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Analysis of Ivacaftor Drug Approval For Cystic Fibrosis Patients With Gating Mutations

Samitha Nemirajaiah

Cystic fibrosis is an inherited monogenetic disorder that leads to chronic respiratory and lung infections. These infections result in decreased quality of life in patients. Quality of life (QOL) can be attributed to many disease characteristics such as hospitalization, organ transplant, depression, and bacterial infections. Ivacaftor is the drug approved to treat cystic fibrosis patients with G551D gating mutation. The goal of this paper was to demonstrate how an earlier approval of Ivacaftor for all gating mutations would have helped the QOL for the subset of cystic fibrosis patients with non-G551D gating mutation. After reviewing studies from reputed sources about Ivacaftor treatment effects on disease characteristics, a total of twenty studies were reviewed, and nine studies were selected to conduct a meta-analysis. In the meta-analysis, forest plots for QOL outcomes were generated. Meta-analysis showed that Ivacaftor improved the disease characteristics/bacterial infections and quality of life in cystic fibrosis patients.

Keywords: CFTR, cystic fibrosis, gating mutations, Ivacaftor

Introduction

Cystic fibrosis is a progressive, monogenetic life-threatening lung disease that affects about 35,000 people in the United States and 70,000 worldwide. Cystic fibrosis is considered an orphan and a rare disease (defined as a disease in which the number of patients affected is less than 200,000). Life expectancy has improved from five years in the 1950s to 50 years currently. The mortality rate for cystic fibrosis patients is about four percent. Cystic fibrosis causes severe damage to the lungs, and there is no cure. This research will concentrate solely on cystic fibrosis caused by gating mutation.

The condition is caused by a dysfunction, or a missing protein called Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CFTR protein regulates the salt and water balance at the surface of lung cells. When there is a malfunction in the saltwater balance, the lungs get infected (Pittman & Ferkol, 2015). CFTR exists at the epithelial cell surface, where it facilitates chloride transport across the membrane to maintain salt and pH balance in multiple organs. CFTR mutations disrupt Chloride transport causing an accumulation of sticky mucus in the lungs. (Yu et al., 2012) There are over 1800 different CFTR mutations; one among them is gating mutation. Gating refers to the opening and size of the gates or pores on the CFTR protein surface for salt and water movement.

Literature Review

The Present State of Cystic Fibrosis and CFTR Modulators

CFTR modulators have various modes of action, different from those of other therapies. One of the variations is that it restores and improves the defec-

tive CFTR protein's functioning. The latter is mostly useful to individuals who have CFTR mutations. CFTR modulators that are highly effective can provide many transformational benefits by facilitating improvements along with several significant endpoints in clinical care and trials (Clancy, et.al, 2019). An essential objective of the cystic fibrosis care and research community is to provide CFTR-based therapies to any individual diagnosed with cystic fibrosis. In this case, the modulators can be termed as tiny molecules whose goal is to improve "mutant CFTR proteins" by using various approaches. One approach is potentiators that promote the advancement of gating CFTR variants. They raise the probability of having an open channel for the gating of the mentioned variants (Strub & Mccray, 2020). Another approach is correctors, which augment the trafficking of the processing variants for CFTR to the plasma membrane. Readthrough agents suppress premature termination codons (PTCs) and produce readthrough that is transnational through the ribosomes. Amplifiers are another approach, which increases the level of variant CFTR available for successive modulation by small molecules that are protein active. Potentiators and correctors are two categories of modulators that have gained approval as treatments for cystic fibrosis brought about by discrete CFTR variants. The various mentioned approaches are used by recent clinical trials in examining the CFTR modulators.

Gating Processes and Mutations

Similarly, in some cases, gating mutation leads to defective channel gating. Gating mutations represent about ten percent of all CFTR mutations. The gating mutations are G551D, which represents about five percent of all CFTR mutations, and ninety percent of all gating mutations, and non-G551D mutations (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D), which represent ten percent of all gating mutations. There are approximately one hundred and fifty people with non-G551D gating mutations in the United States of America. (Yu et al., 2012). Since discovery of the disease in the 1940s, cystic fibrosis treatment and drug development were mainly based on the symptoms. The drug development for cystic fibrosis moved from treating the symptoms and secondary infections to primary prevention of chronic lung disease. Since discovery of the gene and significant advances in knowledge at the molecular level, it has become possible to develop proper drugs. It was well established that CFTR gene mutation caused cystic fibrosis (Mayer-Hamblett et al., 2007). In the early part of the 2000s, A biopharmaceutical company called Vertex Pharmaceutical started developing a treatment that specifically targeted the CFTR gene mutation, explicitly gating mutations.

Vertex Pharma developed oral molecules to increase mutated CFTR gene gating activity using high-throughput screens, resulting in many pre-clinical hits in *in vitro* screening assays. (McPhail & Clancy, 2013) The name of the drug molecule developed by Vertex Pharma was VX-770 (Ivacaftor). Ivacaftor was considered a CFTR potentiator since it enhanced salt and water movement through the defective gates/channels. Vertex Pharma conducted various *in vitro* studies, Biopharmaceutics studies, animal toxicity studies, Drug-drug interaction studies, Pharmacokinetics studies, and placebo-controlled, randomized safety and efficacy clinical trial studies. Ivacaftor is an oral 150 mg oral tablet taken twice daily. The company, Vertex Pharmaceuticals, conducted *in vitro* analysis for both gating mutations G551D and non-G551D.

