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CFTR Modulator Therapies in Pediatric Cystic Fibrosis: Focus on Ivacaftor

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Abstract

Introduction—Mutations in the cystic fibrosis transmembrane conductance regulator protein (CFTR) cause cystic fibrosis (CF), a disease with life threatening pulmonary and gastrointestinal manifestations. Recent breakthrough therapies restore function to select disease-causing CFTR mutations. Ivacaftor is a small molecule that increases the open channel probability of certain CFTR mutations, producing clear evidence of bioactivity and efficacy in pediatric CF patients. CFTR modulators represent a significant advancement in CF treatment. Extending these therapies to young CF patients is proposed to have the greatest long term impact, potentially preventing later disease.

Areas covered—Here we summarize the research experience of CFTR modulators in pediatrics, focusing on ivacaftor and highlighting challenges in pediatric studies. As a result of these studies, ivacaftor has been approved in CF patients age 2 years and older who have one of ten CFTR mutations.

Expert Opinion—Conducting studies in young CF patients presents unique challenges, including small numbers of patients and difficulty selecting sensitive biomarkers and meaningful outcome measures. Adverse events may be more pronounced in children and deserve special attention. Ongoing efforts must focus on expanding and validating new biomarkers, innovative study design, and thorough monitoring of adverse events in children treated with CFTR modulators.

Keywords

CFTR; CFTR modulator; cystic fibrosis; ivacaftor; pediatrics; VX-770

1. Introduction

Cystic fibrosis (CF) is the most common lethal genetic disorder in the Caucasian population, affecting >70,000 people worldwide and ~30,000 people in the US [1–3]. Median survival in the US is slightly over 41 years, which varies considerably across different countries and

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Declaration of Interests

JP Clancy has clinical contracts for trials with Vertex Pharmaceuticals, the manufacturer of ivacaftor. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

healthcare systems [4]. Lung disease is the major cause of morbidity and mortality, with frequent symptoms in the pancreas (exocrine and endocrine), GI tract, sinuses, liver and biliary tree, sweat gland, and vas deferens. CF is caused by autosomal recessive mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator protein (CFTR), with >2,000 mutations reported [5]. CFTR is part of the traffic ATPase family, which are characterized by conserved membrane-anchored transmembrane domains and cytoplasmic nucleotide binding domains (NBD-1 and NBD-2) that transport a variety of substrates across cell membranes. The NBDs form a heterodimer complex that binds and hydrolyzes ATP, providing gating (opening and closing) to the channel [1]. CFTR is unique in that it is regulated by cAMP and PKA-dependent phosphorylation of its regulatory (R) domain. CFTR is a bicarbonate and chloride channel that also regulates other epithelial other ion transporters, such non-CFTR chloride channels and the epithelial sodium (Na) channel (ENaC), as well as the transport of other compounds such as thiocyanate and glutathione [1, 6–10]. CFTR is a master regulator of the ion and fluid content of several epithelial surfaces, and most CF-affected tissues demonstrate abnormal mucus obstruction contributing to disease manifestations. In the lungs, CFTR expression is highest in submucosal glands, with lower amounts in the pseudostratified epithelium of the medium and large airways and distal small-airways [11, 12]. CFTR expression in airway smooth muscle and cartilage may also contribute to CF airway disease, but their relative contribution to airway obstruction is unclear [13–19].

1.1. Pathophysiology of Cystic Fibrosis

The pathophysiology of CF lung disease relates to CFTR regulation of ion transport in submucosal glands and surface airway epithelia, airway surface liquid (ASL) volume, pH, and mucus hydration and release [20–27]. Submucosal gland regulation is through an intricate paracrine and neurogenic network driving mucus hydration and release. Reports from studies in neonatal pigs with CF have identified subtle but detectable airway defects at birth, with reduced bacterial killing by the airway surface (due to reduced pH) and reduced mucus release from submucosal glands [26, 27]. These may reflect bicarbonate transport defects that require CFTR. The release and unfolding of mucus granules on epithelial surfaces is also postulated to depend on pH and bicarbonate, with results from the murine CF gut demonstrating thick and adherent mucus along the mucosal surface [28–32]. The airway surface fluid volume is also regulated by airway epithelial cells, which produce and control an overlying airway surface liquid (ASL) compartment. The ASL and periciliary compartment have differentially expressed free and cell-attached mucins, which are high molecular weight glycoproteins with complex and carefully regulated structures [33, 34]. Most of the mucus gel mass is produced by water, and normal hydration of the ASL allows unimpeded ciliary activity and mucociliary clearance [1, 35, 36]. Loss of CFTR releases tonic inhibition of ENaC that increases sodium absorption from the airway surface. This dehydrates the ASL in polarized human airway epithelial monolayers, increasing the percent solid content of gel-forming mucins and compression of the periciliary compartment [35, 37, 38]. Mucus clearance is thus stagnated and produces an airway surface vulnerable to infection and the downstream symptoms of the disease. CFTR deficiency in airway cells also produces inflammation that is persistent and out of proportion to local stimuli. Airway

