International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 7|Issue 03 (May-June) |2024 Page: 536-539

Review Paper

Cystic fibrosis medication causing antibiotic resistance

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Article Received: 14-April-2024, Revised: 04-May-2024, Accepted: 24-May-2024

ABSTRACT:
Cystic fibrosis (CF) is a progressive, life-threatening condition that causes severe respiratory and digestive issues in addition to other consequences. It is an autosomal recessive genetic disease caused by the cystic fibrosis transmembrane regulator (CFTR). According to reports from the past ten years, CF is present in India, although its exact prevalence is unknown. In India, managing CF is challenging because to a lack of skilled personnel, a lack of availability, and the high cost of pharmacologic agents. Supplements, antibiotics, penicillin, and mucolytic agents are frequently employed as treatments, however this condition cannot be treated and occasionally even results in antibiotic resistance, which causes additional complications. Trikafta, the first triple combination therapy ever approved by the FDA, is being used to treat CF in patients 12 years of age and older who have the genetic mutation that afflict the great majority of CF patients which results in the decrease risk of antibiotic resistance. In the case of antibiotic resistance, even lung transplantation is significant.

Keywords: Cystic fibrosis, CFTR, Antibiotic resistance, Trikafta.

Abbreviation: Cystic fibrosis – CF, Cystic fibrosis transmembrane regulator – CFTR, Food and Drug Association – FDA.

INTRODUCTION:

Cystic fibrosis is a genetically inherited autosomal recessive disorder which is life threatening that eventually damages majorly lungs, pancreas, liver and digestive tract slowly problems along with other complications like intestinal blockage, nasal polyps, chronic respiratory failure, infertility, coughing up blood, etc. Cystic fibrosis affects the cells that produce mucus, sweat, and digestive secretions. Normally, these produced fluids are thin and slippery. But in people with CF, a defective gene causes these secretions of fluids to thicken and become sticky. They then seal off tubes, ducts, and passageways. The excessive production of mucus leads to difficulty in breathing, if coughed uncovered can also infect a healthy individual.

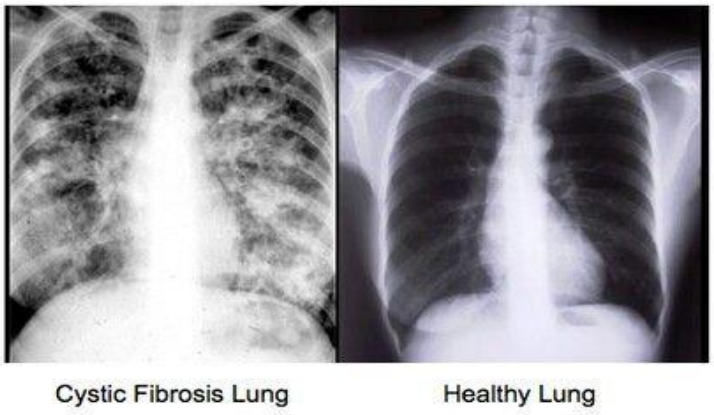

Figure 1. X-Ray difference between lungs

CF is a rare genetic disorder, fewer than 1 million cases per year. CF is caused due to mutation in the CFTR gene which helps in the normal production of the mucus. In every single individual there is only two mutated copies

of CFTR gene, however there are over 700 mutations of CFTR gene identified till today. The most common mutated codons are F508del and G542X. The G542X is a nonsense mutation that introduces a stop codon into the mRNA, thus prevents normal CFTR protein synthesis. CFTR with the F508del mutation presents a deletion of three base pairs, involving the loss of an amino acid, phenylalanine, at position 508 which results in a threefold problem that leads to loss of chloride channel function. This mutation is seen on chromosome 7 due to certain bacteria like Staphylococcus aureus, Haemophilus influenzae (common), Pseudomonas aeruginosa and Burkholderia cepacia.

