Recent advancements in treatment of Cystic Fibrosis

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***Abstract*: Cystic fibrosis (CF) is the most usual life-shortening autosomal recessive disease(1). It is generally result of mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene (2). This result into the accumulation of exocrine secretions in various systems, specifically the respiratory, and gastrointestinal systems, causing serious comorbidities (5). Still, lung disorder accounts for important reason for the excessive morbidity and mortality in CF (6)Cystic fibrosis also influences epithelial cell lining of reproductive tract and lead to faulty exocrine secretion. Patients with cystic fibrosis have regular gastrointestinal issues like Fatty liver, Rectal prolapse, Constipation, malabsorption, Distal intestinal obstruction syndrome, Gastro-oesophageal reflux, etc(3). Most general CF-causing mutation is F508del. Other CFTR mutations may additionally impair mRNA and protein expression, function, stability or a combination of these. Gene modifiers, social status, patient's lifestyle, respiratory infections and adherence to treatment plans like quite a few different elements impact disorder severity beyond CFTR mutations. Most of the new drugs availablee in market for CF remedy have been deliberate and developed from acquired advances on genetics and proteomics (6) Kalydeco® (Ivacaftor),is a drug referred to as a CFTR "potentiator" was at the beginning supposed for use in the therapy of patients with the G551D mutation in Cystic Fibrosis(7).Research is being carried out into gene therapy that aims at introducing a normal copy of CFTR into lung epithelial cells(4).**

***Keywords*: CFTR modulators, Ivacaftor, Mucociliary clearance, Physiology, PTC124,**

I.INTRODUCTION

Cystic fibrosis is a progressive, monogenic disorder considered to have an effect on at least 100 000 human beings worldwide via Mutations in CFTR gene. In 1989, Lap-Chee Tsui led a team of scientists at the Hospital for Sick Children in Toronto that discovered the gene responsible for CF i.e. CFTR gene. CFTR gene codes for epithelial ion channel that generally transports chloride and bicarbonate epithelial cell's membrane, mutation of it leads to impaired mucus hydration and clearance(8). The noun "cystic fibrosis" refers to the characteristic fibrosis and cysts that shape inside the pancreas (15). Cystic fibrosis is additionally called as Mucoviscidosis. Cystic fibrosis is caused by pathogenic mutations in a single large gene located on human chromosome no. 7 that encodes for cystic fibrosis transmembrane conductance regulator (CFTR) protein (1). CFTR is concerned in sweat production, digestive fluids, and mucus production (14). It is a multi-organ disorder (affects pancreas, liver, kidneys, and gut also) however it substantially causes lung tissue destruction, which remains the predominant motive of morbidity (9). In the 1930s, Dorothy Anderson identified CF after autopsy research in malnourished children, and gave the ailment title "cystic fibrosis of the pancreas" (10). The majority of CF patients also developed sinus disease (11). More than 95% of males with CF are infertile because of defects in sperm transport (12). Approximately two-thirds of CF patients shows exocrine pancreas insufficiency (15).

II.EPIDEMIOLOGY

Cystic fibrosis affects more than 30,000 persons in the United states and is one of the most frequent genetic ailments of Caucasian people. On an average, thousand new cases are recognized annually within

one year of birth. It is estimated that more than 70,000 human beings worldwide are residing with CF. The disorder occurs in 1 in 2,500 to 3,500 white newborns in United States. In Asia, the incidence remains underestimated; however, Middle Eastern nations shows a greater incidence than East Asia. CF influences each male and female persons equally, women with CF exhibits a shorter life expectancy than their male(16). Due to the implementation of newborn screening, more than 75% of CF diagnoses in the United States manifest earlier than a baby reaches two years of age.

In 2012, of the 111 humans who died from cystic fibrosis, 54 were adult males and 57 have been females, 105 had been aged 15–64 years old, 4 had been aged 0–14 years; and 2 had been 65 and above.

