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PharmGKB summary: ivacaftor pathway, pharmacokinetics/ pharmacodynamics

Alison E. Fohner^a, Ellen M. McDonagh^c, John P. Clancy^d, Michelle Whirl Carrillo^a, Russ B. Altman^{a,b}, and Teri E. Klein^a

^aDepartment of Genetics, Stanford University, Stanford, California ^bDepartment of Bioengineering, Stanford University, Stanford, California ^cGenomics England, Queen Mary University of London, London, England ^dDepartment of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio

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Ivacaftor; CFTR; pharmacogenetics; pharmacogenomics; cystic fibrosis; pharmacokinetics; pharmacodynamics; potentiator

Introduction

Ivacaftor [VX-770; N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide] is one of the first drugs developed to treat an underlying cause of cystic fibrosis (CF) rather than the symptoms. It is a selective small molecule potentiator of the Cystic Fibrosis Transmembrane Conductance Regulator protein (CFTR). Potentiators are a new drug class of CFTR modulators designed to restore CFTR function [1]. The Food and Drug Administration (FDA) has granted ivacaftor orphan drug status because it is indicated in a subset of patients with particular *CFTR* variants, specifically class III variants. Approximately 30,000 people have CF in the United States, which is below the 200,000 patient threshold for orphan drugs in the United States [1].

CF is an autosomal recessive disorder characterized by sweat chloride concentration above 60 mmol/L, leading to progressive obstructive lung disease and premature mortality, as well as problems in the liver, pancreas, vas deferens, and intestine [2]. CF affects approximately 70,000 people worldwide [3], including approximately 1 of every 3500 infants born in the United States [4], and is caused by inheriting two detrimental copies of the *CFTR* gene. The CFTR protein is a chloride channel, which maintains ion and water balance intra- and extra-

Corresponding author: Dr. Teri E. Klein, Shriram Center for Bioengineering and Chemical Engineering, 443 Via Ortega, Room 213, MC: 4245 Stanford, CA 94305, Phone: (650)-725-0659, FAX: (650)-725-3863, feedback@pharmgkb.org.

Requests for reprints: Dr. Teri E. Klein, Shriram Center for Bioengineering and Chemical Engineering, 443 Via Ortega, Room 213, MC: 4245 Stanford, CA 94305, Phone: (650)-725-0659, FAX: (650)-725-3863, feedback@pharmgkb.org.

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cellularly [5]. The channel opens and closes through ATP binding, hydrolysis, and phosphorylation, which changes the protein conformation to allow chloride ions to flow through the ion gradient between the intracellular and extracellular regions [2]. Defective CFTR function prevents the flow of chloride ions across epithelial cells, which leads to the mucus buildup, infection, inflammation, and progressively decreasing lung function that is characteristic of cystic fibrosis [5].

Pharmacokinetics

Administered as an oral dose, ivacaftor absorbs readily from the gut, but has low solubility in water (< 0.05 ug/mL) [6]. Taking a 150 mg dose of ivacaftor with a high fat meal improves absorption, increases AUC by 2.5 times, and delays $T_{\max}$ from 3 to 5 hours [7]. Dose/time pharmacokinetics follows a linear profile to a dose of 250 mg, though $C_{\max}$ plateaus for doses 375 mg and higher [6]. Ivacaftor is transported in the plasma highly bound (99%), preferentially to alpha-1-acid glycoprotein but also to albumin, to its site of action, which is the apical membrane of epithelial cells [7, 8]. However, no drug-drug interactions related to protein binding competition are expected [6].

As shown in figure 1, ivacaftor is metabolized in the liver by cytochrome P450 3A (CYP3A), including both CYP3A4 and CYP3A5, into a metabolite hydroxymethyl-ivacaftor (M1), which is considered to be active with a potency $1/6^{\text{th}}$ that of ivacaftor itself, and the inactive metabolite ivacaftor-carboxylate (M6), which not considered active and has an activity level $1/50^{\text{th}}$ that of ivacaftor [9]. Elimination of the parent drug and metabolites occurs predominantly (87%) through the bile, with 22% being the M1 metabolite and 43% being the M6 metabolite [8]. The M6 metabolite is excreted in the bile through the solute carrier organic anion transporter 1B1 (SLCO1B1) transporter, but the mechanism for the elimination of M1 is unknown [10]. Ivacaftor has a half life of 12–14 hours [10].

