Cystic Fibrosis Gene Therapy: A Treatment Worth Considering?

Fiona Wang
ENGL299
University of Washington
Christina Ma, Instructor
November 21, 2022

Abstract

In recent years, gene therapy has emerged as a novel form of treatment for many genetic illnesses, one of the most notable being cystic fibrosis (CF). Gene therapy can be used to deliver a correct, non-mutated copy of the cystic fibrosis transmembrane conductance regulator (CFTR) gene into the body via a virus cell to replace the mutated copy of the CFTR gene in CF patients, which causes the illness. If done correctly, gene therapy can offer a non-invasive, versatile treatment that can cure cystic fibrosis at the source (or in other words, at the mutation). However, the viral vectors used to transport the CFTR gene can cause fatal inflammation and infection, along with the vectors attacking the wrong tissue. These two deadly side effects in conjunction with the hundreds of thousands dollar price tag make CF gene therapy an ineffective form of treatment.

Introduction

Think back to the last time you had a cold. More likely than not, your symptoms consisted of a runny and/or stuffy nose, sore throat, some congestion, and possibly a headache. For the majority of the world's population, the common cold and its symptoms come around once a year. However, for those living with cystic fibrosis (CF), these symptoms don't start and end within a week or season. Patients diagnosed with CF have to deal with amplified versions of these symptoms every day, with common symptoms being persistent cough with phlegm, shortness of breath, and constant nasal drip.

Over 35,000 people are affected by cystic fibrosis (CF) in the United States, and according to (Boyle, 2007), the number of people affected worldwide is close to 100,000. For these 100,000 individuals, their average life expectancy decreases about half, from an average of 70 years to 40 years, generating a spate of interest in cystic fibrosis treatments. Antibiotics has been the frequently turned-to method of treatment for centuries; however, in recent years, gene therapy has emerged as a novel new form of treatment. As Leonard and Heintz (2020) describe in their video, cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator gene, or CFTR gene, where the phenylalanine codon is missing. The idea behind gene therapy is that a normal working CFTR gene can be introduced into an individual's genome, or gene sequence, through vector transport. Most commonly, vector transport is done through viral vectors. These viral vectors are viruses that have been altered to not cause a viral infection, but rather are infused with the correct DNA sequence that will replace the mutated gene. Hence, the newly transformed cells reproduce and generate normal gene products, reducing the symptoms of disease or eliminating disease altogether.

With its non-invasive, versatile application, gene therapy presents a promising avenue of exploration to proactively eliminate CF in those affected. Proponents of this treatment argue that if done correctly, new genes could be delivered via vector transmission, and the vector particles would be cleared from the recipient's body after inserting in the genes, leaving only a positive effect on the patient. But despite its promising outlook, gene therapy is fraught with concerns surrounding the possibilities of unexplored side effects, possibly even worse than those of tested, existing treatments. Cystic fibrosis gene therapy treatment is not an effective form of treatment due to its possibility of attacking wrong target cells, unexplored immune responses, and lack of affordability.

Opposing Gene Therapy

On one hand, plenty of information exists to validate the concerns of the opposition of CF gene therapy. Viral vectors can negatively impact other cells that weren't targeted, opening up potential to cause damage or additional illness or disease. For genetic diseases, the afflicted tissue is the intended target, however, in studies such as the one conducted by Boyd (2013), tissues other than the intended range can be affected. While the majority of these participants in this study showcase a positive outcome of increased forced expiratory volume (FEV), a measure of airway clearance in CF patients, there were a couple notable cases where a patient's FEV declined by 68%. In this study, the writer specified the vectors targeting epithelial cells, which do not contain DNA, and hence are not affected by the genetic DNA mutation that causes CF. This attack of non-target cells caused a weakened inflammatory response for the airway cells, hence leading to a decline in the patient's health. Another case of this occurring is in more rare

forms of cystic fibrosis, such as cystic-fibrosis liver disease, viral vectors could direct themselves to target lung cells, where cystic fibrosis cell mutations usually reside (Staufer, 2020). Both cases are examples of viral vectors incorrectly targeting non-affected cells, causing infections or inflammation in a new tissue, where there wasn't before.

Additional inflammation and infection are not just limited to vectors targeting the wrong tissue. Sometimes, the vectors used to transmit the CFTR gene can cause inflammation itself. In their paper "Toward Cystic Fibrosis Gene Therapy", Wager and Gardner (1997) highlight the dangers of adenoviruses being the most commonly used viral vector in CF gene therapy. Adenoviruses, while being effective transport vectors, are viruses that a human body's immune system considers an intruder, and may initiate an immune response against. Compared to other forms of gene therapy which may use non-viral vectors such as liposomes that will not trigger an immune response, adenoviruses pose a significant concern in initiating inflammation and infection. This again, poses a big concern for CF patients who already have a weakened immune system and could have difficulty fighting the virus.

