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UNLOCKING HOPE: THE PROMISE OF IVACAFTOR, LUMACAFTOR, THEIR COMBINATION IN CYSTIC FIBROSIS TREATMENT AND GENE THERAPY

Poojitha Modepalli, Ramesh Chinnabala, Om Vinay Dappu, Ramarao Tadikonda, Gayatri Devi Yasa*

CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India.

Abstract:

Cystic fibrosis (CF) is an inherited disorder that causes severe damage to the lungs, digestive system and other organs in the body. A protein that controls the flow of salt into and out of cells are altered in cystic fibrosis due to a flaw (mutation) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. As a result, sweat becomes more salted and the respiratory, digestive, and reproductive systems produce thick, sticky mucus. A novel medicinal drug called ivacaftor modifies the function of the CFTR channel. For patients who are homozygous for the F508del mutation in the CFTR gene, lumacaftor is a protein chaperone that is used in conjunction with ivacaftor to treat cystic fibrosis. Lumacaftor-ivacaftor is indicated for treatment of CF in patients homozygous for the Phe-508del CFTR gene mutations. Without the treatment and perfect knowledge on the disease leads to death of the patient on suffering with CF. A significant step in the development of CF gene therapy was the cloning of the CFTR gene. This review mainly describes about the cystic fibrosis and its treatment ways and procedures. The drugs like ivacaftor, lumacaftor, different combinations of drugs and also discussed about the gene therapy and agents of gene therapy for cystic fibrosis.

Key words: *Cystic fibrosis, ivacaftor, lumacaftor, gene therapy.*

Corresponding author:

Mrs. Gayatri Devi Yasa,

Assistant Professor,

Department of Pharmaceutical Chemistry,

CMR College of Pharmacy,

Kandlakoya, Medchal, Hyderabad, Telangana, INDIA - 501 401.

E-Mail: sunilgayatridevi@gmail.com

Mobile: +91 6300 357 345

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INTRODUCTION:

Cystic fibrosis (CF) is a multisystemic autosomal recessive disease caused by a defect in the expression of CFTR (Cystic fibrosis transmembrane conductance regulator) protein, i.e. chloride channel present in the apical membrane of respiratory, digestive, reproductive, and sweat glands epithelium. Cystic fibrosis (CF) affects more than 30,000 people in the United States and 80,000 people worldwide, according to the American Cystic Fibrosis Foundation patient registry. As per the 2018 Registry Report by the Cystic Fibrosis Foundation, the average estimated survival time for CF patients in the United States is roughly 47.4 years (95% CI, 44.2-50.3) (1,2). CF occurs in about 1 out of 3,500 births per year in whites and northern Europeans (3). In the year 1989, CFTR was identified, this helps in developing of cystic fibrosis gene therapy.

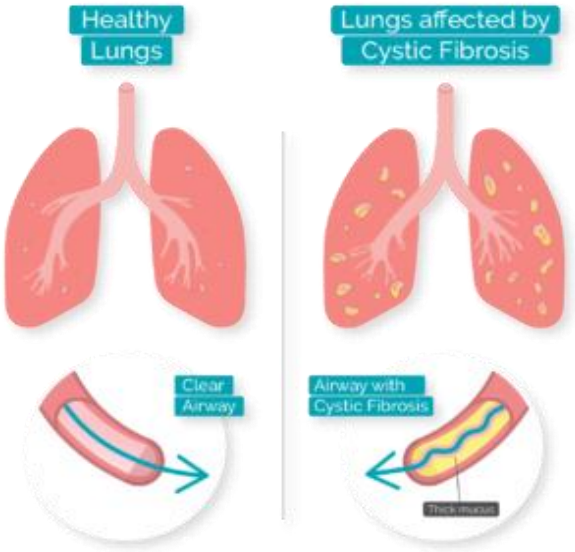

Figure 1: Cystic fibrosis

It predominantly affects Caucasians, and people of other ethnic backgrounds experience it very infrequently. It is a chronic illness that often results in inadequate functioning of the pancreas and chronic sinopulmonary infections. End-stage lung disease is the leading cause of death (4). Inadequate absorption of salt and chloride in the sweat glands and mucosal hyper concentration in the respiratory, digestive, and reproductive systems are caused by deficiencies, absences, or abnormalities in the structure or function of the CFTR protein (5). Management requires drug therapy, extensive physiotherapy and nutritional support. Respiratory system and GIT are primarily involved but eventually multiple organs are affected leading to life threatening complications (6). Mutations in the sole gene that encodes the CFTR protein on the long arm of chromosome 7 result in CF, an autosomal recessive disease (7).