However, they ran the efficacy and safety trial for only G551D gating mutations. Vertex Pharma ran two placebo-controlled randomized trials STRIVE and ENVISION, for cystic fibrosis patients with G551D gating mutation. The results were statistically significant, meeting the primary endpoint. In the Vertex trials, the FEV1 was improved by more than ten percent, which was statistically significant and clinically meaningful. In February 2012, The Food and Drug Administration (FDA) approved Ivacaftor for patients with G551D gating mutation. Vertex Pharma conducted another small cross safety and efficacy clinical trial named KONNECTION (39 patients) for cystic fibrosis patients with non-G551D gating mutations. The test met the primary endpoints, and subsequently, FDA approved Ivacaftor for non-G551D gating mutations (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D) in 2014 (Discussion 2015). After Ivacaftor's approval for cystic fibrosis with gating mutations, it was evident that the drug improved the outcomes and hospitalization rates. Ivacaftor was significant for multiple gating mutations (Robison, 2012). It was not a surprise that the

ivacaftor uptake was rapid, and 80% of the eligible patients were on the drug within the first twelve months after FDA approval in 2012.

Furthermore, a study conducted on 143 patients on the drug ivacaftor showed a 55% decrease in general hospital admission and an 81% decrease in cystic fibrosis-related hospital admission. A reduction in hospitalization rates leads to an increase in quality of life. (Feng et al., 2018). Ivacaftor has proven in clinical trials that it works for all gating mutations (G551D and non-G551D). Ivacaftor has demonstrated in *in vitro* studies that it works in all gating mutations. The primary function of Ivacaftor is to increase the opening of the CFTR channel or gate. Research by (Eckford et al., 2015) found that CFTR potentiator Ivacaftor opens the defective channels/gate of mutant CFTR, agreeing with the findings by (Goor et al., 2009) that showed Ivacaftor increased the probability of an open CFTR channel. According to (Elborn 2011), research has shown in *in vitro* studies that gating mutations similarly respond to Ivacaftor to G551D. Also, J Elborn notes that there are too few patients with these mutations (non-G551D gating) to allow conventional clinical trials. According to the FDA reviewer (Ivacaftor approval for G-551D modification), the *in vitro* results appear to be consistent with classifying ivacaftor as a potentiator of the CFTR protein (Robison, 2012). Before conducting the placebo-controlled randomized clinical trials for clinical trials, Vertex pharmaceutical conducted a detailed *in vitro* study of Ivacaftor's potential for CFTR gating mutations. Mutant CFTR was obtained from Fischer Rat Thyroid (FRT) cells.

Also, single-channel patch-clamp technology was employed to measure the channel open probability of CFTR directly. The results showed that the chloride transport and channel/gate open probability increased in both gating mutations after administering Ivacaftor. (Both G551D and non-G551D). (Yu et al., 2012) The data suggested that the mechanism of action increases chloride ion transport by increasing the CFTR channel/gate's open probability (Welsh & Smith,1993). The studies show that Ivacaftor increases the available probability in CFTR "gating defect" mutant channels (G551D, S549N, S549R, S1251N) (Robison, 2012). Three results from the actual randomized placebo-controlled clinical trial for G551D gating mutation (STRIVE and ENVISION studies) correlated to the *in vitro* results in terms of gate/channel opening. The increase in chloride transport and gate/channel opening demonstrated in *in vitro* studies resulted in improvement in FEV1 of the patients in clinical trials.

Similarly, in the clinical trials conducted for non-G551D gating mutation (KONNECTION study), the FEV1 improved correlating to *in vitro* studies. (Yu et al., 2012) The improved chloride transport and gate/channel opening link to improvement in FEV1 based on clinical trials. However, a second clinical trial needed to be conducted, and two and half years were spent to get the approval.

Gap in Research

The FDA approved Ivacaftor for a G551D gating mutation in February 2012. The FDA approved Ivacaftor for non-G551D (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D) gating mutation in February 2014. The *in vitro* data in 2009 showed that Ivacaftor worked similarly for all gating mutations (G551D and non-G551D). Ivacaftor *in vitro* data for gating mutations directly correlated to the improvement of FEV1 in the clinical trial. The number of patients for non-G551D gating mutations is meager (about one hundred and fifty patients and represents one half percent of all cystic fibrosis patients) and difficult to recruit. The literature states that *in vitro* study is an excellent predictor of clinical trial outcomes for CFTR gating mutations in cystic fibrosis patients. According to Professor Elborn (2011) of Queens University, U.K., "There are too few patients in the world with these mutations to allow the conventional clinical trials to be conducted" (p. 4). Cystic fibrosis is a dreaded disease with no cure, and Ivacaftor has proved to reduce hospitalization and improve life quality based on studies.

Additionally, the FDA has approved drugs for rare diseases based on smaller clinical trials, *in vitro* data, and animal clinical studies (Clancy et al., 2019). By first approval in February 2012, Ivacaftor had already proved safety and efficacy in clinical, *in vitro*, and animal studies for gating mutations. Essential factors for earlier approvals are efficacy and safety of the drug, clear disease cause (gating mutations), clearly known disease pathology, no available alternative therapy, the precise mechanism of action (Ivacaftor), the severity of the disease, and rarity of the disease. The gap leads to the specific research question: 'How could the in-

clusion of non-G551D gating mutations in the 2012 drug approval for Ivacaftor by Vertex Pharma have increased patient quality of life before the subsequent approval for non - G551D gating mutations?'

Purpose and Hypothesis

The purpose of this research is to explore whether the results from *in vitro* data and studies based on gating mutations can be used for drug approval for rare disease treatments, hence improving the patient's quality of life with earlier drug availability. Thus, the hypothesis is that "If the cystic fibrosis patients with non-G551D mutations had been given Ivacaftor in 2012, then their quality of life would have improved with the earlier approval."