On top of the health risks gene therapy poses, it can become extremely costly due to the extensive upfront costs that come from designing the viral vectors. Opposed to traditional medications or therapy treatments which have been tested for years, gene therapy performance remains indeterminate and limited to the handful of published clinical trial results. As a result, gene therapy insurance coverage is essentially non-existent, making it exponentially more expensive than traditional medications which are often partially, if not fully covered, by one's medical insurance. A direct example of this would be the drug tobramycin, used to treat lung

infections in CF patients. Drugs such as tobramycin have had the luxury of undergoing decades of experimentation and revision, allowing researchers to figure out ways to lessen both manufacturing and administration costs of the drug. As Chopra (2015) describes, dry powder inhaled forms have been developed as an alternative to an IV drip version of tobramycin, which are much faster and easier to administer, and decrease cost for the patient as it "does not require the care and cost of maintenance of a nebulizer". Instead, projected costs of gene therapy treatments can range up to hundreds of thousands, or even millions, due to their experimental nature and costs for a company to pass all regulatory approvals before the drug can be administered to patients.

Supporting Gene Therapy

On the other hand, there has been considerable advancement in CF gene therapy to build a strong argument in support for this treatment. Gene therapy has a component called vector shedding that allows vector particles to be cleared from the recipient's body through excretion. Being able to shed foreign particles from the body reduces the probability of lingering or prolonged reactions, and reduces the body's ability to develop a resistance to the cells. Bell, De Boeck, and Amaral (2015) describe in their study how the "safety concerns associated with vector shedding is extremely low for replication-deficient viral vectors". With adenoviruses being an example of these replication-deficient, or devoid of genetic information for replication, vectors, CF gene therapy can reap the benefits of this easily shedded vector.

The flexibility in specializing a gene therapy treatment for a patient's needs has also been cited as a positive element of gene therapy. As opposed to standardized drugs that have a specific

purpose and usually are intentional in treating at most one condition/disease, viral vectors can be customized to contain multiple corrected pieces of DNA to treat multiple conditions at once. This can be particularly beneficial for CF patients that have other genetic mutations that each require an extensive treatment process that cannot be overlapped. Rather than being forced to undergo multiple lengthy administrations of treatment which may require periods of waiting in between administrations, customized gene therapy can tackle all the diseases at once and shorten treatment time.

Counter Argument

However, it is important to note that the extent of these gene therapy positives extend to the few clinical trials that have been conducted to test this CF therapy. Clinical trials for this treatment are not only sparse, but often only contain a small sample size of patients. For example, the clinical trial conducted by Alton and Armstrong (2015) contained only 140 subjects, suggesting it is only a Phase II trial that is still obtaining preliminary data on whether the drug works in people who have CF. This is a considerably smaller population than the thousands or millions of people that drug therapy and/or enzyme therapy have been tested on (Chopra, 2015). The novelty of this treatment also implies that trials haven't had the opportunity to explore long-term effects of treatment, both years and decades after it has been administered. This combination of both small testing populations and the novel treatment highlights the possibility of unexplored long-term effects of gene therapy treatment components, such as vector shedding, might have on a patient's health. One of the hypothesized, but not tested, negative side effects include risk of seropositive pregnancies, or pregnancies where the newborn is infected with viral vectors at birth.

Similar counter arguments can be made against the novelty of gene therapy specialization. Despite the supposed benefits of personalizing therapy for a patient, this treatment can quickly become costly with no promise of its efficacy. CF gene therapy itself is a very theoretical treatment which has sparse clinical trial results to support its successfulness, let alone gene therapy to treat multiple conditions at once. Additionally, as Fajac and De Boeck (2017) describe in their paper, patients with CF often need treatment for conditions or illnesses that develop from their weakened immune system from battling CF. Oftentimes, these are non-genetic, or not mutation-induced illnesses that cannot be treated with gene therapy, but are instead treated with antibiotics and drugs such as ivacaftor, which are readily accessible at hospitals and pharmacies.

Conclusion

While both opponents and proponents of CF gene therapy have well-supported arguments for their positions, it's clear that the negatives of gene therapy far outweigh the positives. Gene therapy's method of transmission can lead to unprecedented infections and inflammation, and for the hundreds of thousands to million dollar price tag that patients would have to pay, antibiotic treatments that can be covered by insurance are a better option. In a couple decades, it is possible for gene therapy to emerge as a more profoundly tested form of treatment that is comparable in price to drugs and antibiotics. However, due to their easy accessibility, affordability, and rigorous testing, drug treatments such as ivacaftor and tobramycin remain as the superior form of CF treatment over gene therapy.