Pathophysiology of cystic fibrosis

The pathophysiology of cystic fibrosis is broken down into following:

- Defective CFTR protein
- Impaired ion transport
- Mucus accumulation
- Respiratory complications
- Pancreatic dysfunction
- Other manifestations

CFTR defective protein:

The CFTR gene, which controls the CFTR protein's synthesis, is mutated in CF patients. Normally, this protein serves as a chloride channel, assisting in controlling the passage of chloride ions through cell membranes. Chloride ion transport is disrupted when CFTR gene mutations result in CFTR protein that is missing or malfunctioning.

Impaired ion transport:

The CFTR protein serves in preserving the proper ratio of sodium and chloride ions in the epithelial cells that line the pancreas, sweat glands, airways, and other organs in healthy people. However, poor chloride ion transport and increased sodium ion absorption are the outcomes of faulty CFTR protein in CF patients. The epithelial surfaces get dehydrated as a result, and thick, sticky mucus is produced.

Mucus accumulation:

Thick, viscous mucus is produced in many organs, including the pancreas and lungs, due to improper ion transport. It is challenging to remove germs, viruses, and other foreign particles from the respiratory tract because the thick mucus clogs the airways. This causes inflammation, lung damage that worsens over time, and recurring lung infections.

Respiratory complications:

Mucus buildup in the airways provides the perfect habitat for bacteria to flourish, which can result in persistent respiratory infections like those brought on by Staphylococcus aureus and Pseudomonas aeruginosa. Breathing problems worsen and lung tissue is further damaged by the inflammatory reaction that these illnesses cause.

Pancreatic dysfunction:

The ducts that transport digestive enzymes across the pancreas to the small intestine are blocked in the pancreas by the thick mucus. Consequently, people with cystic fibrosis (CF) may develop pancreatic insufficiency, which is typified by insufficient nutrient digestion and absorption, especially for fats and fat-soluble vitamins. Malnutrition, stunted growth, and vitamin shortages may result from this.

Other manifestations:
The liver, sweat glands, reproductive system, and bones are among the various organs and systems in the body that can be impacted by cystic fibrosis. The accumulation of thick mucus in the bile ducts can lead to liver problems, including gallstones and liver disease. Pancreatitis can lead to the development of diabetes associated with cystic fibrosis. Due to aberrant ion transport, sweat glands may produce overly salty sweat, which can cause electrolyte imbalances and dehydration.

Different drugs used in treatment of cystic fibrosis
Though there is no cure for CF, a number of medications and therapies have been created that can control its symptoms and enhance the lives of those infected. The main goals of the treatment/ medication of cystic fibrosis typically involves managing symptoms, preventing complications and enhancing the quality of life.

The treatment mainly includes, CFTR modulators, Mucolytics, Bronchodilators, Antibiotics, Pancreatic Enzyme Replacement Therapy (PERT), Gene therapy.

- ❖ The **CFTR modulators** mainly targets the defected gene of CF by two ways – by enhancing the function of defective CFTR protein (or) by increasing the production of functional CFTR protein.
  - Some of the well marketed CFTR modulators are:
    - Ivacaftor (Kalydeco)
    - Lumacaftor/Ivacaftor (Orkambi)
    - Tezacaftor/Ivacaftor (Symdeko)
    - Elexacaftor/tezacaftor/ivacaftor (Trikafta)
- ❖ The **Mucolytics** aid in thinning and relieving the viscous mucus in the airways, facilitating its removal from the lungs.
  - Some of the mucolytic drugs are:
    - Dornase alfa (Pulmozyme)
- ❖ The **Bronchodilators** relaxes the smooth muscles around the bronchioles and helps in open up the airways and makes the breathing easier.
  - Some of the Bronchodilators in market are;
    - Albuterol (ProAir, Ventolin), Ipratropium bromide (Atrovent)
- ❖ The **Antibiotics** are typically prescribed to CF patients to treat the respiratory infections which are highly common in patients suffering with CF.
  - Some commonly used antibiotics are:
    - Tobramycin (TOBI, Bethkis), Azithromycin (Zithromax), Ciprofloxacin (Cipro)
- ❖ The **Pancreatic Enzyme Replacement Therapy (PERT)** plays an important role in treatment of CF patients. PERT is necessary to support nutrient absorption and digestion in people with pancreatic insufficiency.
- ❖ Exogenous pancreatic enzymes are supplied by PERT supplements to aid in the digestion of lipids, proteins, and carbohydrates in the diet.
  - This includes:
    - Pancrelipase (Creon, Pancreaze, Zenpep)

The above treatments differ based on the condition of individual patient suffering with CF and stage of the CF. Some of the popular marketed drugs are Ivacaftor (Kalydeco), Lumacaftor / Ivacaftor (Orkambi), Tezafactor / Ivacaftor (Symdeko) and Elexacaftor / tezacaftor/ ivacaftor (Trikafta).

