



## Combination Therapy with Lumacaftor–Ivacaftor in Cystic Fibrosis Keeping It Real

Ivacaftor was approved by the U.S. Food and Drug Administration in 2012 for patients with cystic fibrosis (CF) carrying the G551D mutation and represented the first treatment that targeted mutant CFTR (cystic fibrosis transmembrane regulator) protein, the underlying cause of CF. Subsequently, several real-world studies have expanded our understanding of ivacaftor's effects on long-term pulmonary and nonpulmonary outcomes (1–3). Because it is approved for only about 10% of patients with CF, there remained a substantial unmet need. The most common mutation in patients with CF is a phenylalanine deletion at amino acid 508, termed F508del, which results in complex protein abnormalities that require multiple drugs to effect clinically meaningful CFTR restoration. The combination of a CFTR corrector and potentiator, lumacaftor–ivacaftor, was approved in 2015 after two concurrent phase 3 trials that established its efficacy in increasing FEV<sub>1</sub> and reducing pulmonary exacerbations (4). During the phase 3 studies and in subsequent reports, it was noted that the combination (likely resulting from lumacaftor) was associated with significant adverse effects, most notably chest tightness (8.7% vs. 5.9% in placebo) and dyspnea (13.0% vs. 7.8%), with an overall discontinuation rate of 4.2% in treated subjects compared with 1.6% in the placebo group. In this issue of the *Journal*, Burgel and colleagues (pp. 188–197) report on the real-world effectiveness and safety of lumacaftor–ivacaftor in French patients treated for 1 year (5). This is an important follow-up study to the phase 3 trials for a few reasons, two of which are that this study includes patients excluded in the phase 3 trials and that it reports on nonpulmonary outcomes.

There are several strengths to the study by Burgel and colleagues. These include the large number of participants ( $N = 845$ ) from many CF clinics (47 centers), prospective data collection, near complete follow-up (>98%), and inclusion of a relatively high proportion of adolescents and patients with severe liver disease. The authors stratified the population into 3 subgroups according to whether treatment was continuous, discontinued, or intermittent, and intermittent was defined as successful resumption after temporary discontinuation. The increase in FEV<sub>1</sub>, body mass index, and reduction in pulmonary exacerbations mirrored the pivotal trial results in the overall population while adding granularity to the heterogeneity of clinical response. About 20% of the overall population had a 10% or greater increase in FEV<sub>1</sub>, whereas patients who discontinued treatment had a fall in FEV<sub>1</sub> and body mass index, and no reduction in pulmonary exacerbations. Interestingly, adolescents demonstrated a steady FEV<sub>1</sub> rise over the course of 1 year, and an overall greater increase compared with adults, who had a peak effect after 1 month of

treatment that remained stable out to 1 year. Surprisingly, measures of vitamins A, D, and E levels and Hb A1C were unchanged after 1 year of lumacaftor–ivacaftor treatment. The heterogeneity in clinical trajectories and in response to CFTR modulators remains poorly understood and highlights the need for personalization of CFTR modulator use (e.g., biomarkers to predict responsiveness), especially in light of the high cost burden.

Of particular focus to CF clinicians in using lumacaftor–ivacaftor has been a relatively high incidence of respiratory adverse effects (e.g., dyspnea, chest tightness, and/or wheezing) compared with that reported in the pivotal trials, which excluded patients with FEV<sub>1</sub> < 40%. In this study, Burgel and colleagues noted a discontinuation rate of 18.2%, almost half of which was a result of respiratory adverse events. Patients with more severe disease, such as those older than 18 years and with an FEV<sub>1</sub> < 40%, more intravenous antibiotics use, and diabetes mellitus were at higher risk for discontinuation. These data confirm earlier smaller reports that noted that the incidence and severity of bronchospasm leading to discontinuation was higher in patients with FEV<sub>1</sub> < 40% (6–10). Of note, fewer patients in the French cohort compared with the subjects in the pivotal trials were chronically treated with bronchodilators and hypertonic saline, which may have also affected the differential rates of respiratory adverse effects.

Discontinuation resulting from nonrespiratory adverse events included mostly gastrointestinal intolerance (diarrhea or abdominal pain), but reassuringly, only a very small frequency of patients discontinued treatment because of abnormalities in liver function tests (0.24%). This is noteworthy, as 5% of the overall population had cirrhosis or portal hypertension, a group of patients that was excluded from the phase 3 trials. On the basis of improvements in sweat chloride and acceptable safety profiles in a small number of patients, lumacaftor–ivacaftor is now approved for patients as young as 2 years of age, and a similar study will be required in patients aged 2–11 years to assess long-term safety and effectiveness in a group of patients not included in this study.

Because the study reported here only followed patients for 1 year, there was no ability to assess other outcomes of interest such as FEV<sub>1</sub> decline, need for lung transplantation, and survival. Although large U.S. and UK registry analyses have suggested ivacaftor attenuates FEV<sub>1</sub> decline and lowers the risk for death and lung transplantation (1), similar real-world follow-up is lacking but needed for lumacaftor–ivacaftor. The data reported in the lumacaftor–ivacaftor phase 3 extension study are promising, as it reported that the combination led to a 42% reduction in FEV<sub>1</sub> decline compared with the matched registry control group (11).

Finally, as lumacaftor–ivacaftor was released, an additional combination consisting of the novel corrector tezacaftor and ivacaftor has been approved. This combination has a better safety profile and fewer drug–drug interactions compared with lumacaftor–ivacaftor (12) and has supplanted lumacaftor–ivacaftor in many U.S. patients with CF. The tezacaftor–ivacaftor combination, with a second corrector (elixacaftor) added, forms the basis for the

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triple-combination modulator therapy, which has shown greater efficacy than either dual combination and has been approved by the U.S. Food and Drug Administration. With the approval of the triple-combination drug, 90% of patients with CF will be eligible for a CFTR modulator (13). It is plausible that in the not-too-distant future, most infants diagnosed with CF will begin a highly effective CFTR modulator, such as the triple-combination treatment, shortly after birth, and continue receiving it indefinitely. This possibility highlights the continuing need for postmarketing observational analyses, such as this one by Burgel and colleagues, as we know relatively little about the long-term efficacy or safety of any CFTR modulator. ■

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## Coming to “Grp(s)” with Senescence in the Alveolar Epithelium

According to the current paradigm of idiopathic pulmonary fibrosis (IPF) pathogenesis, injury to and dysfunction of the lung epithelium play a major role in driving the disease process (1). Over the past two decades, studies of families with PF implicated rare mutations in genes related to surfactant biology as monogenic causes of PF (2), and subsequent work from multiple groups has indicated that

at least a subset of surfactant protein mutations lead to misfolding of the proprotein, leading to endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) (3–5). Although surfactant protein mutations appear to be rare causes of adult PF, evidence of UPR activation in the lung epithelium is a common, if not ubiquitous, feature of IPF lungs (6, 7). Studies using several different pharmacologic UPR inducers and transgenic mouse models have demonstrated links between UPR activation, epithelial cell death by apoptosis or necroptosis (4, 5, 8, 9), and chronic inflammation (10). Conceptually, these studies suggest that high-level expression of misfolded proteins can overwhelm ER chaperone function, promoting a proinflammatory epithelial cell phenotype and premature death of the alveolar epithelium. Consistent with this hypothesis, global haploinsufficiency for the ER chaperone Grp78 (glucose-related peptide 78, also known as the immunoglobulin heavy-chain chaperone protein, Bip) appears to

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