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Systemic effects of CFTR modulator therapy in cystic fibrosis: implications for organ function and quality of life

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Abstract

Background: Cystic fibrosis (CF) is a chronic autosomal recessive disease caused by CFTR mutations, leading to impaired chloride and bicarbonate transport and the production of thick secretions. This results in progressive damage, mainly in the respiratory and gastrointestinal systems. CFTR modulators have recently transformed CF treatment by targeting the underlying defect.

Aim: To review the pathophysiology and clinical manifestations of CF and evaluate the effects of CFTR modulators on pulmonary and extrapulmonary systems.

Materials and Methods: A narrative literature review was conducted using PubMed and Google Scholar with keywords such as “cystic fibrosis”, “CFTR mutations”, “clinical manifestations”, and “CFTR modulators”.

Results: CFTR modulator therapies, have demonstrated significant clinical benefits. These include improvement in lung function, reduction in pulmonary exacerbations, and enhanced quality of life. Additionally, extrapulmonary effects were observed, such as partial restoration of pancreatic function, reduction of gastrointestinal symptoms and inflammation, improvement in nutritional status, and positive effects on reproductive health.

Conclusions: CFTR modulators represent a major advancement in CF therapy, improving both pulmonary and systemic outcomes. However, limitations such as variable response and limited access remain. Further studies are needed to assess long-term effects.

Keywords: cystic fibrosis; CFTR; CFTR modulators; ivacaftor; elexacaftor; tezacaftor; pulmonary function; pancreatic insufficiency; fertility; tripple therapy.

1. INTRODUCTION

Cystic fibrosis (CF) is a chronic, multisystem genetic disorder inherited in an autosomal recessive manner, caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene located on chromosome 7 [1,3]. The CFTR protein belongs to the ATP-binding cassette (ABC) transporter family and functions as a cAMP-regulated chloride and bicarbonate ion channel expressed at the membrane of epithelial cells in multiple organs, including the respiratory tract, pancreas, and gastrointestinal system [1,2].

Impaired chloride and bicarbonate transport due to dysfunctional CFTR protein, leading to disrupted epithelial ion and fluid homeostasis [2]. Reduced chloride secretion and altered sodium and water transport result in dehydration of the airway surface liquid and the formation of thick, viscous mucus [1,2]. This abnormal mucus impairs mucociliary clearance, promoting chronic bacterial colonization and persistent neutrophil-dominated inflammation, particularly in the lungs [3]. Over time, these processes lead to progressive organ damage, including bronchiectasis, respiratory failure, and dysfunction of the pancreas and gastrointestinal tract [2,3].

There are more than 2,000 known mutations in the CFTR gene [3]. These mutations are grouped based on how they affect CFTR protein [3]. These mutations include missense, nonsense, frameshift, and splicing defects, each affecting CFTR protein synthesis, processing, or function [1].

- **Class I** mutations result in defective protein production, often due to premature stop codons or abnormal mRNA splicing [1].
- **Class II** mutations, including the most common F508del variant, cause protein misfolding and degradation before reaching the cell surface [1,3].
- **Class III** mutations are characterized by defective channel regulation (gating defects), where CFTR reaches the membrane but fails to function properly [1,2].
- In **class IV** mutations, the protein is present at the cell surface but exhibits reduced ion conductance [1,2].
- **Class V** mutations lead to reduced synthesis of functional CFTR protein [1,2].
- **Class VI** mutations are associated with decreased stability and accelerated turnover of CFTR at the cell membrane [1,2].

Mutations in classes I–III are generally associated with more severe disease phenotypes, whereas classes IV–VI tend to result in milder clinical manifestations [2].

Understanding the molecular basis of CFTR dysfunction and the classification of CFTR mutations is essential for the development of targeted therapies. In particular, CFTR modulators have emerged as a cornerstone of precision medicine in cystic fibrosis, offering mutationspecific treatment approaches that directly address the underlying protein defects.

2. RESEARCH MATERIALS AND METHODS

This study is based on a comprehensive review of the current scientific literature concerning cystic fibrosis (CF), with a particular focus on the molecular mechanisms of CFTR dysfunction and the clinical effects of CFTR modulator therapies.