cells in CF patients demonstrate excessive NF- κ B activation and cytokine release that drives neutrophil-dominated inflammation but fails to resolve normally [39–41].

1.2. Treatment of Cystic Fibrosis

Traditional treatment of CF is supportive, addressing the downstream manifestations of defective CFTR activity. These treatments are effective but create a high care burden for CF patients and families. Treating the underlying cause of CF prior to significant lung damage offers the potential to dramatically alter the disease course, reduce the care burden, and improve the quality of life of CF patients and their families. Therapies would likely require very early initiation for maximal benefit, as end organ damage can be detected at birth (pancreatic insufficiency) or within the first few years of life (bronchiectasis) [42, 43].

2. CFTR modulators to assist mutant CFTR function

Several molecules have been identified through high throughput screening efforts that help restore function to mutant, disease-causing mutations in CFTR. These molecules target common and uncommon CFTR mutations, and several have advanced to clinical trials. The most efficacious of these is ivacaftor, which helps to restore gating function to mutant CFTR at the plasma membrane [44]. The most common gating defect mutation in CF, G551D, is found in approximately 4% of CF patients; non-G551D gating mutations are rare and together are present in only 1% of patients [3, 45, 46]. Ivacaftor has profound positive effects on CFTR function and clinical status in CF patients possessing mutations with gating defects.

2.1. Restoring activity of G551D and other CFTR Gating Defects Through Ivacaftor

G551D CFTR is the most common gating defect mutation in CF, and is the third most common disease-causing mutation[3]. Ivacaftor is a first-in-class molecule that increases the open channel probability of both wildtype and G551D CFTR [47]. Pivotal clinical trials of ivacaftor (Kalydeco®, Vertex Pharmaceuticals Incorporated, formerly known as VX-770) in patients possessing the G551D CFTR mutation culminated in FDA approval of this CFTR modulator in 2012 for patients > 6 years of age, and have ignited research focused on CFTR modulation[44, 48–50]. These studies have provided strong support to develop small molecules that target various disease-causing CFTR mutations to treat CF, generating excitement about the development of novel drugs that restore function to other common CFTR mutations. Since approval, ivacaftor has been studied in new pediatric CF patients (patients with non-G551D CFTR gating mutations and the R117H CFTR mutation). More recent studies have extended ivacaftor use to children as young as two years of age. These studies have included standard and novel outcome measures, and have carefully examined safety, tolerance, pharmacokinetics, and drug exposure (Table 1).

2.2. Phase 3 Ivacaftor Monotherapy Clinical Trials in Patients with a G551D Mutation, with a Focus on Pediatric Investigation

The pivotal Phase III clinical trial of ivacaftor enrolled 161 CF patients ages 12 and older with at least one copy of the G551D CFTR mutation and a baseline FEV₁ of 40–90% of predicted (Table 1) [44]. Patients were randomized to ivacaftor 150 mg every 12 hours or

placebo for 48 weeks. The ivacaftor group had dramatic improvements in sweat chloride (SC) values, respiratory symptom scores, rates of pulmonary exacerbations, weight, and FEV₁ at 24 and 48 weeks compared to those receiving placebo. SC values in the ivacaftor group decreased by -48 mMol/L compared to the placebo group (treatment effect $p < 0.001$), and the mean FEV₁ in the ivacaftor group increased by +10.5% predicted at week 48 compared with the placebos (treatment effect $p < 0.001$). The increase in mean weight in the ivacaftor group vs the placebo group was +2.7 kg at week 48 (treatment effect $p < 0.001$). Respiratory symptom scores also improved in the ivacaftor treatment group (treatment effect $p < 0.001$), and treated patients demonstrated a 55% relative reduction in the risk of pulmonary exacerbation ($p < 0.001$). The adverse event rate in treated patients was less than that observed in the placebo group, and together these results supported the regulatory approval of ivacaftor in several countries.

