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MONOGRAPH

IVACAFTOR

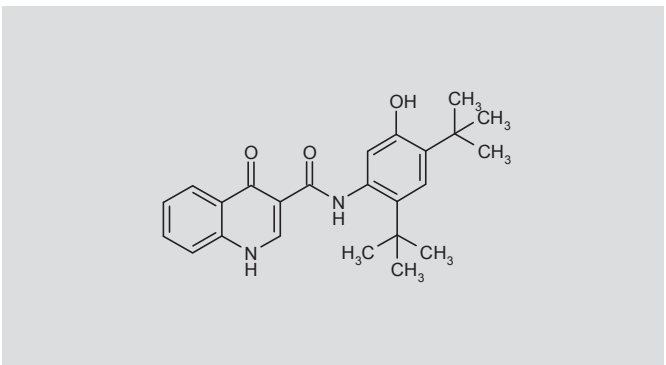
Prop INN; USAN

CFTR Potentiator
Treatment of Cystic Fibrosis

VX-770
Kalydeco™

N-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

InChI: 1S/C24H28N2O3/c1-23(2,3)16-11-17(24(4,5)6)20(27)12-19(16)26-22(29)15-13-25-18-10-8-7-9-14(18)21(15)28/h7-13,27H,1-6H3,(H,25,28)(H,26,29)



$C_{24}H_{28}N_2O_3$
Mol wt: 392.4907
CAS: 873054-44-5
EN: 418632

SUMMARY

Twenty years after discovering the cystic fibrosis gene, new therapies that treat the underlying defect are coming to fruition. Recent advances in our understanding of the effect of cystic fibrosis transmembrane conductance regulator (CFTR) mutations on the ion channel function of the protein have enabled the discovery of small molecules that restore absent or dysfunctional CFTR activity. Ivacaftor is a CFTR potentiator that improves chloride transport by enhancing channel gating (conformational change between opening and closing states of a channel), and is particularly effective in restoring the activity of G551D-CFTR. In phase III clinical trials, ivacaftor was associated with marked improvements in the clinical status of cystic fibrosis (CF) patients with G551D-CFTR mutations, including improvements in pulmonary function and frequency of exacerbations, in addition to improved quality of life and weight gain. Ivacaftor has also demonstrated activity in other CFTR mutations, including patients with F508del-CFTR co-treated with CFTR folding correctors (e.g., VX-809). As such, ivacaftor represents a major advance in CF therapeutics, opening a new era of mutation-specific therapy to treat the disease.