A literature search was conducted using electronic databases, including PubMed and Google Scholar. The following keywords and their combinations were used: “cystic fibrosis”, “CFTR mutations”, “CFTR mutation classification”, “CFTR protein function”, “clinical manifestations”, “CFTR modulators”, “ivacaftor”, “tezacaftor”, “elexacaftor”, “lumacaftor”, “triple therapy”, “pancreatic insufficiency”, “pulmonary manifestations”, “gastrointestinal symptoms”, and “fertility”.

The search included articles published primarily in the last 5–10 years to ensure up-to-date information, although older, widely cited studies were also included when necessary to provide essential background knowledge. Articles were selected based on their relevance to the topic, scientific credibility, and contribution to understanding the pathophysiology of CF and the clinical impact of CFTR modulator therapies. Studies focusing on both pulmonary and extrapulmonary manifestations of cystic fibrosis were included to provide a comprehensive, multisystem perspective. The collected data were analyzed and synthesized in a narrative manner to present an integrated overview of current knowledge regarding cystic fibrosis and advances in targeted therapy.

3. RESEARCH RESULTS

3.1. CLINICAL PRESENTATION

Cystic fibrosis presents with a variety of symptoms that can range from mild to severe and often change over time. The course of the disease is progressive, with some issues appearing early in life and others developing later. This section will summarize the main clinical features of CF.

Pulmonary Manifestations

Cystic fibrosis is characterized by excessive thickening of mucus in the airways, leading to obstruction and impaired clearance [4]. This results in frequent chronic infections, which manifest as persistent productive cough and dyspnea [1,4]. Radiographic imaging and spirometry typically show hyperinflation and obstructive changes [1]. Chronic colonization of the airways by bacteria such as Staphylococcus aureus, Pseudomonas aeruginosa, Burkholderia cepacia, and fungi including Aspergillus fumigatus further sustains inflammation and damages the bronchi [1,3]. P. aeruginosa colonization often begins in early childhood and becomes lifelong; bacteria adapt and shift into a biofilm lifestyle [6]. In fact, biofilms are the dominant mode of P. aeruginosa growth in CF lungs, providing enhanced antibiotic resistance and protection from the immune response, which enables chronic infection persistence [6].

Recurrent infections and inflammation lead to structural destruction of the bronchi, resulting in irreversible bronchiectasis [1,4]. This condition perpetuates airflow obstruction and contributes to progressive loss of lung function [1,4]. Advanced pulmonary disease in patients with CF is the main cause of mortality, accounting for approximately 60% of deaths [3]. In advanced CF, secondary pulmonary hypertension is often seen, primarily due to chronic hypoxemia and pulmonary vascular remodeling [5]. One study found pulmonary hypertension in 41% of end-stage CF patients [5]. When FEV falls below ~50% of predicted values, lung transplantation is considered [3].

Pulmonary exacerbations are characterized by an acute increase in respiratory symptoms, including worsened cough, increased sputum production, and worsening dyspnea, along with declines in lung function [1,3]. These episodes are often accompanied by systemic symptoms such as loss of appetite, weight loss, and fatigue. Persistent or recurrent exacerbations cumulatively accelerate the decline in lung function.

Sinonasal manifestations

In patients with cystic fibrosis, chronic sinusitis almost always develops in the upper airways due to the accumulation of thick mucus [7]. Typical symptoms include persistent purulent nasal discharge, nasal congestion, and recurrent headaches, often accompanied by hyposmia [8]. The inflammatory process leads to swelling of the sinus mucosa, resulting in the formation of nasal polyps and mucous cysts [8]. These symptoms tend to worsen with age and significantly reduce patients' quality of life [8]. Consequently, many patients require otolaryngological interventions, such as sinus irrigations or endoscopic surgery, due to persistent sinus-related symptoms [7,8].

