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Change in Lung Function after Initiation of Elexacaftor–Tezacaftor–Ivacaftor: Do Not Forget Anatomy!

To the Editor:

In their recent paper titled "Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis: A Clinical Trial," Nichols and colleagues described a prospective postapproval study in 487 people with cystic fibrosis (PwCF) with at least one F508del allele starting elexacaftor–tezacaftor–ivacaftor (ETI) in a diverse U.S. patient population (1). At 6 months after ETI therapy onset, the authors confirmed a large improvement in lung function (mean percentage predicted FEV_1 [$ppFEV_1$] improvement of 9.76 percentage points from baseline) and a sweat chloride concentration decrease of −41.7 mmol/L, indicating improvement in epithelial ion transport. The authors reported a modest correlation between the change in $ppFEV_1$ and the change in sweat chloride concentration from baseline to 6 months (Pearson coefficient = −0.19, $P < 0.005$); the correlation remained statistically significant even when excluding influential points or when using a Spearman rank-based association. As acknowledged by the authors, such statistically significant correlation was not observed in previous studies of CFTR (cystic fibrosis transmembrane conductance regulator) modulator drugs. Nichols and colleagues proposed several explanations for their findings, including *1*) the large effect size caused by ETI; *2*) the heterogeneity in the cohort by genotype and prior CFTR modulator use; and *3*) the large sample size. Although these explanations are all valid, our view is that they do not fully account for the modest association reported between improvement in ion transport and lung function after ETI initiation. We would like to propose an alternative explanation for the heterogeneous lung function response to ETI, based on the anatomical determinants of lung function impairment.

In PwCF, CFTR-related defective ion transport is responsible for altered properties of airway mucus (2, 3). The resulting abnormal mucus clearance results in airway infection and inflammation, leading to progressive mucus plugging (4, 5) and abnormalities and destruction of small conducting airways (5). Among these anatomical abnormalities, some might be reversible, but others may be less reversible using CFTR modulators; for example, recent studies comparing findings on computed tomography scans before the initiation of lumacaftor–ivacaftor and one year afterward have shown reductions in mucus plugging, but not in bronchiectasis extent and severity (6). These data suggest that the effects of CFTR modulators on lung function occur by allowing effective clearance of mucus from plugged airways. Under this assumption, the effect of a given CFTR modulator on $ppFEV_1$ would depend on *1*) its ability to correct ion transport to a degree that permits sufficient mucus hydration leading to effective clearance of mucus, in which regard it appears logical that drug combinations that allow better ion transport correction in airways (e.g., ETI vs. lumacaftor–ivacaftor [7]) show greater impact on lung function; and *2*) the proportion of $ppFEV_1$ decrease that is related to mucus plugging rather than to less reversible lung anatomical abnormalities (e.g., small-airway destruction, airway wall fibrosis), as improvement in lung function is less likely to occur when destructive lesions predominate rather than mucus plugging.

A recent study showed that ETI restores CFTR function to a degree approximately 45–50% of normal CFTR function (7). An open question remains whether newer drug combinations, designed to provide greater correction of the CFTR-related ion transport defect, will result in greater improvement in lung function. One hypothesis is that greater improvement in ion transport may eventually result in improved mucus clearance; however, as there are no clear data on how much ion transport correction is necessary to trigger effective mucus clearance in PwCF, it is unclear whether the clinical effect of newer, more effective CFTR modulator combinations will indeed result in better mucus clearance and improved lung function compared with ETI. Furthermore, CFTR modulators may be most effective in improving lung function when the decrease in $ppFEV_1$ is related mostly to mucus plugging (e.g., earlier in life), but they may result in less improvement in lung

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function when the decrease in ppFEV$_1$ is related largely to airway destruction or fibrosis. Ongoing real-world studies (8) using morphometric analysis of computed tomography scans before and after the initiation of ETI may help in further understanding the anatomical determinants of lung function improvement after the initiation of CFTR modulators. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Martin *et al.*

From the Authors:

We thank Martin and colleagues for their interest in our publication reporting early effects of elexacaftor–tezacaftor–ivacaftor (ETI) in people with cystic fibrosis (PwCF) (1), and we wish to respond to three key topics addressed in their letter to the editor. First, the authors propose that the relative contributions to percentage predicted FEV$_1$ from reduction in mucus obstruction in the airways versus less reversible airway damage (e.g., fibrosis or small-airway obliteration) may be a key factor in the modest correlation we identified between improved lung function and improved CFTR (cystic fibrosis transmembrane conductance regulator) activity measured by sweat chloride concentration. We agree with this premise, which is consistent with our explanatory framework of heterogeneity of response to ETI in our large study cohort with varied baseline disease status and medication use before initiating ETI. We concur that it is likely that early gains in FEV$_1$ after starting highly effective CFTR modulator drug therapy occur primarily through improved mucociliary clearance and reduced airway obstruction, as seen with ivacaftor (2). Whether additional improvement in lung function can develop with continued use of modulator therapy, perhaps related to reduced airway inflammation or structural disease, is unclear but of great interest (3).

Second, the authors raise the question of whether CFTR correction greater than that achieved by ETI will result in additional airway clearance improvement. This query is also important, and significantly greater change in FEV$_1$ with newer agents, if seen, would suggest that further enhancement of airway clearance is possible. Our study (PROMISE [A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function]; NCT 04038047) includes a substudy focused on mucociliary clearance and mucus properties in sputum samples, which may offer additional outcomes to consider in future work

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