Methodology

The research goal was to analyze and demonstrate how the inclusion of non-G551D gating mutations in Ivacaftor's initial drug approval would have increased patients' quality of life. A meta-analysis was warranted to show the improvement in cystic fibrosis disease characteristics across studies and to obtain a precise estimate of the effect of treatment. The meta-analysis was performed under the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Liberati et al., 2009). Various studies have shown disease characteristic improvements, but a systematic review was conducted to conclude a definitive trend. The data was also analyzed to measure improvements demonstrated in patients using Ivacaftor, thereby showing how those improvements could have helped the subset of non-G551D cystic fibrosis patients who had to wait two extra years for approval.

Study Selection

A comprehensive search was performed to find relevant studies and data sources. Sources implemented in the data search were extracted from databases selected by credibility and related sources. All published sources considered for implementation in the study were peer reviewed and taken from PubMed, British Medical Journal, Elsevier, U.S. cystic fibrosis data registry, U.K. cystic fibrosis data registry, and ScienceDirect databases. In each database, an advanced search was employed based on keywords such as, 'G551D and non-G551D gating mutations', 'Ivacaftor pre-clinical studies,' 'Ivacaftor and Cystic Fibrosis,' 'Ivacaftor effects on cystic fibrosis patients,' 'Ivacaftor and hospitalization' and 'Disease progression in cystic fibrosis patients.' Specific studies that showed a numerical improvement in disease characteristics and bacterial infections were selected. A quality assessment was done using Grading of Recommendations, Assessment, Development, and Evaluation, or GRADE (Guyatt et al., 2008). The studies were assessed based on the type of evidence (such as a randomized trial, observational study, or any other evidence), study quality, inconsistency, sparse data, strong evidence of association, very strong evidence association, and evidence of dose-response. The GRADE system has four levels based on the quality of evidence: high, moderate, low, and

Table 1:

Quality assessment of studies

Study Names	Type of Evidence	Sudy Quality	Inconsistency	Strong Evidence	Very Strong evidence	Dose Response	Selected	Reason
Lisa B Feng, 2018	Moderate	Moderate	Moderate	High	High	High	Y	
Shahid I. Sheikh, 2015	Low	Moderate	High	High	Low	Low	N	Very low N
Frank J Accurso, 2010	High	High	Moderate	High	High	High	Y	
Bonnie W ramsey, 2011	Moderate	High	Moderate	High	High	High	Y	
Jane C Davies, 2013	High	High	Moderate	High	High	High	Y	
US Data Registry, 2018	Moderate	High	low	High	High	High	Y	
UK Data Registry, 2018	Moderate	High	low	High	High	High	Y	
Scott C. Bell, 2019	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Y	
Patrick A Flume,2017	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Y	

very low. Studies with low population, lack of numerical disease characteristics, or bacterial infection data were excluded from the meta-analysis. The phases of the systematic review process are documented using the PRISMA flow chart in Appendix A.

Data Extraction and Statistical Analysis

Meta-analysis was used to analyze data to measure improvements shown in patients using Ivacaftor, thereby showing how those improvements could have helped the subset of non-G551D cystic fibrosis patients who had to wait two extra years for approval. The patient data for Ivacaftor and comparator was collected from cystic fibrosis registries and other studies, including disease characteristics and bacterial infections, and extrapolated to the patient set with non-G551D gating mutations. STATA was used to perform all statistical analysis.

The data was initially tabulated and represented using descriptive statistics. An exploratory analysis was conducted to describe the characteristics of the population included in this meta-analysis. The incidence of each postoperative outcome (i.e., Quality of Life [QoL] items) was extracted as a dichotomous variable (present or absent) and compared using Odds Ratios (OR) with their respective 95% confidence intervals (CI). Forest plots were used to illustrate the estimations and overall effect sizes with pooled Odds Ratio (OR) represented as a solid diamond at the bottom of the forest plot. Predetermined subgroup analyses were performed based upon bacterial infections or type of outcome. Heterogeneity (I^2) was assessed by with the correspondent chi-squared test ($I^2 < 50\%$ and $I^2 > 50\%$ were considered insignificant and significant heterogeneity, respectively). The meta-analysis of the binomial data was performed using a random-effects model and the DerSimonian & Laird method (DerSimonian & Laird, 2015).

Bias in the meta-analysis was tested by calculating publication bias and running funnel plots using Egger's test (Egger et al., 1997). Funnel plots were constructed to represent any tendency for publishing in favor of the positive effect. Significant publication bias was considered when there was an asymmetry in the plot, and a statistically significant bias coefficient was noted according to Egger's test. P values < 0.05 were considered statistically significant in all statistical analyses.