Combination of drugs therapy is highly used in the treatment of CF.CF is not a common disease, yet most dangerous disease with very low chances of recovery. Researches are going on currently to develop a better cure of the patient. It becomes a boon to the CF patients.

GENE THERAPY:
In the year 1989, CFTR was identified, this helps in developing of cystic fibrosis gene therapy. The first of several clinical trials involving gene therapy was conducted in 1993 in an effort to treat the CF deficiency in airway epithelia. There is still no FDA-approved gene therapy for cystic fibrosis (CF), despite the early excitement (8).

The first nonviral gene therapy experiment to investigate the potential for clinical benefit from recurrent nonviral gene transfer (12 doses over 12 months) was completed in the fall of 2014 by the U.K. Cystic Fibrosis Gene Therapy Consortium.

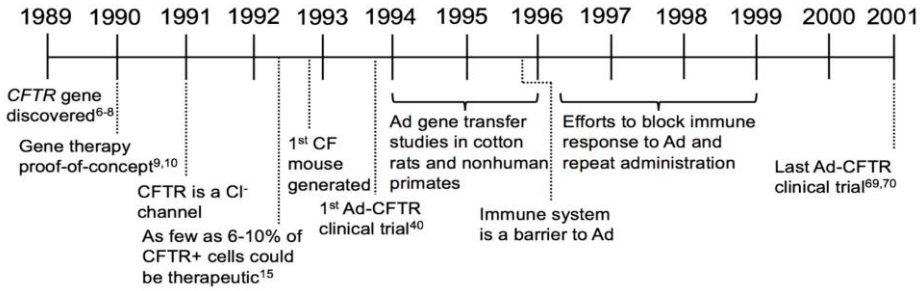

Figure 2: Timeline of CF gene therapy

Evidence indicating that the molecular flaw in small-molecule medications can be used to correct CFTR, and interest in CF gene therapy is growing due to the effectiveness of gene therapy in treating other monogenic disorders. A significant step in the development of CF gene therapy was the cloning of the CFTR gene. Due in large part to the noninvasive accessibility of the lung and the pressing need for more effective treatments, the majority of efforts over the last 20 years have been directed at developing gene therapy for CF lung disease (9).

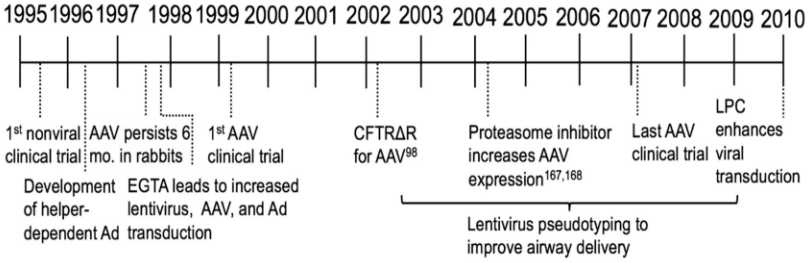

Figure 3: Important milestones for the second era of CF gene therapy (1995–2010)

Gene transfer agents

Since naked DNA has such a low transfection effectiveness, gene transfer agents (GTAs) have been developed to improve entrance into the cell or nucleus. These often fit into the viral and non-viral groups, the latter of which are often lipid-based but can also contain nanoparticles. Given their presumed inherent ability to infect the respiratory system, viruses were an obvious first choice. Early CF clinical trials11 included engineered adenovirus (Ad), yet at high titers, some of these produced marked inflammatory reactions and unacceptable toxicity; this issue has mainly been resolved with the introduction of next generation viruses. Many substances, like polidocanol13 and perflurochemicals14, have been employed to open up tight junctions and provide access to these receptors; however, it is still unclear if these methods are safe and useful for use with humans. Adeno-associated virus (AAV) is a tiny Parvovirus family member with single-stranded DNA. The Sendai virus (SeV) is a member of the Paramyxoviridae family of single-stranded RNA viruses. Cationic liposomes, bare DNA, and compacted DNA nanoparticles are examples of non-viral techniques (10).