A phase 3 study of ivacaftor in younger CF patients with the G551D CFTR mutation ($n = 52$, age 6–11 years) confirmed many of the findings observed in older CF patients (Table 1) [49]. The mean age of enrolled patients was 8.9 years, with a baseline predicted FEV₁ of 84.2%. Thus, these patients were much younger and demonstrated far less advanced disease compared with the larger study in older CF patients (mean age of 25.5 years, baseline predicted FEV₁ of 63.6%)[44]. Importantly, ivacaftor treatment again demonstrated a large impact on predicted FEV₁, with a treatment effect of 12.5% at 24 weeks and 10% at 48 weeks ($p < 0.001$). Thus, there did not appear to be a ceiling effect on lung function benefit for these patients with near normal baseline testing, but post-hoc analysis did demonstrate greater drug effect in those patients with more airway obstruction. SC likewise significantly decreased by 53.5 mMol/L ($p < 0.001$) in the ivacaftor treatment group compared to placebo. Weight gain was also profoundly impacted by ivacaftor, with an absolute weight gain treatment effect of 1.9 kg at 24 weeks and 2.8 kg at 48 weeks ($p < 0.001$). Body mass index (BMI) for age z scores also increased substantially in the treatment group compared with placebo (week 24 treatment effect = 0.34, week 48 treatment effect = 0.45, $p < 0.001$), but respiratory symptoms and pulmonary exacerbations did not differ statistically between the ivacaftor and placebo groups. Safety monitoring was similar between the two groups, including serious adverse events (pulmonary exacerbations), laboratory abnormalities, and study withdrawal. Some symptoms were reported more commonly in the ivacaftor treatment group (eg: headache, oropharyngeal pain, nasopharyngitis, upper respiratory infection, otitis media, diarrhea, blood eosinophil count) but their relationships to study drug use are unclear.

The above phase 3 trials focused on relatively short term effects of ivacaftor on FEV₁; a study to examine longer term changes in FEV₁ decline was recently performed using a comparison of clinical trial data with a disease control population selected from the Cystic Fibrosis Foundation (CFF) Patient Registry [51]. In this comparison, G551D patients 6 years of age (average age 22.6 years, average baseline FEV₁ 65.7%) treated with ivacaftor during clinical trials were matched with F508del homozygous patients from the CFF registry. The ivacaftor treatment period lasted up to 3 years. The annual rate of FEV₁ decline in G551D patients treated with ivacaftor was -0.91%, compared with -1.72% in F508del matched controls ($p = 0.03$). The data suggests that ivacaftor reduces the rate of FEV₁ decline by approximately half, and that ivacaftor causes not only rapid improvement in lung function but also a sustained impact on lung function decline.

SC is a potentially valuable proxy for CFTR activity, as it is a portable, repeatable and objective measurement that can be obtained across a wide range of age groups [52]. As mentioned above, SC was significantly reduced in patients aged 6–11 years and 12 years with a G551D mutation treated with ivacaftor for 48 weeks [44, 49]. This SC reduction was further verified in a study of patients aged 6 and older with a G551D mutation who were assessed at 1, 3, and 6 months after ivacaftor initiation; interestingly, the SC reduction was readily apparent at early time points (decrease of 47.3 mEq/L compared to baseline following 1 month of treatment, $p < 0.001$) [53]. SC in these studies has failed to directly correlate with an individual's clinical response to ivacaftor or FEV₁ [53, 54]. Thus, while SC is a useful endpoint on a cohort level to assess changes in CFTR activity, it currently fails to be predictive of a patient's individual pulmonary benefit.

Ivacaftor treatment has been shown to impact the airway microbiome in cystic fibrosis patients. In a small study of three children (age 10–16 years) with a G551D mutation treated with ivacaftor for over a year, increases were seen in microbiota diversity with increases in anaerobes such as *Prevotella* correlating with improved FEV₁ [55]. A longitudinal cohort study (a substudy analysis of the G551D Observational - GOAL study) compared sputum cultures collected before and during ivacaftor treatment from 14 G551D patients age 10 years and older (mean age 27 years, baseline mean FEV₁ 84%) [53]. In this group, although microbial diversity did not increase, the burden of traditional CF pathogens did trend down while *Prevotella* abundance increased with ivacaftor treatment. Finally, a longitudinal observational study of 151 G551D patients age 6 years participating in the GOAL study examined *Pseudomonas aeruginosa* burden in cultures obtained the year prior and the year after ivacaftor initiation [56]. Ivacaftor treatment significantly reduced *Pseudomonas aeruginosa* culture positivity, although this was not correlated with clinical markers such as improvement in FEV₁ or hospitalizations. Alterations in the pulmonary microbiome caused by ivacaftor may be directly due to restoration of CFTR activity, and thus more robust innate host defenses. One publication has reported that ivacaftor has antibacterial properties, suggesting potential direct effects on CF pathogens [57]. These studies also raise the question of whether changes in the CF airway microbiome may serve as biomarkers for clinical impact and improvement after treatment with CFTR modulators.

