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Evidence for Early Cystic Fibrosis Transmembrane Conductance Regulator Modulator Treatment for Children with Cystic Fibrosis Keeps Growing

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies have led to dramatic improvements in clinical outcomes for many persons with cystic fibrosis (CF) eligible for these medications (1). In the 2020 U.S. Cystic Fibrosis Foundation Patient Registry, median lung function improved across all age groups, reflecting for the first time a reversal of the historically described annual decline in lung function (2). Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), the most recently developed CFTR modulator, results in clinical improvements larger than those with lumacaftor/ivacaftor (LUM/IVA) or tezacaftor/ivacaftor (TEZ/IVA) and similar to those with ivacaftor, which is only approved for a small population with responsive *CFTR* variants (1). ELX/TEZ/IVA was approved by the Food and Drug Administration for patients 12 years and older with at least one *F508del-CFTR* allele in the United States in 2019, and regulatory approvals followed in other countries, including the European Union (2020), Canada (2020), and Australia (2021). In June 2021, ELX/TEZ/IVA was approved by the Food and Drug Administration for children ages 6 to 11 years after a phase 3 open-label study demonstrating safety and efficacy (3). Although this study demonstrated substantial improvements in clinical outcomes, it was designed primarily to evaluate safety and did not include a control group.

In this issue of the *Journal*, Mall and colleagues (pp. 1361–1369) report results from a phase 3b randomized, double-blind, placebo-controlled study of ELX/TEZ/IVA in 121 children with CF, 6 to 11 years of age, and heterozygous for *F508del-CFTR* and a minimal function *CFTR* variant (4). Children were included if they had an elevated baseline lung clearance index ($LCI_{2.5}$) of $\geq$7.5, suggestive of small airway disease. Participants were randomized to receive either ELX/TEZ/IVA or placebo for 24 weeks. ELX/TEZ/IVA resulted in a significant improvement in $LCI_{2.5}$, the primary study outcome, with a between-groups difference of -2.26 units ($P < 0.001$). Reduction in sweat chloride (-51.2 mmol/L, $P < 0.0001$); improvement in percent predicted forced expiratory volume in 1 s ($ppFEV_1$) (11.0%, $P < 0.0001$); and improvement in scores on the Cystic Fibrosis Questionnaire–Revised, respiratory domain (5.5 points, $P = 0.0174$), were also observed and were similar to changes seen in the open-label study. Notably, less improvement on the Cystic Fibrosis Questionnaire–Revised, respiratory domain, was noted in this age range compared with adolescents and adults treated with ELX/TEZ/IVA, despite impressive improvements in lung function and sweat chloride, possibly because of relatively mild symptom scores at baseline (5, 6). Thus, in clinical practice, children and caregivers may not notice a substantial difference in symptoms after starting therapy, despite benefits to lung health.

Results from this study add information about the potential benefits of ELX/TEZ/IVA in this age range. Additionally, important comparisons related to adverse events were made between the treatment and placebo groups, providing additional insights into safety and benefits. Headache and rash were reported more frequently with ELX/TEZ/IVA, compared with placebo, whereas cough, abdominal pain, and pulmonary exacerbations were decreased relative to placebo, likely reflecting overall improvement in underlying CF disease. No new safety concerns were identified compared with previous clinical trials. Adverse events related to mental health or behavior changes were not measured in this trial, although concerns around mental health effects have been raised in older age groups.

As in several other recent clinical trials of CFTR modulators in younger children (7, 8), $LCI_{2.5}$ served as the primary outcome rather than $ppFEV_1$, which has generally been used as the primary efficacy outcome in studies of adolescents and adults (5, 6). Increases in $LCI_{2.5}$ appear more sensitive for the detection of early lung disease and may detect improvements in small airway disease that are not captured with $ppFEV_1$ measurements. The impact of

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ELX/TEZ/IVA on LCI in those with normal baseline values is not known, as these children were excluded from the study, potentially reducing the generalizability of these results. Although the *ad hoc* subgroup analysis suggests greater improvement in $LCI_{2.5}$ in those with worse baseline values (>10 versus <10), those with normal baseline $LCI_{2.5}$ may still benefit from therapy, especially if annual worsening of $LCI_{2.5}$ is attenuated by ELX/TEZ/IVA. Additionally, a recent study found that $LCI_{2.5}$ was elevated in approximately 70% of school-age children with CF, despite most having normal $ppFEV_1$ (9). For CFTR modulator studies in children less than 6 years of age, $LCI_{2.5}$ takes on added value, as spirometry is less reliable in these age groups.

Although the use of $LCI_{2.5}$ as an outcome measure has gained traction within the CF community, the minimal clinically important change has not been defined. Improvements in $LCI_{2.5}$ observed in this study were substantially greater in those seen with hypertonic saline in young children (mean difference versus placebo in $LCI_{2.5}$, −0.63) (10) or dornase alfa (mean difference versus placebo in LCI, −0.9) (11), both of which are generally viewed as improving mucociliary clearance and small airway disease. The change in $LCI_{2.5}$ was also comparable with findings in the open-label study of ELX/TEZ/IVA in this age range (3) and larger than in studies of LUM/IVA and TEZ/IVA (7, 8). Although the authors reported that the device required updates to correct for cross-sensitivity in the device's oxygen and carbon dioxide sensors, the changes in calculations were not expected to alter the interpretation or treatment response.