The cDNA encoding the cystic fibrosis transmembrane conductance regulator protein needs to be successfully transported to the nucleus of the epithelial cells lining the bronchial tree within the lungs for gene therapy to be effective in treating cystic fibrosis patients. Throughout the patient's life, sufficient transgenic expression must be maintained, either by repeating the vector dosage or by focusing on airway stem cells.

Strategies for CF gene therapy

This strategy provides a potentially long-lasting remedy by substituting a "correct version" of the CFTR gene for the genetic mutation. In fact, numerous research has sought to fix the CFTR mutations through gene therapy procedures since the CF gene was discovered. Analyses conducted in vitro have revealed that normal epithelial activities can occur without all cells expressing normal CFTR (11).

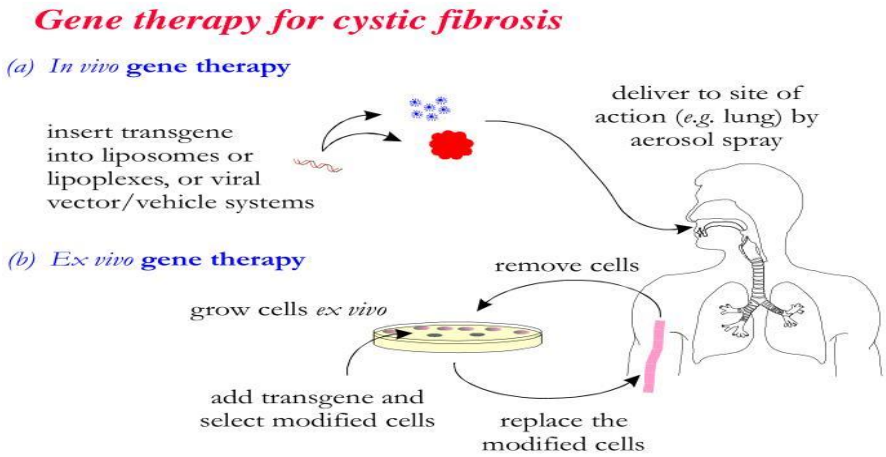

Figure 1: Gene therapy for cystic fibrosis

It is also possible to combine or replace traditional methods of focusing on the disease-causing variant with enhanced pre-clinical models and mutation-agnostic methods of treating complicated CF symptoms.

To treat complicated CF symptoms, mutation-agnostic approaches and enhanced pre-clinical models may also be used in place of or in addition to traditional methods of focusing on the disease-causing variation. At present gene therapy became boon to the patients suffering from CF. Hope this procedure get highlighted and becomes more interested for the research.

Ivacaftor

Ivacaftor is an aromatic amide that synthesizes via the condensation of the 5-amino-2,4-di-tert-butylphenol amino group with the carboxy group of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid. utilized as a cystic fibrosis therapy. It functions as both an orphan medication and a CFTR potentiator. It is an aromatic amide, a monocarboxylic acid amide, a quinolone, and a member of the phenol family. Ivacaftor, frequently referred to as VX-770 or Kalydeco.

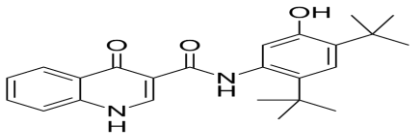

Figure 2: Structure of ivafactor

KALYDECO is available as a light blue, film-coated, capsule-shaped tablet that can be used orally and contains 150 mg of ivacaftor along with other inactive ingredients. Additionally, KALYDECO provides the product as white to off-white, sweetened, flavorless granules for oral use that come in unit-dose packets containing 5.8 mg, 13.4 mg, 25 mg, 50 mg, or 75 mg of ivacaftor. 5.8 mg, 13.4 mg, 25 mg, 50 mg, or 75 mg of ivacaftor as well as the following inactive ingredients are included in each unit-dose packet of KALYDECO oral granules: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate.