Key words: CFTR potentiator – Cystic fibrosis – Ivacaftor – VX-770 – Kalydeco

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SYNTHESIS*

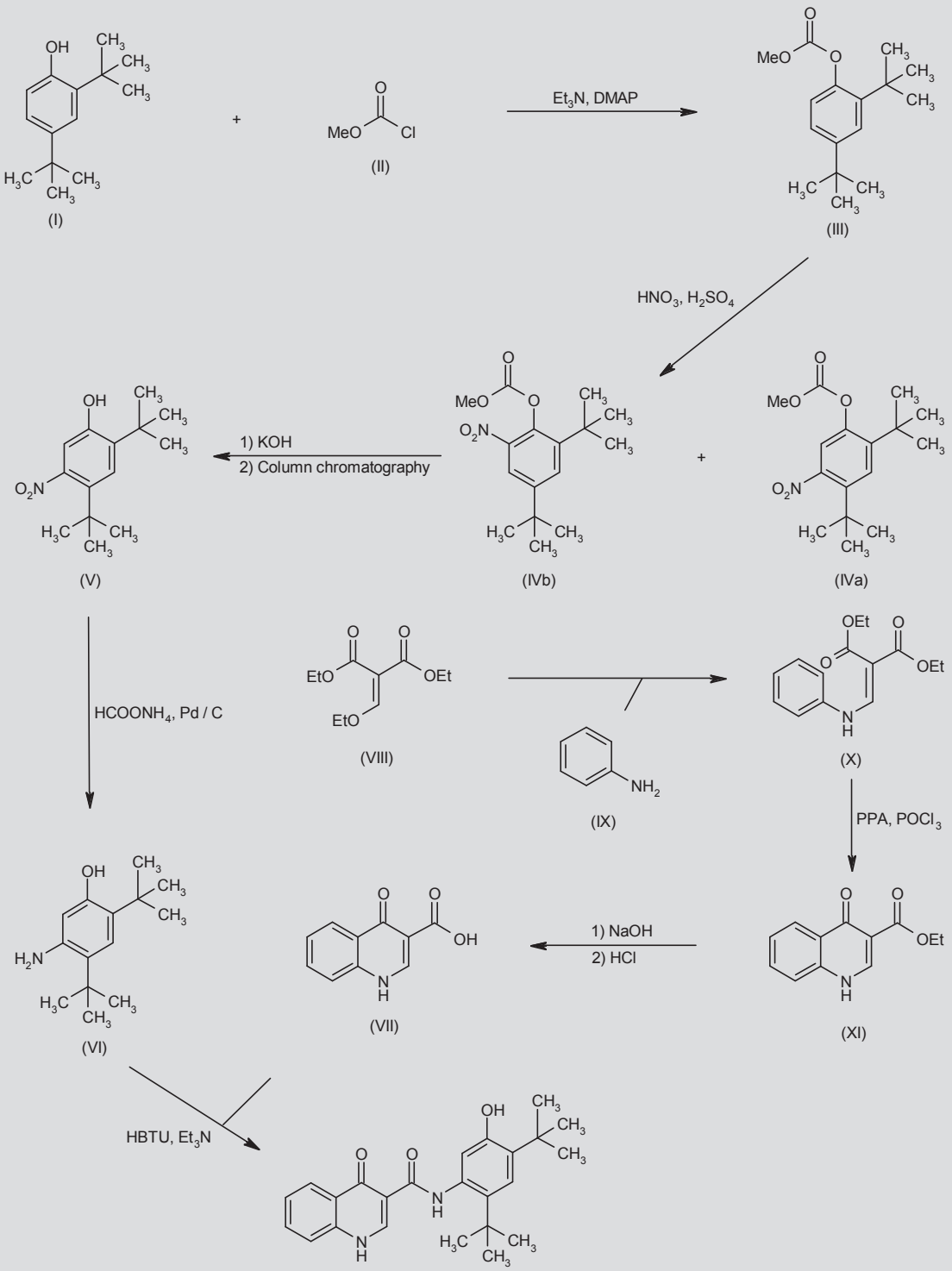
O-Protection of 2,4-di-*tert*-butylphenol (I) with methyl chloroformate (II) in the presence of Et_3N and DMAP in CH_2Cl_2 gives 2,4-di-*tert*-butylphenyl methyl carbonate (III), which by nitration with HNO_3 and H_2SO_4 provides a mixture of the 5- and 6-nitrophenyl carbonates (IVa) and (IVb), respectively. Hydrolysis of the mixture of carbonates (IVa) and (IVb) by means of KOH in MeOH followed by chromatographic separation of the resulting mixture of nitrophenols affords 2,4-di-*tert*-butyl-5-nitrophenol (V), which is reduced by transfer hydrogenation with $HCOONH_4$ in the presence of Pd/C in refluxing EtOH to the amine (VI). Finally, amine (VI) is condensed with 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (VII) by means of HBTU and Et_3N in DMF (1) or CH_2Cl_2 (2). Scheme 1.

4-Oxo-1,4-dihydroquinoline-3-carboxylic acid (VII) is prepared by coupling of diethyl 2-(ethoxymethylene)malonate (VIII) with aniline (IX) by heating at 140-150 °C to afford diethyl 2-(anilinomethylene)malonate (X), which by cyclization by means of PPA and $POCl_3$ at 70 °C yields ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (XI). Finally, ethyl ester derivative (XI) is saponified with NaOH at reflux, followed by acidification with HCl (1, 2). Scheme 1.

BACKGROUND

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disorder in people of European descent and is caused by mutations in the *CFTR* gene. Approximately 1 in every 3,000 Cau-

Scheme 1. Synthesis of Ivacaftor



casian Americans are diagnosed with CF and 1 in every 25-30 people of European ancestry carry a *CFTR* mutation. Currently, there are approximately 30,000 CF patients in the U.S. and the worldwide prevalence is estimated at approximately 70,000 (3).

