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AN OVERVIEW ON CYSTIC FIBROSIS

Dr. Rama Brahama Reddy*1, Ch. Sri Lakshmi*2, G. Suvarna*3

*1Principal & Professor, Department Of Phytochemistry, Nalanda Institute Of Pharmaceutical Sciences, Guntur, AP, India.

*2Associate Professor, Department Of Pharmaceutical Analysis, Nalanda Institute Of Pharmaceutical Sciences, Guntur, AP, India.

*3Student, Nalanda Institute Of Pharmaceutical Sciences, Guntur, AP, India.

ABSTRACT

Cystic fibrosis is an autosomal recessive disease caused by mutations of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). Here we summarize, at the basic descriptive level, clinical and genetic characteristics of cystic fibrosis gene mutations, while emphasizing differences between CF mutations found in Chinese pediatric CF patients compared to those found in Caucasian CF patients. In addition, we describe animal models used to study human cystic fibrosis disease and highlight unique features of each model that mimic specific human CF-associated signs and symptoms.

CF is as a result in mutation in cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation in CF gene is (ΔF508). In ΔF508 mutation the Δ is deleted from three nucleotides result in loose of phenyl alanine amino acid at 508th location on protein. CF caused by mutation of (ΔF508) account two third of cases worldwide and difficulty in breathing and eventually severe lung infection. The most common signs is salty skin, growth rate retardation and loss of weight, however the food intake is normal, accumulation of thick sticky mucous in chest region which is difficult to control because of it's sticky in nature. Different diagnosis categories are used in screening of CF, such as sweat test or genetic testing and new born screening. In new borns, measuring the level of immunoreactive trypsinogen is valuable in detecting CF. Although there is no healing in CF patients, many ways are available for treatment. [1]

Keywords: Animal Model, CFTR, Chinese, Clinical Feature, Cystic Fibrosis, Mutation.

I. INTRODUCTION

CF is a lifelong genetic disease that result in formation of thick, sticky mucous in lung, pancreas and other organs. In lung, the airway is blocked by mucous causing lung damage and difficulty in breathing and eventually severe lung infection. In pancreas the most common feature is obstruction of pancreatic duct, which is lead to limitation in passage of pancreatic enzyme resulting in digestive problems. According to many surveys which have been done by health organizations, survival age from CF has improved significantly over past 50 years, with increasing of median age of death by CF (Elborn, 2000 and Dodge, 2007). This improvement has been attributed by several factors including nutritional improvement, early monitoring of the individuals with early symptoms of CF and using drug of choice for treatment.

CF is caused by mutation in genes that encode cystic fibrosis transmembrane conductance regulator protein, which is expressed in many epithelial cells and blood cells (Reisin,1994 and Mehta, 2005).CF is vary between patients and even children of same CFTR genotype and polymorphism. Severe pulmonary disorder with evidence of gene to gene interaction has been shown that result from polymorphism in transforming mannose binding lectin 2 gene and growth factor B1(Drumm, 2005 and Collaco, 2008). In addition, the prevalence of CF is varied from country to country and depends on ethical background, for example the incidence of CF in white American is higher than Latin American and the incidence of CF in African American is very low comparing to other ethical backgrounds.[2]

EPIDEMOLOGY:

Worldwide, approximately 89 000 individuals are living with cystic fibrosis, including approximately 31 450 people in the US. The prevalence of cystic fibrosis is similar between the US (7.97 per 100 000) and European Union (7.37 per100 000). Among people with cystic fibrosis in the US, approximately 3.5%identified as Black or African American, 91.4% as White, and 5.1% as other, which included people who identified as American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, some other race, or 2 or more races. Among

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people with cystic fibrosis in the US, approximately 9.8% identified as Hispanic ethnicity and approximately 91.2%as non-Hispanic ethnicity.