Clinical pharmacology

Mechanism of action

Ivacaftor is a potentiator for the chloride channel on the surface of epithelial cells in different organs, the CFTR protein. Ivacaftor stimulates the channel's open probability, or gating, to allow for increased transit of chloride ions. The amount of CFTR protein on the cell surface and the degree to which a particular mutant CFTR protein responds to the potentiation effects of Ivacaftor determine how much CFTR chloride transport is facilitated by the drug (12). Using a panel of FRT cell lines transfected with distinct CFTR mutations, Ussing chamber electrophysiological investigations were conducted to ascertain the chloride transport response of the mutant CFTR protein to ivacaftor. In FRT cells carrying CFTR mutations, ivacaftor enhanced chloride transport, causing CFTR protein to be transported to the cell surface. Since the in vitro CFTR chloride transport response threshold is predictive or logically predicted to predict clinical benefit, it was defined as a net increase of at least 10% of normal over baseline. The amount of the net change over baseline in CFTR-mediated chloride transport in vitro for particular mutations does not correspond to the amount of the clinical response. For a patient to be recommended, they must have at least one CFTR mutation that is sensitive to ivacaftor.

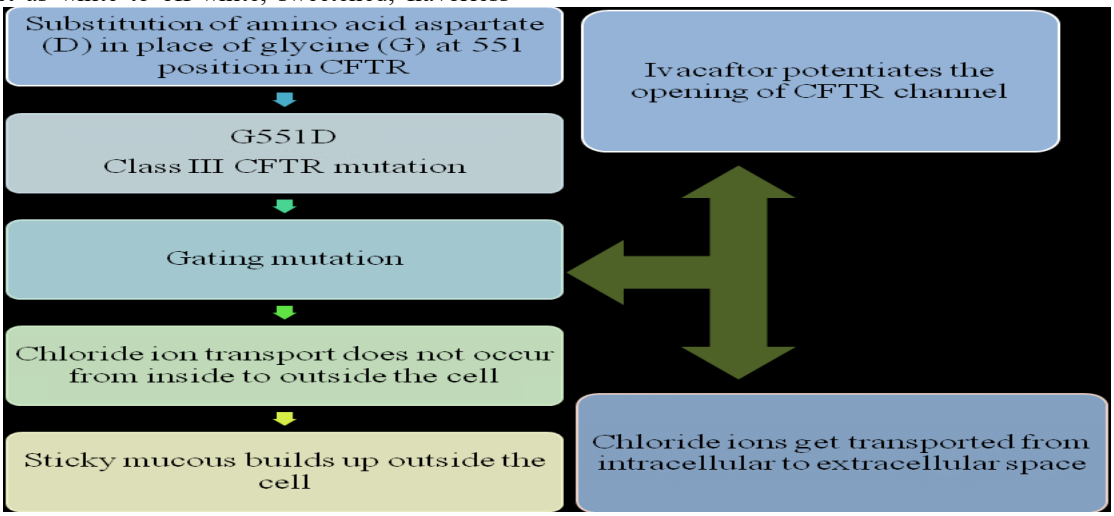

Figure 3: Mechanism of action of ivacaftor

Adverse reactions

- Transaminase elevations
- Cataracts

Lumacaftor

Lumacaftor is an aromatic amide that is produced by formally condensing the aromatic amino group of 3-(6-amino-3-methylpyridin-2-yl) benzoic acid with the carboxy group of 1-(2,2-difluoro-1,3-benzodioxol-5-yl) cyclopropane-1-carboxylic acid. utilized as a cystic fibrosis therapy. It functions as both an orphan medication and a CFTR potentiator. It belongs to the class of aromatic amides, benzoic acids, pyridines, cyclopropanes, benzodioxoles, and organo-fluorine compounds. Lumacaftor is a medication that is used when combined with [DB08820] as part of the fixed dosage combination product Orkambi to treat people with cystic fibrosis (CF) who are six years of age or older.

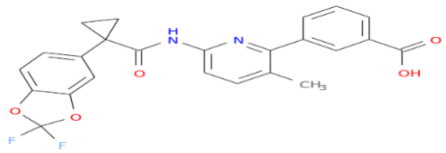

Figure 4: Structure of lumacaftor

Mechanism of action of lumacaftor

Lumacaftor helps the F508del-mutated CFTR maintain its conformational stability, which increases the processing and trafficking of mature protein to the cell surface and ameliorates the symptoms of CF and the underlying pathophysiology of the disease. More precisely, lumacaftor functions as a chaperone that fold proteins, preventing CFTR ion channels from being misfolded and subsequently destroyed during endoplasmic reticulum processing.