Hepatobiliary manifestations

Cystic fibrosis (CF) can cause a range of hepatobiliary complications including cholestatic liver injury, focal biliary cirrhosis, gallstones (cholelithiasis), portal hypertension, and liver failure [3,9]. Pathophysiologically, CFTR dysfunction in biliary epithelial cells causes thick, inspissated bile and biliary stasis, leading to focal fibrosis and "biliary cirrhosis" [1,3]. Some of the patients with CF may later develop periportal fibrosis progressing to true cirrhosis with portal hypertension and variceal bleeding [1]. Patients are often asymptomatic until advanced disease; late findings include hepatomegaly or splenomegaly, cholestatic jaundice, vitamin K– deficiency coagulopathy, and bleeding from esophageal or gastric varices [1,3]. Laboratory tests typically show a cholestatic pattern (high alkaline phosphatase, GGT, bilirubin), whereas transaminases may be normal or only mildly elevated [1]. Abdominal ultrasound often reveals steatosis or a heterogeneous, nodular liver and signs of portal hypertension such as ascites and splenomegaly [9]. Extrahepatic biliary disease (e.g. gallbladder stones or strictures) may occur, and large-duct involvement can cause acute cholangitis with right-upper-quadrant pain, fever and jaundice [9]. The natural course of the disease is usually slow: many patients remain clinically stable for years; however, gradual progression and progressive liver failure may sometimes necessitate transplantation [9].

Pancreatic Manifestations

Pancreatic exocrine insufficiency (EPI) is the most common pancreatic complication of CF. Approximately 85% of CF patients have EPI [1,3]. The insufficiency causes malabsorption of fat, protein and carbohydrates: patients present with chronic steatorrhea (frequent, bulky, foulsmelling stools) and poor weight gain [1,3]. Malnutrition and failure to thrive are direct consequences of fat malabsorption [1,3]. EPI also leads to fat-soluble vitamin deficiencies: vitamin A deficiency causes night blindness and xerosis, vitamin D deficiency leads to rickets or osteopenia, vitamin E deficiency can cause neuropathy or myopathy, and vitamin K deficiency produces coagulopathy [13]. CFTR dysfunction eventually impairs the endocrine pancreas. Thick inspissated secretions and ductal obstruction lead to progressive pancreatic damage [3]. As a result, insulin-secreting β-cell mass decreases and Cystic Fibrosis Related Diabetes (CFRD) develops. CFRD typically presents after age 10, affecting about 20% of adolescents and ~50% of adults with CF [12]. Pancreatitis in CF usually occurs only in those with remaining pancreatic function [12]. In pancreatic-sufficient CF patients (usually with milder mutations), chronic ductal obstruction and inflammation can trigger acute pancreatitis [12].

Gastrointestinal Manifestations

CFTR dysfunction in the gut leads to thick, sticky secretions throughout the intestines [3,14]. Meconium ileus (neonatal intestinal obstruction) occurs in about 10–20% of infants with CF [14]. It presents within the first days of life with abdominal distension, bilious vomiting and failure to pass meconium [14]. Distal Intestinal Obstruction Syndrome (DIOS) affects older children and adults (10–22% prevalence). DIOS is characterized by partial or complete blockage of the terminal ileum due to sticky stool and mucus, causing sudden periumbilical or right-lower-quadrant abdominal pain, marked distension, nausea/vomiting and a history of reduced stooling [3,14]. Risk factors include dehydration, pancreatic insufficiency, and prior meconium ileus [3,14]. Chronic constipation (fecal impaction in the colon) affects over half of CF patients, presenting with gradually progressive abdominal pain/distension,

hard stools and infrequent bowel movements [14]. Other intestinal issues include rectal prolapse due to chronic cough [14]. Patients with CF have higher risk of intussusception [14].

Patients with CF are at risk for gastroduodenal inflammation or ulcer disease so dyspeptic symptoms (epigastric discomfort, nausea) should raise suspicion of infection with H. pylori or ulcers [14]. Gastroparesis (delayed gastric emptying) is reported more often in older patients with CF [14]. GERD is very common in CF, especially in children [14]. It is driven by factors like chronic cough, negative intrathoracic pressure, and weak lower esophageal sphincter [14]. CF-related GERD often worsens lung disease by aspirating acid or bacteria [14]. Eosinophilic esophagitis (EoE) – marked by allergic inflammation of the esophagus – is also seen more often in CF [14].

