

Review Article

Exploring the Mechanism behind G551D and the Effects of Ivacaftor

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Abstract

Much research has been done to explain the mechanism behind the third most common cause of Cystic Fibrosis (CF), a missense mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. The G551D mutation is caused by a glycine to aspartic acid substitution at the 551st position of the CFTR protein. This causes a malfunctioning in the diffusion of chloride anions across specific cell membranes. A missense mutation involving an amino acid other than Glycine will result a 100x lower probability in the opening of the chloride channel. This is because the mechanism behind G551D-CFTR is multi-faceted and requires that the amino acid filling this position not possess a side chain and/or be negatively charged. The presence of a mutation at Position 511 impairs ATP's ability to effectively bind at the NBD. Once ATP is able to bind, it is often prohibited from releasing and allowing another ATP molecule to bind in its place. This causes an ineffective conductance of current that prevents the channel from fully opening. Ivacaftor is a drug formulated to increase the potentiation of the CFTR to increase the transference of chloride anions across the cell membrane. It has the ability to provide relief to this subset of CF patients. While we know much about the effects of the drug, research is still being conducted to enhance its efficacy. The use of Ivacaftor has a promising future. However, there are still areas of its use that we still don't know and, as lung function declines and infections go uncontrolled, its ability to provide relief to patients with the G551D mutation begins to diminish. This paper will elaborate of the mechanism behind the G551D missense mutation and how Ivacaftor can be used to improve the lung function and quality of life of patients with this fatal disease.

Keywords

- CFTR
- G551D mechanism
- Ivacaftor effects
- PFT
- CPET

ABBREVIATIONS

CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; CF: Cystic Fibrosis; WT: Wild Type; ATP: Adenosine Tri Phosphate; NBD: Nucleotide-Binding Domain; TMD: Transmembrane Domain; mM: Millimoles; FEV₁: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; FEF_{25-75%}: Forced Expiratory Flow 25-75%; VO_{2max}: Maximal Oxygen Uptake; SV_{max}: Maximal Stroke Volume; Q_{max}: Maximal Cardiac Output; BMI: Body Mass Index; IV: Intravenous; CFQ-R: Cystic Fibrosis Questionnaire-Revised

INTRODUCTION

Cystic Fibrosis (CF) is one of the most common genetic diseases among the Caucasian population. It affects about 1 in 2500 Caucasian newborns [1]. This disease is a multi-organ recessive disorder and limits the lives of 70,000 people worldwide [2,3]. In 1938, Dorothy Hansine Andersen was the first person to describe and document CF [4]. More than 900 CF mutations are currently known [5]. In 1989, a recessive mutation on the

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene on Chromosome 7, F508Δ, was linked to the pathogenesis of CF [3,6]. Later in 1997, the second most common mutant allele of CF, G542X, was discovered [7]. A replacement of glycine with aspartic acid at the 551st position (G551D-CFTR) is the third most common genetic defect associated with Cystic Fibrosis [8]. This missense mutation results in a gating dysfunction of the CFTR protein and causes a reduction in the transference of chloride anions across the cell membrane [9].

The CFTR protein is located in the apical membrane of cells that line the airways, sweat glands, intestinal, reproductive, hepatic, and renal epithelia [10]. CFTR is a chloride anion channel that is responsible for facilitating the transport of chloride anions in and out of many epithelial tissues [11]. CFTR is a complex glycoprotein that is composed of 1,480 amino acids [12]. This protein has two nucleotide binding domains, NBD1 (cyan) and NBD2 (grey), that use Adenosine Triphosphate (ATP) as an energy source and two transmembrane domains, TMD1 (red) and TMD2 (blue), that are folded in such a way to allow a chloride

to pass through to the outside of the cell (Figure 1) [13,14]. The natural CFTR protein is typically called wild-type CFTR (WT-CFTR) [9,15] and has the ability to directly down-regulate Na⁺ channels. This explains the observed differences in Na⁺ transport of the airway epithelia between WT-CFTR and G551D-CFTR [16]. This paper discusses G551D-CFTR, reviews the current literature on the mechanism behind this protein, and elaborates on the effect of Ivacaftor as a treatment.

Glycine to aspartic acid substitution at position 551

In some patients with CF, there is a mutation of the CFTR protein. Glycine (Gly or G) is present in position 551 on the native protein (Figure 2). In some patients with CF, a missense mutation has occurred causing Aspartic Acid (Asp or D) to replace Glycine (G551D-CFTR) (Figure 3) [17]. This Glycine/Aspartic Acid mutation results in the decreased probability of an open chloride channel, about around 100 times less than the WT-CFTR protein [9]. For this reason, researchers are attempting to find reagents that will possibly increase the conduction of current in this protein resulting in the increased probability of an opened channel [17].