The cystic fibrosis transmembrane conductance regulator (CFTR) has pleiotropic functions and plays an important role in transepithelial fluid and electrolyte transport. It is a protein kinase A (PKA)-activated channel that selectively conducts chloride and bicarbonate ions (4, 5). It is expressed in the epithelium of various organs, including the lungs, gastrointestinal tract, pancreas, reproductive tract and skin. Consequently, genetic mutations that alter protein (proteins/channels are interchangeably used to describe CFTR) function affect each of these organs. Respiratory problems remain the principal cause of morbidity and mortality in CF patients (6). The loss of transepithelial anion transport and CFTR-dependent fluid secretion coupled with imbalanced sodium absorption through the epithelial sodium channel (ENaC) cause depletion of the airways surface fluid and delayed mucociliary clearance (7). These changes lead to mucus plugging, bacterial colonization, infection, inflammation and airways remodeling, ending in bronchiectasis and end-stage lung disease (8). Current mainstays of CF therapy are supportive in nature and include chest physiotherapy, mucolytics, antibiotics and antiinflammatory drugs to treat CF lung disease. These are coupled with pancreatic enzyme replacement therapy and nutritional supplements to address gastrointestinal manifestations.

Collins, Riordan and Tsui identified the *CFTR* gene in 1989, and to date, more than 1,800 *CFTR* mutations have been discovered (9, 10). These *CFTR* mutations are grouped into six different classes based on their pathophysiological mechanism of genetic defect (6, 11, 12). Among those included are the F508del-CFTR mutation, a class II mutation that confers protein misfolding whereupon little or no protein is trafficked to the cell surface, and the G551D-CFTR mutation, a class III mutant that causes defective channel gating and regulation of CFTR residing in the apical plasma membrane. Gating mutations such as G551D-CFTR cause the channel to open infrequently and exhibit prolonged periods of channel closure, resulting in poor channel function through low open probability. Other mutations also reside at the cell surface but exhibit reduced function because of poor conductance (class IV mutations), reduced number of transcript levels (class V; e.g., splicing mutations) and accelerated protein turnover (class VI mutations). Due to the variety of functional consequences caused by *CFTR* mutations, a number of therapeutic strategies are being studied to address defective protein function. Among these are CFTR potentiators such as ivacaftor, which augment channel function by potentiating cAMP-mediated gating.

Here, we review the current understanding of ivacaftor, a CFTR "potentiator" that increases ion flow through CFTR channels by improving channel open probability (P_o) (13). We also discuss the potential of combining ivacaftor with investigational "CFTR correctors" (e.g., VX-809), drugs that rescue cell surface expression of F508del-CFTR by overcoming its defects in cellular processing and trafficking to the cell surface.

PRECLINICAL PHARMACOLOGY

Following the disappointing results of gene therapy in the 1990s and significant improvements in the understanding of the defects in *CFTR* folding, trafficking and gating caused by various mutations, Cystic Fibrosis Foundation Therapeutics (CFFT), the non-profit drug development arm of the Cystic Fibrosis Foundation (CFF), focused considerable resources on new treatments for CF through small-molecule drugs that improve CFTR function. Buoyed by a highly successful model of venture philanthropy, partnership with CF patients and a robust clinical trial network, ivacaftor was discovered and developed by Vertex Pharmaceuticals using their expertise in a novel high-throughput screening (HTS) strategy for membrane-localized ion channels. Precursors to ivacaftor were originally identified following HTS of 228,000 chemically diverse drug-like compounds using a cell-based fluorescence membrane potential assay dependent on fluorescence resonance energy transfer and designed to discover potentiators of F508del-CFTR localized to the membrane surface following low-temperature growth (14). From this original screen, a lead scaffold was identified and synthesized for medicinal chemistry optimization with due consideration for potency, selectivity and chemical tractability. Ivacaftor was ultimately synthesized following multiple rounds of analogue chemistry and bioassay optimization. The agent was specifically attractive due to its ability to potentiate multiple forms of *CFTR* (including F508del, G551D, R117H and wild-type *CFTR*), selectivity for *CFTR* (compared to ENaC, calcium-activated chloride channels [CaCC] or other ion channels) and a favorable preclinical pharmacokinetic profile.

Ivacaftor potentiates channel gating of apical membrane-bound CFTR channels that have been activated through cAMP/PKA signaling pathways. As opposed to constitutive channel activators, ivacaftor is expected to work only in the background of endogenous levels of activation (15) (e.g., β-adrenoceptor stimuli) and may be less susceptible to adverse effects related to irreversible channel activation. Van Goor et al. assessed the effects of ivacaftor on CFTR-mediated Cl^- transport in Fischer rat thyroid (FRT) cells expressing G551D, F508del and wild-type CFTR chloride channels or human bronchial epithelial (HBE) cells isolated from CF and non-CF individuals (13, 14). Compared to the cells expressing wild-type *CFTR*, forskolin-induced *CFTR* activation is reduced (measured as short circuit current, Isc) in FRT cells expressing G551D-CFTR mutations, a property that indicates compromised CFTR channel function. Ivacaftor potentiated forskolin effects in these G551D-CFTR cells by about fourfold with nanomolar potency.