Reproductive Manifestations

Cystic Fibrosis reduces the chances of conception [15]. Most women with CF have anatomically normal reproductive organs; however, abnormal CFTR function leads to the production of thick, viscous cervical mucus, which impairs sperm penetration [15]. Most women also have an altered pH of cervical secretions, which reduces sperm viability [15]. Delayed puberty and malnutrition, typical for CF, additionally reduce the chances of conception [15]. Studies suggest that pregnancies in women with CF generally result in live births, although they are associated with certain increased risks [15]. One large study reported a higher frequency of congenital anomalies in children born to mothers with CF (14.3% vs. 6.4% in the general population) [15]. Premature birth and low birth weight are primarily observed in patients with severe respiratory insufficiency [15]. Women with CF are more prone to recurrent vaginal infections, particularly with Candida and may experience stress urinary incontinence [16].

Men with cystic fibrosis also experience significant reproductive complications. The vast majority (over 95–98%) suffer from male infertility, mainly due to congenital bilateral absence of the vas deferens (CBAVD) [17,19]. Despite this, most patients have preserved spermatogenesis [18]. Approximately 25–45% of men with CF develop hypogonadism (low testosterone levels), caused by chronic inflammation and recurrent infections [17]. Secondary sexual dysfunctions are also reported, such as reduced libido or erectile dysfunction, influenced by hypoxia [18]. A characteristic feature is also decreased semen volume, resulting from the absence or degeneration of the vas deferens and seminal vesicles [17,18].

3.2. CFTR MODULATOR THERAPY

CFTR modulators are small molecules designed to correct the underlying protein defect in cystic fibrosis (CF). They are grouped into classes [22,23]:

- ### Potentiators

  These drugs help the CFTR protein work better. Potentiators help the channel open more often so important substances (like salt and water) can move in and out of cells more easily [20,21].

- ### Correctors

  Sometimes the CFTR protein is made incorrectly and never reaches the cell surface where it’s needed. Correctors act like quality-control helpers—they help the protein fold into the right shape so it can travel to the cell surface and do its job [20,21].

• **Amplifiers**

These drugs increase the production of the CFTR protein [23].

• Stabilizers

Stabilizers help keep the protein on the cell surface for longer, so it can continue working instead of being quickly removed [23].

• Read-through agents

Some genetic mutations create a "stop signal" too early, so the CFTR protein is cut short and doesn't work. Read-through agents help the cell ignore this early stop signal, allowing it to produce a full-length, more functional protein [22,23].

Four modulators are clinically approved: ivacaftor (a potentiator) and combinations of ivacaftor with lumacaftor, tezacaftor, or elexacaftor (correctors) [20,22]. Monotherapy involves the use of a single drug—ivacaftor (a CFTR potentiator)—in patients with gating mutations, in which the Cl^- channel opens less frequently [30]. Dual therapy (corrector + potentiator) typically includes combinations such as lumacaftor + ivacaftor or tezacaftor + ivacaftor [30]. It is indicated in patients with specific mutation (F508del) or when monotherapy has proven insufficient [30]. CFTR modulators generally have a favorable safety profile, and decisions regarding therapy escalation are primarily based on genotype and clinical response [30].

Triple therapy (elexacaftor/tezacaftor/ivacaftor) is a highly effective modulator therapy (HEMT) [21]. In trials, ELX/TEZ/IVA produced rapid, large FEV_1 improvements (mean ~+10%), dramatically reduced exacerbations, and marked weight gain [21]. In real-world use ELX/TEZ/IVA are now approved for ~85–90% of CF patients age ≥6 [21]. Importantly, modulators do not work for all mutations – for example, patients with Class I mutations need the read-through drugs, which are under study to enable some CFTR function in these patients [22,23].

Both pulmonary and extrapulmonary benefits include improvements in organ function and a reduction of some of the symptoms described above, which together contribute to enhanced quality of life; these effects will be discussed in more detail in the following sections of this work.

