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Lauren G. Culver

Wayne State University, gg2449@wayne.edu

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Cystic fibrosis transmembrane conductance regulator modulation may improve intestinal inflammation in adults with cystic fibrosis

LAUREN G. CULVER, BS, Wayne State University School of Medicine, gg2449@wayne.edu

ABSTRACT A clinical decision report using:

Ooi CY, Syed SA, Rossi L, Garg M, Needham B, Avolio J, Young K, Surette MG, Gonska T. Impact of CFTR modulation with Ivacaftor on Gut Microbiota and Intestinal Inflammation. *Sci Rep*. 2018 Dec 13;8(1):17834. <https://doi.org/10.1038/s41598-018-36364-6>

for a patient with cystic fibrosis experiencing small bowel obstruction.

Keywords: *cystic fibrosis, gastrointestinal, small bowel obstruction, CFTR*

Clinical-Social Context

Mr. David Wallace [pseudonym] is a 27-year-old Caucasian man with a history of cystic fibrosis, nonalcoholic steatohepatitis, pancreatic insufficiency, and diabetes mellitus who presented to the emergency department with nausea and vomiting. Mr. Wallace has experienced similar episodes in the past, which were diagnosed as distal intestinal obstructions. He has undergone several exploratory laparotomies for this issue, revealing functional bowel obstruction as well as extensive adhesions.

On initial evaluation, Mr. Wallace reported bilious vomiting and right-sided abdominal pain that he rated 6/10 in severity. He was unable to keep any food down that day but had a bowel movement and was able to take his medications. Mr. Wallace is on an extensive medication regimen consisting of over 10 medications, including but not limited to pancreatic enzymes, vitamins, insulin, and Trikafta. Trikafta contains a combination of elexacaftor, texacaftor, and ivacaftor, which modulate the cystic fibrosis transmembrane conductance regulator (CFTR). Because it is non-formulary, Mr. Wallace states that “my insurance won’t really cover that medication, so I have to buy my own.” He is currently living at home with a single mother, who works as a nurse, and he does not have an income of his own.

Overnight, Mr. Wallace’s condition deteriorated. The following morning, his abdomen was severely distended. He rated his pain 10/10, and he was actively vomiting bilious emesis. This was accompanied by tachycardia, tachypnea, and diaphoresis. He was taken to the OR, where emergent exploratory laparotomy was performed. A small bowel perforation was found and repaired, and the bowel was decompressed. Following surgery, he reported feeling much better, denying any symptoms except for mild incisional pain.

LAUREN G. CULVER, BS, is a medical student at the Wayne State University School of Medicine.



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Since beginning Trikafta in 2019, Mr. Wallace reports improvement in his respiratory symptoms, however he has undergone 5 abdominal surgeries for obstructive symptoms, begging the question of whether this medication is optimizing his treatment or adding an unnecessary yet significant expense.

Clinical Question

Do CFTR-modulating therapies have a role in preventing gastrointestinal symptoms in adults with cystic fibrosis?

Research Article

Ooi CY, Syed SA, Rossi L, Garg M, Needham B, Avolio J, Young K, Surette MG, Gonska T. Impact of CFTR modulation with Ivacaftor on Gut Microbiota and Intestinal Inflammation. *Sci Rep*. 2018 Dec 13;8(1):17834. <https://doi.org/10.1038/s41598-018-36364-6>¹

Description of Related Literature

Literature search was performed with key word searches in PubMed. Publication date was limited to the past 10 years.

The search for an article began with the terms “cystic fibrosis” and “therapy” or “treatment” and “gastrointestinal”, “intestine”, “gut”, or “bowel”. This search yielded 911 results. When filtered to only clinical trials or randomized controlled trials, 41 results were included. The list of relevant articles was narrowed further with the addition of “adult” to the search terms, which led to 25 results. Adding “CFTR” produced 4 articles, all of which were reviewed.