Additional mechanistic studies of ivacaftor revealed that: 1) it does not alter cellular cAMP levels; 2) it does not increase membrane CFTR channel density; and 3) it robustly enhances open channel probability. The effect on gating has been further substantiated by the increase in the ATPase activity of CFTR following ivacaftor treatment. Furthermore, ivacaftor increased forskolin-induced Isc in HBE cells isolated from CF patients with G551D/F508del mutations to levels approximately 33-50% those of wild-type CFTR activity (depending on specific donor of epithelial cells expressing G551D-CFTR) (13), and also increased lung function (as measured by spirometry) in a concentration-dependent fashion. Using well-differentiated G551D/F508del-CFTR cultures, ivacaftor successfully increased vasoactive intestinal peptide-stimulated airways surface liquid (ASL) volume and ciliary beat frequency, suggesting a beneficial effect on the epithelial function of CFTR on the surrounding mucociliary transport (MCT) apparatus. More recently, our laboratory confirmed these findings using alternate methods estimating the MCT in CF epithelia with impaired CFTR function (16).

In summary, in vitro pharmacological data indicate that ivacaftor is a potent and efficacious CFTR potentiator that increases chloride transport by increasing its open channel probability, and is further associated with improved MCT in well-differentiated epithelia.

PHARMACOKINETICS AND METABOLISM

Ivacaftor is extensively metabolized through oxidation, reduction and dehydration, undergoes sulfate and glucuronide conjugation, and is excreted via the feces (17). In vitro studies have demonstrated it to be metabolized by the cytochrome P450 3A4 enzyme, and consequently, ivacaftor exhibits significant drug–drug interactions with other agents that modulate cytochrome P450 3A4. Inhibitors of cytochrome P450 3A4 such as ketoconazole and fluconazole increase the systemic concentration of ivacaftor about threefold and activators of cytochrome P450 3A4 such as rifampicin decrease systemic ivacaftor by 80% (18). These interactions need to be considered on an individual basis in the clinic.

CLINICAL STUDIES

Given the resemblance of the CF phenotype with in vitro experimental models and the lack of an appropriate animal model of CF lung disease at the time, ivacaftor was evaluated in human subjects without further efficacy testing in animals. Following the requisite safety and pharmacokinetic evaluation of ivacaftor in preclinical models and normal human subjects, the efficacy was first tested in CF patients by Accurso et al. (19). The results obtained from various phase II and III trials are summarized in Table I. The initial trial was designed as a randomized, placebo-controlled, dose-ascending study and included crossover (Part 1) and parallel (Part 2) components. No serious safety concerns were raised in the study and dose escalation was achieved successfully. CFTR activity was measured by nasal potential difference (NPD), with a dose-dependent improvement in CFTR activity in Part 1 that was successfully replicated in Part 2. The effect on $\Delta_{\text{low chloride + isoproterenol}}$, the principal NPD measure of CFTR-dependent chloride transport, in the 150-mg dose group (the most common dose tested) was 4.6 mV in Part 1 of the study, whereas improvement in the 250-mg dose group was even greater (7.6 mV), but was limited by a small sample size (n = 7). Lower doses also demonstrated a significant but lesser degree of benefit, lending further confidence in the findings. The –5 mV change in NPD is notable, as it was defined previously as a clinically meaningful change by genotype–phenotype correlation in CF (20).

In addition to the effects on nasal potential difference, a pronounced effect on sweat chloride was observed and clearly indicated the rescue of CFTR activity. The median reduction in sweat chloride of about 59 mEq/L at the maximally effective dose (150 mg) resulted in a mean sweat chloride of about 55 mEq/L, a value below the traditional diagnostic threshold of CF. Unlike NPD, the effect on sweat chloride was maximal at 150 mg and less in the 250-mg dose group, suggesting tissue specificity for the dose–response relationships. Ivacaftor also dose-dependently increased lung function, as measured by spirometry. The maximal effect was about a 10% relative improvement in FEV1 in the 250-mg dose group.