3.3. CFTR MODULATOR THERAPY – EFFECTS AND BENEFITS

Impact on Pulmonary Function

CFTR modulator therapies (potentiators and correctors such as ivacaftor, lumacaftor, tezacaftor, elexacaftor) improve respiratory outcomes in people with cystic fibrosis. Across multiple studies, modulators consistently raise lung function (FEV_1) and percent-predicted

FEV_1 ($ppFEV_1$) [2,24]. For example, elexacaftor–tezacaftor–ivacaftor (ETI) raised $ppFEV_1$ by ~15 percentage points on average in one-year studies [2,24]. CFTR modulators dramatically cut exacerbation frequency [24]. Studies report 80–97% fewer exacerbations after one year of ETI [24]. Studies report

that modulators improve airway surface liquid hydration and change pH, which leads to enhanced ciliary beating and mucus transport [25]. In practice, this leads to thinner, more easily cleared secretions. For example, one study showed reduction of mucus plugging and airway wall thickening within months of ETI [24]. Improved mucus clearance generally reduces cough and sputum. For example, one study summarized that sputum output was markedly lower in most patients after prolonged ETI use [2]. Clinical studies show reduced inflammatory biomarkers (e.g. IL-6, CRP, TNF) after therapy [2]. A key effect of CFTR therapy is reduced airway pathogen load. Modulators do not instantly cure chronic infections, but they make the airway less hospitable to bacteria. In one cohort, nearly half of previously culture-positive samples became pathogen-negative after one year of ETI [24]. In one study of ivacaftor, 29% of patients initially positive for *Pseudomonas aeruginosa* became culture-negative after one year [25]. Patients also report improved exercise tolerance and respiratory quality-of-life on modulators [24].

Impact on Sinonasal Manifestations

CFTR modulator therapy leads to an overall improvement in symptoms of chronic rhinosinusitis as well as imaging and endoscopic findings. Imaging studies (CT and MRI) show a significant reduction in inflammatory changes, particularly in the maxillary and ethmoid sinuses. A decrease in mucopyoceles, mucosal edema, and the prevalence of nasal polyps has also been observed. However, its impact on olfaction is limited [8].

Impact on Hepatibiliary Function

The direct impact of CFTR modulators on liver-related symptoms remains unclear. There is no evidence demonstrating a halt in the progression of fibrosis, cirrhosis, or beneficial changes in ultrasound findings [29]. In clinical studies involving lumacaftor/ivacaftor, treatment discontinuation occurred in some cases due to significant abnormalities in liver function tests [24]. In studies on ETI, mild and transient elevations in liver enzymes were most commonly observed after initiating CFTR modulator therapy [24]. In one large study involving 255 patients, ETI treatment led to a significant increase in AST, ALT, and bilirubin after 3 months, which persisted up to 12 months (although the values remained within normal ranges) [24]. Monitoring of liver parameters is therefore required. Experts recommend regular assessment of liver enzymes during therapy and dose adjustments, especially after treatment initiation [24,29]. A case has been described in which a marked elevation in ALT resolved after reducing the ETI dose [24]. The effect of CFTR modulation on the biliary tract in cystic fibrosis is poorly understood and is mainly based on individual case reports. A series of adult cases has been reported in which acute biliary colic occurred within days to a week after starting ETI therapy, and some patients were diagnosed with acute or chronic cholecystitis with gallstones. The authors suggest that the sudden restoration of CFTR function in the biliary tract may have revealed previously subclinical gallbladder stones [24].

Impact on Pancreatic Inufficiency

CFTR modulators have demonstrable effects on cystic fibrosis (CF) pancreatic pathology. A systematic scoping review found that CFTR modulators reduce Acute Pancreatitis (AP) hospitalizations by ~85% [11]. The effect was strongest in pancreatic sufficiency patients [11]. This likely reflects decreased

ductal obstruction and enzyme activation on treatment [11]. 54 of 253 pancreatic insufficiency patients (21.3%) converted to pancreatic sufficiency during CFTR modulator therapy [11]. About half of the patients with severe insufficiency and fecal elastase (FE-1) levels below the lower limit of normal (<200 µg/g) achieved normal FE-1 levels [11]. These findings suggest partial recovery of enzyme output in some patients. However, results vary: in a real-life ETI study, mean FE-1 did not increase after 6 months, indicating that established insufficiency may be irreversible in many [24]. CFTR therapy lowered markers of pancreatic inflammation [11]. Raports suggest that modulators may improve glucose metabolism: small studies of ETI have shown better glucose tolerance and insulin secretion in CF patients [24]. For example, adolescents on ETI showed significant improvement in OGTT results [24]. Insulin secretion (C-peptide) tended to rise on treatment [24]. Overall, data from mechanistic models and clinical series indicate that CFTR modulators can restore ductal physiology and ameliorate pancreatic inflammation in CF, especially when pancreatic damage is incomplete [10,11].

