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# Getting Near to "Closing the Gap" in the Pediatric Age Group for the First Personalized Treatment of Cystic Fibrosis

With the approval of highly effective modulators, the treatment of cystic fibrosis (CF) has been transformed, and the progression of the disease will be further modified in people with CF. CFTR (cystic fibrosis conductance regulator) modulators are small molecules administered orally that treat the basic defect by correcting specific deficiencies in the CFTR protein and therefore restoring CFTR function. Potentiators such as ivacaftor improve the channel opening duration of CFTR in so-called gating mutations.

A phase III study in patients with CF (aged ⩾12 yr) with the G551D mutation demonstrated that ivacaftor improved the percent of predicted $FEV_1$ ($ppFEV_1$) by 10.6% after 24 weeks of treatment ($P < 0.001$). It reduced the frequency of pulmonary exacerbations by 55% ($P < 0.001$), induced a weight gain of 2.7 kg ($P < 0.001$), and decreased sweat chloride concentration by 48 mmol/L compared with placebo ($P < 0.001$) (1). These results demonstrated that correction of CFTR at the molecular level translates into impressive clinical improvements (2). Ivacaftor became the first CFTR modulator approved in 2012 for people with CF in this age group.

Clinical benefit was also confirmed in further studies. Patients with CF with eight further gating mutations showed improvement in $ppFEV_1$, weight, sweat chloride, and quality of life. Even in children, a patient population with still normal $ppFEV_1$ due to "silent" CF lung disease, a significant improvement in $ppFEV_1$ and lung clearance index was shown (2–4). Furthermore, ivacaftor demonstrated effectiveness in preschool children (5). In this age group, the increase in FE-1 (fecal elastase-1) as an outcome parameter is remarkable, indicating a potential reversal of early pancreatic insufficiency previously thought to be irreversible (5, 6).

Therefore, these promising data, combined with real-life experience, hold promise for its use in very young children when disease manifestations can still be modified. However, new therapies in this vulnerable patient group need careful assessment of pharmacokinetics and safety.

In this issue of the *Journal*, Davies and colleagues (pp. 585–593) provide results of ivacaftor in infants aged 4–12 months with a gating mutation (7). A total of 25 patients received ivacaftor in a phase III, single-arm, two-part multicenter clinical trial.

An important finding of this study was that ivacaftor was generally safe in this very young age group. The majority of infants showed plasma drug concentrations within the accepted range from prior clinical studies consistent with ranges for older children.

This study reveals that most adverse events (AEs) were mild to moderate and considered not related to the study drug, with cough being the most frequent AE (Part B). Five infants had serious AEs, interestingly also all considered not or unlikely related to the study drug.

An important concern regarding CFTR modulators is the risk of inducing abnormalities of liver function in this young population. Fortunately, only one child demonstrated a reversible transaminase elevation. Interestingly, the incidence of liver function abnormalities was lower than expected compared with previous trials.

A striking finding was that one infant aged 3 months had drug levels above the adult 95th percentile, a fact that led to an adjustment of age and dose during the ongoing trial.

This raises the question of whether the dosages need to be adjusted to weight/body composition and whether the ranges are really comparable between the various age groups. The authors



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conclude correctly that drug administration in the age group <4 months has to be further studied before dose recommendations can be made. So, for now, ivacaftor can be safely administered in the age group ⩾6 months.

A remarkable finding was the substantial improvement of sweat chloride as a biomarker for CFTR function; three children even reached normal values once during the trial. So, the question is, if we go further down the age cohorts until the newborn age, can we revert elevated sweat chloride levels to normal values and maintain these? Would this translate into substantially better outcomes or even an absence of CF lung disease? Also, are small infants more susceptible to positive impacts of CFTR modulation therapy? We do not know—yet. However, this study fuels the hope that by giving a CFTR modulator in the newborn period, disease manifestations could be modified enormously.

Although Davies and colleagues can be congratulated for examining such young infants in a CF modulator trial for the first time, there are some limitations.

As the authors state correctly, the study was not powered to detect treatment effects. Unfortunately, the sample size was too small to learn more about this special age group, and there are clear opportunities missed here!

Utilizing a larger sample size, with the addition of a control group, we would have gained more knowledge about disease trajectory both with and without treatment in this early age (e.g., the striking variability of the FE-1 measurements in this study). The questions remain, which positive change would be clinically (not statistically) significant, and is the response in FE-1 (or sweat chloride, etc.) related to study drug levels?

Furthermore, the whole field of clinical pharmacogenomics determining drug metabolizing enzyme activity is not explored in these modulator trials (8). Understanding the relative change in enzyme activities or rate of clearance of modulator treatments relative to an individual's genetic variance is an important component in the interpretation of data (8). Additionally, age-dependent body composition may necessitate individualized dosing regimens. Because of the large interindividual variability, individual dosage adjustments based on the monitoring of drug plasma concentrations are highly recommended in children with CF (9). Despite the development of new techniques for determining levels of modulators and their metabolites in body fluids, there are no recommendations to date for therapeutic drug monitoring (9).

Lung clearance index, one of the most important, albeit also elaborate, outcome parameters in young children, was measured in one infant; studies like this could offer an opportunity to gain more knowledge about early CF lung disease and its possible modification by CFTR modulators.

An additional field that is missed in these pediatric trials of CFTR modulators is the evaluation of neurodevelopment. Potentially, this could be negatively influenced by side effects of the study drug in this vulnerable age group but also positively affected by inducing CFTR function in the developing human brain. Different expression and localization of CFTR depending on the brain structure or the cell maturation stage has been shown in fetuses (10). These findings suggest that CFTR may play previously unsuspected roles in neuronal maturation or function (10).

We need further investigation when evaluating new therapies treating the basic defect in this very young age group. So, there is still more to explore! Additionally, these new treatments provide a unique opportunity to explore the changes in pathophysiology in early age.

The current study is of major importance, as the data of this trial favored an indication approval in the age group 6–12 months. We are making steady progress toward "closing the gap" for treating the basic defect right after infants are diagnosed with CF via newborn screening. ■

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