Improved lung function along with increased CFTR activity firmly established CFTR as a viable therapeutic target in CF. These results provided the first example of a systemic drug that restored CFTR activity, normalized sweat chloride and conferred meaningful clinical improvements in lung function (21). As such, this study provided confidence that CFTR modulators that restore CFTR activity can also be associated with meaningful improvements in the clinic. An additional effect of this landmark study was to validate the use of sweat chloride as an outcome measure. Previously, the use of this test had been relatively limited (22, 23). The sweat chloride study results, bolstered by a long history of phenotype–genotype data, helped establish the sweat chloride test as a useful biomarker to detect even low levels of clinical efficacy. The test has proven to be a robust assay suitable for widespread use in clinical trials evaluating CFTR modulators, and we expect it will be widely used in future studies with other CFTR modulators.

The dramatic effects of ivacaftor on sweat chloride secretion and lung function in phase II testing enabled a rapid progression to phase III trials in G551D-CFTR patients, which included two long-term, randomized, placebo-controlled clinical trials using the 150-mg dose. In a long-term trial in older children and adults (aged 12 and above) (24), the primary endpoint was achieved, establishing an approximately 10.5% absolute improvement in FEV1% at 24 weeks, an effect lasting through 48 weeks of testing. In addition, all secondary clinical endpoints showed meaningful and statistically significant improvements, including a 55% reduction in the probability of experiencing a pulmonary exacerbation during the course of the study, a 3.1-kg weight gain (compared to 0.9 kg in the placebo group) and an improvement in respiratory symptoms as assessed by the Cystic Fibrosis Questionnaire Revised (CFQ-R), a patient-reported quality-of-life index. Sweat chloride testing also exhibited marked improvements (mean of sweat chloride was about 55 mEq/L in the ivacaftor treatment group at the 24- and 48-hour time points, confirming the prior findings). Of note, the improvement in spirometry was rapid; within 2 weeks, 90% of the maximal improvement was observed, suggesting that the mechanism may be clearance of inspissated mucus from plugged airways, rather than the reversal of long-standing structural lung disease. Similar results were reported in a smaller study that enrolled pediatric G551D-CFTR patients aged 6-12 years (25). Like the study in adults, the lung function improvements were sustained through 48 weeks. The mean improvement in FEV1 was 12.5% following 24 weeks of treatment and sweat chloride also improved similarly to the adult study. The degree of improvement in spirometry among participants of the phase III trial of ivacaftor compares favorably to that of commonly used therapies for chronic CF care, including inhaled recombinant human DNase (26), inhaled tobramycin (27), azithromycin (28) and hypertonic saline (29).

In both phase II and III clinical studies, ivacaftor appeared to be safe and well tolerated. Moreover, potential mechanistic-based toxicities related to CFTR activation, such as secretory diarrhea, were not observed. While principally designed as a safety study, ivacaftor has also been tested in CF patients homozygous for F508del-CFTR and served to test whether surface-localized F508del-CFTR could be a therapeutic target in CF. A 4-month placebo-controlled trial revealed no statistically significant change in FEV1 following ivacaftor treatment (30). Sweat chloride did improve by a small amount

Table I. *Summary of clinical trials evaluating ivacaftor in cystic fibrosis (CF) patients.*

Study	Phase	Enrollment age	N	Duration	Δ FEV1% predicted	Δ in CF exacerbation rate	Δ Sweat chloride	Other	Conclusions
Ivacaftor in G551D-CFTR subjects									
Accurso et al. (40)	II	18 years and older	39	14-28 days	10.8% relative improvement[a]	N/A	−46 mEq/L[a]	Δ NPD of −4.6 mV[a]	Established safety of ivacaftor in G551D-CFTR; tested proof of concept that CFTR rescue can alter outcomes in CF
Ramsey et al. (24, 41, 42)	III	12 years and older	161	48 weeks	10.6% absolute improvement; 16.7% relative improvement	55% reduction	−40 mEq/L	Improved CFQ-R below MCID	Marked improvement in all primary and secondary outcomes; no important safety limitations
Ahrens et al. (25)	III	6-12 years		48 weeks	12.6% absolute improvement; 17.4% relative improvement	Uncommon in both arms	−54.3 mMol/L	NA	Results similar to Ramsey et al.; no important safety limitations in this age group
Ivacaftor in F508del-CFTR subjects									
Flume et al. (43)	II	18 years and older	140	16 weeks	No significant change	No statistically significant change	−3.0 mEq/L		Ivacaftor safe in F508del homozygous subjects, but not efficacious; very small residual fraction of F508del at cell surface
Ivacaftor in combination with the CFTR corrector VX-809 in F508del-CFTR subjects									
Boyle et al. (33)	II	18 years and older		1 week of combination therapy following 2 weeks of VX-809	No significant change compared to placebo	N/A	13.2 eEq over baseline following combination treatment[b] with 250 mg but not with 150 mg		Interim results suggest combination is safe; also demonstrate potential for additive effects of combination treatment; longer duration warranted for further testing