A new analysis of 213 CF patients enrolled in the phase 3 trials described above [44, 49], age 6 years with the G551D mutation, examined changes in weight and BMI after 48 weeks of ivacaftor [58]. In patients 20 years (mean baseline predicted FEV₁ of 77.7%), patients treated with ivacaftor gained 2.7 kg more than those treated with placebo ($p = 0.0008$). Weight for age z score also increased, with treatment effect 0.35 ($p < 0.0001$). Interestingly, there was no correlation between weight gain and sweat chloride or % predicted FEV₁, which are more widely used biomarkers of restored CFTR function and improving CF lung disease.

One concern that has been raised in regards to studies of new therapies in young CF patients is the insensitivity of pulmonary biomarkers such as FEV₁ % predicted or pulmonary exacerbations to detect lung disease and treatment effects [59, 60]. Bronchiectasis can be detected within the first few years of life and prior to detectable changes in FEV₁ [42]. Novel biomarkers such as the lung clearance index (LCI) and hyperpolarized gas magnetic

resonance imaging (MRI) detect defects in lung ventilation in early CF lung disease that are not yet apparent with spirometry [60, 61]. Given the growing concern that CF lung disease begins in infancy, prior to the onset of symptoms or changes in FEV₁ (which is not routinely monitored until patients are several years old), more sensitive tools need to be developed and validated to assist clinicians in using evidence based therapies for our youngest CF patients. To address this in the context of CFTR modulator development, a small pediatric crossover study was performed to compare the capacity of multiple breath washout and LCI to detect ivacaftor treatment effects in young CF patients with the G551D CFTR mutation and minimal detectable lung disease [62]. All patients were 6 years of age, had a predicted FEV₁ of >90%, and a screening LCI value outside of the normal range (>7.4). 21 patients were enrolled and treated with 28 days of ivacaftor or placebo in a crossover format. Treatment with ivacaftor led to significant improvements compared with placebo in LCI (difference between groups in the average of mean changes from baseline at days 15 and 29 was -2.16 [95% CI -2.88 to -1.44]; p<0.0001).

2.3. Ivacaftor Use in CF Patients with non-G551D CFTR Mutations

Ivacaftor has been evaluated in new populations of patients with non-G551D gating mutations, including patients possessing G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N and S549R CFTR mutations (Table 1) [63] (KONNECTION study). De Boeck and colleagues recently reported the results of an eight week, double blind crossover trial of ivacaftor (150 mg every 12 hours) compared with placebo (n=39). The mean age and range of enrolled patients was 22.8 years and 6–57 years respectively, with a mean predicted FEV₁ of 78.4% (range 42.9% – 118.7%). Patients demonstrated a significant increase in FEV₁ % predicted while receiving ivacaftor compared with placebo (treatment effect = 10.7%, p<0.0001). In addition, significant improvements in BMI, SC and symptoms were reported during ivacaftor treatment compared with placebo in this short protocol. During the open label study extension (16 weeks), the mean absolute increase in predicted FEV₁ was 13.5% compared with baseline, and large improvements in BMI, SC, and symptoms were sustained. Safety and tolerability were similar across the two groups, and based on this additional data regulatory agencies have extended approval of ivacaftor to treat CF caused by nine different gating mutations (FDA approval was not obtained for the G970R CFTR mutation, which was the genotype of 4 subjects in the above trial).

Ivacaftor has also been investigated in CF patients with a mutation that primarily produces conductance defects (Table 1) [64] (R117H-CFTR, the KONDUCT study). This mutation is unique in that the phenotype depends on the number of thymidine repeats within one of the introns of the CFTR gene. The 5T genotype (i.e., five thymidine repeats) leads to aberrant gene splicing and absence of exon 9, which correlates with R117H individuals who have a more severe disease phenotype [65]. In contrast, patients with 7T and 9T genotypes demonstrate normal splicing and typically a milder phenotype [66, 67]. Recent clinical evaluation of ivacaftor in 69 CF patients 6 years and older (average age 31 years, average baseline FEV₁ 72.9%) with the R117H mutation (independent of T status) failed to meet the primary endpoint of improved predicted FEV₁ vs placebo across all study subjects [64]. Interestingly, improvements in the FEV₁ % predicted and respiratory symptoms were statistically significant in the adult subjects (18 years old) treated with ivacaftor compared

with placebo controls (n= 50). As expected, the effects on lung function and SC were smaller than those observed for ivacaftor in patients with CFTR gating mutations. Based on these results and the below study in younger CF patients, ivacaftor has received FDA approval for use in patients age ≥ 2 years with the R117H mutation independent of T status [64, 68].

