The PROSPECT Is Bright for CFTR Modulators

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Cystic fibrosis (CF) is an autosomal recessive inherited disorder in which absence or dysfunction of an epithelial sodium channel, the CFTR (CF transmembrane conductance regulator protein), leads to thick secretions and multisystem complications, including suppurative lung disease, sinus disease, pancreatic insufficiency, liver disease, and male infertility (1). The gene coding for CFTR was discovered in 1989 (2) and led to great hopes for gene therapy, but thus far, this has largely been unsuccessful. Despite this, improvements in CF survival have been a dramatic success story over the last several decades. The median predicted survival in CF has risen from 29 years in the late 1980s to approximately 43 years in 2017 (3). Before 2010, these improvements were due solely to improvements in supportive care, such as better antipseudomonal antibiotics and better management of nutrition, rather than treatment of the underlying cause of CF.

However, in 2010 the first CFTR-modulator drug, ivacaftor, was approved by the U.S. Food and Drug Administration (FDA). Ivacaftor works on CFTR variants known as gating mutations, in which the chloride channel is present on the epithelial cell surface but does not open properly. Phase 3 clinical trials showed that ivacaftor resulted in a dramatic 10.6 percentage-point increase in forced expiratory volume in one second (FEV_1) at 24 weeks and improvements in symptoms, weight, and pulmonary exacerbations (4). Because gating mutations are relatively uncommon, ivacaftor was only available for about 5% of all patients with CF in the United States.

In 2015 a combination of two drugs, lumacaftor and ivacaftor (LUM/IVA), was approved for people with CF who had two copies of the F508del mutation, the most common CFTR mutation. This greatly expanded the pool of people with CF who could receive treatment with a CFTR modulator, and although FEV_1 improved significantly, the impact on clinical outcomes in trials was more modest than those seen with ivacaftor alone for gating mutations. Observational studies, including PROSPECT (Prospective Longitudinal Study of CFTR-dependent Disease Profiling in CF), provide a unique opportunity to study longer-term clinical effects of LUM/IVA but also to study biomarkers such as sweat chloride and to perform smaller more mechanistic studies on lung clearance and gastrointestinal effects of CFTR modulators.

In this issue of *AnnalsATS*, Sagel and colleagues (pp. 75–83) present their findings from the PROSPECT cohort in which people with CF (≥6 yr), homozygous for the F508del mutation, started therapy with LUM/IVA and were followed for 12 months (5). Among the 193 study participants, the authors found significant improvements in nutritional status and sweat chloride levels. Among those < 20 years of age, there was a 3.1% (95% confidence interval [95% CI], 0.6 to 5.6) average increase in body mass index (BMI) percentile from a baseline mean of 58.3% (standard deviation [SD], 23.5) to a 12-month mean of 61.5% (SD, 22.6). Similarly, those ≥ 20 years of age saw a 0.42-kg/m^2 (95% CI, 0.07 to 0.78) increase at 12 months. Results also demonstrated significant improvements in sweat chloride, with an average decrease of −16.5 mmol/L (95% CI, −19.4 to −13.6) at 12 months from a baseline mean of 100.4 (SD, 11.5) to a 12-month mean of 83.6 (SD, 18.0). In contrast to these findings, the authors found no statistically significant difference in lung function measured by percent predicted FEV_1 ($ppFEV_1$), hospitalization rates for pulmonary exacerbations (PEx) or infection with *Pseudomonas aeruginosa* in the 12 months after initiation of LUM/IVA.

Although there was no improvement in $ppFEV_1$ or rates of PEx, as shown in other placebo-controlled trials, this study is important for a number of reasons. The authors offer insight into the real-world clinical effectiveness of LUM/IVA in a prospective longitudinal cohort that extends beyond the 24-week duration in prior studies (6–9) while achieving an 85% retention rate at 12 months. Furthermore, participants ≥ 6 years of age were included in the study allowing the authors to evaluate clinical effectiveness in the 6- to <12-year age group, which are not typically included in phase 3 or other real-world CFTR-modulator studies. The authors stratified the cohort into four different age groups (<12 yr, 12 to ≤18 yr, 18 to ≤30 yr, and ≥30 yr) and three different groups on the basis of disease severity ($ppFEV_1$ < 50%, $ppFEV_1$ of 50% to ≤90%, and $ppFEV_1$ ≥ 90%). Improvements in nutritional status achieved through an increase in BMI after initiation of LUM/IVA confirmed the results of prior studies (6–8, 10), but the authors also found that these changes were more pronounced in younger patients (<18 yr). Furthermore, the authors present the largest study to date evaluating the change in sweat chloride in response to LUM/IVA in a homozygous F508del cohort comprising individuals ≥ 6 years of age and confirmed that sweat chloride is an optimal biomarker to evaluate CFTR function in future studies.

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DOI: 10.1513/AnnalsATS.202007-881ED

The authors evaluated the association of several baseline covariates (age, sweat chloride, sex, and BMI) with an increase in $ppFEV_1 > 5\%$ at 6 months, which they defined as being a "responder." Although no variables were statistically associated with this improvement, male sex was most associated with being a responder (relative risk, 1.46; 95% CI, 0.98–2.18). This potential benefit contrasts with a recent study that demonstrated that females with at least one G551D mutation on ivacaftor had a greater reduction in sweat chloride and rates of PEx, indicating that females had a differential response profile compared with males (11). Although there were differences in the two study cohorts regarding genotype and modulator treatment, these findings underscore the need for future studies to evaluate the effect of sex and treatment response to CFTR-modulator therapies. In addition to the significant findings presented, the study design allowed for creation of a robust biorepository of specimens as well as substudies that will provide further biologic data on the effectiveness of increased CFTR activity achieved through LUM/IVA.

Although $ppFEV_1$ did not increase significantly in this report of the PROSPECT study, this should not be interpreted to mean that LUM/IVA does not improve lung function. This study enrolled people with a wide range of lung function, and the ability to detect an effect of LUM/IVA may have been blunted by the heterogenous nature of responses to the drug. In addition, this study was underpowered to detect the 3.5% change in lung function seen in the much larger phase 3 clinical trial (6). More importantly, this study has further demonstrated the ability to use sweat chloride as a biomarker in CF studies and has provided the foundation to further investigate the effects of CFTR modulators on lung clearance and gastrointestinal pathology.

Since LUM/IVA was approved, two additional CFTR-modulator drugs have been approved. The CF community is especially excited about the triple-combination drug elexacaftor/tezacaftor/ivacaftor, which has the trade name Trikafta. This combination demonstrated large effects on FEV_1, respiratory symptoms, weight, and exacerbations in phase 3 trials and was approved by the FDA in October of 2019 (12). The PROSPECT study and the knowledge gained from it will be instrumental in designing future observational studies in people with CF receiving the newer triple-combination CFTR modulator. This is an exciting time for the CF community, given the development and approval of this new class of medication. We applaud the PROSPECT investigators for a well-designed, well-conducted study that represents one more positive step toward finding a cure for CF. ■

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

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