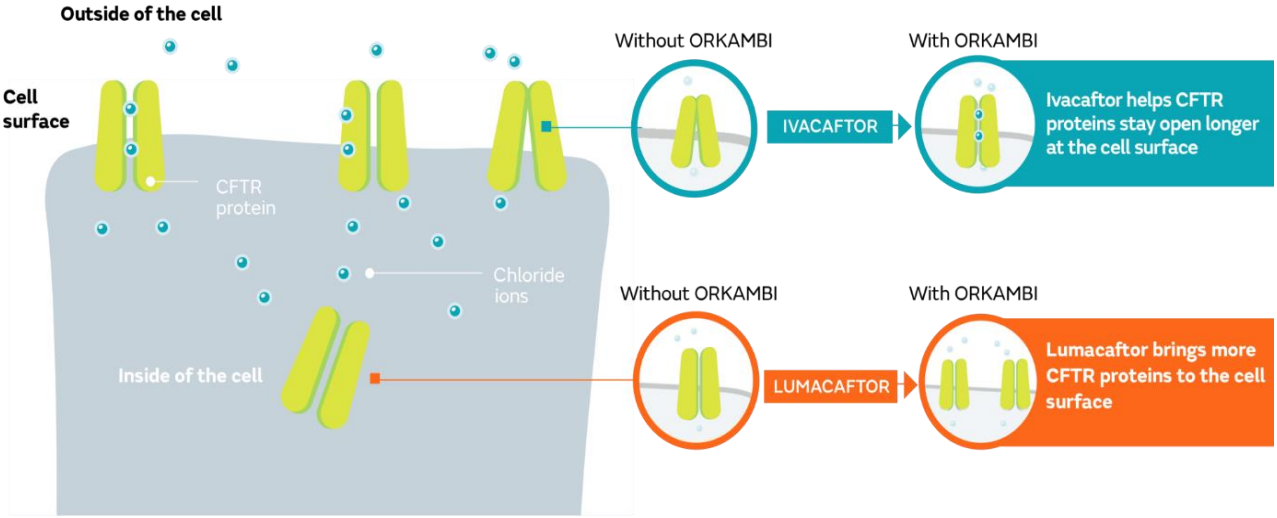

Figure 5: Mechanism of action of lumacaftor

Adverse reactions

- Abdominal pain
- Breathlessness
- Tight chest

Combination of ivacaftor and lumacaftor

Lumacaftor-ivacaftor is indicated for treatment of cystic fibrosis (CF) in patients homozygous for the Phe-508del cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations.

Some of the other combinations are:

- Ivacaftor (Kalydeco)
- Lumacaftor/Ivacaftor (Orkambi)
- Tezacaftor/Ivacaftor (Symdeko)
- Elexacaftor/tezacaftor/ivacaftor (Trikafta)

The combination treatment of lumacaftor and ivacaftor was generally well tolerated in CF patients homozygous for the F508delCFTR mutation, aged 6–11 years (12). Combination therapy is the most successful treatment followed by the physicians on the patients of CF.

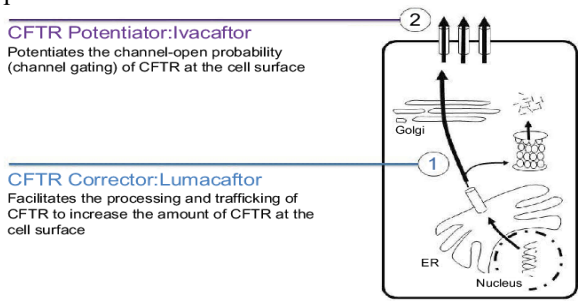

Figure 6: Mechanism of action of combination of drugs

Adverse reactions

- Bloating
- Extreme fatigue
- Diarrhoea

CONCLUSION:

For CF patients, an integrated therapy approach is necessary, incorporating a variety of aspects that improve the patient's overall health through suitable and well-balanced pharmaceutical and non-pharmacological therapies. For the future, the current process is highly crucial. The collaborative effort of researchers, pharmaceutical companies, Physicians, Health care professionals leads to the development of efficient treatment for the cystic fibrosis. Essentially, it is impossible to overestimate the potential of gene therapy, ivacaftor, lumacaftor, and their combination therapies in the treatment of cystic fibrosis. In addition, there is great hope that gene therapy will eventually lead to a permanent cure for cystic fibrosis. Gene therapy offers the possibility to permanently fix the underlying genetic issue by directly delivering functioning copies of the CFTR gene to afflicted cells. Even with persistent issues with immune response, long-term efficacy, and administration strategies, clinical trials and ongoing research are expanding the realm of what is feasible for treating cystic fibrosis. Finally, through the continued innovation the life of patient with CF can be improved.

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