UK

Disease Characterestics	Ivacaftor	Percentage	Comparator	Percentage	P-Value
Death	3	0.7	29	1.4	0.388
Hospitaizations	107	26	937	45.3	<0.0001
Pex	140	34.1	1157	55.9	<0.0001
Organ transplantation	2	0.5	18	0.9	0.5586
CFRD	85	20.7	602	29.1	0.0007
Gastrointestinal	83	20.2	484	23.4	0.185
Pulmonary	256	62.3	1363	65.9	0.2012
Bone/Joint	75	18.2	573	27.7	0.01
Depression	18	4.4	122	5.9	0.2563
Heptobilliary	92	22.4	579	28	0.023

Bacterial Infections	Ivacaftor	Percentage	Comparator	Percentage	P-Value
Staphylococcus aureus	122	29.8	689	33.9	0.1706
MRSA	11	2.7	75	3.7	0.4116
Psuedomonas aeruginosa	188	46	1113	54.7	0.0014
Influenza	53	13	220	10.8	0.2105
Stenostrophomonas	21	5.1	166	8.2	0.0522
Mycobacterium	1	0.2	10	0.5	1
Aspergillus Spp	42	10.3	410	20.2	0.001
Acromobacter	18	4.4	67	3.3	0.311
Burkholderia Complex	17	4.2	104	5.1	0.522
Klebsiella spp	4	1	7	0.3	0.0935
Pandoraea spp	0	0	0	0	

The data analysis resulted in measurements of Quality of Life (QOL) improvements such as percentage reduction in hospitalization, the percentage reduction in hospital visits, improvement in mortality rate, improvement in lung function, disease progression, organ transplants, and pulmonary exacerbation for non-G551D patients had they been administered

Table 2:

Data selected from selected studies

US

Disease Characterestics	Ivacaftor	Percentage	Comparator	Percentage	P-Value
Death	8	0.6	97	1.6	0.011
Hospitaizations	346	27.5	2671	43.1	<0.0001
Pex	349	27.8	2684	43.3	<0.0001
Organ transplantation	2	0.2	68	1.1	0.0017
CFRD	382	30.4	2449	39.5	<0.0001
Gastrointestinal	467	37.2	2474	39.9	0.0719
Pulmonary	431	34.3	2207	35.6	0.3747
Bone/Joint	222	17.7	1389	22.4	0.0002
Depression	178	14.2	1060	17.1	0.0099
Heptobilliary	58	4.6	484	7.8	<0.0001

Bacterial Infections	Ivacaftor	Percentage	Comparator	Percentage	P-Value
Staphylococcus aureus	784	63.9	4166	69.9	0.001
MRSA	286	23.3	1751	29.4	0.0001
Psuedomonas aeruginosa	565	46.1	3354	56.3	0.0001
Influenza	162	13.2	675	11.3	0.0605
Stenostrophomonas	133	10.8	893	15	0.0002
Mycobacterium	66	9.9	430	11.8	0.1479
Aspergillus Spp	131	10.7	1123	18.8	0.0001
Acromobacter	68	5.5	471	7.9	0.0043
Burkholderia Complex	38	3.1	197	3.3	0.7121
Klebsiella spp	17	1.4	90	1.5	0.7452
Pandoraea spp	2	0.2	12	0.2	1

Table 2: Continued

	Ivacaftor	Percentage	Comparator	Percentage
Rowe et al				
Hospitalization	21	12	41	27
Heltshe et al				
Psuedomonas aeriginosa	63	42	93	62
Mycobacterium	45	30	63	42
Aspergillus Spp	8	5	23	15
Feng et al				
Hospitalization	20	13	48	31
Flume et al				
Pex	28	33.7	44	56.4
Bell et al				
Depression	21	28.8	58	42.3
Bone/Joint	24	33.3	74	54
Sheikh et al				
Hospitalization	0	0	1	10

Ivacaftor along with G551D patients. The data analysis shows how the patient's Quality of Life (QOL) would have improved if they started using Ivacaftor with initial approval for all gating mutations.

Justification and Limitations of Methodology

Meta-analysis is conducted to assess the strength of evidence present on disease and treatment to obtain a single summary estimate of the effect. It is a quantitative, systematic assessment of previous research studies to derive conclusions about that body of research (Haidich, 2010). Statistical analysis shows the various measurement and trends for patient Quality of Life improvement and is useful to ensure that the interpretations are correct. According to the research by Vendrusculo et al. (2018), a meta-analysis on benefits and risks of antibiotic therapy in cystic fibrosis patients was conducted, and the study used UK Cochrane Centre for optimal recall of Randomized Controlled Trials (RCT) for search strategy. RCT was rated based on a quality index. Five parameters were used to rate, namely, an adequate description of patient groups, an adequate description of the intervention, adequate assessment of outcomes by clinical assessment, outcome assessments, and an adequate description of effects of the intervention. For statistical analysis, dichotomous and continuous outcome measures were used. Additionally, according to the research done by Florescu et al. (2009), an electronic patients' record was used to collect clinical data. The study was conducted at a single pediatric cystic fibrosis center in Paris. It was important to know the patient characteristics before the treatment was started, and hence the patient data collection was started before the azithromycin treatment was started. Then the data was collected every twelve months until discontinuation. Characteristics such as Body Mass Index (BMI), Forced Expiratory Volume in one second (FEV1), the annual rate of acute respiratory exacerbations, arterial blood gas, microbiological analysis, and pulmonary function tests were recorded. Statistical analysis was conducted using multiple imputations for missing pulmonary function data. These published papers were successful in deriving a conclusion, and their methodology is similar to the methodology of this research. Essentially, these outside research papers make use of the meta-analysis method, using similar components to the methodology of this research.

In 2012, there was not much awareness about gene-level treatment for cystic fibrosis patients. Ivacaftor was the first drug to be approved as a targeted treatment for this rare disease's gating mutation. There is enough material to concur that Ivacaftor works for all gating mutations and would have improved the life of cystic fibrosis patients with non-G551D gating mutation earlier if ivacaftor had been approved initially for all gating mutations.