Ivacaftor and M1 are thought to be weak inhibitors of CYP3A4, increasing midazolam area under the curve of drug concentration in the plasma over time (AUC) by 54% [9]. They are also weak inhibitors of P-glycoprotein (*ABCB1*), increasing digoxin AUC by 32% [9]. CYP3A inducers, such as rifampin, carbamazepine and phenytoin, reduce exposure to ivacaftor and CYP3A inhibitors increase exposure to ivacaftor [9, 11]. When administered with known CYP3A inhibitors, it is recommended that the frequency of ivacaftor administration be reduced from twice to once daily [6].

Pharmacodynamics

Ivacaftor is indicated for use in CF patients who carry at least one of 11 genetic variants, most of which are class III variants, which affect the activation of the chloride channel of CFTR and thereby inhibit normal chloride movement [12, 13]. These variants, called “gating” variants, are listed in Table 1. The functional consequence of class III variants means that CFTR localizes to the apical cell membrane as normal, but cannot undergo cAMP-mediated activation and so is nonfunctional [13, 14]. Ivacaftor is a selective potentiator of CFTR and is believed to stabilize the open state of the channel, enabling chloride transport (figure 1) [15]. The exact mechanism of how this potentiation works is

unknown, though it may be through decoupling the gating cycle and ATP hydrolysis cycle, or by increasing the ATP-dependent opening rate and slowing the closing rate [15, 16]. It is believed that by binding to CFTR in the epithelial cell membrane, ivacaftor improves the function of both CFTR with gating mutations and CFTR with normal function [8, 15].

Initial validation studies were conducted in patients with CF and at least one G551D *CFTR* gating variant (c.1652G>A, rs75527207); treatment was reported to improve lung function by >10%, enough to see a marked improvement in symptoms of CF [17]. Ivacaftor treatment was reported to result in improved pulmonary function tests as measured by the Forced Expiratory Volume in 1 second (FEV-1) by 10.4 – 17.5% over the course of 24 weeks, and this difference was maintained to the trial end at 48 weeks [18, 19]. Ivacaftor treatment was reported to improve weight gain (3.7 kg on ivacaftor compared with 1.8 kg on placebo over 24 weeks) and to decrease chloride concentration compared to baseline (–55.5 mmol/L ivacaftor compared to –1.8 mmol/L on placebo) in clinical trials with 6–11 year olds [18]. Changes in sweat chloride concentrations are often used as a biomarker of drug bioactivity for cystic fibrosis, though there is debate as to the validity of this measure [20–22]. Improvement in chloride transport was reported in patients 12 years and older [19]. Respiratory improvements were reported after 2 weeks of treatment with ivacaftor compared to placebo [19].

Trials in patients homozygous for the F508del variant (c.1521_1523delCTT; rs113993960 or rs199826652), which is not a gating variant and instead prevents CFTR protein from exiting the endoplasmic reticulum and localizing to the cell membrane (figure 1), showed no improvement with ivacaftor treatment alone [23]. However, a combination drug of ivacaftor with lumacaftor (VX-809) was approved by the FDA and European Medicines Agency (EMA) in 2015 for use in patients homozygous for the F508del allele [24]. Lumacaftor is reported to restore CFTR function to about 15% of normal in lower airway epithelial cells derived from patients homozygous for the F508del allele by chaperoning protein folding [11]. By ameliorating the folding malfunction caused by that allele, lumacaftor is thought to enable the localization of F508del CFTR to the cell membrane [11]. When lumacaftor is combined with ivacaftor, the F508del CFTR folding repair from lumacaftor combined with increased potentiation from ivacaftor is reported to result in a 30% improvement of CFTR function in lower airway epithelial cells derived from individuals homozygous for the F508del allele [11]. Phase 2 and 3 trials have also shown clinically meaningful efficacy in patients homozygous for the F508del allele, with results measured by change in chloride concentration and FEV-1 [11].