[a]Pooled data at 14 days from day 14 (Part 1) and day 28 (Part 2) of the study; all changes with the 150-mg dose group; [b]ivacaftor 250-mg dose group; MCID, minimal clinically important difference; NPD, nasal potential difference; CFQ-R, Cystic Fibrosis Questionnaire Revised.

in the ivacaftor treatment group (3 mEq/L reduction compared to placebo), suggesting that efficacious correctors will be needed to provide the requisite CFTR substrate at the cell surface for ivacaftor to confer improvements in lung function.

The sum of the findings outlined above has formed the basis for a new drug application (NDA) for ivacaftor that was approved by the U.S. FDA for use in CF patients with G551D mutations in January of 2012. Furthermore, these remarkable results of a first-in-class medication open new and exciting questions regarding the long-term benefit of effective CFTR modulation and additional CF populations that might benefit from this approach.

To overcome the limitations in the efficacy of VX-809 as a monotherapy in CF patients homozygous for F508del-CFTR (31), and since F508del-CFTR channels exhibit defective gating and membrane residence time, along with a well-characterized misfolding defect, addition of ivacaftor to potentiate CFTR gating and augmenting the activity of subnormal levels of surface CFTR constitute a rational approach towards increasing the function of F508del-CFTR homozygotes. This approach is also substantiated by in vitro results demonstrating that combination therapy increased Isc in F508del-CFTR homozygous HBE cells (32). Interim results of the first CF clinical trial assessing the benefit of ivacaftor in addition to an F508del-CFTR corrector were recently described. In this placebo-controlled trial, 2 weeks of treatment with 200 mg VX-809 was followed by the addition 150 or 250 mg of ivacaftor twice daily for 7 days (33). Data obtained demonstrated that addition of 250 mg ivacaftor further decreased sweat chloride by 9 mEq/L compared to VX-809 alone. The total decrease in sweat chloride following ivacaftor and VX-809 in combination was 13 mEq/L, providing the proof of concept that significant improvements in sweat chloride are possible upon combined treatment of F508del-CFTR homozygous individuals with ivacaftor and an efficacious CFTR corrector. Convincing changes in spirometry were not seen; however, this initial trial was limited by the short duration of administration of the CFTR corrector and potentiator in combination (i.e., only 7 days). Further testing of CFTR correctors with ivacaftor are justified, and may confer clinical improvement upon long-term testing, particularly if the activity of each agent in the combination can be optimized. The results also suggest that ivacaftor may be useful as an agent to augment the rescue of other mutant forms of CFTR, such as premature termination codons or other processing mutants (e.g., class II mutations) sensitive to the effects of CFTR correctors.

FUTURE DIRECTIONS

Other CF populations with the G551D-CFTR mutation

Confirmation of the therapeutic efficacy of ivacaftor in adults and older children with the G551D-CFTR mutation has raised the exciting possibility that rescue of the channel early in life may have pronounced beneficial effects over the long term. For example, the rate of pulmonary function decline approaches about 2% per year according to the latest analysis of the CFF Patient Registry (34). Treatment of CF patients with G551D-CFTR with ivacaftor at a very young age could stall the progressive decline in lung function by preventing early onset of bronchiectasis, a process that can occur prior to a decline in spirometry, as detected by high-resolution CT imaging (35). While some CF patients are born with pancreatic insufficiency, in others it is thought to progress postnatally, reflected by a later onset of malnutrition. Thus, in CF infants with G551D-CFTR, it is reasonable to postulate that ivacaftor treatment could partially reverse pancreatic insufficiency. These considerations have engendered significant interest as the effects of ivacaftor are evaluated in younger CF patients.