Mechanism behind G551D: Currently, to our knowledge, there is only one drug available that targets G551D-CFTR. Ivacaftor (VX770), also known by its trade name - Kalydeco, has been shown to increase the potentiation of G551D-CFTR by about 8 times [18]. While this is an improvement in protein function, its effect is still less than a tenth of the WT-CFTR protein [19]. There have been prior studies that have shown that ATP's ability to open the channel is obliterated by the G551D mutation despite

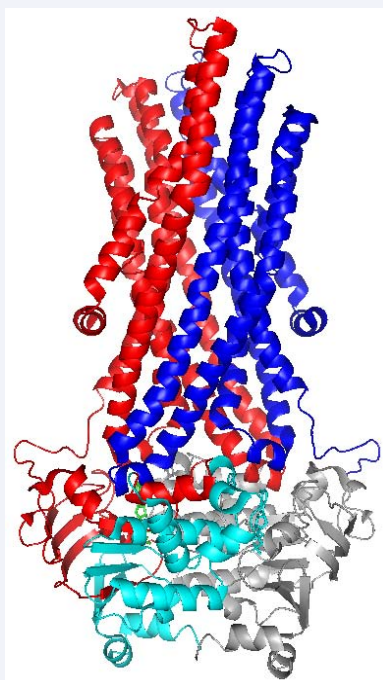


Figure 1 A PyMol rendering of the Cystic Fibrosis Transmembrane Conductance Regulator. The two transmembrane domains, TMD1 & TMD2, are colored in red & blue, respectively. The two nucleotide binding domains, NBD1 & NBD2, are colored in cyan & grey, respectively [61].

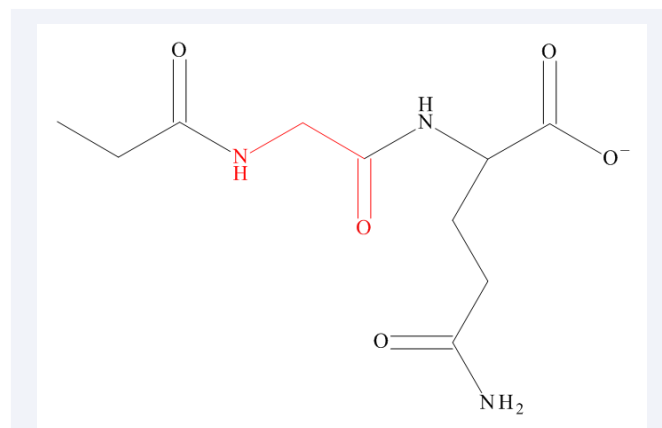


Figure 2 A peptide structure showing Glycine at Position 551 (red) of WT-CFTR. Figure was created using BIOVIA Draw [62].

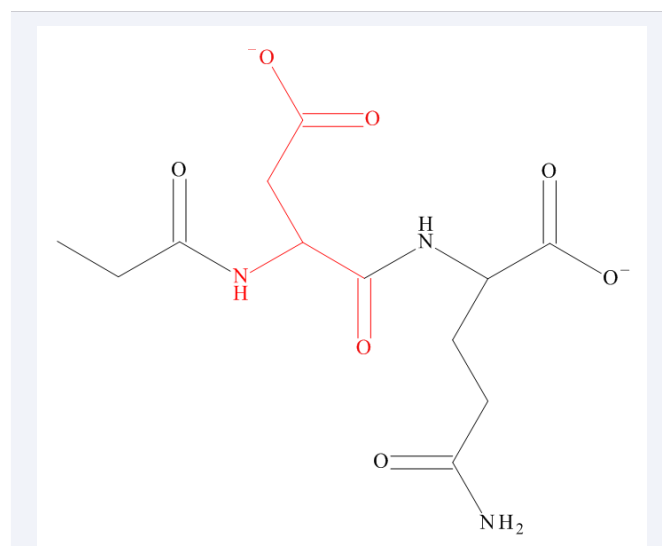


Figure 3 A peptide structure showing Aspartic Acid at Position 551 (red) of G551D-CFTR. Figure was created using BIOVIA Draw [62].

the fact that the CFTR proteins appear on the apical surface of epithelial cells [9,20]. There is a presumption that this mutation impedes ATP-induced dimerization because of where the mutation occurs on the protein [21]. This mutation hasn't been fully investigated due to low activity in the G551D channel [9]. Furthermore, since Glycine doesn't contain a side-chain, its small size exposes the peptide backbone so ATP can form a hydrogen bond at the Nucleotide-Binding Domain (NBD). G551D results in a longer side chain creating a complication in the phosphorylation-induced dimerization of the NBD [22].