III.GENETICS/CAUSES

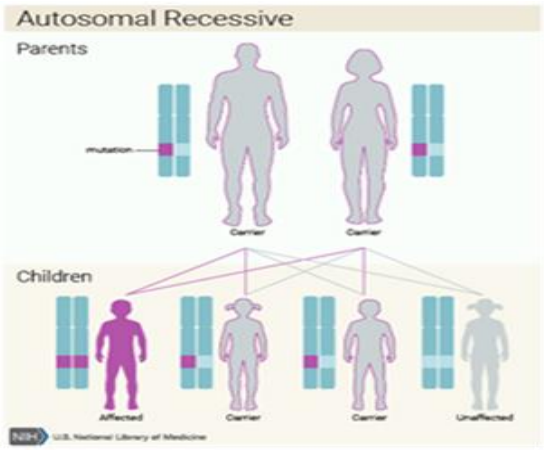

Figure 1:Autosomal recessive

Cystic fibrosis is caused via any of a range of mutations in the gene that produces the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CF gene was recognized in 1989. Since then, a magnificent deal has been realized about this gene and its protein product..CFTR gene is 230,000 base pairs long and formulates a protein that carries 1,480 amino acids. Structurally, the CFTR is a kind of gene recognized as an ABC (ATP-binding cassette transporters) gene. Most persons have two working copies (alleles) of the CFTR gene,Out of which solely one is wished to prevent cystic fibrosis. A man or woman who has a mutation on simply one allele is a carrier. CF develops when neither allele can produce a functional CFTR protein. Thus, CF is viewed an autosomal recessive disease.(17)(fig. 1).

CFTR mutations are currently categorised according to reason of dysfunction, which include dysfunctional protein translation, cell processing, or CFTR channel gating.It consists of Missense (single amino acid substitution) mutations, frameshift (insertion or deletion) mutations, splicing (incorrect intron splicing) mutations, nonsense (early termination codon) mutations(18)(fig.

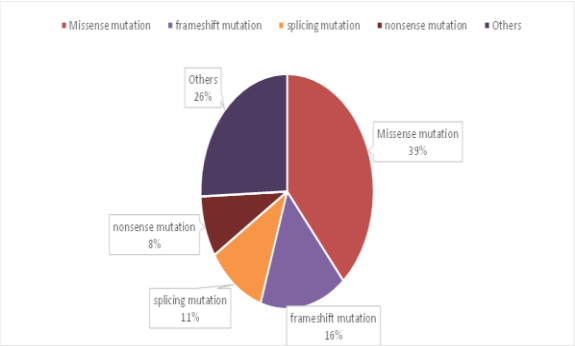

Figure 1:Types of mutations

2).Mutations of the CFTR gene categorize into six particular types of CFTR dysfunction(19)(Fig-2).According to this classes.

*Class-I mutations:*It includes Defective protein production. It typically entails mutations like nonsense, frameshift, or splice-site mutations, effects in premature termination of mRNA. G542X, W1282X, R553X, 621 G>T, and 1717-1G>A are examples of class –I mutations(20).

Class-II mutations: Class-II mutations:It includes Defective protein processing.These mutation reasons atypical post-translational processing of the CFTR protein(20). F508del(deletion of three nucleotides) mutation results in a loss of the amino
acid phenylalanine which is the most frequent kind of mutation (occurs in about 70% of victims with CF), N1303K, A455E are examples of this type (21).

Class-III mutations:It entails Defective regulation of CFTR protein. These mutations diminishes CFTR channel functionality even when ATP levels are sufficient.Ex G551D mutations (20).In this mutation, amino acid glycine (G) on position 551 is exchanged with aspartic acid.

Class-IV mutations:There is Defective conduction by CFTR channel.Here CTFR protein is produced and transported correctly to cell surface. But there is mark reduction in rate of ion flow and the duration of channel opening(20). Ex. R117H mutation.

Class-V mutations: There is Reduced amounts of purposeful CFTR protein. It includes various mutations that alter mRNA stability(17). A455E mutation is the example of this class.

