diagnostics and therapeutics in the application of precision medicine in ARDS. These challenges are currently being tackled by others (https://clinicaltrials.gov/ct2/show/NCT04009330), and it is possible that we will have rapid diagnostics in the not-so-distant future. The best lesson, one that we can act on starting today, is that the bedside to bench to bedside approach is a powerful method for understanding clinically relevant biology. This illustrates that the path toward clinical application of personalized interventions in ARDS requires synchronized research by multiple groups with complementary expertise. If these steps are taken in the coming years, the field may look back at this study as a pioneering step toward a treatable trait approach for ARDS (10). ■

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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 function, promoted weight gain, reduced exacerbation frequency, and improved the quality of life for patients with an FEV_1 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, FEV_1 (by ∼14% absolute predicted), nutritional status, exacerbation frequency, and quality of life for individuals with an FEV_1 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

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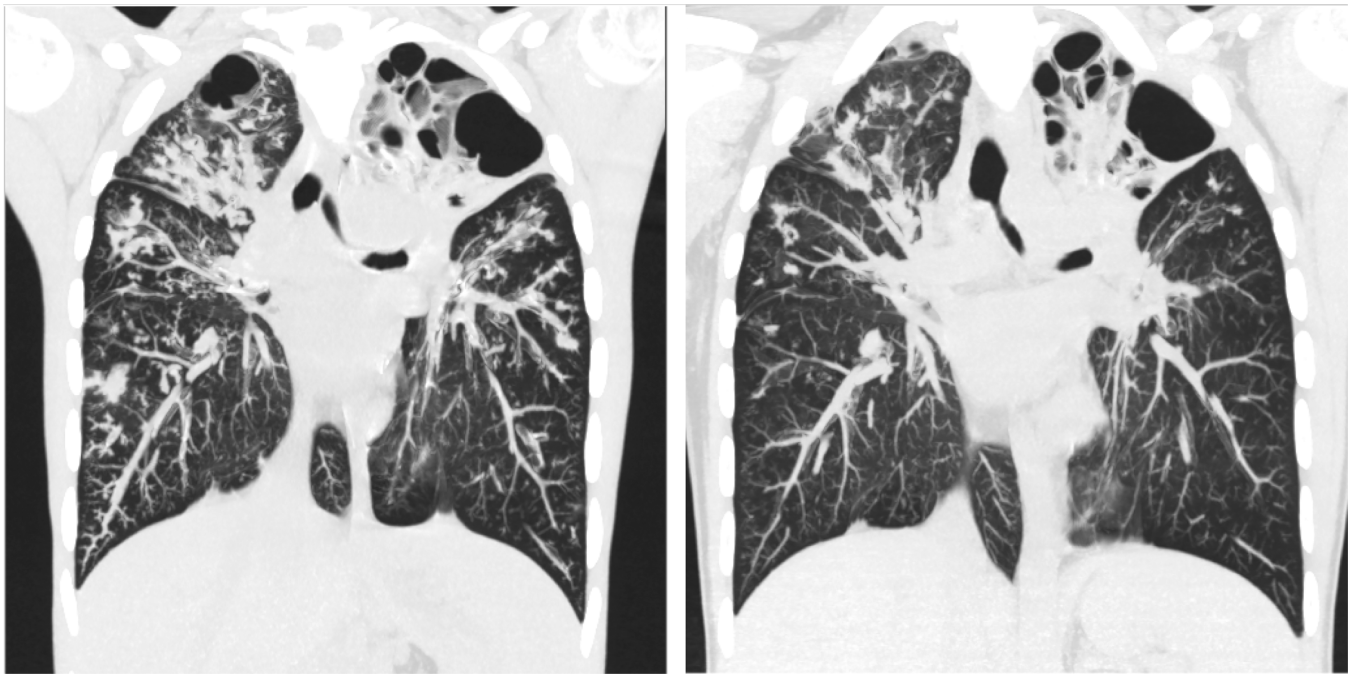

Figure 1. Effect of elexacaftor–tezacaftor–ivacaftor (ETI) on lung disease in a young man homozygous for 508del CFTR mutations. After his first visit to our center in January 2019, he received nine courses of antibiotics and was evaluated for lung transplantation. Since initiating ETI through a compassionate use program in September 2019, he has not had a cystic fibrosis exacerbation, his FEV_1 improved from 26% to 50% predicted, his body mass index improved from 14.5 to 17.6, and he returned to full-time employment. Computed tomographic imaging in October 2019 (right), after 1 month of ETI, demonstrated marked reduction in areas of mucus impaction compared with before (left).

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 FEV_1 <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 FEV_1% predicted was consistent with the subset of patients in the phase 3 studies whose FEV_1 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 O_2 by 50%, noninvasive ventilation by 30%, and enteral tube feeding by 50%. Even in those on O_2 and/or noninvasive ventilation at initiation of ETI, mean FEV_1% 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 FEV_1 <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 FEV_1 of 30–40%, and other markers of severe disease as well as referral for all patients with an FEV_1 < 30% predicted (13). These recommendations were informed by the observation in the Cystic Fibrosis Foundation Patient Registry that individuals with CF and an FEV_1 < 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. ■

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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 0.95×10^9/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.

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