2.4. Expanding Ivacaftor use to Younger Patients

Safety, pharmacokinetics and pharmacodynamics of ivacaftor have recently been reported in CF patients age 2–5 years with gating mutations in the KIWI study (Table 1) [69]. Patients were treated with one of two doses of ivacaftor (50 mg every 12 hours if < 14 kg or 75 mg every 12 hours if ≥ 14 kg) for 4 days in Part A to establish short-term safety and pharmacokinetics. Subjects were then treated for 24 weeks with open label ivacaftor to assess safety and longer term pharmacodynamics in Part B (primary outcome measures). The secondary outcomes were absolute change in SC, weight, BMI and height z scores. Nine patients were enrolled in Part A and 34 in Part B, with 33 completing the 24 week treatment period. Exposures to ivacaftor at both dosages were similar to that seen adults, supporting the doses evaluated. The most common adverse events reported were cough and vomiting (56% and 29%, respectively). Liver function tests >8-fold above the upper limit of normal were reported in 15% of patients, with interruption of ivacaftor in four subjects and discontinuation in one. Six subjects reported serious adverse events, with the elevation of liver transaminases in one subject reported as related to ivacaftor. There were significant increases in growth parameters over the course of treatment (weight z score and BMI z score, $p<0.0001$). Ivacaftor is now approved for use in children with CF age 2–5 years with specific CFTR mutations as described above.

2.5. Novel Endpoints in Studies of Ivacaftor in Pediatric Patients

Given the difficulty in studying subtle improvements in CF related lung pathology in children, several studies have investigated novel potential endpoints. Although high resolution computed tomography (HRCT) of the chest carries the risk associated with exposure to ionizing radiation, it offers the chance to measure changes in airway and parenchymal structure. In a small single center study in 2015, ten CF patients with the G551D mutation age 10–44 years (average age 20.9 years, average predicted FEV₁ 78%) were placed on ivacaftor for one year [70]. HRCT scans of the chest were obtained at enrollment and after one year of therapy and were scored using the modified Brody method to record the amount of bronchiectasis, mucus plugging, parenchymal opacities, bronchial wall thickening, and air trapping in the images. The total Brody scores significantly improved by 13.6 points, and this scoring correlated with improvements in predicted FEV₁ ($p<0.01$).

In another study from this group, 12 CF patients with a G551D mutation (median age 17 years, mean predicted FEV₁ 82.5%) had sinus CT scans performed prior to therapy and after one year of ivacaftor therapy [71]. Sinus CT scans were graded empirically as mild, moderate, or severe; improvement in scoring was noted in all patients (except one who had a normal sinus CT both before and after therapy). These studies demonstrate that radiographic

improvement may serve as an important biomarker in pediatric patients treated with ivacaftor.

Magnetic resonance imaging (MRI) is another imaging modality that avoids exposure to ionizing radiation, a major drawback to serial CT imaging. Specifically, hyperpolarized gas MRI provides morphologic as well as functional data in children with CF and other pulmonary diseases [72]. In the past decade, hyperpolarized ^3He MR has been shown to sensitively detect changes in ventilation in pediatric CF patients with normal lung function, as well as show regional ventilation changes after chest physiotherapy [73–75]. Even more recently, the cost of ^3He has caused a shift towards use of ^{129}Xe in hyperpolarized gas MRI. Two recent studies in CF children aged 8–16 years (average FEV_1 97.9%) have shown the safety and tolerability of ^{129}Xe MRI as well as the sensitivity of ^{129}Xe MRI in showing ventilation defects in young CF patients with normal FEV_1 [61, 76]. Preliminary reports of a phase 2 study in G551D patients 12 years old (average 20.3 years, average baseline FEV_1 79.3%) showed significant decreases in total ventilation defect volume as measured by hyperpolarized gas MRI after ivacaftor treatment for 28 days [77]. The sensitivity of hyperpolarized gas MRI to subtle lung disease makes it an exciting potential biomarker; however, children must still be able to perform a prolonged breath-hold for some techniques, which precludes their use in our youngest patients.

