CFTR Modulators to the Rescue of Individuals with Cystic Fibrosis and Advanced Lung Disease

The development of CFTR modulators has been one of the most remarkable stories in respiratory medicine. Defining the genetic, molecular, and cellular biology of cystic fibrosis (CF) mutations enabled high-throughput screening to identify compounds that partially restore CFTR function. The first highly effective CFTR modulator became available in 2012 when the U.S. Food and Drug Administration approved ivacaftor (Kalydeco, IVA) for individuals with the G551D CFTR mutation. IVA substantially decreased sweat chloride, increased respiratory frequency, promoted weight gain, reduced exacerbation frequency, and improved the quality of life for patients with an FEV1 40–90% predicted (1). Since that time, IVA was approved for several other gating mutations such that by early 2020, ~20% of individuals with CF had access to an efficacious disease-modifying oral medication. Several studies have examined the effect of IVA on patients with advanced lung disease and demonstrated similar improvements to what was observed in patients with modest lung disease (2–5). More recently, the second highly effective CFTR modulator therapy, elexacaftor–tezacaftor–IVA (Trikafta, ETI) was approved for individuals with the F508del CFTR mutation. ETI also dramatically improves sweat chloride, FEV1 (by ~14% absolute predicted), nutritional status, exacerbation frequency, and quality of life for individuals with an FEV1 40–90% predicted (6–8). Because F508del is the most common CFTR mutation, now ~90% of individuals with CF have access to an efficacious disease-modifying therapy. Although the transformative effects of ETI have been extensively studied in...
individuals with mild to moderate CF lung disease, the clinical impact for individuals with severe lung disease has been less well described; small studies and early real-world experience suggest a similar degree of benefit (9) (Figure 1). In this edition of the Journal, Burgel and colleagues (pp. 64–73) report the effect of ETI for individuals with CF and advanced lung disease who received ETI through an early access program in France (10). Between December 2019 and August 2020, 245 patients with at least one F508del CFTR mutation and an FEV₁, 40% predicted and/or who were under evaluation for lung transplantation received ETI. Consistent with prior studies, ETI was well tolerated and associated with dramatic improvements in lung function and weight. The 15% mean increase in absolute FEV₁% predicted was consistent with the subset of patients in the phase 3 studies whose FEV₁ was just below 40% predicted (7). The current study provides additional evidence for a transformative effect of ETI for individuals with severe lung disease, as ETI use reduced the need for supplemental O₂ by 50%, noninvasive ventilation by 30%, and enteral tube feeding by 50%. Even in those on O₂ and/or noninvasive ventilation at initiation of ETI, mean FEV₁% predicted increased by 13%. Notably, before the initiation of ETI in this population, 16 patients were on the lung transplant waiting list and 37 were undergoing transplant evaluation. Although somewhat confounded by the coronavirus disease (COVID-19) pandemic, only two patients underwent lung transplantation, one died, and five remained on the path to transplant. Given the duration of the study, these results are extraordinary.

The current study by Burgel and colleagues and recent reports of the long-term impact of other CFTR modulators have important implications for the care of individuals with CF and advanced lung disease as defined by an FEV₁ <40% predicted (10–12). CF providers have struggled for decades trying to optimize the timing for lung transplant referral and listing. Despite multiple attempts using large registries and other data sets, predictive models for short-term mortality remain suboptimal, and many individuals with CF die without careful consideration of lung transplantation. These observations were the impetus to update transplant referral guidelines, which recommend early discussion of lung transplant as a treatment option for individuals with CF, an FEV₁ of 30–40%, and other markers of severe disease as well as referral for all patients with an FEV₁ < 30% predicted (13). These recommendations were informed by the observation in the Cystic Fibrosis Foundation Patient Registry that individuals with CF and an FEV₁, 30% predicted have a median survival of 6.6 years compared with a 10-year median survival after lung transplantation (14). However, these data were collected before the advent of highly effective CFTR modulators, which will clearly reduce the rate of progression of CF lung disease. Long-term studies recently demonstrated that IVA significantly reduced the progression of CF lung disease over 5 years (12). This, coupled with the short-term effects of both IVA (4) and ETI (10) for individuals with CF and advanced disease, suggests that survival with advanced CF lung disease will increase significantly.