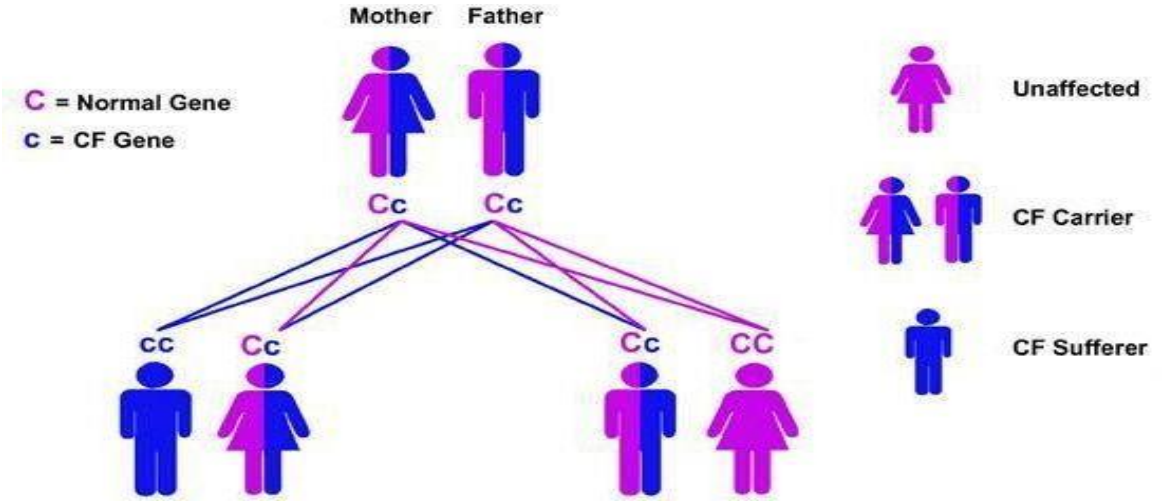

Figure 2. Genetic Representation of CF Gene transfer

It occurs genetically when each of the parents contributes a gene to their child, they could pass on either their CF gene or their non-CF gene which results in 50% chances of the child with CF. The bacteria causing CF is Pseudomonas aeruginosa which is a dangerous pathogen. This bacterium quickly colonises the lungs of persons with CF, resulting in chronic infections that are nearly impossible to resolve and is even fatal as it feeds on lungs of the individual.