Class-VI mutations: It includes Decreased CFTR stability.This type motives plasma membrane instability and consists of Phe508del mutation(17). Ex. Q1412X mutation. above mutations are a lot common, but over a thousand other mutations have been identified.

IV.SYMPTOMS

1) *Very salty-tasting skin:* Patients with cystic fibrosis lose immoderate salt in their sweat, and we can regularly observe salt crystallizing on the skin,imparts salty taste to skin.

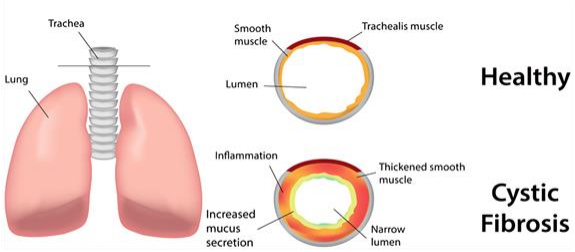

Figure 1: Lung infection in Cystic fibrosis.

2) *Frequent lung infections including pneumonia or bronchitis*: It is the primary motive of morbidity and death in human beings with cystic fibrosis which can be consider as strong symptom.Lung infections are normally due to Pseudomonas aeruginosa, fungi, and mycobacteria, Staphylococcus aureus, Haemophilus influenzae (5).It additionally result in Wheezing or shortness of breath, Persistent coughing, at times with phlegm,further Pneumonia,Bronchitis subsequently leads to respiratory failure. Lung ailment outcomes from clogging of the airways due to mucus build-up, decreased mucociliary clearance.(Fig.-3)

3) *Nasal polyps:* Inflammation of the upper respiratory tract results in well-known runny nose and nasal obstruction due to Nasal polyps.Nasal polyps are noncancerous growths within the nose or sinuses. It represents an overgrowth of the mucous membranes.

4) Frequent greasy, bulky stools or difficulty with bowel movements: Newborns and infants with cystic fibrosis tend to have frequent, large, greasy stools ,It is a end result of malabsorption.These children are normally underweight for their age group(22*)*.

5) Rectal prolapse: Increased fecal volume, malnutrition, and expanded intra–abdominal pressure due to coughing,causes protrusion of interior rectal membranes i.e.rectal prolapse.

*6)Pancreatitis***:** The pancreatic ducts are definitely plugged due to thickened secretions from the pancreas. These secretions block the exocrine movement of the digestive enzymes into the duodenum and result in irreversible damage to the pancreas(23). Problems with digestion can lead to diarrhea, malnutrition, bad growth, and weight loss..Certain victims with CF can also boost DIOS (distal intestinal obstruction syndrome).

*7) Cystic fibrosis-related diabetes***:**Blockage of Passage with thick mucus or Damage to the pancreas can lead to loss of the islet cells, leading to a type of diabetes unique to those with the disease indicates traits of type 1 and type 2 diabetes, and is one of the principle nonpulmonary issues of CF(24).

8) Infertility: 20% of females with CF have fertility difficulties due to thickened cervical mucus and malnutrition.of ovum ,disrupts ovulation process and results in absence of menstruation(26). At least 97% of men with cystic fibrosis are infertile, however not sterile. The fundamental purpose of infertility in males with cystic fibrosis is CBAVD (congenital bilateral absence of the vas deferens) a condition in which the tubes that carry sperm are blocked via mucus and do not longer developes desirably , other mechanisms includess no sperm, abnormally formed sperm, and few sperm with less motility(25).

Various other clinical problems includes weight attain in spite of a exact appetite, Poor growth, Chronic sinus infections, Clubbing or expansion of the fingertips and toes, cor pulmonale (enlargement of the right side of the heart), gassiness (too much gas in the intestine), gallstones, pneumothorax (rupture of lung tissue and trapping of air between the lung and the chest wall), hemoptysis (coughing of blood).

