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Cystic Fibrosis: A Disease in Transformation, yet More Work to Be Done!

What have we learned from real-world experience about highly effective CFTR modulation and its impact on the lives of patients with cystic fibrosis? In 2019, the triple combination CFTR (cystic fibrosis transmembrane regulator) modulator elexacaftor-tezacaftor-ivacaftor (ETI) was approved for patients with cystic fibrosis (PwCF) aged 12 years and older with at least one copy of the *F508del* variant in the United States and several European countries based on supportive phase 3 efficacy and safety data (1, 2). Over the past 2 years, the international cystic fibrosis (CF) community has begun collecting and analyzing real-world experience with ETI based on several large and comprehensive post-approval observational studies evaluating its biologic and clinical impact on PwCF. In this issue of the *Journal*, two papers provide initial findings from complementary studies, one by Nichols and colleagues (pp. 529–539) focused on clinical outcomes (3), and the second by Graeber and colleagues (pp. 540–549) on CFTR channel function across multiple epithelia (sweat duct, airway, and intestine) (4). The findings are exciting and impactful, indicating that the CFTR channel function is likely approaching 50% normal levels and we are just beginning to understand the longer-term clinical impact of this biological milestone for PwCF.

Why is it so important to continue to collect prospective post-approval biological and clinical data? First, it allows us to understand the generalizability of the phase 3 findings across a broad range of ages (≥12 yr), geography, populations, disease severity, and comorbidities. The ETI phase 3 trials excluded patients with mild (FEV_1 > 90% predicted) and severe (FEV_1 < 40% predicted) lung disease and comorbidities such as active *Mycobacteria abscessus* and *Burkholderia cepacia* complex infections. In addition, phase 3 trials focused on a few key pulmonary endpoints, such as percent predicted FEV_1 ($ppFEV_1$), and not the multiple other organ systems affected by this genetic disease. In addition, the CF community needs to better understand the biologic basis of these remarkable changes in lung function and patient well-being. The international CF community should be commended for the foresight and commitment to collect real-world data and should serve as a model for other orphan genetic diseases as they develop new therapies.

What New Insights Have These Two Papers Provided?

These two papers have demonstrated that ETI leads to ∼50% functional correction of the CFTR protein channels in epithelial cells across multiple organs, leading to impressive clinical impacts for patients 12 years and older with at least one copy of the *F508del* variant (plus a small number of other ETI-responsive variants) (3, 4).

The article by Nichols and colleagues (3) reports the initial findings of a planned 6-month interim analysis of a 30-month observational study of PwCF who were 12 years and older with at least one *F508del* variant at the time of initiation of ETI (Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function [PROMISE], NCT04038047). These patients were assessed before drug initiation and at 1, 3, and 6 months after therapy. The outcomes being evaluated are changes in $ppFEV_1$, sweat chloride concentration (SCC), body mass index, and patient-reported outcomes (Respiratory Domain of the Cystic Fibrosis Questionnaire-Revised [CFQ-R, RD]). The PROMISE study has multiple substudies examining other disease manifestations, including airway microbiology, gastrointestinal (GI) symptoms, and glucose metabolism, which will be reported at a later date (5). Among the 487 study participants across 56 U.S. sites, ∼50% had received earlier generations of CFTR modulators, potentially reducing the magnitude of the ETI therapeutic impact. Yet, even with previous modulator exposure, the mean clinical changes at 6 months were remarkable in $ppFEV_1$ (9.79%; 95% confidence interval [CI], 8.76% to 10.76%), SCC (−41.7 mmol/L, 95% CI, −43.8 to −39.6), and CFQ-R increased (20.39 points; 95% CI, 18.3 to 27.50) (Figures 1 and 2 and Table 2) (3). Treatment effect was robust across all CFTR variant grouping, race, sex, age, and disease severity. These findings undertaken in real-world settings are comparable to the data from the phase 3 trials and set a new benchmark for clinical impact measures, surpassing the robust ivacaftor studies (6, 7). In addition, with the large study population and effect size, a modest correlation (at 6 mo) between sweat chloride and FEV_1 change was seen for the first time (Figure 4) (3).

The article by Graeber and colleagues (4) comes from five German CF centers and examines the effect of ETI on CFTR function in airway and intestinal epithelia, using CFTR biomarkers, SCC, nasal potential difference (NPD), and intestinal current measurement (ICM). The study included 107 patients with one or two *F508del CFTR* variants (55 with *F508del* and minimal function variant; 52

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with *F508del/F508del*) over a 6-month period. Some of the patients with *F508del/F508del* migrated from tezacaftor/ivacaftor to ETI. The biomarkers show changes in the biomarkers in parallel with clinical change observed (Table 1 and Figures E2–E4) (4). Only weak correlations were seen between CFTR biomarker response and changes in lung function with ETI (Figure 4) (4).

Two key issues that emerge from this study include the gene–dose effects comparing variants with one versus two *F508del* alleles and the impact of ETI on different epithelial surfaces. The study seems to indicate that improvement in CFTR function in *F508del*/minimal function participants had a lesser impact on SCC than the *F508del/F508del* participants, suggesting a gene–dose effect in the sweat duct. Yet, changes in NPD and ICM (Table E6) did not demonstrate this dose effect in airway and intestinal epithelial surfaces. A related finding is the heterogeneity of biomarker response to ETI in individual patients, such as strong SCC and yet limited NPD ± ICM responses. The authors speculate that tissue-specific differences in pharmacokinetic/pharmacodynamic responses to ETI and/or differences in genetic modifiers (e.g., inflammation/microbiome of the airway and GI versus sweat duct) may be responsible for these observations.