References

Alton, E. W., Armstrong, D. K. (2015). Repeated nebulisation of non-viral CFTR gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial. The Lancet Respiratory Medicine, 3(9), 684–691. https://doi.org/10.1016/S2213-2600(15)00245-3

The authors of this study explore an alternate method of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene therapy delivery. As opposed to the more well-known viral gene therapy where plasmid DNA is delivered intravascularly, or through the blood vascular system, the study explores the method of lung delivery of plasmid DNA complexed with a cationic liposome, which are positively charged lipids. They presented the results of 140 randomly assigned patients that either received a placebo treatment or pGM169/GL67A CTFR treatment to treat CF, finding a significant treatment effect in the pGM169/GL67A group at 12 months follow-up. compression.

Though the study notes that further improvement in consistency of response must be made to the current gene therapy formulation, a monthly application of the pGM169/GL67A therapy formulation indicated a stabilization of lung function in the treatment group. This information will be helpful in distinguishing what the most effective method of CTFR gene therapy delivery is, through comparison of how effective the treatment was within a specified period of time as well as what kind of side effects patients that received either method of therapy experienced. Additionally, this clinical trial can be used in conjunction with the other clinical trial source that I evaluated to help develop my support for gene therapy in my research paper in comparison to other therapies.

Bell, S. C., De Boeck, K., & Amaral, M. D. (2015). New pharmacological approaches for cystic fibrosis: Promises, progress, pitfalls. *Pharmacology & Therapeutics (Oxford)*, *145*, 19–34. https://www.sciencedirect.com/science/article/pii/S0163725814001223?via%3Dihub

The authors of this study detail pharmacological approaches to treating cystic fibrosis, providing a pharmacological therapy guideline for the years following diagnosis. For the first years of life after diagnosis, treatment is based on oral dicloxacillin or flucloxacillin to treat S. aureus, the predominant pathogen that is often the first to infect the respiratory tract. When progressive deterioration of respiratory function occurs, the oral antibiotic recommendation changes to ciprofloxacin or ceftazidime. This is meant to treat P. aeruginosa, which causes the most severe chronic pulmonary infection. If pulmonary deterioration continues, it is recommended to switch to amoxicillin-clavulanic acid to prevent antibiotic resistance from developing. In addition to these progressions, the writers emphasize the important of maintaining an optimal nutritional state as well as keeping the airway clear of secretions using mechanical aids such as a positive expiratory pressure mask or high-frequency chest compression.

At the end of the article, it is detailed that oral and/or intravenous therapy has been replaced by inhaled treatments, which allow prolonged treatments with high doses and minimal toxicity. This evidently provides a strong argument for using traditional medication therapy for cystic fibrosis, however, I intend to argue that having to constantly modify antibiotic treatment can be confusing and costly for patients. As opposed to gene therapy that is a more streamlined, one-type process, constantly changing antibiotic treatment during different stages of infection can be demoralizing for patients. Additionally, antibiotics are more likely to induce problems to develop, such as bronchoconstriction, the narrowing of the arteries, which will need to be treated by more medications.

Boyd, A. C., Cheng, S. H., Cunningham, Porteous, D. J. (2013). A randomised, double-blind, placebo-controlled phase IIB clinical trial of repeated application of gene therapy in patients with cystic fibrosis: Table 1. *Thorax*, *68*(11), 1075–1077. https://thorax-bmj-com.offcampus.lib.washington.edu/content/68/11/1075

This article detailed the results of a multi-dose clinical trial of a non-viral, liposome-based formulation of gene therapy for patients with cystic fibrosis. In the clinical trial 130 subjects were randomly assigned to receive the active treatment or placebo; out of each of the active treatment or placebo groups, there were nasal and bronchoscopic subgroups where either their nasal cavity was assessed for prevalence of CFTR expression, or their airways were assessed through bronchoscopies to see airway potential difference. The patients received 12 doses of either the nebulized study drug (gene therapy) or the placebo at intervals of 28 days, and their symptoms were evaluated on day 2 following each dose.

The primary outcome measure of the treatment was the change in percent forced expiratory volume (FEV), with patients receiving the treatment having 80% in exhalation compared to their initial baseline 6%. There was also a secondary outcome of increase in lung clearance index. This source will be helpful in solidifying my argument of the effectiveness of gene therapy, as I can provide concrete, statistical evidence from clinical trials that gene therapy has positive effects. The results of the study can be used in conjunction with the other clinical study that I read and evaluated to formulate a strong argument, as well as compared to alternative methods of CF treatment to measure how FEV may have increased more in one method versus another.

