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Short Communication

Cystic Fibrosis: Improving quality of life

Sunil Chaudhry[1,*]

[1] *Honorary Médical Director, Bioclinitech Technologies Pvt Ltd, Mumbai, India & GPATtutor.com*

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ABSTRACT

Cystic Fibrosis (CF) or Mucoviscidosis is an inherited condition. In cystic fibrosis transmembrane conductance regulator (CFTR) protein does not functions properly i.e regulation of fluids and salts outside the cells. Cystic fibrosis affects exocrine glands eg., the mucus-secreting and sweat glands in the respiratory and digestive systems. The frequency of common mutation F508del (deletion of phenylalanine residue at position 508) in children is between 19% and 34%. The estimate frequency of CF as 1:10,000 to 1:40,000 in children. There is no cure for cystic fibrosis, but treatment can reduce symptoms and complications to improve quality of life. Close monitoring and early, aggressive intervention is recommended to slow the progression of CF, which can lead to possible longer life.

1. Introduction

Cystic fibrosis is a genetic, autosomal recessive disease that involves different organ systems with particular damage occurring to the respiratory and gastrointestinal tracts.[1,2] The most common mutation worldwide, found in approximately 66% of patients with CF, is a class II mutation caused by a deletion of phenylalanine in position 508 (F508del) of CFTR. F508del CFTR is misfolded and trapped in the endoplasmic reticulum (ER) and subsequently proteolytically degraded.

The gene that encodes the CFTR protein, which is called CFTR, is located on chromosome 7. Mutations in this gene lead to CF. CFTR's soluble domains, which include two nucleotide binding domains (NBF1 and NBF2) and a regulatory domain (R). The cystic fibrosis transmembrane conductance regulator (CFTR) is defective in cystic fibrosis (CF). The CFTR gene provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator. This protein functions as a channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes. The channel transports negatively charged particles called chloride ions into and out of cells.

Table 1: Grades of cystic fibrosis

Class	Mutation
Classic or typical CF	
Class 1	CTFR is not synthesized
Class II	CTFR is synthesized but in abnormal form
Class III	CTFR is synthesized but there is disruption at cell membrane
Non Classic or Atypical CF	
Class IV	Reduced chloride conductance
Class V	CTFR synthesis or processing is partly defective
Class VI	Impaired conductance of ions other than chloride

* *Corresponding author*.
E-mail address: sunil.r.chaudhry@gmail.com (S. Chaudhry).

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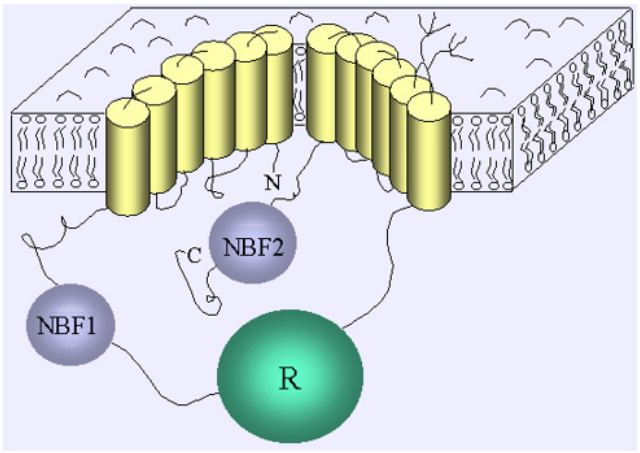

Fig. 1: Proposed structure of CTFR protein

1.1. Symptomatology

CF is characterized by mucoviscid respiratory tract secretions that impair ciliary clearance. There is salty skin, persistent cough, frequent lung infections, wheezing, poor growth and weight gain, greasy bulky stools, and male infertility. *Early colonization with Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae* is followed by chronic infection of the lower respiratory tract due to *Pseudomonas aeruginosa*.[3]

Pancreatic insufficiency is the most common gastrointestinal complication of cystic fibrosis (CF), affecting approximately 85 percent of patients at some time in their lives**.** In rare cases, cystic fibrosis can manifest itself as a coagulation disorder.[4]

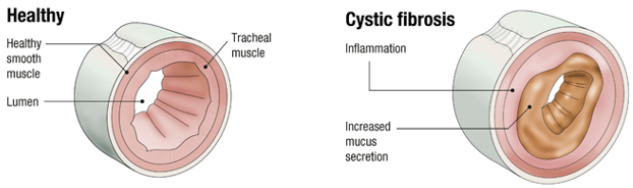

Fig. 2: Narrowing of respiratory passages by cystic fibrosis

1.2. Differential diagnosis

Gastro-esophageal reflux (GERD), fibrosing colonopathy. Celiac disease, inflammatory bowel disease, strictures and adhesions after surgery, and short bowel syndrome can mimic CF gastrointestinal symptoms[5]