Final search terms were as follows: ((cystic fibrosis) AND (gastrointestinal, or intestine, or gut, or bowel) AND (adult) AND (therapy, or treatment) AND (CFTR)).

Among the 4 articles, Rosenfield et al. 2018 reported on a clinical trial using ivacaftor in children. It was excluded due to the inclusion of only subjects less than 24 months old.²

Bell et al. 2019 discussed a new CFTR corrector named GLPG2222. While this new therapy was found to be more potent than other CFTR modulators and may serve as an interesting future direction for research, this article focused mainly on the safety and potential adverse effects of GLPG2222. Mention of the gastrointestinal system was limited to the discussion of mild side effects experienced while undergoing GLPG2222 therapy.³

Halilbasic et al. 2020 focused on the link between sphingosine-1-phosphate (S1P) and CFTR activity. It was found that total S1P levels did not differ between controls and cystic fibrosis patients, but unbound plasma S1P levels were lower in patients with CF. This difference was most drastic in those with heterozygous mutations, who also reported the most gastrointestinal symptoms. Though again offering an interesting direction for future therapy, this article does not discuss the role of CFTR modulators on intestinal symptoms. Rather, it offers a different target for monitoring and therapy.⁴

Ultimately, the article chosen was published by Ooi et al. in 2018. This article discusses a clinical trial of ivacaftor, a component of Mr. Wallace’s current medication regimen, and its role in preventing gastrointestinal symptoms.¹ This was the only study that sought to answer a question similar to that in Mr. Wallace’s case. The overall Grade of Recommendation using the SORT criteria for implication of CFTR-modulating therapy for gastrointestinal symptoms in patients with cystic fibrosis is B, based on a paucity of limited-quality, patient-oriented evidence.⁵

Critical Appraisal

This study is a prospective observational study focusing on the effect of ivacaftor, a CFTR-potentiating therapy, on gastrointestinal inflammation and gut microbiome in patients with cystic fibrosis. 16 patients from hospitals in Canada and Australia were included. At initial assessment, stool samples were collected, as well as measurement of FEV1, anthropometrics, and sweat chloride levels. A second stool collection and set of measurements was taken after a median of 6.1 months of CFTR-modulating therapy. DNA



extraction and genomic sequencing was carried out to calculate presence of inflammatory markers, which included fecal calprotectin and M2-pyruvate kinase (M2-PK). Microbial composition was also evaluated using DNA sequencing, as well as classification to operational taxonomic units using the Ribosomal Database Project classifier.

The study used paired stool samples stored at the same temperature and processed together. The researchers also excluded patients who may have altered gut microbiome due to pre-existing gut disease or use of steroids or NSAIDs within 2 weeks of initial assessment and collection. While funding was provided for the DNA extraction, sequencing, and microbial composition by Vertex Pharmaceuticals, the company was not involved in study design, data collection, analysis, or interpretation. One author was a consultant for Vertex Pharmaceuticals, but it was noted to be unrelated to the manuscript. No other conflicts of interest were identified.

This trial found that CFTR-modulating therapy, specifically ivacaftor, resulted in significantly increased FEV1 and patient weight as well as decreased sweat chloride levels. The researchers also found significantly increased Akkermansia after treatment, which is known to be associated with normal gut mucosa. This increase was associated with normal stool M2-PK levels in the study population. Additionally, Enterobacteriaceae was found to be significantly decreased, which was associated with decreased stool calprotectin. These findings indicated improvements in CFTR function, resulting in better lung function, nutritional status, and gut health. This was noted to be the first study of its kind to look at the role of CFTR modulation in intestinal inflammation and microbiome composition.