Results

Included Studies

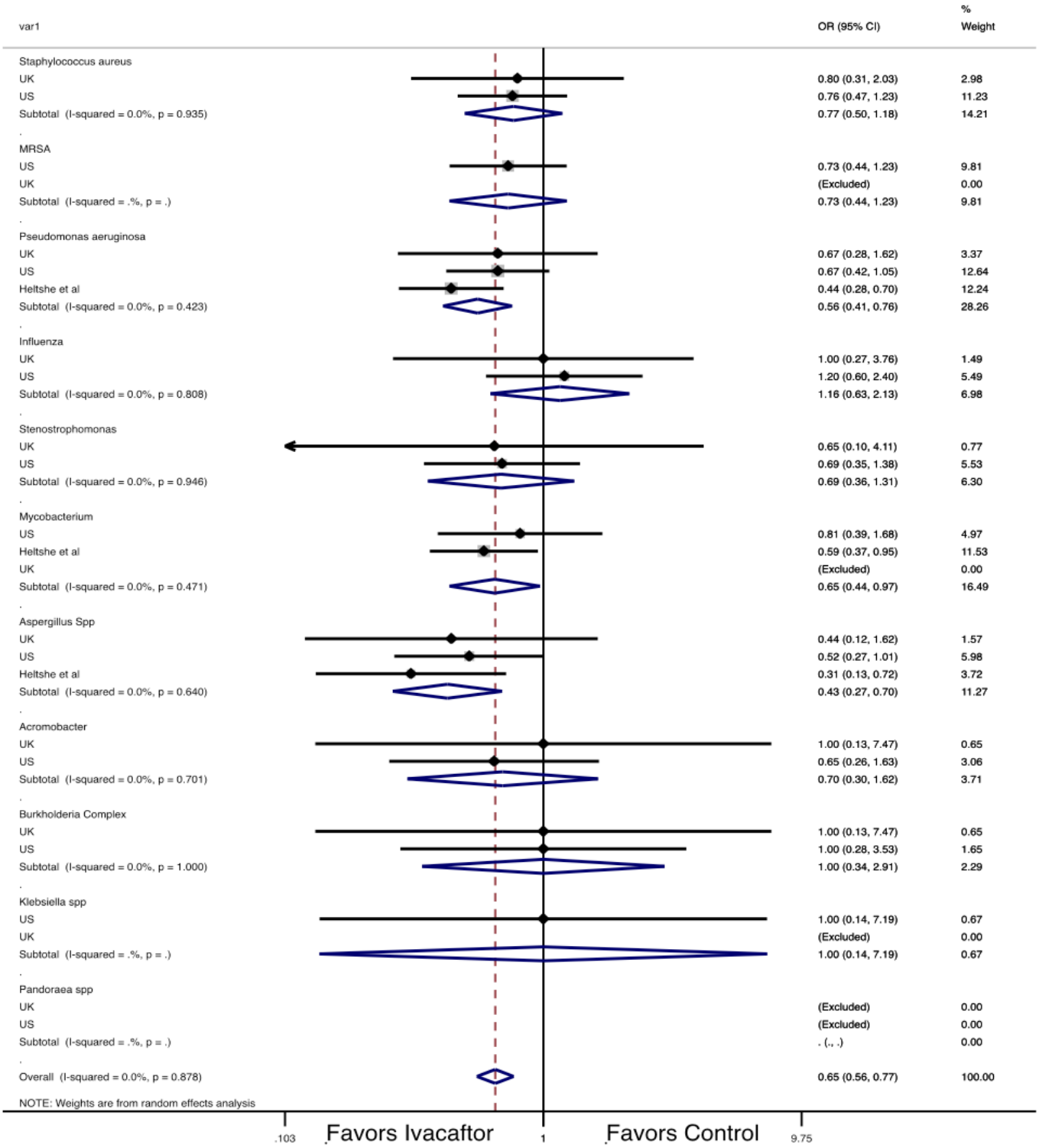
After using the GRADE system (Guyatt et al., 2008) to evaluate studies, seven studies were used for meta-analysis. This includes 21 sets of data from all the studies containing disease characteristics and bacterial infection data (Quality of Life data). The goal here is to use the data collected from these studies and extrapolate it to a 150 patient population comprising non-G551D gating mutation. The data was divided into ten different groups for disease characteristics and eleven groups for bacterial infections.

Forest plot based on diseases characteristics

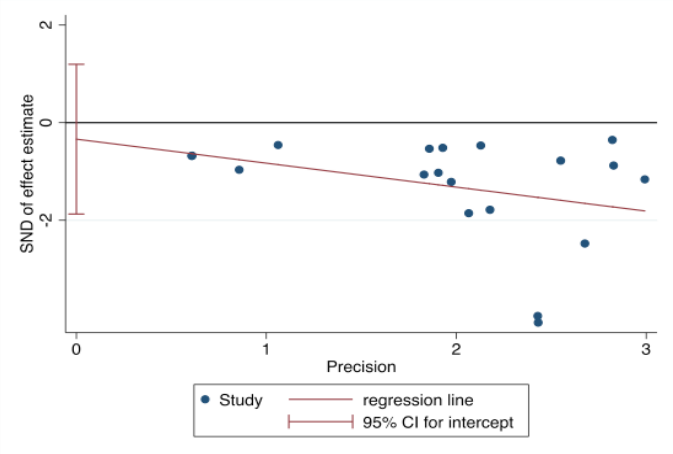
Figure 1

Forest plot for non-G551D Quality-of-Life outcomes comparing Ivacaftor vs. control