1.3. Pathogenesis

CF lung may be attributed to endogenously increased levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 8 (IL-8), and IL-1 (According to some reports, the levels of these cytokines may be altered in CF subjects even before a bacterial infection can be documented. Intriguingly, reduced levels of the anti-inflammatory cytokine IL-10 have been recently reported in CF patients. Chronic bacterial airway infections are characteristically seen in the majority of individuals with CF. These infections are commonly polymicrobial and rarely can be eradicated with antimicrobial treatment.[6,7]

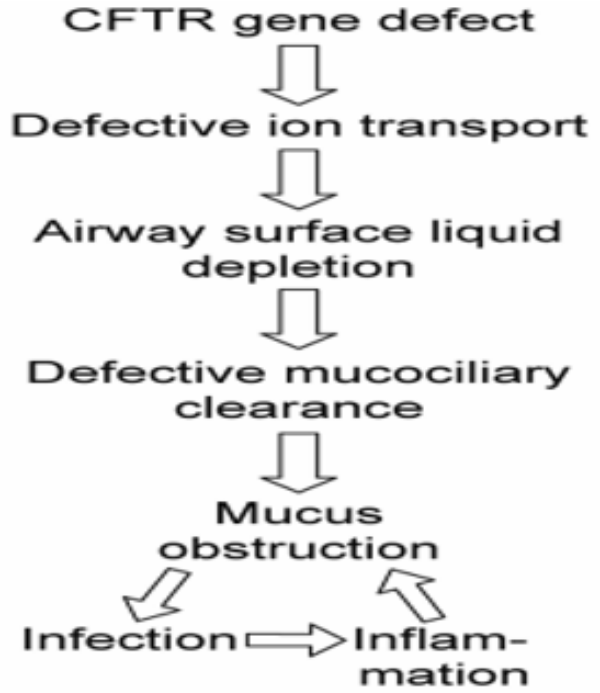

Fig. 3: Cascade for cystic fibrosus

1.4. Associated conditions

1. Diabetes occurs in about 10% of adolescents with CF. Beginning at age 10, children should be tested annually with an oral glucose tolerance test to monitor for impaired glucose tolerance
2. Pancreatic *insufficient* patients may have recurrent episodes of pancreatitis.
3. Small bowel obstruction should be suspected anytime an individual with CF presents with abdominal pain.
4. Meconium ileus is reported in 10–15% of CF new born and is usually but not invariably related to exocrine pancreatic insufficiency. In most infants this intestinal obstruction can be successfully treated with hyper-osmolar enemas
5. People with CF may have early aquagenic wrinkling of the skin, in which the palms wrinkle in less than 3 minutes of exposure to water, compared to 7 minutes in carriers and 11 minutes in controls.

2. Diagnosis

Sweat chloride: 60 mmol/l is considered diagnostic of CF. Values of sweat chloride of 40– 60 mmol/l are considered highly suggestive of CF. Patients with CF usually have a sweat sodium: chloride ratio > 1. DNA testing for the more common CF transmembrane regulator (CFTR) mutations is a valuable diagnostic test. The identification of increased immunoreactive trypsinogen (IRT) levels in the blood of infants with CF has made neonatal screening for CF possible. Trypsinogen is one of the secretory products of the pancreas making its level in the blood a specific marker of pancreatic function. Immunoreactive Trypsinogen (IRT) ≥ 120 ng/mL is confirmatory [8]

3. Treatment

3.1. Preventing and controlling lung infections

Antibiotics are prescribed. These mainly consist of inhaled forms of azithromycin, tobramycin, aztreonam and levofloxacin. Other antibiotics recommended are ciprofloxacin, cephalexin, amoxicillin and doxycycline depending on the sensitivity pattern.

Aztreonam inhalation solution is an alternative antibiotic for patients with chronic colonization of P aeruginosa. Aztreonam 75 mg is administered by nebulization route three times daily for 28 days on and then 28 days off.

For chronic use, Tobramycin is administered by nebulization (300 mg) or dry powder inhalation (112 mg) twice daily for 28 days on and 28 days off.

Azithromycin 22-30 mg/kg/week is the lowest recommended dose.

The treatment of multidrug-resistant gram-negative bacteria in patients with CF with advanced lung disease is challenging given the intrinsic resistance of these organisms to antimicrobials of several different classes.