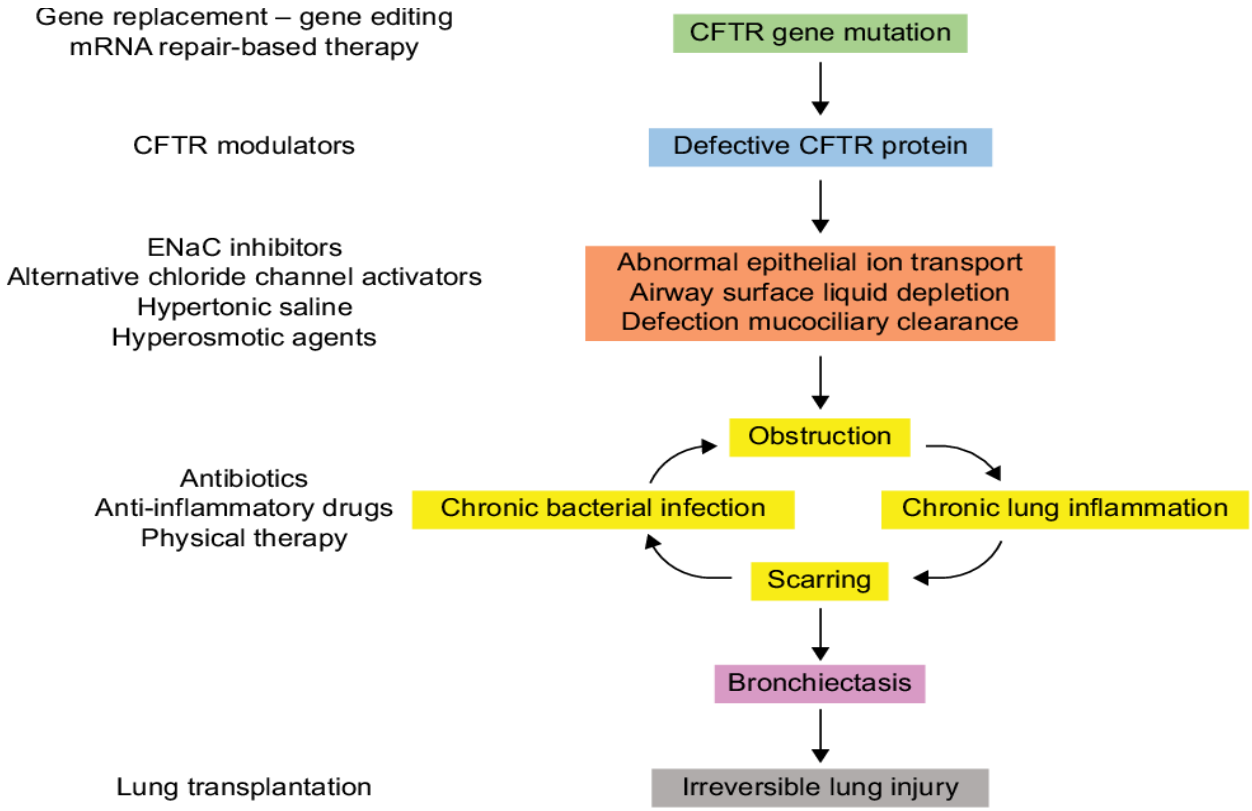

Figure 3. Pathway of damage of lungs

CF mutations have traditionally been classified according on their cellular phenotype. Protein synthesis defect (class I); maturation defect (class II); gating defect (class III); conductance defect (class IV); quantity defect (class V); and stability defect (class VI). CF cannot be completely cured as it is inherited, recessive and rare but, infection can be cured by non – pharmacological as well as pharmacological means. Non – pharmacological means include postural drainage, keeping atleast 6 feet distance from a healthy individual, covering their nose and mouth with mask, wearing gloves to reduced their own condition, using regular sanitising methods, physiotherapy, oxygen therapy, high-frequency chest wall oscillation and positive expiratory pressure technique. Medications used to treat patients with cystic fibrosis may include pancreatic enzyme supplements, multivitamins (particularly fat-soluble vitamins), mucolytics, antibiotics (including inhaled, oral, or parenteral), bronchodilators, anti-inflammatory agents, and CFTR potentiators (eg, ivacaftor) and correctors (eg, elexacaftor, lumacaftor, tezacaftor). Mutation in the CF gene causes this condition. These mutations lead to defects in a specific protein CFTR. As a result of these defects, the CFTR proteins don't work the way they should. In CF, biofilms permit the installation of a microenvironment that promotes maturation and overall shielding of pathogens against both antibiotic actions and host immune mechanisms. FDA approved three drug combination medication for CF named Trikafta was introduced manufactured by Vertex pharmaceuticals, Boston, England. Trikafta adds elexacaftor to tezacaftor and ivacaftor to target CFTR protein defects caused by the f508del mutation or another mutation responsive to Trikafta. But, before administration of the Trikafta drug combination physician should check about the condition of other organ system as this may lead to further more damage especially to liver and kidneys. The patient should inform the physician about the medications like rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, ketoconazole, itraconazole, fluconazole, clarithromycin or erythromycin if they are taking. Antibiotics from which bacteria can develop resistance are Penicillin (Piperacillin, Tazabactam), Cephalosporins (Ceftazidime, Cefepime), Carbapemens (Impene), Aminoglycosides (Tobramycin and TOBI, Gentamicin and Amikacin), Quinolones (Levofloxacin, Ciprofloxacin). While being on Trikafta medication it is compulsory to avoid food or drink that contains grapefruit.

CONCLUSION:

Based on the articles reviewed the article concludes the Cystic fibrosis is a life threatening condition which is genetically transferred from parents to child and it cannot be cured completely, only by proper medications and precautions the death of the patient can be delayed. Even the transplant of the lungs can only increase the life span of the CF individuals by 4-5 years. Due to a genetic mutations that happen in the DNA which functions abnormally, this results in the excessive production of mucus in the individual resulting in CF. In order to help this condition from excessive worsening, Vertex pharmaceuticals along with FDA approval introduces a medication named Trikafta which is a three drug combination of elexacaftor, tezacaftor and ivacaftor which directly targets the mutated gene. But, as there are multiple antibiotics advised in CF patients, results in causing antibiotic resistance in the individual.

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