The forest plot for Quality-of-Life outcomes comparing Ivacaftor vs. control (Figure 1) favors ivacaftor in the overall summary of all disease characteristics. It shows a significant reduction in hospitalizations (OR 0.42, 95% CI 0.31-0.57), Pulmonary exacerba-



tions (PEX) (OR 0.44, 95% CI 0.32-0.61), CFRD (OR 0.65, 95% CI 0.42-1.00), and depression (OR 0.51, 95% CI 0.27-0.97). The rest of the outcomes were not significantly improved, as shown in the graph (diamonds crossing the unit line). The overall summary measure of complications was also reduced significantly (OR 0.57, 95% CI 0.5-0.66). As desired, these results did not have statistically significant heterogeneity (I^2=6.0%). Hospitalization is a critical criterion when it comes to treatment effect and quality of life improvement. Each disease characteristic shows in favor of using Ivacaftor. These results show that the cystic fibrosis patients with non-G551D gating mutation would have a favorable improvement in quality of life with ivacaftor.



Publication bias for QOL

Figure 2
Publication bias analysis for QOL

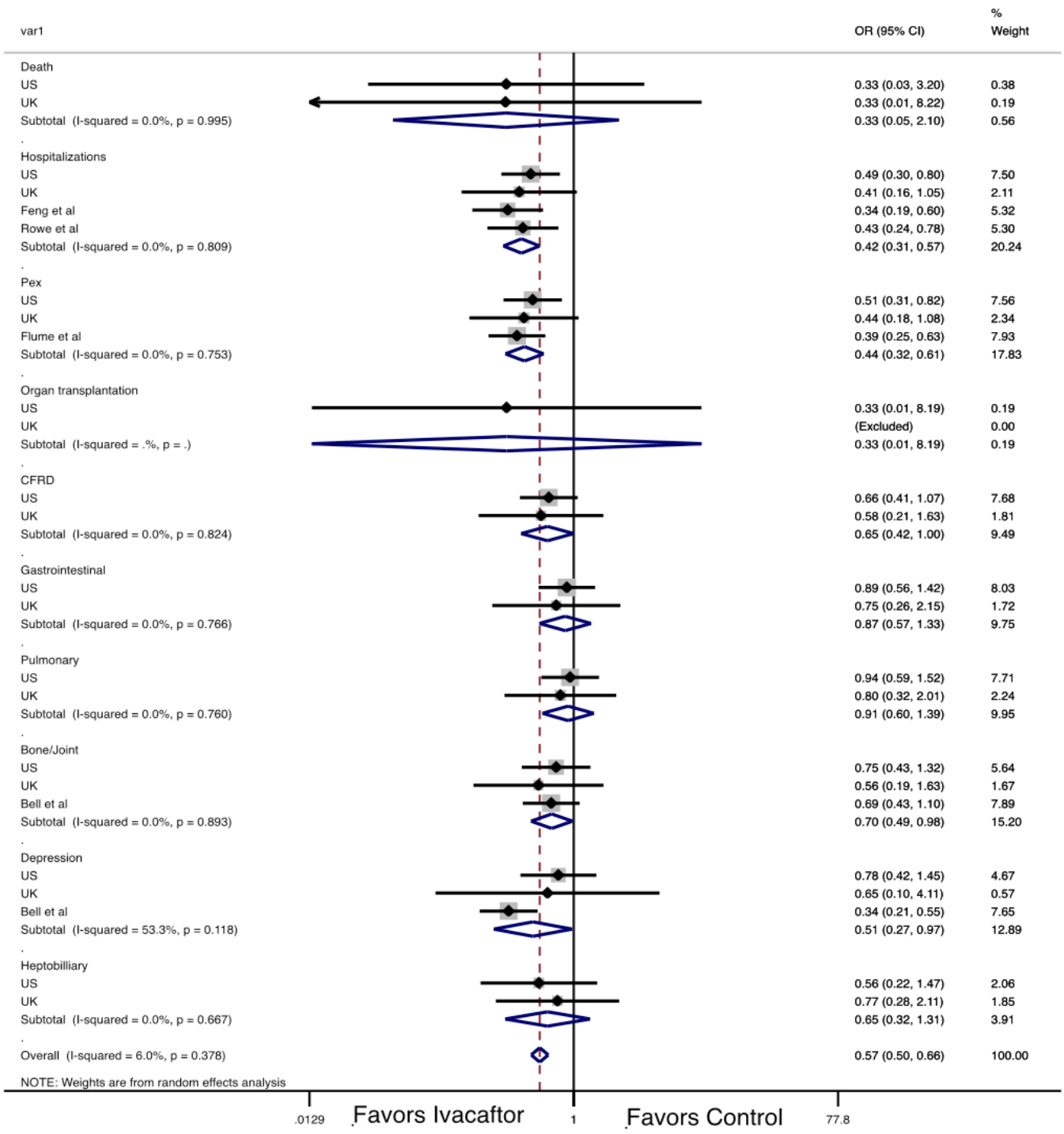
In Egger's plot for publication bias analysis for QOL (Figure 2), each point represents a dataset for QOL outcomes. The regression line follows the direction of the points, and there are no outliers in this graph, which suggests no evidence of publication bias. This was subsequently demonstrated by calculating the bias coefficient (coefficient 0.9, P = 0.65), which was non-significant.