Another novel biomarker for improvement in CF related lung disease after beginning ivacaftor is fractional exhaled nitric oxide (FENO). CF patients have reduced airway NO, which has been associated with more severe lung disease and increased risk for infections [78–80]. A potential difficulty inherent in using FENO as a biomarker for restored CFTR function is the many factors that can affect FENO, such as pulmonary exacerbations, oral bacteria load, polymorphisms in NOS1, infection status, and use of dornase alpha [81–84]. These potential confounders are important to consider when interpreting FENO measurements. In two studies published in 2015, FENO was measured before and after initiation of ivacaftor therapy in CF patients with a CFTR gating mutation. In the first study, 15 patients (mean age 23.3 years, average predicted FEV_1 69.7%) were placed on ivacaftor for 4 weeks [85]. After treatment, FENO improved by 7.7 ppb ($p=0.002$); this improvement was more pronounced in pediatric patients. However, improvements in FENO did not correlate with average predicted FEV_1 . In the second smaller, exclusively pediatric-focused study, 5 children with CF (mean age 13.6 years, mean predicted FEV_1 95.2%) had FENO measurements obtained before and after 4 weeks of ivacaftor treatment [86]. FENO increased by 5.2 ppb after ivacaftor treatment ($p<0.05$). Thus, FENO may represent a novel, sensitive lower airway biomarker capable of detecting restoration of CFTR function.

The study of exhaled breath from CF patients is a valuable and noninvasive tool; beyond FENO, other breathomics tools applicable to CF include electronic noses, nuclear magnetic resonance (NMR) spectroscopy, and gas-chromatography/mass spectrometry [87]. NMR spectroscopy of exhaled breath condensate has been shown to discriminate CF patients from healthy controls, CF patients from patients with primary ciliary dyskinesia, and stable (no clinical or FEV_1 change from baseline in the last 4 weeks) from unstable CF patients [88, 89]. Electronic nose analysis of exhaled breath samples can detect *Aspergillus fumigatus* colonization and chronic *Pseudomonas aeruginosa* infection in CF patients; furthermore, the

pH of exhaled breath condensate has been shown to be lower in CF than in healthy controls and is further reduced in CF patients during a pulmonary exacerbation [90–92]. Further studies are needed to determine if exhaled breath analysis can be a sensitive biomarker to assess response to CFTR modulators in pediatric patients.

3. Conclusion

Ivacaftor is a first-in-class CFTR modulator now approved for CF patients age 2 years and older with one of nine gating mutations (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R) or with the R117H mutation in CFTR. A series of studies have shown improvement in typical biomarkers such as FEV₁ % predicted, sweat chloride, and weight/BMI [44, 48, 49, 63, 64]. There continues to be concern that these typical endpoints are insensitive to subtle improvements in lung disease in the youngest patients who have minimal detectable lung disease; LCI may be a more sensitive alternative, but is currently not sufficient to support FDA approval [62]. Other novel potential endpoints, such as CT imaging, MRI, hyperpolarized gas and FENO, may prove beneficial in younger CF patients but are not routinely used [70, 71, 85, 86]. Pulmonary exacerbations are not a reliable nor sensitive indicator of improvement in young children with CF given their mild lung disease and rarity of severe exacerbations. Finally, there are a relatively small number of pediatric CF patients available to take part in clinical trials; only approximately 5% of patients with cystic fibrosis have one of the ten mutations approved for ivacaftor use, and the total number of young CF patients is static. Finally, the already small number of modulator naive patients available for studies will continue to shrink as eligible patients begin therapy with approved CFTR modulators.

4. Expert Opinion

There are multiple unmet needs in ivacaftor and CFTR modulator development in general that are relevant to the pediatric population. These include basic questions about studying and gaining approval to use these (and other) novel therapeutics in young children with CF. These obstacles will be similar in other slowly progressive chronic lung diseases of childhood; thus, it is worthwhile to consider the lessons learned throughout the ivacaftor clinical studies. First, the more subtle extent of lung disease in children makes typical endpoints such as pulmonary exacerbations and FEV₁ insensitive. Evidence from the AREST CF trial from Australia indicates that airway damage is common in young CF patients, with approximately 1/3 of children demonstrating bronchiectasis on CT by age 3 years [42]. Unfortunately, the lack of measurable lung disease in children with CF is precisely what makes them the group that may benefit the greatest from disease modifying agents such as ivacaftor. By lessening the early lung remodeling in CF, the trajectory of the disease may be permanently improved. Another roadblock in pediatrics is the inability to reliably perform and obtain certain established endpoints, such as spirometry, in many children <5 years old. It will be up to investigators and industry to identify, study, and validate sensitive new biomarkers and endpoints. Sweat chloride has performed quite well to demonstrate ivacaftor bioactivity and dose-dependent effects, and will certainly be incorporated into future modulator trials building upon current treatment. Already, researchers have identified subtle changes in lung structure and function in young CF

