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-(methylnitrosamino)-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. Specimens 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 percentage predicted forced expiratory volume in 1 second (FEV₁,pp) and Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory scale.

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 59.2 mmol/L (95% CI, 54.3 mmol/L–64.1 mmol/L) in smoke-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 FEV₁,pp (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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Discovering symptom clustering patterns during a pulmonary exacerbation in people with cystic fibrosis

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Background: Pulmonary exacerbations (PEXs) in people with cystic fibrosis (CF) are characterized by worsening symptoms, and more research is needed to understand how symptoms group together during PEX. A symptom cluster is defined as co-occurrence of two or more related symptoms. Symptom clusters in chronic obstructive pulmonary disease are associated with greater health care use and mortality. Symptom clusters have not been systematically studied in CF. The purpose of this study was to identify distinct symptom clustering patterns during a CF PEX.

Methods: This study (N = 120) was a secondary, longitudinal analysis. Children aged 10 and older and adults being treated with intravenous (IV) antibiotics for a CF PEX were enrolled from six Cystic Fibrosis Foundation–accredited centers across the United States. The CF Respiratory Symptom Diary (CFRSD), a valid, reliable tool, was used to measure eight symptoms accredited centers across the United States. The CF Respiratory Symptom Diary (CFRSD), a valid, reliable tool, was used to measure eight symptoms (scored 0–4) and symptom burden (scored 0–24), with higher scores indicating worse symptoms. Information on symptoms was collected on treatment days 1, 7, 14, and 21. K-means clustering was performed in R Studio to detect clustering patterns; t-tests, Wilcoxon rank-sum tests, and chi-square tests were used to test differences between discovered groups.

Results: Symptoms measured using the CFRSD were found to be significantly clustered based on symptom severity on days 1 (n = 72) and 7 (n = 79) of a PEX. On day 1, cluster 1 (n = 42) was low symptom severity, mean symptom burden was 6.6 ± 2.9, and cluster 2 (n = 30) was high symptom severity, mean symptom burden was 14.3 ± 2.7. On day 7, symptoms continued to cluster based on severity. Cluster 1 (n = 60) was low symptom severity, mean symptom burden was 2.6 ± 1.7, and cluster 2 (n = 19) was high symptom severity, mean symptom burden was 8.7 ± 3.3. All eight symptoms continued to be significantly different between clusters 1 and 2 except for feverish and chills or sweats. Most symptoms significantly improved between days 1 and 7 in both clusters.

Conclusions: Symptoms cluster significantly based on severity on days 1 and 7 of a PEX in people with CF. There was no significant difference in lung function between clusters 1 and 2 on day 1, suggesting that higher symptom burden is not associated with worsening lung disease severity. On day 1, participants grouped into cluster 2 spent significantly more days in the hospital than those in cluster 1, suggesting that people with higher symptom burden may be at greater risk of spending more days in the hospital. The findings that symptoms improved significantly between days 1 and 7 suggest that symptoms are sensitive to IV antibiotic therapy.

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Lung function and airway inflammatory markers in children with cystic fibrosis transmembrane conductance regulator–related metabolic syndrome

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Background: Newborn screening for cystic fibrosis (CF) has led to an increase in the diagnosis of children with cystic fibrosis (CF) transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS) who are at risk for developing CF. There is limited literature on stratifying children with CRMS who are at risk for progression to CF.

Methods: We conducted a cross-sectional study of children with CRMS and age-matched control children using exhaled breath condensate (EBC). LCI and functional residual capacity (FRC) were measured according to sulfur hexafluoride multiple-breath washout (MBW) using the Innocore LCI. At least two acceptable LCI and FRC values were recorded. EBC samples were collected using the R-Tube method. EBC metabolites were analyzed using liquid chromatography coupled with high-resolution mass spectrometry covering 472 validated metabolites and detection of novel molecules using data-dependent ion fragmentation. Methionine sulfoxide, a metabolite associated with inflammation in early CF bronchoalveolar lavage, was detected. We conducted a hypothesis that it is high in people with CRMS who progress to CF. Other EBC metabolites were used for untargeted analysis to assess risk progression to CF diagnosis.

Results: Seven children with CRMS (aged 4–14) and 26 with CF (aged 5–15) were enrolled. In CRMS, CFTR variants included F508del and R117H;7T/9T (n = 4), 2789 + 2insA and R117H;7T/7T (n = 2 siblings), and 2789 + 5G > A and R117H;[TG]12–5T (n = 1). In the CRMS group, mean LCI was 6.55 ± 0.56 and mean FRC was 1.35 ± 0.91 L. One child with CRMS had an abnormal LCI (>7) of 7.39. In the CF group, mean LCI was 6.90 ± 0.88, and mean FRC was 1.15 ± 0.35 L. Nine (35%) children with CF had abnormal LCI between 7.1 and 9.2. There was insufficient evidence to conclude that LCI differed between days 1 and 7 of a PEX.