Impact on Gastrointestinal System

CFTR modulators, especially the triple therapy elexacaftor/tezacaftor/ivacaftor (ETI), significantly improve gastrointestinal function and reduce intestinal inflammation in individuals with cystic fibrosis [26]. Regarding intestinal symptoms, studies show that CFTR modulator therapy may alleviate abdominal pain and bloating in some patients. Mainz et al. reported a reduction in abdominal pain intensity by approximately 20% and bloating by about 12% after 24 weeks of ETI [27]. Studies show that gastrointestinal adverse effects may occur with CFTR modulator therapy. The most common gastrointestinal side effects include mild abdominal discomfort, nausea, and changes in bowel habits (diarrhea or constipation) [26,27]. In most cases, these symptoms can be managed by dose adjustment or symptomatic treatment. CFTR modulators generally have a beneficial effect on symptoms of gastroesophageal reflux and upper gastrointestinal motility [24]. After initiating ETI therapy, significant improvement in gastroesophageal reflux symptoms, as well as laryngopharyngeal reflux, has been observed [24]. It is believed that improved lung function and reduced intra-abdominal pressure (associated with coughing) indirectly decrease reflux [24]. At the same time, modulators may directly influence gastroduodenal pH, improving esophageal motility and accelerating gastric emptying [24]. A reduction in the frequency of DIOS (distal intestinal obstruction syndrome) has also been reported [27]. Intestinal inflammation is markedly reduced following treatment with CFTR modulators. Clinical studies have confirmed that fecal calprotectin levels decrease significantly with both dual therapies (lumacaftor/ivacaftor or tezacaftor/ivacaftor) and triple therapy (ETI) [28]. These effects are attributed to improved hydration of the intestinal mucosa and reduced activation of the intestinal immune system, which also correlates with changes in microbiota composition. Modulators help restore a relative bacterial balance, with an increased proportion of beneficial strains [26]. CFTR modulator therapy also leads to significant improvements in nutritional status. In both children and adults treated with ETI, notable increases in body weight and BMI have been observed [26]. The mechanisms include enhanced nutrient absorption (due to higher intestinal pH and reduced inflammation) and decreased energy expenditure (fewer pulmonary exacerbations) [26]. Due to dynamic changes in body composition following the initiation of ETI (increases in both fat and lean mass), careful monitoring and individualized dietary adjustments are necessary. Modulator therapy typically also improves the absorption of fatsoluble vitamins—after one year of ETI, serum levels of vitamins A, D, and E increase significantly, and isolated cases of mild hypervitaminosis A have been reported in children [24,26].

Impact on Reproductive Function

In women with CF, the main barrier to fertility is thick, dehydrated cervical mucus with low pH, which impairs sperm penetration [15]. Clinical reports indicate that CFTR modulators improve the consistency and hydration of cervical mucus, enabling conception [15]. Better hydration of the mucus facilitates sperm migration through the cervix [15,18]. In one study, 7 out of 12 previously infertile patients became pregnant after starting treatment with ivacaftor [15]. Improvements in nutritional status and overall health resulting from the therapy may also indirectly increase female fertility [15]. In animal models, CFTR modulators administered at therapeutic doses did not cause significant developmental defects, and cases of pregnancies exposed to CFTR drugs have not shown an increased rate of congenital malformations or miscarriages [15].

CFTR modulators improve ion transport in the epithelium of the male reproductive tract, leading to increased fluid secretion in the seminiferous tubules, epididymal duct, and accessory glands [18]. As a result, semen volume and quality improve (better hydration and reduced sperm damage) [18]. However, CFTR modulators do not restore the anatomical patency of the vas deferens [18]. Since infertility in most men with CF is mechanical in nature, while spermatogenesis is preserved, achieving pregnancy is possible through assisted reproductive technologies (ART) [18,19]. By improving semen quality, CFTR modulators may indirectly increase the chances of conception. The primary method of achieving pregnancy remains assisted reproduction (ICSI with sperm retrieval) [18,19]. In one study, pregnancy was achieved in the partners of 40 out of 42 men using ART, with 35 of these 40 patients continuing CFTR modulator therapy at the time of sperm retrieval [19]. The same study did not show an increased rate of first-trimester miscarriages, and no developmental abnormalities were reported in newborns [19]. None of the newborns had cystic fibrosis (they inherited only one mutated allele), and no concerning delivery complications related to paternal exposure to CFTR modulators were reported [19]. These findings suggest that sperm exposure to CFTR modulators at the time of fertilization does not increase the risk of genetic defects [19].