Approximately 85.5%of people in the US have the phenylalanine deleted at position508(pPhe508del) gene variant, also known as F508del. A meta-analysis described 24 to 54 CFTR gene variants in regions from South Asia, the Middle East, and East Asia, but populations of European ancestry are likely underestimated due to ascertainment bias. In populations from 10 countries in Latin America, F508delwas the most frequent CFTR variant, ranging from 23%to 59%. Rare variants (<1% of individuals) in Latin American populations reflect diverse Native, African and European heritages.[3]

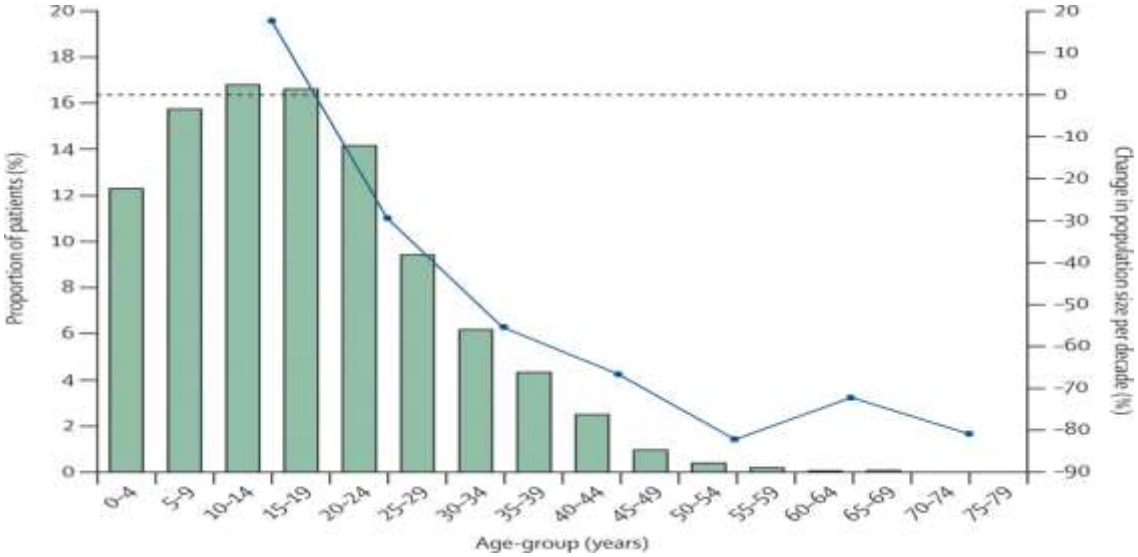

Figure 1: Epidemology of cystic fibrosis

PATHOPHYSIOLOGY:

Pathophysiological changes in cystic fibrosis are primarily due to loss of CFTR protein function and its essential role as an anion channel in apical epithelia. Loss of function of the CFTR protein alters hydration and pH concentration in exocrine ducts, leading to obstructed and dilated exocrine glands in multiple organs. Reduced CFTR function in the sweat gland leads to increased salt losses and higher chloride concentrations in sweat. The mucinous obstruction of pancreatic acini and ducts biliary ducts and glandular obstruction of the vas deferens and submucosal glands in the airways leads to organ destruction and fibrosis.

The endobronchial space of airways in people with cystic fibrosis typically becomes infected initially with bacterial pathogens such as Staphylococcus aureus and Haemophilus influenzae and later with Pseudomonas aeruginosa. These infections are associated with a neutrophilic inflammatory response and persistent mucopurulent plugging that leads to bronchiectasis. With the availability of CFTR modulator therapies, the pathogenesis of clinical disease is changing, and early intervention may partially prevent development of multiorgan pathology. In utero administration of the CFTR modulator ivacaftor to ferret foetuses with the glycine at residue551 replaced by the aspartic acid (pGly551Asp; legacyG551D*)* variant reduced meconium ileus and improved pancreatic exocrine function, growth, and survival.

Morethan700disease-causinggenevariants of CFTR have been identified. The most common are grouped into 6 classes by the processes through which they can cause CFTR dysfunction. Three classes (I, II, III) typically result in minimal or no CFTR and are often associated with the highest sweat-chloride values, severe lung disease, and pancreatic insufficiency whereas classes IV, V, and VI are associated with some residual protein function, may have lower sweat chloride, and milder disease. Although there are examples in which single variants affect multiple mechanisms, matching of cystic fibrosis variants with biological pathways.