V.DIAGNOSIS

Assessment of Cystic fibrosis can be carried out via following measures,

1.Sweat chloride concentration test: Sweat chloride concentration test measures the electrolyte(particularly Cl- ion) concentration in sweat. Sweat sample is collected through pilocarpine

iontophoresis. In this test, an region of the pores and skin (usually the forearm) is made to sweat by means of the usage of a chemical referred to as pilocarpine and applying a mild electric powered current. To collect the sweat, the region is covered with a gauze pad or filter paper and wrapped in plastic. After 30 to 40 minutes, the plastic is removed, and the sweat accumulated in the pad or paper is analyzed.

This is an vital approach so it must be employed carefully to avoid inaccurate consequences by making sure that enough sample is collected. A common reason for failure of the test is an insufficient sample in a small infant (limit 3kg).A sweat chloride concentration >60mmol/L is suggestive of CF. A sweat chloride of 40-60mmol/L is borderline and be repeated. A single sweat test is now not enough to diagnose CF, a 2nd test or identification of genetic mutation confirms the diagnosis. There are a number of reasons for a false positives/negative results.

2.immunoreactive trypsinogen test (IRT): As the sweat test may also not work nicely in newborns because they do no longer produce sufficient sweat. In that case, any other type of test, such as the immunoreactive trypsinogen test (IRT), may also be used. In the IRT test, blood drawn 2 to 3 days after birth is analyzed for a specific protein called trypsinogen. Positive IRT take is primary test as a result ought to be validated via sweat and other tests.

3.Genetic tests : Genetic chemical assessments are carried out to find out what kind of CFTR defect is inflicting CF. A small proportion of humans with CF have normal sweat chloride levels. They can only be diagnosed via chemical tests for the presence of the mutated gene. As there are greater than 200 kinds of CF mutations ,Its necessary to become aware of the Mutation kind to initiate the treatment.

4.Chest x ray : Prognostication of the lung lesion in cystic fibrosis (CF)can be done by traditional chest radiographs, computed tomography (CT), and magnetic resonance imaging (MRI) .These methods reveal some of the traditional chest radiographic findings that reflects Inflated lung, lungs fibrosis ,Searing chronic bronchiectasis: hyperinflation, bronchial thickening and dilatation, peribronchial coughing, mucoid impaction, cystic radiolucencies, an amplify in interstitial markings, and scattered nodular densities(27).

5.Sinus x ray: Sinus X-rays may also be used to diagnose sinusitis, any other common complication of cystic fibrosis in which the sinuses are persistently infected with bacteria.

6.A sputum culture: CF patients may additionally have their airways chronically colonized by filamentous fungi (such as Aspergillus fumigatus, Scedosporium apiospermum, Aspergillus terreus) and/or yeasts(28). Allergic bronchopulmonary aspergillosis is the most frequent fungal disease in the context of CF, involving a Th2-driven immune response to Aspergillus species(29). Children with extra superior cystic fibrosis are regularly inclined to infection with a certain kind of bacteria, Pseudomonas aeruginosa, which can increase inflammation in the airways and irritate lung function. If Pseudomonas is found, Physicians prescribe inhaled antibiotics to cut off the micro organism and improve lung function.

7.Lung function tests: Lung function tests, carried out each time When child visits health center The Doctor measure how much and how quickly air is inhaled and exhaled from the lungs. This can help to recognize if there is a blockage in the lungs that can be treated with medication. Other lung tests measure the amount of oxygen in the lungs and in the blood, which is an additional way to see if mucus in the airways is interfering with breathing and the absorption of oxygen.

8.Stool examinations: This test take a look to assess your stool sample for two enzymes made through the pancreas particularly trypsin and chymotrypsin. The test measures how nicely your pancreas is working to see if you have pancreatic insufficiency or cystic fibrosis (CF).

VI.NORMAL PHYSIOLOGY OF CFTR**:**

Epithelial cells are connected together by using tight junctions (TJ)and gap junctions (GJ). Epithelial Sodium Channels (ENaC) is involved in absorption of Na ions from airway to the cell.Further Na ions are sent across epithelial cell lining in exchange of K ions with the assistance of Na / K -ATPase.Secretion of Cl- ions is facilitated with the aid of CFTR and other Cl- channels mutually in the apical membrane. CFTR was suggested to coordinate the rate limiting steps for both secretion and absorption, specifically Cl- secretion via

CFTR, and Na absorption by means of the epithelial sodium channel (ENaC).