Potential use of ivacaftor for other *CFTR* mutation forms

The molecular basis underlying the potentiation of G551D-CFTR suggests that individuals with other *CFTR* mutations may also benefit from ivacaftor treatment. The most obvious group where testing is warranted is among individuals with other gating (e.g., class III) mutations, since the effect of ivacaftor is to potentiate channel opening (e.g., P_o). In vitro studies indicate that ivacaftor has a broad applicability to other gating mutations, and provide a strong scientific basis for testing the effects of ivacaftor in individuals who harbor them (36). If ivacaftor is as efficacious in individuals with other class III mutations as observed for those with G551D, an additional 1% of the CF population could benefit from ivacaftor therapy (34). CF mutations, such as conductance (class III), processing (e.g., incomplete class II mutations) or other mutants (class V, VI), may also benefit from augmentation of P_o, although P_o is typically not reduced in these CFTR forms. Since transepithelial chloride transport is the product of channel open probability, conductance and channel number, alterations in one or more of these properties can be partially overcome by augmentation of P_o to supernormal levels (wild-type open CFTR is about 40%, suggesting the potential for enhanced activity to confer a therapeutic benefit). Evidence that ivacaftor augments Isc, ASL depth and MCT rates of non-CF epithelia provide a further rationale for this approach, and indicate that CFTR activity is not maximal under basal (unstimulated) conditions (13, 37). In this way, ivacaftor will be effective in a broader group of "surface" *CFTR* mutants.

The addition of ivacaftor treatment to other therapeutics directed towards repairing *CFTR* mutation forms also deserves further testing. For example, the addition of ivacaftor to cells and animals with premature termination codons in *CFTR* has enhanced the efficacy of aminoglycosides, which induce translational readthrough to partially restore protein expression and function. For further information on this topic, see the review by Sloane et al. (37).

New questions regarding impact of ivacaftor on disease mechanism

The significant efficacy of ivacaftor towards rescuing CFTR function and clinical outcomes has provided a new opportunity to evaluate the mechanistic basis of how ivacaftor alters CF pathogenesis. While CFTR clearly functions as a chloride transporter on the epithelial surface, there is emerging interest towards the role of CFTR in regulating mucociliary clearance, and whether CFTR has important effects on the physical properties of mucus itself due to its role as a bicarbonate transporter. We do not yet fully understand how the rescue of CFTR activity resulted in such a rapid improvement in lung function. Improved airways obstruction, as depicted by improved aeration as measured by He^3 MRI, suggests increased mucociliary

clearance, a hypothesis further supported by in vitro data demonstrating improved ASL depth and MCT in primary HBE cells following ivacaftor administration. Important questions that need to be addressed in the future include whether ivacaftor might also have an impact on the CF mucus rheology or adherence through its role in CFTR-mediated bicarbonate transport (38), glandular function of CFTR in the airways (39), and other questions arising from the large magnitude of weight gain observed in G551D-CFTR CF patients following ivacaftor treatment.

Some of these exploratory outcome measures will be tested in upcoming studies led by the G551D Observational Study (GOAL) by Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network following the approval of ivacaftor for CF patients with the G551D-CFTR mutation (ClinicalTrials.gov Identifier: NCT01521338). Other potential avenues for exploration include the effect of ivacaftor on other manifestations of CF, such as glucose metabolism, osteopenia, pancreatic insufficiency and gastrointestinal absorption.

CONCLUSIONS

The discovery of the *CFTR* gene and an improved understanding of the role of ion transport in the pathogenesis of CF have led to the development of ivacaftor, a novel therapeutic that targets the underlying defect in individuals with the G551D-CFTR mutation, and is approved for use at an oral dose of 150 mg every 12 hours in CF patients with a G551D mutation in al least one CFTR allele. Based on ambitious HTS efforts, these new treatments have begun to come to fruition for CF patients. Results from clinical trials demonstrate that the rescue of the CFTR protein by ivacaftor treatment is associated with marked improvements in the clinical outcome, which compares favorably to previous therapies widely used by CF patients. Further advances in evaluating the effects of ivacaftor in other CF populations, including in combination with other CFTR-based therapies, promise to usher in a new era of CF therapeutics. These results also provide a clear path towards the rescue of CFTR caused by other more common CFTR mutations, providing a potential pathway to an optimistic future for CF patients and their families.

SOURCE

Vertex Pharmaceuticals, Inc. (US).

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DISCLOSURES

S.M. Rowe is a member of the Advisory Boards of the Cystic Fibrosis Foundation Therapeutics, PTC, Vertex Pharmaceuticals and Novartis. S. Raju states no conflicts of interest.

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