3.2. Preventing adequate nutrition and electrolyte

Oral rehydration and osmotic laxatives (incomplete blockage) and hyperosmolar contrast enemas. Providing appropriate nutrition and preventing dehydration—a high-calorie-fat diet, supplemental vitamins ADEK, and minerals including fluoride and zinc are recommended. Additionally sodium chloride supplementation is given tailored to patient's age and environmental conditions.

3.3. Pancreatic enzyme replacement therapy

As long been considered as a safe, well-tolerated. Consensus Committees recommend pancreatic enzyme replacement with approximately 1800 U lipase/g fat or 1000–3000 U lipase/kg body weight/meal with an upper limit dose of 10,000 U lipase/kg body weight/d. The amount of lipase prescribed ranges from 2,600 to 40,000 lipase units per capsule. (2,500 lipase units x weight in kilograms).

The main functions of enzymes are to:

1. Digest fat, protein and carbohydrate (to supply the body with energy
2. Promote nutrition absorption
3. Help with weight gain and growth
4. Improve bowel motions

Pancreatic enzyme replacement products are generally well tolerated. Common adverse effects include headache, dizziness, abdominal pain, and flatulence.

Oral corticosteroids at a Prednisolone equivalent dose of 1-2 mg/kg alternate days appear to slow the progression of lung disease in CF but this benefit needs to be weighed against the occurrence of adverse events, in particular, development of cataracts and effect on linear growth. [9,10]

Megestrol acetate (MA) has been used in several controlled studies. MA 40-80mg seems to facilitate significant weight gain in treatment subjects. It has been successfully used in patients with CF who have failed conventional nutrition interventions. Appetite improvement is reported with significant weight gain consisting of both fat mass and lean body mass [11]

3.4. Cystic fibrosis transmembrane regulator replacement therapy

There are four CFTR modulators for population with CFTR mutations:

1. **Ivacaftor**: is a drug used to treat cystic fibrosis in people with certain mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (primarily the G551D mutation), who account for 4–5% cases of cystic fibrosis. The target CFTR-mutation of ivacaftor, G551D, is a Class III defect. Ivacaftor is a "potentiator" of CFTR, meaning it increases the probability that the defective channel will be open and allow chloride ions pass through the channel pore. *Doses in 25, 75, or 150 mg were studied for 14 days followed by a dose of 150 or 250 mg for 28 days. It was concluded that ivacaftor was associated with few severe side effects.*
2. **Lumacaftor/ivacaftor**: is a fixed-dose tablet (200mg of Lumacaftor and ivacaftor 150ng) containing a corrector (lumacaftor) and potentiator (ivacaftor) of the cystic fibrosis transmembrane conductance regulator (CFTR) and is the first therapy approved to treat the underlying cause of cystic fibrosis in patients (aged ≥12 years) homozygous for the most common CFTR mutation, F508del. Lumacaftor improves the processing of F508del CFTR and its transport to the cell surface, while ivacaftor increases the channel's open probability and transport of chloride. *lumacaftor 400 mg plus ivacaftor 250 mg, administered every 12 h in combination with standard therapy*, was associated

Table 2: Antimicrobials preferred

Organism	Antibiotic	Child Dose	Adult Dose	Side Effects
Gram positive	Vancomycin	15mg/kg every	1gm, IV, 12	Oto/
Organism, MRSA	Linezolid	6 hour, IV 10mg/ kg IV or	hourly 600mg, orally	nephrotoxicity Optic/ Peripheral
		Oral	or IV, 12 hourly	neuropathy
Gram negative	Tobramycin	0mg/ Kg IV	!0mg/ Kg IV	Oto and
Organism, Ps	Meropenem	every 24 hour	every 24 hour	Nephrotoxicity
Aeruginosa	Ciprofloxacin	40mg/ kg, 8 hourly, IV	2g, 8 hourly, IV 400mg/ kg IV	Rash, hepatitis
		15mg/ kg jg IV or 20mg / kg orally every 12 hour	12 hourly or 750mg BD	GI, Insomnia
Stenothrophomas	Trimethoprim +	4- 5mg/kg	4- 5mg/kg	GI, Neutropenia
maltophilia	Sulfamethoxazole	Orally or IV	orally or IV	
	Doxycycline	2mg/ Kg orally or IV, every 12	100mg IV or orally, every 12	GI. Phototoxicity
	Tigecycline	hours 1.2mg / kg every 12 hours	hours 50mg IV 12 hourly	GI, cholestasis
Achromobacter species	Imipenem Ciprofloxacin	15-25mg/ kg IV, 6 hourly Same as above	500mg-1g, IV, 6 hourly Same as above	GI, Seizures GI, Insomnia
	Minocycline	2mg. kg. oral or IV 12 hourly	100mg. 12 hourly	GI, Photosensitivity

with an ≈3% statistically significant improvement in lung function relative to placebo