Boyle, M. P. (2007). Adult Cystic Fibrosis. JAMA : the Journal of the American Medical Association, 298(15), 1787–1793. https://jamanetwork.com/journals/jama/fullarticle/209168

This American Medical Association Journal article details a step-by-step explanation of how cystic fibrosis (CF) develops in the body, focusing particularly on the differences of cell membrane channel protein functionality between a healthy human and one diagnosed with CF. It starts by giving a general overview, stating that CF affects cells that produce mucus, sweat, and digestive juices. These secretions, however, in CF patients become abnormally concentrated and sticky, causing them to clog passageways that are vital to human functions, such as breathing. Onn a molecular scale, these concentrated secretions are due to defects in a transmembrane protein called CFTR, that allows passage of Cl- ions across the membrane. Instead of having a regulated rate of Cl- ions being transported, CF patients have a reduced rate of Cl- ions being move, causing reducing the amount of water being pulled from cells by osmosis to maintain proper mucus consistency inside the airways. The lack of water causes the thick mucus and blocking of the airways.

Though this information doesn't provide insight towards the efficacy of CF gene therapy treatment, it does provide me important basis knowledge that furthers my understanding of how CF affects the cells. Since gene therapy is a treatment that specifically targets DNA bases, which are located inside cells, it is important to learn about how the function of cells are changed in CF patients. Additionally, this article helped me deconstruct my understanding of CF in a non-medical jargon filled manner, which I can relay to my audience in the first few paragraphs of my research paper.

Chopra, R., Paul, L., Manickam, R., Aronow, W. S., & Maguire, G. P. (2015). Efficacy and adverse effects of drugs used to treat adult cystic fibrosis. Expert Opinion on Drug Safety, 14(3), 401–411. https://www.tandfonline.com/doi/full/10.1517/14740338.2015.994503

The authors of this journal sought to investigate the efficacy and adverse effects of drugs, such as inhaled antibiotics, anti-inflammatory drugs, mucolytics, and pancreatic enzymes. Hypothesizing that antibiotics and anti-inflammatory drugs provide the most significant effect on cystic fibrosis (CF) patients, they actually concluded that antibiotics and mucolytics had the best short term effect in increasing forced expiratory volume (FEV) and forced vital capacity (FVC). On the other hand, inhaled antibiotics and mucolytics offered a more sustainable, long-term treatment due to their ease of use and reduction of infective organisms, in addition to being more affordable.

These results provided promising results for both short-term and long-term drug treatments that have been available by prescription for years and often don't cause more than mild to moderate intensity side effects. This information will be useful in creating a counterargument towards the more underdeveloped, trial-based gene therapy that is far less accessible and likely much more costly. However, I intend to argue that reliance on antibiotics can offer a gateway towards antibiotic resistance while gene therapy is able to attack the problem at the source, not allowing any sort of rejection or resistance to develop.

Fajac, I., & De Boeck, K. (2017). Modulating the CFTR protein is possible: the potentiator ivacaftor. *Pharmacology & Therapeutics (Oxford)*, *170*, 205–211. https://www.sciencedirect.com/science/article/pii/S0163725816302352?via%3Dihub

This journal publication provides history on the evolution of CFTR treatment, talking about Ivacaftor, the first drug aimed at correcting the DNA correcting the basic defect in cystic fibrosis that was approved for marketing. Ivacaftor's treatment purpose was to enhance chloride transport across cell membranes and increase ciliary beat frequency in airway cells expressing the G551D CFTR mutation. This drug was tested in a placebo-controlled clinical trial, testing both children and adult patients with CF, either administering them Ivacaftor or a placebo over the course of 144 weeks.

The treatment showed evidence of sustained and robust improvement in respiratory function, through a mean increase of 10% in force expiratory volume and reduced sweat chloride concentrations upon the oral administration of Ivacaftor. Clinical improvement was also observed among more patients after the drug was marketed and long-term effects were apparent. This information will be helpful in exploring drug treatments for cystic fibrosis. However, the end of this article does note that ivacaftor is a very high cost treatment (around $294,000 per year) which is significant for a lifelong therapy. This will be helpful in my argument in supporting gene therapy, a one-time treatment, as opposed to oral drugs.