When Chloride channel is open it facilitate movement of Cl- ions , additionally it inhibit opening of sodium channel. So either Sodium or Chloride channel will remain open at a time.In normal physiology Cl- ions are secreted with the aid of chloride channel simultaneously sodium channel is closed. Na stays in airway only. This, in term, creates a salt concentration gradient(30). Salt concentration gradient across the epithelium provoking water to be absorbed passively by means of osmosis inflicting thinning of mucus(31).Thin mucus is cleared effortlessly through Mucocilliary clearance(MCC).

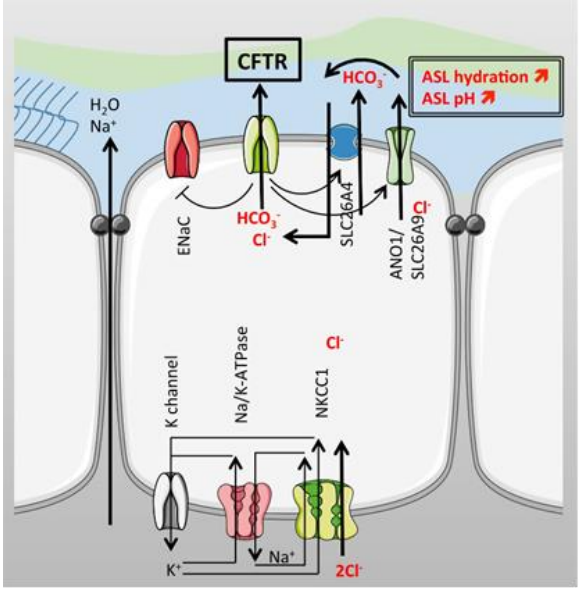

Figure 4:: Normal Physiology of CFTR.

VII.PATHOPHYSIOLOGY

The cilia exist in between the cell's apical surface and mucus in a layer recognized as airway surface liquid (ASL). The flow of ions from the cell and into this layer is determined through ion channels i.e. CFTR. Mutated CFTR inhibits Chloride channel. Due to closure of Cl- channel, Cl- ions does not pass in the ASL, this decrease the inhibitory response on ENaC channel. As a end result, Na ions moves from airway to respiratory epithelial cells. Again this creates a salt concentration gradient(30). Salt concentration gradient throughout the epithelium provoking water to be absorbed passively by way of osmosis in epithelial cells. Water present in thin mucus is absorbed in epithelial cells Causing mucus dehydration and mucus thickening As water follows sodium, the depth of ASL will be depleted and the cilia will be left in the mucous layer(32). As cilia can't successfully move in a thick, viscous environment, mucociliary clearance is deficient and a buildup of mucus occurs, clogging small airways(33). The accumulation of greater viscous, nutrient-rich mucus in the lungs lets in bacteria to hide from the body's immune system, causing repeated respiratory infections(34).

VIII.TREATMENT

Treatment of Cystic fibrosis can be broadly catagerized in 3 classes:

1) Treatment to get symptomatic relief: Here, Cystic fibrosis allied conditions or signs and symptoms are treated to elevate lifestyles expectancy of patients. It includes all the strategies to limit the respiratory microbial infection, developing metabolic enzymatic activity, increase Bronchial lumen diameter with the aid of clearing mucus, etc.

a) Antibiotics: The mucus clogs the airways and traps germs, like bacteria, leading to infections, inflammation, respiratory failure, and different complications. For this reason, avoiding germs is a top concern for people with CF. Respiratory infections in Cystic fibrosis causes irritation of upper respiratory organs end result in cytokine storm further decreasing luminal diameter leading to obstructed airway. With the goal of maintaining excellence of life. Intravenous, inhaled and oral antibiotics are used to treat chronic and acute infections. Antibiotics are without a doubt essential whenever pneumonia is suspected or a noticeable decline in lung function is seen. Colistimethate sodium (colistin) has been used in P. aeruginosa-related CF therapy, which acts via disrupting the integrity of the bacterial cell membrane. Aztreonam lysine (AZLI), Tobramycin (aminoglycoside antibiotic) also inhibit P. aeruginosa (35). Trimethoprim–sulfamethoxazole is effective in treating the coinfection of Stenotrophomonas maltophilia and P. aeruginosa.