While the article provides support for ivacaftor, a component of Mr. Wallace's costly medication routine, it is not without limitations. First, the sample size is quite small. Patients represented a wide range of ages, from 5 to 50 years old. As a 27-year-old, Mr. Wallace was within 10 years of only 5 patients, making it more difficult to generalize these findings to his case. Researchers also admitted their lack of complete access to patients' dietary data, which could alter their gut microbiome and confound results. They could have used a control group of cystic fibrosis patients receiving no treatment. Lastly, no patient outcome data was reported. Understanding the consequences of CFTR-modulation on gastrointestinal complaints or need for surgical intervention could demonstrate its utility in a manner more applicable to this case. As defined by the Strength of Recommendations Taxonomy (SORT), this study has Level 2 evidence.⁵

Clinical Application

Life with cystic fibrosis looks different for every patient. In Mr. Wallace's case, it has meant multiple emergent surgeries and countless treatments, with some being more costly than others. It has also meant extensive trial and error, as he and his care team continue to adjust his medication regimen to best complement not only his symptoms, but his lifestyle. Fortunately, Mr. Wallace has strong familial support, with safe housing and access to adequate care. He also enjoys many activities such as walking his dog, playing basketball, and riding his bike, with much to look forward to in his young age. Following shared discussions between medical staff, Mr. Wallace, and his family, the benefit of being able to participate in activities like these with controlled respiratory symptoms outweighed the financial impact of his combination CFTR-modulating therapy, and he elected to continue Trikafta.

The research article validated the use of CFTR-modulating therapy for gastrointestinal inflammation in cystic fibrosis patients. While the study is limited in size and is the first of its kind, this is a reassuring finding for patients like Mr. Wallace who are putting faith into such a costly medication. Though he has experienced multiple small bowel obstructions, there remains uncertainty as to whether these result from adhesions from prior surgeries or inflammation from his primary disease. The action of Trikafta may have prevented additional, more severe episodes on top of the lethal lung complications seen in cystic fibrosis, allowing Mr. Wallace to live his life to the best possible extent.

New Knowledge Related to Clinical Decision Science

This Clinical Decision Report is based on Mr. David Wallace, a 27-year-old man with cystic fibrosis who underwent emergent exploratory laparotomy for small bowel obstruction. Fortunately, Mr. Wallace's outcome was positive. He is doing well and was

satisfied with his care. However, this case highlights an important aspect of medical care that should not go unnoticed: the extreme cost of medications and subsequent social impact.

As mentioned before, Mr. Wallace's medication Trikafta is a combination CFTR-modulator. Annual costs for this drug are estimated at approximately \$312,000 per patient. This is comparable to other CFTR potentiators, which range from \$272,000 to \$312,000 per year.⁶ CFTR-modulating therapies may play a role in reducing gastrointestinal manifestation of cystic fibrosis, an additional benefit to their primary role of reducing respiratory symptoms.

While Mr. Wallace was able to afford the medication, the financial impact on his family cannot be overlooked. Significant financial stress can hinder patients' ability to focus on experiences they find valuable, which can negatively impact their quality of life. Physicians should make note of a patient's goals and how these can be affected by treatment decisions – especially in those with life-shortening conditions. For example, Mr. Wallace may aspire to travel abroad but is abandoning that goal for the ability to achieve better symptom control.

This Clinical Decision Report highlights the need for physicians to practice individualized medicine and consider the expense of therapy for each patient. Physicians can also work to confront the extraordinary cost of medications. This could mean advocating for better financial assistance programs through their institutions. It could also mean lobbying for increased insurance coverage for drugs used to treat chronic conditions, as well as branded drugs that provide documented patient improvement. Physicians should challenge rejections by insurance companies to authorize payment for these medications. Future initiatives could aim to promote more reasonable pharmaceutical pricing, a problem which may require involvement at manufacturing, industry, and government levels.

Overall, this case demonstrates the necessity to deeply understand both the clinical and social impact of chronic health conditions like cystic fibrosis. Considering cystic fibrosis, treatments can delay but not inhibit the progression of lung disease.⁷ It is vital for patients to understand this and be able to weigh the financial and social cost of treatments against that of their disease. Physicians should stay informed on the availability of new therapies and their scope of action. Most importantly, they should maintain open and honest communication with patients to implement a treatment plan that is realistic and aligns with their personal wishes.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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