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Cystic fibrosis transmembrane conductance regulator modulator–induced sweat chloride changes in the cystic fibrosis population from the Characterizing Cystic Fibrosis Transmembrane Conductance Regulator–Modulated Changes in Sweat Chloride Study: 2022 Update

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Background: We previously reported on the preliminary results from the Characterizing Cystic Fibrosis Transmembrane Conductance Regulator–Modulated Changes in Sweat Chloride (CHEC-SC) study [1], a large population-based epidemiological study characterizing the heterogeneity in sweat chloride response to cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators and evaluating the association between sweat chloride and long-term clinical outcomes. With Food and Drug Administration approval of elexacaftor/tezacaftor/ivacaftor (ELE/TEZ/

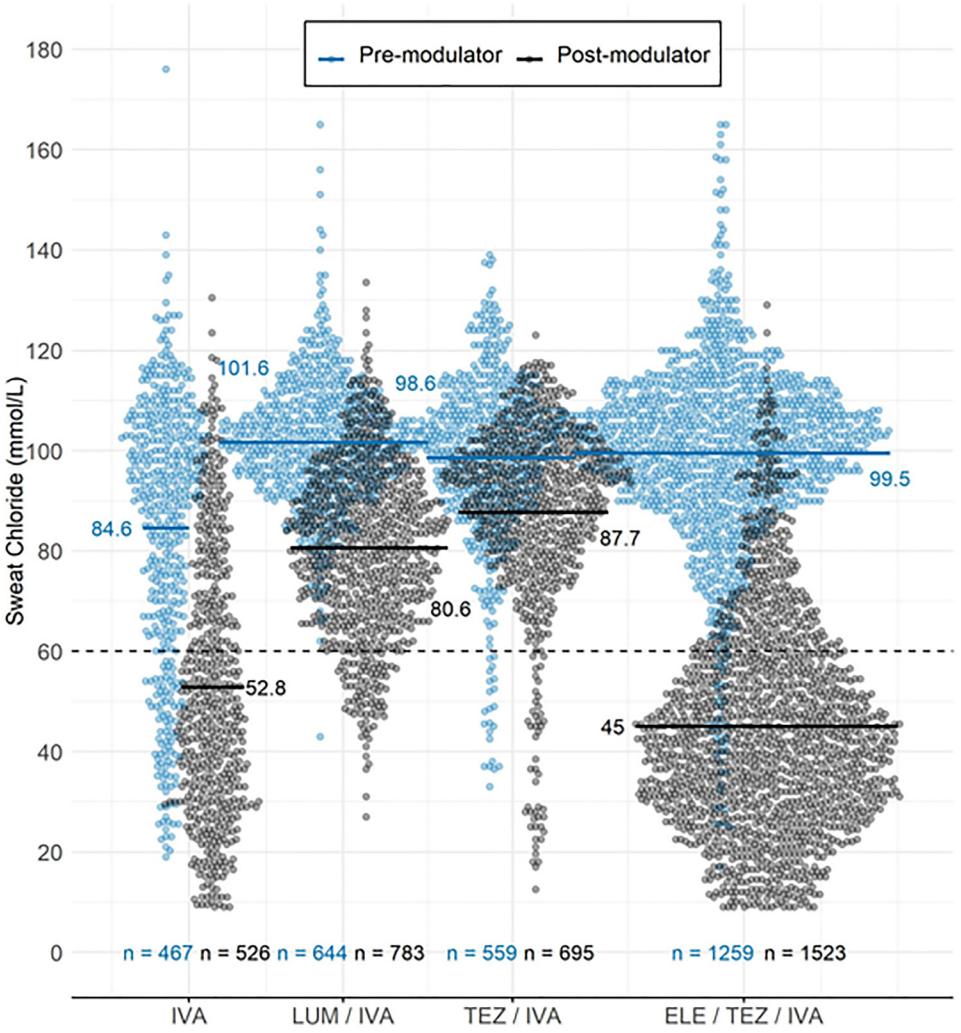

Figure 1 (abstract 43): Pre- and postmodulator sweat chloride in the Characterizing Cystic Fibrosis Transmembrane Conductance Regulator–Modulated Changes in Sweat Chloride study population. For each modulator (ivacaftor (IVA), lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA), elexacaftor/tezacaftor/ivacaftor (ELE/TEZ/IVA)), pre- (blue circles) and postmodulator values (black circles) are shown, with corresponding means indicated by horizontal bars with numerical labels. Sample sizes are indicated below each set of modulator and time point pair.

IVA) in 2019, we now have sweat chloride, demographic, and clinical outcome data for all four commercially available modulators in use in the United States. We present an update on change in sweat chloride after initiation of ivacaftor (IVA), lumacaftor/ivacaftor (LUM/IVA), and tezacaftor/ivacaftor (TEZ/IVA), including new participants at younger ages, and new data on the association between change in sweat chloride after initiation of ELE/TEZ/IVA.

Methods: Eligible subjects who have been prescribed any of the four commercially approved CFTR modulators for 90 days or longer were enrolled for a single visit to collect sweat to be analyzed for sweat chloride at their local laboratory. Diagnostic premodulator sweat chloride values were obtained from chart review. Clinical data obtained at this visit were augmented with data obtained from the Cystic Fibrosis Foundation Patient Registry (CFFPR). Subjects who switched to an alternative prescribed commercially approved CFTR modulator for 90 days or longer were eligible to re-enroll in the study.

