chloride was 42.3 mmol/L in exposed subjects and 58.5 mmol/L in unexposed subjects (p < 0.01) (Figure 1). In multivariable models controlling for age and baseline clinical characteristics, smoke-exposed subjects had 4.5-point less improvement in FEV1pp (95% CI, −8.8 to −0.2; p < 0.01) and 6.8-point less improvement in CFQ-R respiratory scale (95% CI, −13.1, −0.5; p < 0.01) than unexposed counterparts.

Conclusions: Tobacco smoke exposure, assessed according to urinary biomarkers, limits the therapeutic efficacy of ivacaftor in subjects with G551D CFTR. Sweat chloride declined by an additional 15 mmol/L in unexposed subjects, with consequent improvement in lung function and respiratory quality of life. Avoiding smoke exposure may optimize the therapeutic benefit of highly effective CFTR modulators.

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Defining and identifying early-onset lung disease in cystic fibrosis with cumulative clinical characteristics in the first 3 years of life

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Background: Because of variations in cystic fibrosis (CF) lung disease in young children, a clinical method is needed to identify children at risk of early-onset lung disease. As an essential component of a study applying whole-genome sequencing to young children with CF, particularly to discover polygenic risk factors, we designed and developed the CF Early-onset Lung Disease (CFELD) scoring system by using prospectively collected longitudinal data on pulmonary disease manifestations in the first 3 years of life.

Methods: The study population consisted of 145 infants born between 2012 and 2017 enrolled after newborn screening at age 1.8 ± 1.01 months in Feeding Infants Right... from the Start (FIRST), a prospective longitudinal study being conducted at six CF centers (Madison, Milwaukee, Boston, Indianapolis, Salt Lake City, Chicago) who completed 36 months of follow-up. Information was collected on cough severity, pulmonary exacerbations (PEx), respiratory cultures, and hospitalizations on a pulmonary interval history form at each CF center visit every 1 to 2 months in infancy and quarterly thereafter. These longitudinal data were used to construct the novel CFELD system, and overall CFELD scores were used to classify lung disease at 3 years of age into five categories: asymptomatic, minimal, mild, moderate, and severe. Multiple regression analyses were used to identify factors significantly predictive of CFELD scores.

Results: The most frequent manifestation of CF early lung disease was physician-reported PEx episodes, PEx hospitalizations, and positive Pseudomonas aeruginosa cultures. Parent-reported cough occurred in approximately 60% of the FIRST cohort by age 3. Two hundred sixty-six respiratory hospitalizations were documented in 2,469 pulmonary interval history forms (11%) in the first 3 years of life. Cough severity was correlated with number of respiratory hospitalizations (r = 0.48, p < 0.001). Distribution of CFELD categories was 10% asymptomatic, 17% minimal, 29% mild, 33% moderate, and 12% severe. The moderate and severe categories are early-onset phenotypes that occur three times as often in pancreatic-insufficient individuals (49%) as in pancreatic-sufficient individuals (16%) (p < 0.001). Having gastrointestinal or nutrition-related hospitalizations was also a predictor of worse CFELD score. High plasma interleukin (IL)-6 level (a proinflammatory cytokine) was associated with worse CFELD scores, whereas high plasma IL-10 level (an anti-inflammatory cytokine) was associated with better CFELD scores. Ordinal logistic regression revealed that parental education level of community college or above significantly decreased the likelihood of being in the severe CFELD category. Additional analyses of the relationship between breastfeeding and CFELD outcomes are being conducted.

Conclusions: The CFELD scoring system is novel, allows early systematic evaluation of lung disease prognosis, and may aid in therapeutic decision-making. The CFELD system should be especially useful for studies of epidemiological and genetic factors that may play a role in onset of lung disease and for clinical decisions regarding initiation of CF transmembrane conductance regulator modulator therapy.

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