Lin et al (2014) reported that Ivacaftor sensitizes G551D-CFTR to ATP resulting in a biphasic response in current. Despite the absence of ATP, there was an initial spike in current followed by a slow decay [17]. In contrast, WT-CFTR's current shows an immediate increase in the presence of ATP and abruptly falls in the absence of ATP. When ATP's binding affinity with either NBD (NBD1 or NBD2) is manipulated, the G551D mutation forces one of the two ATP-binding sites to become inhibitory [23]. The

second ATP-binding site is formed by the head of NBD2 and the tail of NBD1 (Figure 4) [24]

There are two explanations for this effect. Primarily, a lowered probability of occupancy explains an increase in current despite a decrease in ATP. This is because the various conformations increase the Gibbs free energy of the protein and the instability of the protein results in a lower probability of occupancy [9]. If the molar concentration of ATP is lowered, current will decrease because ATP binding to the NBD is jeopardized. In addition, mutations that alter the affinity for ATP-binding may also alter the stimulatory action of ATP [8,17].

Two millimoles (mM) of ATP is likely to saturate NBD1 and NBD2, 20 micromoles (μM) would allow full occupancy of site 1 [25] (Figure 4); however, a suboptimal probability of binding at site 2, and 1 μM would ensure minimal binding of ATP at both sites. When ATP is decreased from 2 mM to 20 μM , the measured current will increase despite the decrease in ATP. Decreasing the ATP further from 20 μM to 1 μM will result in a lower current than 2mM. This finding indicates that 20 μM of ATP would likely bind to both NBDs and 1 μM is the minimum to bind with one NBD. Because the current increases when lowering the molar concentration of ATP in the absence of Ivacaftor, this inhibitory action must be an intrinsic property of G551D [17].

The second explanation is likely to be explained by altering the ATP-binding affinity at the second NBD site. Evidence of this is found by manipulating the aromatic amino acid at position 1219, Tyrosine (Tyr or Y) [26]. Tyrosine at position 1219 is important because it has an important role in the binding of ATP in the head of NBD2. Three amino acids, two with a side chain and one without, were chosen to demonstrate that a mutation containing a side chain will alter ATP-binding affinity: Phenylalanine (Y1219F), Isoleucine (Y1219I), and Glycine (Y1219G). Y1219F and Y1219I showed a biphasic response in the absence of ATP. However, when Y1219G fills this position, the current falls to baseline as expected. Removing the entire side chain stops the spike in current and the subsequent decay [17]. This means the presence of a side chain causes the biphasic response.

WT-CFTR requires Glycine to be stimulatory and it becomes inhibitory in G551D. However, because Aspartic Acid is anionic, it also implies that a negatively charged molecule at the 551st position would prevent the dimerization of NBD2 due to electrostatic repulsion [17]. It is important to replace the 551st position with a neutral amino acid, a cationic amino acid, and an anionic amino acid to determine if a negatively charged molecule can be implicated as well. Serine (G551S), a neutrally charged amino acid, and Lysine, a cationic amino acid, both show that ATP serves as a pure stimulatory ligand because the current drops to the baseline after the ATP washout. However, when observing the current of Glutamate (G551E), an anionic amino acid, a biphasic response is observed. Since Glutamate and Aspartic Acid are negatively charge amino acids, the inhibition at site 2 must also be caused by the anionic side chain of Aspartic Acid [19].

Ivacaftor (VX770), (Kalydeco)

Ivacaftor (Figure 5) increases potentiation of the mutate CFTR protein to allow the facilitated diffusion of chloride across cell membranes with a projected improvement of 8-fold [18].