b) Nutrient supplementation: People with cystic fibrosis have trouble absorbing fats, which implies they have bother absorbing vitamins that need fat to be absorbed. People with CF want to get fat soluble as well as water-soluble vitamins. Besides eating a nutritious diet, affected person take a CF-specific

multivitamin supplement. Vit D,Vit E,Vit K are essential to be supplied. Most humans with cystic fibrosis (CF) (80% to 90%) need pancreatic enzyme replacement therapy (PERT) to stop malnutrition. Treatment of pancreatic insufficiency with the aid of replacement of missing digestive enzymes approves the duodenum to desirably absorb nutrients and vitamins that would otherwise be lost in the faeces(38). stool softeners, laxatives, and prokinetics (GI-focused treatments) are frequently suggested.

c) Mucolytics*:* Mucolytics acts by thinning the produced mucus.Mucus is prepared via mucin which is internally bonded with disulphide bond(-s-s-). Disulphide bonds make the mucus more thick.So mucolytics acts by means of breaking these disulphide bonds. Ultimately it results into thinning of Mucus.Thin mucus is without any difficulty cleared with the aid of MCC. Herbal Mucolytics encompass Onion ,Garlic whilst N-Acetyl Cystein, CarbaCystein are synthetic Mucolytics.

*d)*Bronchiodilators*:* Bronchodilators can be taken before different treatments, such as mucus thinners, airway clearance techniques, and antibiotics. Bronchodilators, such as albuterol and levalbuterol hydrochloride are frequently inhaled via a biodevice that releases a specific amount of medication. Bronchiodialators widens the respiratory lumen which in the end helps patients with clogged airway to respire.

2) Treatment of Causal root: Because mutations in the CFTR gene are generally small, classical genetics strategies had been unable to accurately pinpoint the mutated gene.

a)Gene Therapy: Transferring the normal CFTR gene into the affected epithelium cells would end result in the manufacturing of functional CFTR protein in all target cells, without unfavorable reactions or an irritation response is the ultimate intention of Cystic fibrosis Gene therapy. There are two types of gene therapy that have potential to treat CF.

Non integrating type of Gene therapy works via introducing a piece of DNA with a correct copy of the CFTR gene in cells. Though DNA stays separate from the genome and is no longer permanent ,still cell can use the new copy of the CFTR gene to make normal CFTR proteins. It is quite particular remedy where there is no disruption to rest of the genome. That implies capacity of danger of side effects, inclusive of cancer, is low.Impact of the gene therapy might remain for several weeks or months. A person with CF would probably want to be treated with the gene therapy repeatedly for it to be effective.

Integrating gene therapy introduces a piece of DNA that consists of a correct version of the CFTR gene in humans affected cells. Here, The new copy of the CFTR gene would combine within host DNA and becomes a permanent part of their genome. It is permanent for the life of the cell. This implies that there is no need of repeated gene therapy. But there may be restricted control over the new copy of the CFTR gene that integrates into the genome. integrating gene therapy could have undesirable side effects, such as increasing the danger of cancer.

b) Gene modulators/CFTR correctors: Gene modulators immediately engaged in modification of root cause i,e, modification/mutation in Gene. CFTR modulator therapies are designed to correct the malfunctioning protein made by the CFTR gene.