patients using techniques such as hyperpolarized gas MRI and LCI [61, 62, 76]. Exploring and validating outcomes such as CT (using low radiation scans and centralized scoring), LCI, hyperpolarized gas MRI, and exhaled breath analysis in young CF patients will be critical to validate and expand CFTR modulator use in the patients who will benefit the most.

Another difficulty is the relatively small number of pediatric CF patients available to participate in clinical trials. The small sample size makes appropriately powering of studies evaluating subtle changes difficult. This difficulty will increase as more CF patients prescribed appropriate CFTR modulators (such as ivacaftor and lumacaftor-ivacaftor), thus causing the pool of therapy-naïve patients to shrink. As new CFTR modulators enter the pipeline, finding sufficient numbers of eligible pediatric CF patients will increase in difficulty. To address this, future clinical trials will need sensitive and carefully defined endpoints, thoughtful study design, and potentially prolonged trial periods to detect the therapeutic effect.

Finally, the pediatric population deserves special attention due to the possibility of unexpected or enhanced side effects. A serious adverse event linked to ivacaftor is elevation of liver transaminases in both adult and pediatric patients; however, the rate of transaminase elevation appeared to be higher in children ages 2–5 years compared with adult studies, reaching 15% [44, 49, 69]. This suggests that young children with CF may be more sensitive to ivacaftor induced liver abnormalities than adults. An ongoing extension study (KLIMB) continues to collect long term safety data in this group. Another concern with pediatric ivacaftor use is the development of ocular lesions, specifically cataracts. Increased incidence of cataracts was seen in pre-clinical studies of ivacaftor treatment in juvenile rats, and non-congenital cataracts have been seen in children treated with ivacaftor although causation is unclear [93, 94]. Given differences in ocular development in rats versus humans and the unclear causative link between ivacaftor and cataracts, there is uncertainty about the clinical relevance of these findings. Nonetheless, ophthalmologic examination is recommended before and during treatment with ivacaftor.

These trials of ivacaftor in pediatric patients reveal ongoing challenges with selecting appropriate and sensitive endpoints, subject recruitment, and side effect monitoring in a rare, progressive pediatric disease. Interinstitutional collaboration, regulatory input, and research innovation have led to the successful approval of ivacaftor for a significant number of CF patients down to age 2 years. Ongoing efforts focused in expanding and validating new biomarkers, innovative study design, and careful monitoring for adverse events will be necessary for both ivacaftor and future CFTR modulators.

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Reference annotations

* Of interest

** Of considerable interest

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Article highlights

- CFTR modulators restore function to select disease-causing CFTR mutations
- Ivacaftor is a CFTR modulator that increases the open channel probability of CFTR mutations with gating defects
- Clinical trials of ivacaftor in pediatrics have led to approval in CF patients 2 years of age and older with one of ten specific CFTR mutations
- Selecting relevant biomarkers and sensitive outcome measures is difficult in studies of pediatric CF patients
- Pediatric CF patients may be more sensitive to adverse liver and ocular effects of ivacaftor
- Future efforts should focus on the development and selection of sensitive endpoints, effectively powering studies, and monitoring for adverse events

Table 1

Summary of major clinical trials leading to the approval of ivacaftor for CF patients age 2 years and older with one of nine gating mutations (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R) or with the R117H mutation in CFTR.