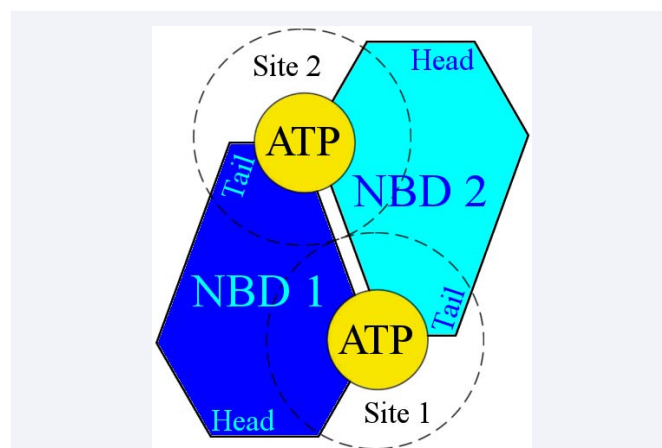


Figure 4 A graphic representation depicting how each site consists of the head of one NBD and the tail of the other NBD.

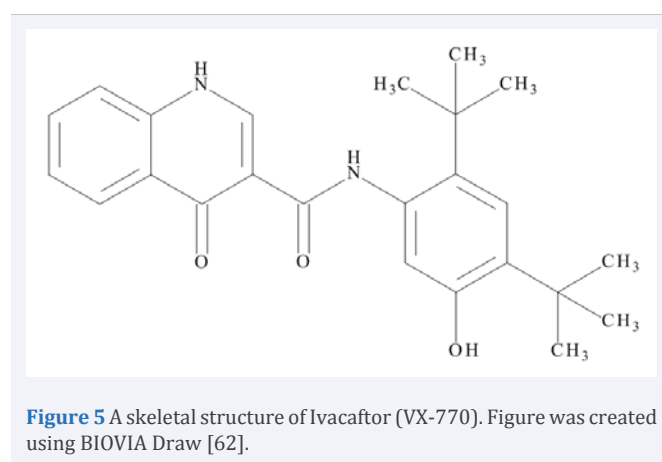


Figure 5 A skeletal structure of Ivacaftor (VX-770). Figure was created using BIOVIA Draw [62].

This drug, Ivacaftor, treats around 4–5% of the cases of CF [27]. It has been reported that Ivacaftor can cost around \$300,000 per year [28]. However, Vertex Pharmaceuticals has made the drug free of charge to patients in the US if they meet certain insurance and income requirements [3,29]. Ivacaftor also been reported to treat other mutations such as, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H [30].

There are some adverse effects of Ivacaftor. The most common are headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness [31,32]. However, most patients that experience these kinds of symptoms find they are of mild to moderate severity and none are serious enough to discontinue treatment [33]. Ivacaftor is transported around the body while chemically bound to albumin and alpha 1-acid glycoprotein. Also, it has been reported that this drug does not have the ability to bind to red blood cells [34]. It has a half-life of 12 hours [35] and most is eliminated in the feces with negligible urinary excretion [36].

Pulmonary function testing / cardiopulmonary exercise testing

Studies show that the administration of Ivacaftor results in an increase in the Forced Expiratory Volume in One Second (FEV₁),

an increase in FEV₁ % Predicted, and an increase in Forced Vital Capacity (FVC) [37-40]. A nominal increase of 0.09 L/s in the Forced Expiratory Flow (FEF_{25-75%}) been reported as well [41]. Some patients reported an increase in maximal oxygen uptake (VO_{2max}). A study published by Saynor et al., (2014) reported an improvement around 30%. However, this improvement was found to be out of proportion with changes in lung function, but it is considered clinically meaningful because this improvement is 20% greater than their expected error. Varied responses in VO_{2max} can be explained by the patient's present lung function. Severely decreased lung function, especially with underlying infections and parenchymal inflammatory changes, explains poor improvement in VO_{2max} [42]. One study showed 292% increase in the 6-minute walk test and a 310 meter increase in the shuttle walk test from their respective baselines [43]. In addition, an increase in maximal stroke volume (SV_{max}) and maximal cardiac output (Q_{max}) were found [41] as well as an increase of 4.5% in overall weight and about 5.8% in BMI (19.1 to 20.2 kg/m²) after the use of Ivacaftor [37]. This can be explained by the decrease in viscosity of mucus in the respiratory tract mucus leading to a decrease in mucus in the sinuses [44] which improves patient's sense of smell and may result in an improved appetite. In addition, a decrease in airway mucus lowers the level of airway obstruction resulting in few exacerbations. This decreased work of breathing leads to a decrease in energy expenditure and can improve the appetite [45]. One notable change was a decrease in the amount of days on IV antibiotics, even when the patient was infected with *Pseudomonas aeruginosa* [46]. However, changes in the microbiota of a patient's lungs do not occur [37] but Ivacaftor seems to enhance bacterial variety [47]. Analysis of the microbiota in CF patients may lead to learning the evolution of the bacteria and using them as biomarkers as a means to evaluate lung function [47].