Pharmacogenetics

CFTR has two nucleotide binding domains and two membrane spanning domains, and variants can occur throughout all regions [25]. Shuttled from the golgi to the apical membrane in secretory vesicles, CFTR turns over at a rate of 10% per minute and has a half life of 12–24 hours [25]. More than 2000 variants have been identified in the *CFTR* gene, though only 127 have been confirmed to be pathogenic [26]. The American College of Medical Genetics guidelines include 23 of these variants in their recommended panel for determining carrier status for cystic fibrosis [27].

Pathogenic variants in *CFTR* are categorized into 5 classes based on their effect on CFTR function. Class I variants affect biosynthesis of CFTR, producing truncated or unstable protein that is quickly degraded. Class II variants affect protein folding, which can reduce protein stability and appropriate localization. The F508del variant, which is a class II variant and prevents localization to the cell membrane, is identified in over 90% of CF cases [2]. Class III variants, those that are targeted by ivacaftor, fold and localize appropriately, but cannot be regulated by ATP or phosphorylation as needed for normal gating function. Class IV variants also affect ion flow, but through decreased permeability of chloride ions, and class V variants usually result in splicing changes that reduce the amount of CFTR expressed in the cell membrane [25].

The most important genetic variants to consider in ivacaftor treatment are the class III variants in *CFTR* that cause problems with gating. The G551D variant is the most common gating variant and that allele is thought to be present in about 4–5% of patients with CF [12]. The FDA and EMA originally approved the use of ivacaftor in the United States and in Europe in 2012 to treat cystic fibrosis caused by the G551D gating variant [8]. Since then, approval has been expanded to include other gating variants. The list of variants approved for treatment with ivacaftor is found in Table 1 and includes G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R [8, 17]. These variants each occur in less than 1% of cystic fibrosis patients [5, 17]. In addition to these other class III variants, the FDA has approved ivacaftor for treatment of patients with the R117H variant, a class IV variant that is primarily a conductance variant, but also has defective gating activity [28].

Conclusion

Ivacaftor monotherapy potentiates CFTR protein with defective gating capabilities, the most common cause of which is the G551D variant. Provided CFTR localization is restored with lumacaftor in patients homozygous for the F508del allele, ivacaftor can also improve chloride transport in these individuals. While the specific mechanism of action is unknown, ivacaftor is thought to restore the flow of chloride ions through the cell membrane via CFTR, and thereby reduce the symptoms of CF in patients with a gating defect.

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Figure 1. Stylized cells depicting the metabolism and mechanism of action of ivacaftor

Ivacaftor potentiates CFTR to restore chloride gating function in CFTR with class III gating defects, such as with the G551D variant. The star symbols on the CFTR-G551D protein icon and the CFTR-F508del protein icon indicate that they are active. The metabolism of ivacaftor and the elimination of its metabolites in the liver is shown. The figure also contains the mechanism of action of lumacaftor, which chaperones the protein folding of the CFTR-F508del and thereby restores correct localization of the protein, where ivacaftor can improve gating function. An interactive version is available at PharmGKB [<https://www.pharmgkb.org/pathway/PA166153178>].

Table 1

Variants in *CFTR* approved for treatment with ivacaftor, with their unique rs numbers, cDNA changes, and resulting amino acid changes.

Amino Acid Change	rs number	cDNA change
R117H	rs78655421	350G>A/C/T
G178R	rs80282562	532G>A
S549N	rs121908755	1646G>A/T
S549R	rs121908757; rs121909005	1645A>C; 1647T>G
G551S	rs121909013	1651G>A
G551D	rs75527207	1652G>A
G1244E	rs267606723	3731G>A/T
S1251N	rs74503330	3752G>A
S1255P	rs121909041	3763T>C
G1349D	rs193922525	4046G>A