Cystic fibrosis transmembrane conductance regulator (CFTR) variants can be generally classified in 6 mechanistic classes based on how they alter CFTR RNA transcription, protein trafficking, channel function, and stability. Reported prevalence, and clinical features (sweat chloride, pancreatic insufficiency) are summarized for exemplar variants per class. The CFTR2 database provides information on all the CFTR variants and updates

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it as information becomes available. The figure is adapted from Boyle and De Boeck. N/A indicates number not available.[3]

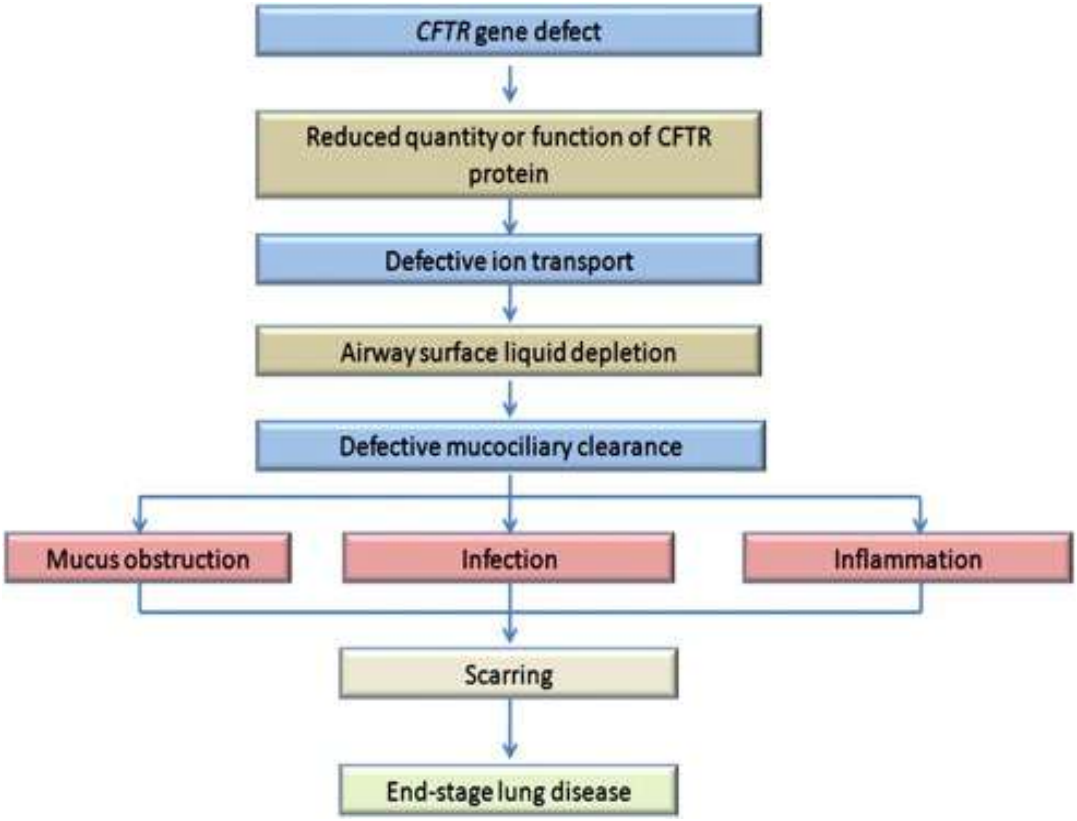

Figure 2: Pathophysiology of CFTR

II. CLINICAL FEATURES OF CYSTIC FIBROSIS

CF is caused by dysfunctional transport of chloride and/or other ions (such as sodium and bicarbonate) that leads to generation of thick, viscous secretions (Eg: mucus) in the lungs, pancreas, liver, intestine, and reproductive tract and increased salt content in sweat gland secretions. Ultimately, progressive lung disease is the main cause of CF complications and patient mortality. The course of disease varies greatly and can begin from a few months after birth to decades after birth, with many patients exhibiting mild or atypical symptoms. Therefore, clinicians should take care to avoid excluding CF as a possible diagnosis in cases where patients exhibit only a few typical CF signs and symptoms.