The Effect of Ivacaftor on Pregnant Patients

Studies regarding the use of Ivacaftor on pregnant patients are limited. However, one norm weighted patient was reported to have had a normal, uncomplicated, spontaneous vaginal delivery while using the drug. Her predicted FEV₁ was 85% before receiving Ivacaftor. After learning she was pregnant, her FEV₁ was 94% while using Ivacaftor (85% without). It's important to note that it is probable that Ivacaftor and/or its metabolites can excrete into human milk. However, to our knowledge, there is no research on the effects of Ivacaftor on infants that are breast-fed [48].

Wellness and quality of life

Studies that perform the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a health-related quality of life measurement for patients with CF, show improvements in the respiratory domain as well as physical functioning, social functioning, eating disturbances, health perceptions, treatment burden, and [40,49]. However, there are no significant differences in emotional functioning, body image, or digestive scale scores [33]. Ivacaftor appears to increase the perceived amount of bronchial secretions, possibly due to improved function. This may result in an increase in the intensity of percussive physiotherapy and frequency of IV antibiotics after initiating Ivacaftor [50]. Patients

receiving Ivacaftor appear to have improved mobility and quality of life. However, the administration of Ivacaftor doesn't appear to eliminate other medications (i.e bronchodilators, steroids, mucolytics) and modalities (i.e chest physiotherapy) that are intended to improve pulmonary function.

DISCUSSION & CONCLUSION

Discussion

Researchers have begun designing a second generation of more effective CFTR potentiators and correctors [51]. In addition, these findings may ultimately lead to a cure for at least a subgroup of patients with the G551D missense mutation. However, there are some limits in our current knowledge of the CFTR protein. Not much research has been done on the role of site 1 (Figure 4). This is partly because it is bound to the tail portion of site 2 and less accessible [52,53]. Studies have shown that site 1 is hydrolysis incompetent and early biochemical studies show that ATP can be trapped in site 1 for minutes implicating a higher binding affinity for ATP [54,55]. To our knowledge, most reported studies aren't able to come to a solid conclusion on the importance of the role of site 1, but most believe the role of site 1 is of less significance when compared to site 2 [25].

Overall, based on this review, we believe there are some drawbacks / limitations with regards to the administration of Ivacaftor to CF patients. In addition, it is reasonable to assume that an improved diffusion of chloride anions resulting from the administration of Ivacaftor can improve mucociliary clearance. However, there isn't enough data that measures that improvement in relation to the types of microbes in the airway. The reduction in the days on IV antibiotics may be explained by Ivacaftor's ability to stimulate the immune system and reduce bacterial survival [56]. By normalizing the function of G551D-CFTR, Ivacaftor is able to correct the degranulation of neutrophils resulting in the controlled destruction of bacteria. The data in some of the reported studies were collected retrospectively. This has the potential to increase the possibility of error due to confounding variables and bias. Ivacaftor has a limitation of ineffectiveness for CF patients suffering from the more common mutation, F508Δ [57]. This is because F508Δ is not found at the apical membrane of cells. F508Δ has a defect in its folding and is unable to leave the endoplasmic reticulum [58]. However, this mutation is currently being treated by another drug called Orkambi, a combination drug that contains Ivacaftor [59]. Another limitation is that medications used in practice are often different and more variable than the medications allowed in clinical trials. It is important to determine how the pharmacology changes in different conditions such as fever, sepsis, and interactions with other medications. Also, to our knowledge, it is currently unknown if Ivacaftor has the ability to overpotentiate other proteins and how the result of that potential overpotentiation will affect the use of Ivacaftor. In addition, to our knowledge, current literature doesn't state whether a reduction in the days on IV antibiotics is reflecting an improvement in the lungs ability to reduce inflammation and clear infection or if the reduced symptoms will result in a patient feeling a lower need to use rescue therapies. For the short term management of CF, current literature doesn't reveal how spirometric changes will impact long-term disease progression.

For the long term management of CF, it is unknown at this time if lung function can be improved [40] Because Ivacaftor appears to provide a short-term improvement of spirometry-assessed lung function and appears to be a viable therapeutic approach in Cystic Fibrosis, [40] more research needs to be done to determine if Ivacaftor is inadvertently targeting and increasing the potentiation of other proteins in the human body [60]

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