What are the implications of this new data for transplant referral and listing for the ~90% of individuals with advanced CF lung disease on highly effective CFTR modulators? Until we have better predictors of survival, early referral for lung transplant seems prudent for all individuals with CF and advanced lung disease to 1) provide patients and families with information about transplant as a treatment option, 2) identify and begin to remediate barriers to lung transplant, and 3) establish a safety net if they develop respiratory failure. Less clear for those on a modulator will...
be the decision to proceed with transplant listing and surgery, as survival with advanced CF lung disease on ETI will undoubtedly improve, allowing individuals to safely delay transplant. As additional data accumulate to provide clarity on best practices, individuals with CF, their families, and providers should continue to celebrate the transformative impact of CFTR modulators on quality of life and survival.

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

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References

1. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al.; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365: 1663–1672.
2. Barry PJ, Plant BJ, Nair A, Bicknell S, Simmonds NJ, Bell NJ, et al. Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease. Chest 2014;146:152–158.
3. Polenakovic HM, Sarville B. The use of ivacaftor in an adult with severe lung disease due to cystic fibrosis (ΔF508/G551D). J Cyst Fibros 2013;12:530–531.
4. Taylor-Cousar J, Niknian M, Gilmartin G, Pilewski JM; VX11-770-901 investigators. Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: safety and efficacy in an expanded access program in the United States. J Cyst Fibros 2016;15:116–122.
5. Salvatore D, Terlizzi V, Francalanci M, Taccetti G, Messore B, Biglia C, et al. Ivacaftor improves lung disease in patients with advanced CF carrying CFTR mutations that confer residual function. Respir Med 2020;171:106073.
6. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, et al.; VX16-445-001 Study Group. VX-445–Tezacaftor-Ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 2018;379:1612–1620.
7. Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, et al.; VX17-445-102 Study Group. Elexacaftor-Tezacaftor-Ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019;381:1809–1819.
8. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al.; VX17-445-103 Trial Group. Efficacy and safety of the exacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394:1940–1948.
9. O’Shea KM, O’Carroll OM, Carroll C, Grogan B, Connolly A, O’Shaughnessy L, et al. Efficacy of exacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced lung disease. Eur Respir J 2021;57:2003079.
10. Burgel P-R, Duriéiu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, et al.: French Cystic Fibrosis Reference Network study group. Rapid improvement after starting exacaftor–tezacaftor–ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. Am J Respir Crit Care Med 2021;64:73–.
11. Higgins M, Volkova N, Moy K, Marshall BC, Bilton D. Real-world outcomes among patients with cystic fibrosis treated with ivacaftor: 2012-2016 experience. Pulm Ther 2020;6:141–149.
12. Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. J Cyst Fibros 2020;19:68–79.
13. Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, et al.; CF Lung Transplant Referral Guidelines Committee. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. J Cyst Fibros 2019;18:321–333.
14. Ramos KJ, Quon BS, Heitshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, et al. Heterogeneity in survival in adult patients with cystic fibrosis with FEV1 < 30% of predicted in the United States. Chest 2017;151:1320–1328.

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Do Circulating Monocytes Promote and Predict Idiopathic Pulmonary Fibrosis Progression?

Despite the availability of pharmacologic therapies, idiopathic pulmonary fibrosis (IPF) is still a clinical challenge. It is a lethal disease with a clinical course that cannot be predicted at the time of diagnosis. The high burden of suffering in IPF, the need to prioritize a select few for transplantation, and the high mortality highlight the need for better, simpler, and clinically applicable prognostic tools. In airways disease, for example (1, 2), eosinophil counts are routinely used for subphenotyping, directed therapy, and assessment of therapy responses. Is there an IPF equivalent to eosinophils?

Growing evidence supports that innate and adaptive immune cells disrupt normal lung repair. Some key studies have brought to light that several circulating immune populations have the potential to reflect and predict disease outcome either by RNA (3), protein (4), or cellular counts (5). Scott and colleagues (5), by performing cell deconvolution analysis of transcriptome data, reported an unexpected finding of an association between absolute and relative numbers of circulating monocytes and survival in individuals with IPF. In their study, patients with high monocyte counts were at higher risk for poor outcomes. Monocyte counts of 0.95 x 10^9/L or greater were associated with mortality after adjusting for FVC, sex, age, and physiology index. These associations were validated in 7,000 patients with IPF through five different cohorts.