Respiratory tract involvement

Typical respiratory manifestations of CF include a persistent productive cough, hyperinflation of lung fields on chest radiograph, and pulmonary function test findings indicative of obstructive airway disease. As the disease progresses, repeated infections associated with inflammatory cell accumulation and release of cell contents damage bronchial walls, leading to loss of bronchial cartilaginous support and muscle tone and eventual bronchiectasis. Disease progression includes acute exacerbations of cough, tachypnea, dyspnea, increased sputum production, malaise, anorexia, and weight loss. These acute events are associated with acute, transient loss of lung function that improves with treatment but that often progresses to permanent loss of lung function over time. Although CF patients often vary, transient airway infection with pathogenic bacteria often first occurs early in life. After years of CF disease, chronic airway infection with either Staphylococcus aureus or Pseudomonas aeruginosa often becomes established and is often detected based on radiographic evidence of bronchiectasis.

In addition, airways of CF patients can be colonized or infected by other species of microbes, including Stenotrophomonas malt philia, Achromobactin xylocopids, Burkholder cepacian complex, nontuberculous mycobacteria (especially Mycobacterium avium complex and Mycobacterium abscesses), and the filamentous

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fungus Aspergillus fumigatus. Continuous airway colonisation and infection by bacteria (especially P aeruginosa) can enhance the inflammatory response by triggering neutrophils to release large amounts of DNA and matrix proteins into airways. These substances, coupled with CF-induced impaired airway clearance functions and chronic inflammation, increase airway mucus viscosity. Current research efforts are underway to identify additional bacterial species in CF patient airways, including obligate anaerobes that may be identified using next-generation sequencing technology.

Sinus disease

The majority of CF patients develop sinus disease. Sinus disease can present with chronic nasal congestion, headaches, cough caused by chronic postnasal drip, and sleep disturbances. Sinus infections can trigger lower respiratory exacerbations in some patients, although organisms found in sinuses do not always match those recovered from lungs. Meanwhile, some individuals with isolated chronic rhinosinusitis have signs and symptoms suggestive of CFTR dysfunction that do not satisfy CF diagnostic criteria, prompting clinicians to refer to this affliction as CFTR-related disorder. Notably, in one case-control study, the single *CFTR* mutation rate for a group of chronic rhinosinusitis cases was significantly higher than the corresponding rate for the general population (7% versus 2%).

Digestive system diseases

Approximately two-thirds of CF patients exhibit CF insufficiency of the exocrine pancreas from birth, with an additional 20% to 25% developing this condition during the first several years of life, and most exhibiting signs of fat malabsorption by one year of age. CF-associated pancreatic disease tends to be progressive; many patients with apparently normal or marginal pancreatic function at birth develop overt evidence of pancreatic insufficiency in childhood or adulthood. Overall, approximately 85% of individuals with CF eventually develop clinically significant pancreatic insufficiency.

Common symptoms and signs of pancreatic insufficiency include steatorrhea, characterized by frequent, bulky, foul-smelling stools that may be oily, as well as failure to thrive or poor weight gain resulting from malabsorption of fat and protein. Infants with severe untreated pancreatic insufficiency occasionally present with edema, hypoproteinaemia, electrolyte loss, and anemia due to malabsorption of macro-and micronutrients. Some patients also may present with symptoms caused by deficiencies of the fat-soluble vitamins A, D, E, and K. Vitamin K deficiency can present as a coagulopathy and vitamin D deficiency as rickets. Continued defective ductular and acinar pancreatic secretion functions lead to progressive pancreatic damage that can trigger acute or recurrent pancreatitis. Moreover, patients with exocrine pancreatic insufficiency often develop dysfunction of the endocrine pancreas, leading to glucose intolerance and CF-related diabetes.

Reproductive system diseases

More than 95% of men with CF are infertile because of defects in sperm transport, although spermatogenesis is not affected. Intriguingly, nearly one-half of all men with congenital bilateral absence of the vas deferens and normal lung function possess two CFTR mutations. Meanwhile, females with CF are less fertile than normal healthy women, due to malnutrition and the production of abnormally tenacious cervical mucus. Nonetheless, females with CF may become pregnant and those who do should be counselled accordingly about contraception and childbearing decisions. Indeed, comprehensive genetic counselling is essential for prospective parents with CF.