3. **Tezacaftor/ivacaftor**: is approved for individuals 12 years and older with two copies of the most common cystic fibrosis mutation, F508del, as well as for individuals who have a single copy of one of 153 specified mutations. *100 mg of tezacaftor once daily and 150 mg of ivacaftor twice daily or matched placebo for 24 weeks.* The adverse events were mild or moderate in severity. None were serious or led to treatment interruption or discontinuation. Tezacaftor/ivacaftor was generally safe, well tolerated, and efficacious in people ≥12 years of age with cystic fibrosis homozygous for Phe508del-CFTR with ppFEV$_1$ of ≥25% and ≤90% who previously discontinued lumacaftor/ivacaftor due to treatment-related respiratory signs or symptoms. It was better than ivacaftor monotherapy
4. **Elexacaftor-tezacaftor-ivacaftor** is used for use is for persons 12 years of age and older with at least 1 F508del mutation for the CFTR gene. This drug combination provides potential therapy to many patients who had previously been excluded from CFTR modulation therapy due to the nature of their genetic mutations. Side effects were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase raised, nasal congestion, rhinorrhea, rhinitis, influenza, sinusitis, and raised blood bilirubin.

The yearly cost CFTR group is expensive with some benefits.[12–14]

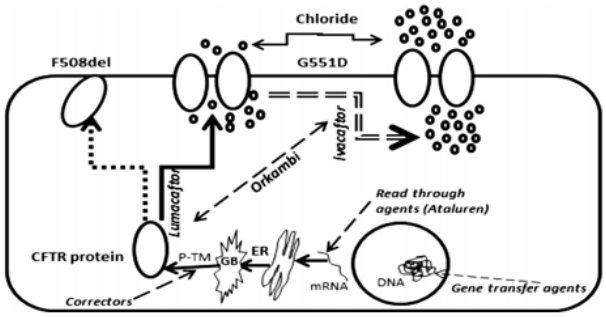

Fig. 4: Lumacaftor and Ivacaftor (Orkambi) action

3.5. Therapeutic strategies to manage cystic fibrosis

3.6. Supportive measures

Airway clearance techniques — also called chest physical therapy (CPT) can relieve mucus obstruction and help to reduce infection and inflammation in the airways. These techniques loosen the thick mucus in the lungs, making it easier to cough up.

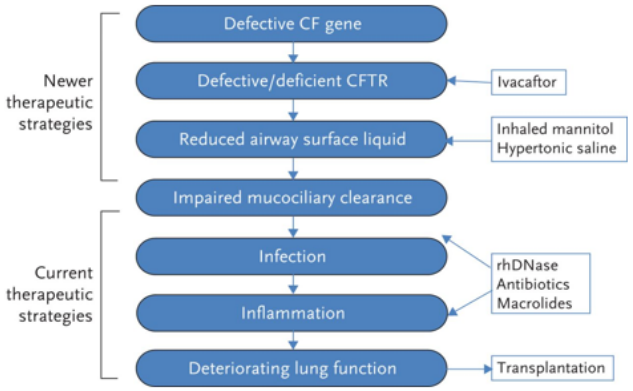

Fig. 5: Cascade of drug action

3.7. Corrector/modifier therapeutic agents in clinical pipeline

3.7.1. Andecaliximab

800mg dose of Andecaliximab binds to MMP9 at the junction between the propeptide and catalytic domains, distal to the active site, and acts by preventing the activation of inactive zymogen. It is under *advanced stages phase III trial* and expected to reduce inflammation and improve lung function. Side effects reported were anemia (20%), DIC, fatigue, anorexia, hypoglycemia, cholangitis, AST elevation and neutropenia.

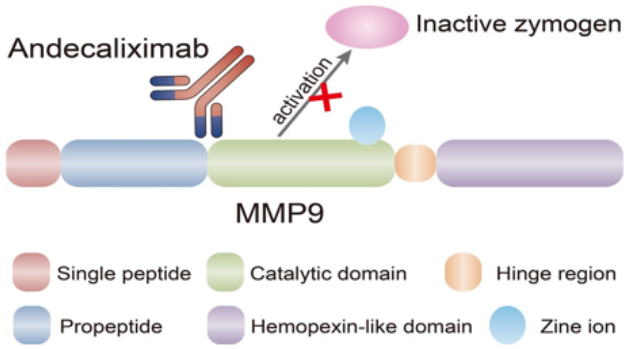

Fig. 6: Action of andecaliximab

3.7.2. Riociguat (also used in Pulmonary Hypertension)

Result in improved function of the CFTR protein as a chloride channel, moving salt and fluids in and out of cells. Side effects reported were headache, dizziness, indigestion, swelling of your hands, legs, feet, and ankles (peripheral edema), nausea, diarrhea, and vomiting.