i) IVACAFTOR(VX-770): FDA permitted Ivacaftor (Kalydeco, Vertex Pharmaceuticals) on January 31, 2012 as CFTR potentiator for the therapy of cystic fibrosis(42).It is chemically 2,4-Di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide.Potentiator implies that it will increase the probability that the faulty channel will be open and allow chloride ions pass through the channel pore. Ivacaftor increases the time the CFTR channel is open, permitting chloride ions to pass through the CFTR proteins on the surface of epithelial cells. ivacaftor majorly acts by enhancing gating function. Ivacaftor has effectively improved lung function and weight in sufferers with G551D. It has been verified to enhance the activity of the CFTR gene, improve lung function, limit exacerbations, and improve quality of life(43).It is used for cure of greater than 35 mutation type of cystic fibrosis. For improved outcomes , It is additionally given in combination with different Gene modulators. The precise mechanism is unknown, even though it may additionally be via decoupling the gating cycle and ATP hydrolysis cycle, or via increasing the ATP-dependent opening rate and slowing the closing rate.

ii) LUMACAFTOR (VX-809): Lumacaftor is chemically 3-{6-{[1-(2,2-Difluoro-1,3-benzodioxol-5-yl) cyclopropane carbonyl]amino}-3-

methylpyridin-2-yl}benzoic acid It was developed pharmacompany Vertex Pharmaceuticals. It is given in combination with ivacaftor under the brand title Orkambi®.This combination was accredited by the FDA in 2015. Lumacaftor had no medical use on its personal as a result it is available in combination. Lumacaftor supervises the protein folding of the CFTR-F508del mutation and thereby restores right localization of the protein. Lumacaftor moreover improves the conformational stability of F508del-CFTR, resulting in elevated processing and trafficking of mature protein to the cell surface.

iii) TEZACAFTOR (VX-661):Tezacaftor is a second generation CFTR corrector. It was developed via Vertex Pharmaceuticals. Tezacaftor was authorised via the FDA on February 12, 2018.FDA approved it in combination with ivacaftor under the brand name Symdeko® to manage cystic fibrosis. Tezacaftor is chemically 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-[1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)indol-5-yl] cyclopropane-1-carboxamide. Clinical studies have proven a massive limit in sweat chloride and an increase in the forced expiratory volume (FEV), a measure of lung function, following Tevacaftor/Ivacaftor therapy. Tezacaftor suggests its impact with the aid of modulating the position of the CFTR protein on the cell surface to the correct position, permitting for sufficient ion channel formation and increased in water and salt movement across the cell membrane. The concomitant use of ivacaftor is supposed to keep open chloride channel, increasing the transport of chloride, reducing thick mucus production. Tezacaftor prevents ivacaftor metabolism via the CYP3A4 pathway.

iv) ELEXACAFTOR (VX-445):Elexacaftor is also a CFTR corrector that works at an alternate binding site than tezacaftor. It promote functionality of the CFTR protein. Elexacaftor is chemically N-(1,3-dimethyl pyrazol-4-yl) sulfonyl-6-[3-(3,3,3-trifluoro-2,2-dimethyl propoxy) pyrazol-1-yl]-2-[(4S)-2,2,4-trimethyl pyrrolidin-1-yl] pyridine-3-carboxamide. It is found in a single pill with ivacaftor and tezacaftor.The combination is registered under trade name Trikafta® . This combination was accepted for medical use in the United States in 2019(44). Elexacaftor is viewed as a next-generation CFTR corrector as it possesses both a exclusive shape and mechanism as compared to first generation correctors. It was first triple combination product for cystic fibrosis manufactured via Vertex Pharmaceuticals. It is given to the patients 12 years of age and older who have at least one F508del mutation in the CTFR gene.

v) PTC124:Premature stop codons inhibit the process of translation before successful completion of process. PTC124 is an orally bioavailable small molecule which induces ribosomes to selectively read through premature stop codons during mRNA translation, to produce useful CFTR.PTC124 is additionally known as Ataluren. Ataluren will be furnished as a vanilla-flavored powder to be blended with water. It seems to work specially well for the stop codon 'UGA'.It is chemically 3-[5-(2-Fluoro phenyl)-1,2,4-oxadiazol-3-yl]benzoic acid.