Nutrition and growth disorders

Patients with CF have reduced bone mineral content and increased rates of fractures and kyphoscoliosis. In all age groups, up to 30% of patients present with clinically significantly reduced bone density, while this proportion approaches 75% in adults with CF, Clubbed fingers (and toes) and hypertrophic osteoarthropathy can also occur in patients, with clubbing of fingers (and toes) found commonly in patients with long-term disease, while hypertrophic osteoarthropathy is only rarely observed.

SIGNS AND SYMPTOMS OF CF:

CF is holistic diseases, i.e. result in several organ impairment in the body with differences in severity and out coming of the condition. The most common signs is salty skin (Quinton, 2006), growth rate retardation and loss of weight, however the food intake is normal (Hardin, 2004), accumulation of thick sticky mucous in chest

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region which is difficult to control because of it's sticky in nature (De Lisle, 2009), coughing is frequent with incidence of chest infection and shortness of breath (O'Malley, 2009). In male symptoms include infertility which is account in 97% of men with CF are infertile, in those men sperm production is normal but missing vas deference make them infertile but recently study showed that they could have baby with assistance of reproductive techniques (McCallum, 2000).

In women, thickening of cervical mucosa and malnutrition cause difficulty infertility and in severe case malnutrition may cause disrupt of ovulation (Gilliam, 2000). In children the most common symptom is meconium ileus and when they grow the need more exercise to eliminate sticky mucous in alveoli (blackman, 2006 and Ratjen, 2009). Mutation of protein in some patient leads to change in mutated epithelial cells and abnormality in mucous viscous production (De, 2009). In CF growth failure is related to multi factor including; abnormality in food absorption in GIT and chronic lung infection due to accumulation of mucous substance (Hardin, 2004). Coagulation disorder particularly during foetal life is another symptom of CF. In young children vitamin K absorption is impaired due to sensitivity of young children to vitamin K absorption and very small amount of vitamin K across placenta result in low reserve of vitamin K.

As a result of Clotting factors (II, VII, IX, and X) highly vitamin K dependent, coagulation problem is happen due to low level of vitamin K (Reaves, *2010*). In pancreatic disorder by CF, both type of diabetes could be seen due to damage of Langerhans cells that responsible for insulin production and blood sugar regulation (Alves, 2007 and Haworth, 1999). In addition poor vitamin intake because of malabsorption which is require for calcium and phosphorous regulation cause bone weakness and osteoporosis which is highly susceptible to fracture (Haworth, 1999).[1]

III. CAUSES

CF is result in mutation in cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation in CF gene is (ΔF508). In ΔF508 mutation the Δ is deleted from three nucleotides result in loose of phenyl alanine amino acid at 508th location on protein. CF caused by mutation of (ΔF508) account two third of cases worldwide (Mitchell, 2007). CF can be prevented in those who have only one copy (alleles) of CFTR gene.

Although most of the people have two copies but when none of the copies produce functional CFTR, CF develops thus it is regarded as an autosomal recessive disease. CFTR is located in 931.2 locus chromosome, and it is 230,000 base pairs in length which produce a protein with 1,480 amino acid length. CFTR genes produce a halide anion channel which is important in sweat, digestive juice and mucous secretion and by having ATP-hydrolysing domain CFTR allow protein to use energy in form of ATP and it possess tow domain which is used by protein to across the cell membrane. In addition, there is increasing evidence that genetic modifiers besides CFTR modulate the severity and frequency of the disease such as mannan-binding lectin, which is involved in innate immunity by accelerating phagocytosis of microorganisms. Polymorphisms in one or both mannan-binding lectin alleles that result in lower circulating levels of the protein are associated with a threefold higher risk of end-stage lung disease and increased burden of chronic bacterial infections (Mitchell, 2007).[2]

DIAGNOSIS AND MONITORING:

Different diagnosis categories are used in screening of CF, such as sweat test or genetic testing and new born screening. In new born, measuring the level of immunoreactive trypsinogen is valuable in detecting CF (Daves, 2007). Trypsinogen level elevated in individuals who have one copy of mutation in CFTR gene or some time trypsinogen level elevated in individuals even with two normal copies of CFTR gene, for this result new born screening causing disagreement (Ross, 2008, Assael, 2002).