One limitation of this study, acknowledged by the authors, is the potential lack of diversity among study participants. Because of local regulations, race and ethnicity data were not collected for 24% of participants; among participants who had data collected, 95% were non-Hispanic White. Persons with CF from racial and ethnic minority groups are less likely to have variants that qualify them for CFTR modulators (12), which places them at risk for widening health disparities and delays in diagnosis because of false-negative newborn screening (13, 14). Minoritized groups in the United States also have been underrepresented in pharmaceutical trials (15). It is imperative, with the support from industry sponsors, that CF researchers strive to recruit and enroll participants into clinical trials to accurately reflect the diversity of the CF community. Because of the significant benefits seen with ELX/TEZ/IVA, worsening health disparities between those eligible and not eligible for CFTR modulators will almost certainly occur; therefore, there is an urgent need for treatments for persons with genetic variants not amenable to modulator therapies.

The availability of ELX/TEZ/IVA in younger populations is exciting and offers hope that disease progression can be slowed or even prevented. Given the substantial benefit demonstrated with ELX/TEZ/IVA, it is unlikely that another placebo-controlled trial will be conducted in this age group. As these are lifelong medications, information about adverse effects and relative benefit compared with prior standard-of-care therapies is critical for families and clinicians deciding to start therapies. Mall and colleagues have made a substantial contribution to this understanding, with implications for studies in even younger children where clinical impact on early disease manifestations such as pancreatic insufficiency may take on added importance. ■

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Particle Constituents and Oxidative Potential: Insights into Differential Fine Particulate Matter Toxicity

The association between fine particulate matter ($PM_{2.5}$) and morbidity and mortality differ widely between and within regions (1–4). It is expected that differences in $PM_{2.5}$ composition play a role in the observed differences by modifying the effects of $PM_{2.5}$ on various biological processes (5). However, there is currently scarce evidence about which components have stronger impacts or health effects (6). It has been hypothesized that constituents that contribute to the oxidative potential (the ability of particles to generate reactive oxygen species by consumption of antioxidants and/or generation of oxidants) are likely to drive many of the observed health effects. Metals from various sources, including traffic and industrial emissions, are likely an important part of the oxidative potential (7). Furthermore, it's also important to consider the influence of sulfate in the toxicity of particles because sulfate found in $PM_{2.5}$ facilitates the dissolution of metals, and solubility is an important determinant of particle oxidative potential (8).

The effects of air pollutants on children's respiratory health have been a focus of research for several decades (3, 4, 9). However, spatial and temporal misalignment in studies of environmental exposures (i.e., measuring a toxicant at a point in space as a weekly aggregate with daily changes in health) can bias the estimation of health risk (10, 11). The development of methods for processing large numbers of samples with low limits of detection, as well as methods to measure the oxidative potential of particles, allows the identification of PM constituents with a time resolution more suitable for the assessment of temporal changes in health effects. However, because of the cost of these analyses, data availability is still low compared with measurements for regulated pollutants (e.g., criteria air pollutants in the United States).

In this issue of the *Journal*, the paper by Korsiak and colleagues (pp. 1370–1378) provides evidence that associations between short-term $PM_{2.5}$ mass concentration and respiratory hospitalizations in children are modified by metal and sulfur content in $PM_{2.5}$, as well as particle oxidative potential (12).

Two major strengths of this study are the large sample size of 10,500 children across 34 Canadian cities and the time-stratified case-crossover design that allowed time-invariant factors (e.g., sex) or factors that do not vary within subjects over short periods of time (e.g., age and body mass index) to be controlled for by design (13, 14). The time-stratified case-crossover design provides an alternative to conventional time series regression for analyzing associations between time series of environmental exposures (air pollution and weather) and counts of health outcomes (15). Another important strength of the Korsiak study is the 2-week per month periodicity of $PM_{2.5}$ samples that were collected in each of the cities and analyzed for metals, sulfur, and oxidative potential (Figure 1), accounting for some of the temporal variability in $PM_{2.5}$ composition over time.

A novel contribution to the field is the integrative analysis of the different PM constituents and oxidative potential using 2-week integrated filters each month. These analyses are likely too time-consuming and costly to be repeated in similarly large studies but can be useful tools to assess the toxicity of $PM_{2.5}$ in more polluted regions of the world. It is likely that 2-week integrated samples were needed to capture enough mass for the Korsiak study, given the low ambient concentrations found in Canada, but it is unclear how rapidly metal concentrations or oxidative potential may change within this 2-week period or if the 2-week period is representative of the full month. More frequent filter samples can likely be collected in regions with higher $PM_{2.5}$ concentrations, providing higher time resolution that reflects the daily variability in $PM_{2.5}$ sources depending on airmass transport and can be better matched to acute health effect measurements.

Interestingly, there was a relatively low correlation between the three metrics of oxidative potential measured (particularly the DDT assay (dithiothreitol) with the other two assays). Although these different metrics can have a variable response to the different PM constituents, it is still not clear which metric should be prioritized for health research. It is possible that the low $PM_{2.5}$ concentrations observed in Canada make it difficult to distinguish between these different metrics, and this remains an important area for future research.

Limitations of the study include that the study was conducted in Canada, where $PM_{2.5}$ concentrations are low compared with much of the world. Ozone concentrations are also quite low year-round in Canada (75th percentile below 30 ppb in both seasons). Thus, there was a small range of exposures considered in the study, and metal

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