Although These Are Encouraging, There Is More to Be Done!

Both studies followed patients for 6 months after commencing ETI and plan ongoing follow-up of the study populations (NCT04038047 and NCT04732910). Longer-term durability of response to ETI is important in real-world practice. The study by Nichols and colleagues will follow the population for 30 months, and the study by Graeber and colleagues will review participants at 12 and 24 months. The investigators in Germany plan to monitor SCC as the selected ongoing CFTR biomarker. Given the heterogeneity of the biomarker response reported here, consideration should be given to measure ICM and/or NPD responses in their ongoing study.

ETI has been approved in the United States and Europe for 6- to 11-year-olds (8) and is under consideration in other jurisdictions. The two studies reported in this issue included children (≥12 yr) and adults. PROMISE has now enrolled children 6–11 years old who are initiating clinician-prescribed ETI. Future studies in the youngest patients will be essential to understand the potential for disease prevention and modification. It has been estimated that 90% of the known CFTR variants are responsive to currently available CFTR modulators (9). Those PwCF who have CFTR variants nonresponsive to current modulators remain a therapeutic development priority, including nondrug approaches such as gene therapy, RNA-based approaches, and gene editing (10). As most nonresponsive variants are ultrarare, classical randomized trials are impractical (11), and the use of CFTR biomarkers reported by Graeber and colleagues (4) may be a feasible alternative approach for studying potential treatment candidates. Although access to ETI (and other CFTR modulators) is increasing, the high cost of therapy means access is not universal for the ∼90,000 global CF population. In fact, even access to standard of care in low- to middle-income countries is limited and known to adversely affect length of life (12).

What Do We Still Need to Learn?

Over the past decade, the G551D Observational Study (GOAL) study has provided long-term, real-world evidence on the impact of ivacaftor on airway microbiology and inflammation, growth and nutrition, GI function, nasal complications, and sleep-related disorders (7, 13, 14). The even more ambitious PROMISE study will continue to evaluate the impact of ETI on many of these features and complications of CF and also endocrine and metabolism complications (5). Recent CF registry studies have demonstrated reduced mortality and lower lung transplant rates in PwCF receiving long-term ivacaftor (15), and similar studies will be required to determine the long-term impact of ETI on prevention and modification of multiorgan complications, including lung disease, CF-related diabetes, and GI cancers.

The PROMISE study reported intriguing information on pregnancy in women with CF receiving ETI. In fact, 11 of the study participants became pregnant (4.5% of all females and ∼6.7% of females ⩾18 yr of age in the study), highlighting the potential impact of highly effective modulators on reproductive health. The patient/clinic dialogue from "Should I have a baby on ETI?" to "I am having a baby on ETI" is an increasingly frequent scenario in many adult centers. To date, there are limited published data on the impact of taking any modulators during pregnancy in women with CF (16). It is crucial such data are collected (17) and reported, and a prospective observational study of maternal and fetal outcomes of pregnancies in women with CF is currently in progress (Prospective Study of Pregnancy in Women with Cystic Fibrosis [MAYFLOWERS]; NCT04828382). In addition, CF registries around the world should also contribute to this work.

There were growing numbers of adults with CF who were overweight or obese even before CFTR modulators became widely available. Nichols and colleagues (3) provide insights into the impact of ETI on nutritional status (increase in body mass index ∼1 kg/m^2) in only 6 months. As was seen in all the phase 3 CFTR modulator studies, weight gain is common (and desired) and may require a lifelong change in the approach to nutritional advice. In adults with CF, longevity is also associated with increased metabolic complications (obesity, hypertension, vascular issues), especially in those with diabetes and those who have undergone transplantation (18).

In summary, the Nichols and colleagues (3) and Graeber and colleagues (4) studies demonstrate in the real-world clinical setting how CFTR modulators are transforming the lives of many PwCF internationally. They also help us understand mechanistically how changes in CFTR channel function in epithelial tissue lead to remarkable clinical impact. As these studies report only the first 6 months of ETI therapy, we look forward to further information from these and other studies in the coming 1 to 2 years to shine a light on the long-term impacts of these remarkable therapies. ■

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Identifying the Risk of Acute Exacerbation in Idiopathic Pulmonary Fibrosis

A Step Forward

The clinical course of idiopathic pulmonary fibrosis (IPF) is unpredictable (1), characterized in a significant number of patients by episodes of acute deterioration that heavily affects the prognosis of the disease. These events, named "acute exacerbations" (AEs), remain idiopathic in some cases, whereas in others, known risk factors, such as lung surgery, chemotherapy, radiotherapy, or other conditions, including pulmonary embolism, heart failure, and infections, are recognized (2). Nevertheless, the pathogenic mechanisms of AE in IPF remain largely unclear, causing a substantial lack of effective therapeutic approaches. In this issue of the *Journal*, McElroy and colleagues (pp. 550–562) explore in detail the role of the response to bacterial and viral infections in AE in patients with IPF (3). The starting point of this interesting research is a previous study published by the same authors showing that an SNP of Toll-like receptor 3 (TLR3), Leu412Phe (TLR3 L412F), is associated with a worse prognosis in patients with IPF (4). In the present study, this

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