Results: CHEC-SC began in 2018. As of February 2022, more than 3,500 subjects aged 0.88 to 77 years were enrolled from 51 U.S. sites in the CF Therapeutics Development Network; 36% of 526 IVA subjects were aged 0 to 11, 35% of 783 LUM/IVA subjects were aged 2 to 11 years, and 9.7% of 699 TEZ/IVA and 7.5% of 1,532 ELE/TEZ/IVA subjects were aged 6 to 11. The IVA group had the greatest percentage of Hispanic subjects (11%). Regarding *CFTR* genotype, 52% of the IVA group had gating mutations, and 100% of LUM/IVA, 90% of TEZ/IVA, and 57% of ELE/TEZ/IVA were homozygous for F508del. Median time from start of prescribed modulator to postmodulator sweat chloride collection was 2.48 years for IVA, 1.76 years for LUM/IVA, 0.57 years for TEZ/IVA, and 1.14 years for ELE/TEZ/IVA.

Pre- and postmodulator sweat chloride results are presented in Figure 1. Average sweat chloride changes tracked consistently with those reported in clinical trials, with the greatest change observed with ELE/TEZ/IVA (–59.9 ± 23.6 mmol/L). This change resulted in the greatest proportion of sweat chloride values falling below the diagnostic value for CF of 60 mmol/L: 79% after ELE/TEZ/IVA (pre 3.5%). The average sweat chloride change with IVA was –31.9 ± 30.5 mmol/L overall; –50.7 ± 25.8 mmol/L for those with gating mutations, and –20.3 ± 21.3 mmol/L for R117H. Average sweat chloride change was –20.8 ± 19.3 mmol/L for LUM/IVA and –10.5 ± 17.6 mmol/L for TEZ/IVA. Pre- and postmodulator sweat chloride less than 60 mmol/L were 19.9% and 64.4%, respectively, with IVA, 0.1% and 10.9% with LUM/IVA, and 3.9% and 6.8% with TEZ/IVA. Heterogeneity in sweat chloride changes across key population factors and among rare genotype groups, as well as changes in patients changing modulator regimens, are being evaluated. The first analysis covering all CFTR modulators evaluating the association between sweat chloride response and FEV_1 change across the large CHEC-SC population, accounting for genotype and age group, will be presented at the North American Cystic Fibrosis Conference.

Conclusions: CHEC-SC is the largest study characterizing changes in modulator-induced sweat chloride and clinical outcome changes and factors associated with these changes across the CF population.

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Factors associated with survival of Mexican patients with cystic fibrosis—a cohort study

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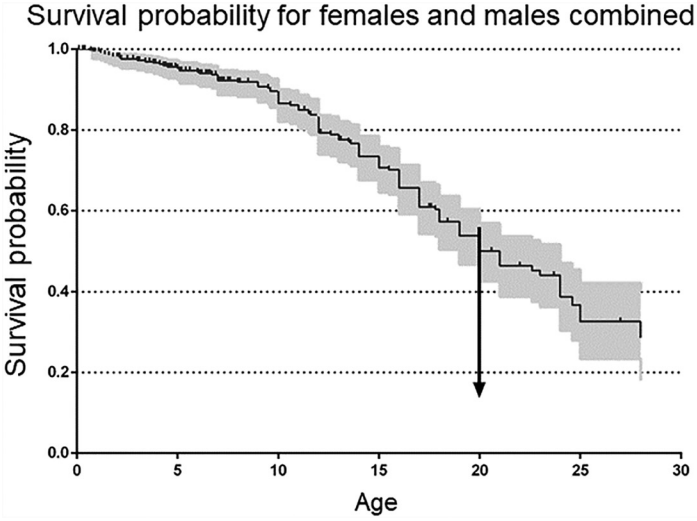
Background: Cystic fibrosis (CF) is one of the most common autosomal diseases in Mexico, with an estimated prevalence of 1 in 8,500. Many factors can affect survival, including nutritional status, colonization by *Pseudomonas aeruginosa,* and pulmonary function. Early identification of these factors allows therapy to be initiated to improve survival and quality of life.

Methods: All patients who attended the CF clinic were registered and underwent an anthropometric evaluation and pulmonary function evaluation with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FCV); values greater than 80% were considered to be optimal lung function. A social evaluation was also performed. Pancreatic exocrine insufficiency was defined as a requirement for regular pancreatic enzyme supplementation. Undernutrition was considered a body mass index more than 2.0 standard deviations below the mean or weight for height more than 2.0 standard deviations below the mean. Government coverage of treatment was defined as the full supply of pancreatic enzymes, dornase alfa, nebulized tobramycin, salbutamol, vitamins, and oral antibiotics needed. Positive *P. aeruginosa* was determined from a sputum sample or cough swab before 7 years old. Survival from date of first assessment to the last visit was calculated using the Kaplan Meier method. Pearson correlation coefficients were calculated to test relationships between predictor variables.

Results: We included 341 patients from 1990 to 2018. Estimated median age of survival was 20 (95% CI, 17.3–23.0), and 55% of patients were diagnosed before the age of 2, with no significant effect on survival. Ninety-



Factors affecting survirval	OR (95% IC)	Valor p.
Diagnosis ≤ 2 years	0.9 (0.58-1.4)	0.65
Pancreatic insufficiency	0.08 (0.01-0.58)	0.001
FEV1 ≥ 80%	0.51 (0.03-0.09)	0.001
FVC ≥ 80%	0.05 (0.03 - 0.11)	0.001
Positive *P. aeruginosa* ≤ 7 years	5.19 (2.97-9.05)	0.001
Undernutrition	15.8 (8.4-29.7)	0.001
Treatment government cover	0.048 (0.02-0.1)	0.001

Figure 1 (abstract 44): Estimated median age of survival in Mexican patients with cystic fibrosis and related factors