Forest plot based on Bacterial Infections

Figure 3

Forest plot for non-G551D bacterial infections outcomes comparing Ivacaftor vs. control

The forest plot for bacterial infections outcomes comparing Ivacaftor vs. control (Figure 3) shows a significant reduction in infections due to Aspergillus (OR 0.43, 95% CI 0.27-0.70), Mycobacterium (OR 0.65, 95% CI 0.44-0.97), and Pseudomonas aeruginosa (OR 0.56, 95% CI 0.41-0.76). The rest of the outcomes were not significantly improved, as shown in

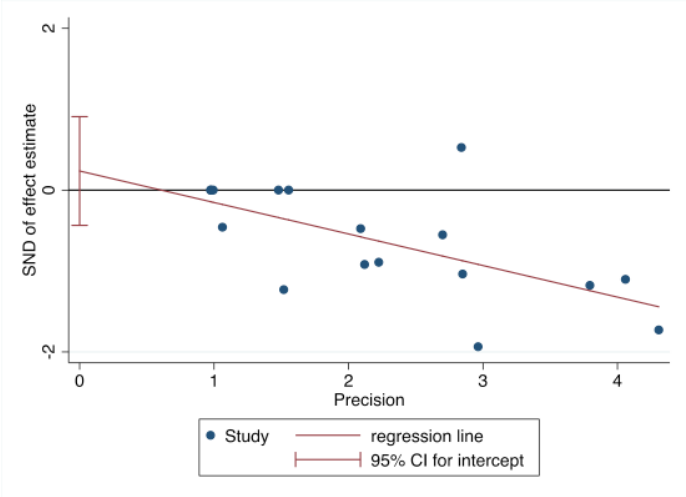


the graph (diamonds crossing the unit line). The overall summary measure of infectious complications was reduced significantly (OR 0.65, 95% CI 0.56-0.77). As desired, these results did not have statistically significant heterogeneity (I^2). Even though the outcomes were not statistically significant, with P value greater than 0.05, but it was clinically meaningful. The majority of bacterial infections outcomes show in favor of using Ivacaftor for cystic fibrosis patients with non-G551D gating mutations.

Publication bias for bacterial infections

Figure 4

Publication bias analysis for bacterial infections.

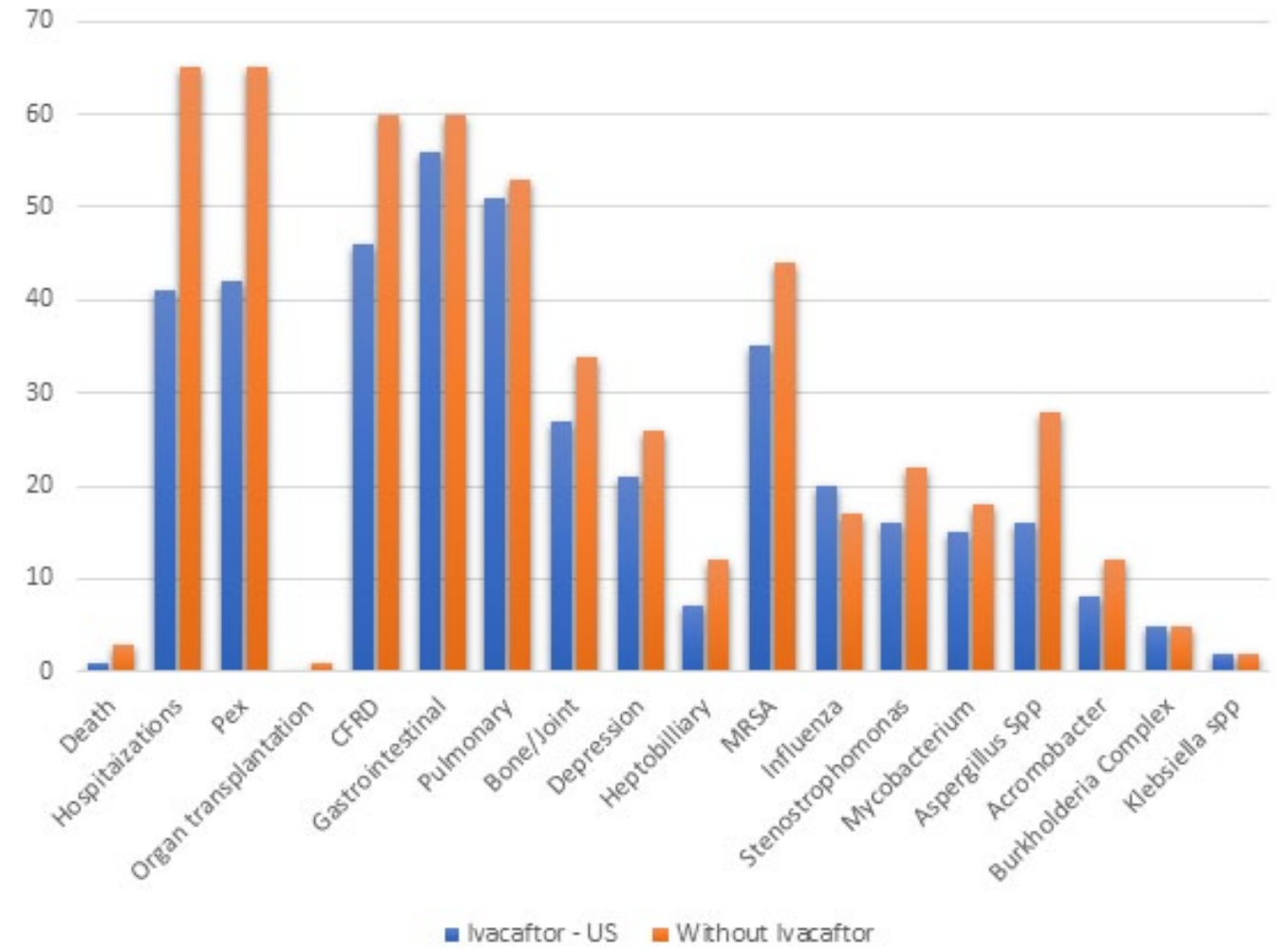


In Egger's plot for publication bias analysis for bacterial infections (Figure 4), each point represents a dataset for each bacterial microorganism. The regression line follows the direction of the points, and there are no outliers in this graph, which suggests no evidence of publication bias. This was subsequently demonstrated by calculating the bias coefficient (coefficient 0.7, P=0.46), which was non-significant.