3.7.3. Cavosonstat

An orally bioavailable inhibitor of S-nitrosoglutathione reductase, promotes cystic fibrosis transmembrane conductance regulator (CFTR) maturation and plasma membrane stability, with a mechanism of action complementary to CFTR correctors and potentiators. Cavosonstat was well tolerated, with no dose-limiting toxicities.

3.7.4. Ataluren

Was developed for potential treatment of nonsense-mutation cystic fibrosis (CF). Trial results are not very encouraging. Ataluren is taken three times a day, and the recommended dose is 10 mg/kg (10 mg per kilogram body weight) in the morning, 10 mg/kg at midday and 20 mg/kg in the evening (for a total daily dose of 40 mg/kg). Granules (125, 250 and 1,000 mg) are available. Side effects of ataluren include vomiting, nausea, headaches, stomach aches, and flatulence.

3.7.5. Tezacaftor in combination with ivacaftor

The combination of tezacaftor and ivacaftor was efficacious and safe in patients 12 years of age or older who had cystic fibrosis and were homozygous for the CFTR Phe508del mutation.[9–15]

3.7.6. Lung transplantation

International Society for Heart and Lung Transplantation (ISHLT) Guidelines:

Table 3: Recommendations for surgery

Oxygen-dependent respiratory failure	**Hypercapnia**
Pulmonary hypertension	FEV_1 < 30% of baseline or rapid decline in FEV_1, particularly if female
Recurrent haemoptysis not controlled by embolism	Refractory and/or recurrent pneumothorax

For severe cystic fibrosis-related liver disease, such as cirrhosis, liver transplant may be an option. In some people, a liver transplant may be combined with lung or pancreas transplants.[16]

3.7.7. Oxygen therapy

Cystic fibrosis may cause hypoxia. Oxygen therapy may down-regulate inflammation, halting the catabolic effects of a pro-inflammatory state. and also reduce complications associated with hypoxia. High-flow nasal cannula oxygen therapy (HFOT) is an oxygen technique offering greater comfort and more efficient oxygenation than standard oxygen. HFOT is increasingly used, particularly in patients with acute hypoxemic respiratory failure

People with cystic fibrosis (CF) suffer from breathing problems. Giving additional oxygen has long been a standard of care for people with chronic lung diseases. Participants receiving oxygen therapy were able to exercise for a significantly longer duration during exercise. Often,

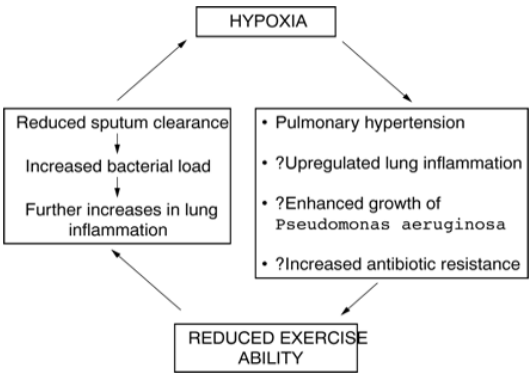

Fig. 7: Hypoxia medicated complications

patients who need oxygen therapy for 15 hours or more use a large oxygen tanks. High-flow nasal cannula oxygen therapy (HFOT). Is an oxygen technique offering greater comfort and more efficient oxygenation than standard oxygen HFOT is increasingly used, particularly in patients with acute hypoxemic respiratory failure. A large randomized controlled trial has found that mortality of patients with acute hypoxemic respiratory failure was lower when they were treated with HFOT than with standard oxygen.[17,18]

4. Conclusion

Treatment for cystic fibrosis (CF) will depend on child's symptoms, age, and general health. *There is no proper for cystic fibrosis, and the disease generally gets worse over time.* Maintenance treatments reduce the risk of pulmonary exacerbations. Antibiotics should be targeted against the common CF bacteria and these could be given orally, but i.v. antibiotics will be required for ongoing symptoms or severe pulmonary exacerbations. Management of comorbidities, like poor nutrition and diabetes, will be critical in improving outcomes. Four CFTR modulators for people with certain CFTR mutations are generally adopted. Management of comorbidities, like poor nutrition and diabetes, will be critical in improving outcomes.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Author biography

Sunil Chaudhry, Honarary Medical Director, Bioclinitech Technologies Pvt Ltd Mumbai India

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