Hollander, F., Ross, N., & Heijerman, H. (2017). The optimal approach to nutrition and cystic fibrosis : latest evidence and recommendations. *Current Opinion in Pulmonary Medicine*, *23*(6), 556–561. https://www.mdpi.com/1422-0067/21/22/8586

The authors of this journal explore the most recent evidence-based and expert-based findings associated with respiratory pulmonary function. They support their emphasis of the need for adequate nutritional intake to improve nutritional status by explaining that increase caloric expenditure is caused by increased work of breathing from loss of pulmonary function due to

cystic fibrosis. Statistically, they recommend that for adolescents 2-18 years old, the target body mass index (BMI) is at or above the 50th percentile for a healthy child. For CF adults of at least 18 years, the target BMI is at or above 22 kg/m^2 for women, and at or above 23 kg/m^2 for men.

The generalized guidelines are not a solidified rule, however, as focus on different micronutrient and macronutrient intake of CF patients vary in different age and disease stages. The article highly recommends CF patients to consult a specialized CF dietitian to help them along their journey. This article does not address gene therapy, but was very enlightening about all the different factors of life that CF patients have to be hypervigilant of during infection. It has changed how I intend to approach my argument, from arguing that gene therapy itself is most effective, to considering a combination of lifestyle changes, such as change in nutritional diet, and gene therapy being the most effective treatment.

Leonard, M., & Heintz, K. (2020). Learn how gene therapy seeks to repair genetic mutations through the introduction of healthy genes. Encyclopedia Britannica.

The producers of this video intended to educate their viewers about how a mutation, the disruption of the number of order of bases in a gene, can lead to genetic diseases such as cystic fibrosis. In particular, they provide a side-by-side comparison of a normal CTFR gene with a mutated CTFR gene, highlighting how the missing phenylanine (TTT pairing) on chromosome 7 is the cause of cystic fibrosis. The video then presents two approaches to gene therapy: 1) a new gene transported through viral material to introduce a normal working gene into an individual's genome, which then replaces the mutated gene, and 2) a new gene is introduced that aids the body in fighting disease, but does not replace the mutation.

Though this video was not very long time-wise, it provided me with a solid and clear understanding on exactly what mutated gene causes cystic fibrosis, as well as the two main approaches towards gene therapy. This information will be useful in helping me investigate the pros and cons of each gene therapy method, and compare their effectiveness against alternate methods of cystic fibrosis treatment. Additionally, this source's unbiased presentation of information can help me develop an initial understanding and opinion about my topic before comparing/contrasting my argument to other sources.

Staufer, K. (2020). Current Treatment Options for Cystic Fibrosis-Related Liver Disease. *International Journal of Molecular Sciences*, *21*(22), 8586–. https://www.mdpi.com/1422-0067/21/22/8586

This journal publication provides insight on a less prevalent form of cystic fibrosis, where CF primarily attacks the liver and other non-respiratory organs as opposed to the lungs and throat. Due to its rarity, cystic fibrosis-related liver disease (CFLD) is harder to treat as there has been less research in drug development for the condition and the understanding of the pathogenesis of CFLD is weak, making it hard to develop efficacious treatments. So far, ursodeoxycholic acid has been the standard treatment for decades, however, its efficacy in CFLD is controversial. Instead, this article highlights the hope that targeted gene therapy brings to provide a more effective treatment for CFLD.

Prior to reading this article, I was completely unaware that CFLD even existed, and has increased my awareness on looking for different forms of CF. It has changed how I think about the topic in terms of the population the disease affects. In particular, I plan to use this article to

my advantage by showing the lack of development of antibiotics or other drugs to treat CFLD, and how gene therapy would be able to provide a more encompassing solution to this disease.

Wagner, M., & Gardner, M. (1997). TOWARD CYSTIC FIBROSIS GENE THERAPY. Annual Review of Medicine, 48(1), 203–216. https://www.annualreviews.org/doi/10.1146/annurev.med.48.1.203

The authors of this journal bring to light how the lethality of and quick progression (often most severe by early adulthood) of cystic fibrosis (CF) has made it a target for gene therapy development. The clinical study that these authors conducted presented results of a variety of vectors, including adenovirus, adeno-associated virus, and liposomes as a variety of vectors designed to correct the genetic mutation in the genome of one affected by cystic fibrosis. They then conclude by saying that further research is needed to refine vector technology.

Though this journal paper was published several decades ago, the promising results extracted from this paper can provide a basis, or resource from earlier years, to illuminate the progression of CF gene therapy. The gene therapy results from this paper can be compared to more recent, modern papers to shape my argument in defending the effectiveness of vector CTFR gene expression through whether vector gene therapy has been further developed or alternate methods have been more heavily pursued instead.