Summary of Quality of Life (QOL) measurements

Figure 5

Non-G551D disease characteristics and bacterial infections improvement



Ivacaftor is favored in almost all disease characteristics and bacterial infections. Had Ivacaftor been approved for non-G551D cystic fibrosis patients in the year 2012 along with G551D patients based on in vitro study data, the mortality rate would be reduced by two patients, and the hospitalization rate would be reduced by about 50%. Data analysis of lung-related infections, Pex, and Pseudomonas aeruginosa shows substantial improvements with use of ivacaftor. Other important quality of life related characteristics such as cystic fibrosis-related diabetes (CFRD), depression, and bone/joint pain also show substantial improvement with the use of Ivacaftor. All bacterial infections show an improvement with the use of Ivacaftor with the exception of Influenza infection, which is considered non-life threatening.

Discussion

The results from the data analysis clearly indicate that the quality of life of cystic fibrosis patients with non-G551D would have improved on both disease characteristics and bacterial infections with the use of ivacaftor. Ivacaftor's use dramatically improved most of the disease characteristics and bacterial infections, and in turn, quality of life. Some of the other research concurs with the findings of this research. For example, Salvatore et al. show how Ivacaftor helped reduce Pex and other characteristics in severe cystic fibrosis patients with non-G551D gating mutations. The study also showed improvement in sweat chloride and FEV1 data, clearly indicating that Ivacaftor significantly affects cystic fibrosis patients. This study also found that Ivacaftor improved weight and BMI, which can be considered as a quality-of-life improvement. Additionally, as explained by De Boeck et al., the KONNECTION study showed lung function improvement between placebo and Ivacaftor with statistical significance. The serious adverse events, which are considered life-threatening, were reduced by 45% in the group using Ivacaftor.

The initial hypothesis was, "If the cystic fibrosis patients with non-G551D mutations had been given Ivacaftor in 2012, then their quality of life would have improved with the earlier approval." The literature also showed that Ivacaftor was equally effective *in vitro* for all gating mutations. This hypothesis led to our research question. The results show that Ivacaftor is favored in almost all disease characteristics and bacterial infections. Thus, had Ivacaftor been approved for non-G551D cystic fibrosis patients and G551D patients based on in-vitro study data, the patient quality of life would have improved with clinical significance. The clinical trials later conducted affirmed that Ivacaftor works similarly for all gating mutations. The results affirm the initial hypothesis.

There are some limitations to the findings of this research. The research is comparing outcomes based on different mutations. The registry data was compared with and without the use of Ivacaftor rather than with and against placebo. Even though it is a reasonable assumption that all cystic fibrosis patients are under treatment, there is a possibility that the disease characteristics might vary to a larger degree among mutations. Furthermore, previous studies have shown that the genotype and phenotype of different mutations have similar characteristics. In the end, each case must be weighed based on the available data.

Conclusion and Future Directions

Cystic fibrosis is a rare disease without a cure. The patient population is meager. As we have seen from the literature, finding a cure or treating rare illnesses is exceedingly difficult. When a drug shows moderate efficacy and a decent safety profile during an earlier phase of a clinical trial in a rare disease such as cystic fibrosis, earlier approval for similar mutations may be desirable. The later clinical trial results, which took over two years to complete proved that Ivacaftor worked similarly for all gating mutations. As we have seen lately, there is a drive for accelerated approval of drugs for rare diseases based on early data. Accelerated approvals have become more common for treating rare diseases with a confirmatory trial requirement after the drug approval based on satisfactory early data. There have been instances where a drug was approved for a rare disease based on an exceedingly small clinical trial, but later confirmatory trials failed. It is a delicate job of risk versus reward. Drug development should include quality of life improvement as one of the criteria. We have a similar situation where a phase two clinical trial for cystic fibrosis nonsense mutation, G542X, represents 37% of all cystic fibrosis non-sense mutations conducted by Eloxx pharmaceuticals. Currently, there is no treatment for nonsense mutations, of which there are about 73. It would be practically impossible to recruit patients for every one of 73 mutations. Given this is a rare disease, it is hard to find patients to conduct clinical trials. The implications could extend to the drug being approved for all nonsense mutation classes, based on the results and data from *in vitro* studies, where it shows that the drug works for all nonsense mutations (G542X, W1282X, R553X, R1162X, E60X, etc.). The earlier approval would result in improved patient quality of life.

Some of the critical factors for early drug approvals in pediatric rare disease settings are promising early data and a strong parents advocacy group. Since there are no cures for these rare diseases, the approval authorities should evaluate the drugs based on early data and supporting *in vitro* data. The current health care

insurance system does not allow unapproved drugs to be covered by insurance. There are drugs with some efficacy that never made it to the treatment regime because of various factors such as not showing statistically significant results (even though clinically meaningful), safety issues, or incomplete data. The patient advocacy group should be involved with approving authorities to facilitate proper resolution. Letting patients decide to try a drug that may not meet all the approval requirements is another aspect to consider as a future direction.

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Appendix A

PRISMA Flow Chart