Reference	Population	Design	Results
Ramsey et al [44]	Age range: 12 y Mean age: 25.5 y Genotype: At least one copy of G551D Baseline FEV ₁ : 64%	Randomized, double-blind, placebo-controlled trial • Duration: 48 wks • Randomized 1:1, IVA 150 mg q12h or placebo • Primary end point: Mean change in baseline FEV ₁ through wk 24 • Secondary end points: Change from baseline FEV ₁ through wk 48, pulmonary exacerbations, CFQ-R score, weight, SC	FEV ₁ change from baseline at wk 24 • Treatment effect: +10.6% (p<0.001) FEV ₁ change from baseline at wk 48 • Treatment effect: +10.5% (p<0.001) Pulmonary exacerbations at wk 48 • 55% reduction in risk in IVA group (p<0.001) CFQ-R score at wk 48 • Treatment effect: +8.6 points (p<0.001) Weight at wk 48 • Treatment effect: +2.7 kg (p<0.001) SC at wk 48 • Treatment effect: -48.1 mmol/L (p<0.001)
Davies et al [49] ENVISION	Age range: 6–11 y Mean age: 8.9 y Genotype: At least one copy of G551D Baseline FEV ₁ : 84.2%	Randomized, double-blind, placebo-controlled trial • Duration: 48 weeks • Randomized 1:1, IVA 150 mg q12h or placebo • Primary end point: Mean change in baseline FEV ₁ through wk 24 • Secondary end points: Change from baseline FEV ₁ through wk 48, CFQ-R score, weight, SC	FEV ₁ change from baseline at wk 24 • Treatment effect: +12.5% (p<0.001) FEV ₁ change from baseline at wk 48 • Treatment effect: +10% (p<0.001) CFQ-R score at wk 24 • Treatment effect: +6.1 points (p<0.001) Weight at wk 48 • Treatment effect: +2.8 kg (p<0.001) SC at wk 24 • Treatment effect: -54.3 mmol/L (p<0.001)
Davies et al [69] KIWI	Age range: 2–5 y Genotype: At least one copy of a CFTR gating mutation (G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N and S549R)	Open-label, single-arm study • IVA dose: <14 kg, 50 mg q12h 14 kg, 75 mg q12h Part A • Duration: 4 days Primary end points: Short term safety, pharmacokinetics Part B • Duration: 24 weeks • Primary end points: Long term safety, pharmacokinetics • Secondary end points: Change from baseline SC, weight, BMI, and height	Part A Pharmacokinetics: Similar exposures to IVA as adults Adverse Events: In 2 patients: pyrexia, vomiting, ecchymosis, and rhinorrhea Part B Pharmacokinetics: Similar exposures to IVA as adults Adverse Events: In five (15%) patients, raised concentration of transaminases >8 times upper limit of normal Change from baseline SC at wk 24 • -46.9 mmol/L (p<0.0001) Mean weight z score change at wk 24 • +0.2 (p<0.0001) Mean BMI z score change at wk 24 • +0.4 (p<0.0001) Mean height z score change at wk 24 • -0.01 (p=0.84)
De Boeck et al [63] KONNECTION	Age range: 6 y Mean age: 22.8 y Genotype: At least one copy of a non-G551D gating mutation (G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N and S549R) Baseline FEV ₁ : 78.4%	Double blind, placebo-controlled crossover study • Duration: 8 weeks • Randomized 1:1 to either 8 wks IVA (150 mg q12h) then placebo or placebo then IVA • Primary end point: Change from baseline FEV ₁ through 8 weeks IVA treatment • Secondary end points: Change from baseline in BMI, SC, and CFQ-R score	Part 1 FEV ₁ change from baseline at wk 8 • Treatment effect: +10.7% (p<0.0001) BMI z score change at wk 8 • Treatment effect: +0.24 points (p<0.0001) SC change at wk 8 • Treatment effect: -49.2 mmol/L (p<0.0001) CFQ-R score change at wk 8 • Treatment effect: +9.6 points (p=0.0004)
Moss et al [64] KONDUCT	Age range: 6 y Mean age: 31 y Genotype: At least one copy of R117H	Double blind, placebo controlled parallel group study Duration: 24 wks with a 3–4 wk washout period	KONDUCT FEV ₁ change from baseline at wk 24 • Treatment effect: +2.1% (p=0.2) BMI change at wk 24 • Treatment effect: +0.31 kg/m ² (p=0.78)

Reference	Population	Design	Results
	Baseline FEV ₁ : 72.9%	Randomized 1:1, IVA 150 mg q12h or placebo Primary end point: Change from baseline FEV ₁ at 24 wks Secondary end points: Change from baseline BMI, CFQ-R, and SC	SC change at wk 24 • Treatment effect: -21.9 mmol/L (p<0.0001) CFQ-R respiratory score change at wk 24 • Treatment effect: +12.6 points (p=0.002)

BMI, body-mass index; CFQ-R, Cystic Fibrosis Questionnaire-revised; IVA, Ivacaftor; q12h, every 12 hours; SC, sweat chloride; wk, week; y, years.