3) Other aspects:

a*) Lung transplantation* : Lung Transplantation is regarded when lung function declines to the factor where assistance from mechanical device is required or someone's survival is threatened(37).

b) *Surgery* : Newborns with intestinal obstruction generally require surgery(38).

c) *Insulin Supplements* : Use of insulin injections or an insulin pump is additionally recommended for cystic fibrosis-related diabetes.

d) *Treatment of Osteoporosis*: Bisphosphonates taken by means of mouth or intravenously can be used to improve the bone mineral density in humans with cystic fibrosis.

e) *Treatment of Infertily* : Female infertility can also be overcome by using assisted reproduction technology(embryo transfer techniques).Surrogacy is also a opportunity for female with CF.. Male infertility may be overcome with testicular sperm extraction (39).

IX.CONCLUSION

Cystic fibrosis (CF) is one of the most widely known and most common monogenetic problems in the Caucasian population. Nearly 200 mutations have been recognized in the CFTR gene. In cystic fibrosis (CF) there is an alteration in the viscosity and tenacity of mucus produced at epithelial surfaces. The ‘low volume’ hypothesis recommended that the absence of CFTR supposed that the total mass of NaCl in CF ASL was reduced, and that the osmotic force for water

transport to the lumen lessened. As a result, the airway surface became dehydrated and mucociliary clearance (MCC) retarded. Further study of parallel tissue-specific regulatory mechanisms, especially in organs that appear to be protected in CF, can also provide insights into CF pathology and plausible disorder treatments. Mechanical devices and inhalation medications can additionally used to alter and clear the thickened mucus. Denufosol, an investigational drug,it opens an alternative chloride channel, helping to liquefy mucus(36). PERT formulations be given to treat abdominal pain, flatulence, constipation. over the years since the CFTR gene was discovered, the proof of principle of gene transfer to the airway has been confirmed and partial correction in ion transport achieved.(41). Ivacaftor is the first FDA-approved therapy to goal the primary defect in CF.CFTR modulators like elexacaftor and different corrects the mutated CFTR Gene.

X.RESULT

The CFTR gene, additionally recognised as ABCC7, contains 27 exons and encodes a chloride channel that is unique within the ABC transporter superfamily. CFTR not only permits chloride ions to be drawn from the cell and into the ASL, however it additionally regulates another channel called ENac, which allows sodium ions to leave the ASL and enter the respiratory epithelium. F508del is the primary type of mutation in CFTR gene in which there is deletion of Phenyl alanine amino acid located in position 508 of the protein chain. Despite CF being primarily a disease of epithelial cells, CFTR expression has also been recognized in nonepithelial cells, for example, hypothalamic neurons and cardiomyocytes. Although relatively widespread, CFTR expression shows tissue-specific regulatory mechanisms that act at multiple levels, including transcription, post-transcription and translation .UK Cystic Fibrosis Gene Therapy Consortium has been formed in recent years to develop cystic fibrosis gene therapy for medical benefit is focusing current efforts on a non-viral approach. Inhaled antibiotics are accessible on the market. Colistin, tobramycin, aztreonam lysine and, more recently, levofloxacin have been permitted in different countries for CF patients. CFTR modulators like ivacaftor, lumacaftor, tezacaftor are found to be finest treatment of cystic fibrosis.

ABBREVIATIONS

CF	- Cystic Fibrosis.
CFTR	-Cystic Fibrosis Transmembrane Conductance Regulator.
mRNA	-Messenger Ribose Nucleic Acid.
ABC -	ATP-Binding Cassette transporters.
CBAVD	- Congenital Bilateral Absence of Vas Deferens.
ENaC	- Epithelial Sodium Channel.
TJ	- Tight Junctions.
GJ	-Gap Junctions.
MCC	-Muco-Cilliary Clearance.
IRT	-Immunoreactive Trypsinogen Test.
CT	-Computed Tomography.
MRI	-Magnetic Resonance Imaging.
UK	-United Kingdom.
ASL	-Airway Surface Liquid.
AZLI	-Aztreonam Lysine.
PERT	-Pancreatic Enzyme Replacement Therapy.
FEV	-Forced Expiratory Volume.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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