4. DISCUSSION

The results of the conducted studies confirm that cystic fibrosis (CF) is a multisystem disease in which mutations in the CFTR gene lead to impaired transport of chloride and bicarbonate ions, resulting in thickened secretions in the respiratory, digestive, and reproductive systems, as well as chronic inflammation [1], [2].

CFTR modulator therapy has significantly changed the clinical picture of CF. The summary of the conducted analyses indicates a substantial improvement in respiratory parameters in patients treated with CFTR modulators, including an increase in forced expiratory volume in one second (FEV1) and a significant reduction in the frequency of disease exacerbations [25]. The increase in FEV1 and improvement in exercise capacity may be attributed to the effective restoration of chloride channel function, as confirmed by numerous clinical reports [25]. The significant reduction in exacerbations suggests a decrease in chronic inflammation in the airways, likely due to the stabilization of ion transport and its impact on inflammatory processes [25]. Triple therapy with elexacaftor–tezacaftor–ivacaftor (ETI) has also demonstrated clear extrapulmonary benefits: a reduction in gastrointestinal symptoms and improved exocrine pancreatic function in patients requiring enzyme supplementation were observed

[10,24]. In our analysis, approximately 21% of patients with pancreatic insufficiency regained partial exocrine function, indicating that some pathological changes may be reversible [10].

A major strength of this study is its comprehensive approach: we used a wide range of data— from clinical studies to in vitro models—allowing for a multidimensional evaluation of therapeutic efficacy [25]. Nevertheless, several limitations exist. CFTR modulator therapies are genetically targeted and primarily apply to patients with the most common F508del mutation, which limits their universality [2,24]. Moreover, access to triple therapy (ETI) remains limited; it is estimated that fewer than 15% of eligible patients worldwide receive it due to treatment costs and reimbursement barriers [24].

It should also be noted that CFTR modulation does not eliminate all aspects of the disease— ETI does not fully restore normal organ physiology nor reverse existing fibrotic changes. Additionally, all cited studies are short-term or observational in nature, highlighting the need for long-term evaluation of both safety and durability of therapeutic effects [24].

Future research should focus on treating patients with rare CFTR gene variants and on developing mutation-independent strategies (e.g., gene therapies) to extend treatment to this group. Modern preclinical models, such as organoids or patient-derived cell cultures, may support the personalization of therapy by predicting individual responses to treatment [24].

5. CONCLUSIONS

The collected evidence underscores that the clinical impact of CFTR modulation is systemic rather than organ-specific. Improvements observed across multiple physiological domains indicate that restoring ion transport has far-reaching biological consequences, influencing epithelial homeostasis, inflammatory pathways, and tissue function. This reinforces the concept that early and sustained therapeutic intervention may alter the natural trajectory of the disease rather than merely slow its progression.

At the same time, the heterogeneity of treatment response emphasizes the need for individualized therapeutic strategies. Variability in genetic background, disease stage, and organ involvement suggests that optimal management of cystic fibrosis will require integration of genotype-driven therapy with patient-specific clinical factors. In this context, precision medicine approaches—supported by emerging technologies such as organoid testing—may play a key role in refining treatment selection and predicting outcomes.

Importantly, the evolving therapeutic landscape raises new clinical and ethical considerations. As survival improves, cystic fibrosis is transitioning into a chronic condition of adulthood, bringing increased attention to long-term complications, quality of life, reproductive health, and healthcare accessibility. Ensuring equitable access to highly effective therapies remains a critical challenge that will influence global disease outcomes.

In conclusion, while CFTR modulators represent a transformative advancement, they also mark the beginning of a new phase in cystic fibrosis research and care. Continued innovation, broader accessibility, and deeper understanding of long-term effects will be essential to fully realize the potential of these therapies and to move closer toward comprehensive, causative treatment for all patients with cystic fibrosis.

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