In most states or countries they do not perform screening for CF and the individuals diagnosed after symptom appearance (Michell, 2007). In general, sweat test is a common test in screening of CF; it's done by applying medicine that enhances sweating (Pilocarpine). Iontophoresis is used to deliver the medication through the skin in which one electrode placed on skin and electrical current passed through it and another electrode placed on to applied medication. After that delivered sweat collected in a capillary tube or on filter paper to detect the amount of sodium and chloride. In CF case, the amount of sodium and chloride increased while the amount of thiocyanate decreased in their saliva (Mina Roski, 2008).

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In individuals with pulmonary symptom related to CF, X-ray and CAT scan are used to detect the size of infection and damage of lung. Bacterial examination of sputum is required for detecting the organism which causes infection of lower respiratory tract. Blood test is also used in diagnosis of CF by detecting vitamin deficiency and liver function. Insufficient digestive enzyme due to pancreatic damage could be detected by using DXA scan for testing faecal elastase. In mild form mutation of CFTR gene, sweat test is insufficient in diagnosis of CF because the change of chloride concentration is less than (60 mM/L), in this case nasal trans epithelial potential differences (TEPD) are commonly used. Abnormalities in exocrine glands related to CF, cause increasing in water and sodium reabsorption and reduction in chloride secretion, these change result in higher TEPD than normal which is used as a useful form of diagnosis in people with mild form of CF (Freudianism, 2009).[2]

IV. TREATMENT

Long-term Therapies

For patients with cystic fibrosis, at least quarterly visits with a specialized, multidisciplinary team, including physicians, nurses, social workers and dietitians, are recommended to monitor for disease progression and treat multiorgan manifestations. Annual screening for psychosocial health concerns is recommended in children aged 12 years or older Monitoring for comorbidities includes annual oral glucose tolerance testing (_10 years) for cystic fibrosis– related diabetes,50 dual-energy x-ray absorptiometry scanning every 2 to 5 years (>8 years) for bone density, and colonoscopy every 5 years (_40 years) for colorectal cancer.

Disease progression is measured by monitoring for trends in nutritional status (height, weight, body mass index [BMI], calculated as weight in kilograms divided by height in meters squared), lung health (spirometry, respiratory microbiology, chest imaging), and assessments for pulmonary exacerbations manifest as an acute worsening of respiratory symptoms and lung function (percent predicted FEV1 [ppFEV1]) and usually require oral or intravenous antibiotic treatments specific for respiratory microbiology, increased airway clearance therapies (eg., high-frequency oscillatory percussive devices), and high-calorie, high-protein diets to limit permanent loss of lung function.44,47 In a randomized clinical trial of 989 participants with cystic fibrosis and pulmonary exacerbation defined by providers as necessitating intravenous antibiotic treatment, antibiotic therapy duration of 10 days was noninferior to 14 days, based on the outcome of lung function (change in ppFEV1) among those who had improved lung function and symptoms within 7 to 10 days of treatment (mean ppFEV1 change, 12.8% vs 13.4%; difference, −0.65%;95%CI, −3.3%to2.0%).

In addition, those without improved lung function or symptoms within days 7 to 10 days, 21days of intravenous antibiotics was not superior to 14days47(mean ppFEV1 change, 3.3% vs 3.4%; difference, −0.10%; 95% CI, −1.3% to 1.1%).47 In subsequent analysis, lung function improvement was higher for those treated in the hospital(meanppFEV1 change,8.0%; 95%CI,6.7%to9.4%) vs at home(meanppFEV1change,5.0%;95% CI, 3.5%to 6.5%).

Long-term pharmacological pulmonary therapies such as mucolytics to thin secretions to facilitate clearance from the upper and lower airways (such as dornase alfa), airway surface liquid hydration (inhaled hypertonic saline, mannitol), and anti-inflammatory drugs (azithromycin, ibuprofen) have been based on phase 3 randomized, placebo-controlled clinical trials. In a clinical trial of968patients with cystic fibrosis, dornase alfa compared with placebo increased the mean percent change inFEV1by5.8%(SE,0.7%) vs0%(SE, 0.6%) and reduced the proportion of patients with 1 or more pulmonary exacerbations from 89 (27%) to 61 (19%).64 In a clinical trial of 164 participants, 7%hypertonic saline compared with 0.9% saline reduced pulmonary exacerbations (mean exacerbations per participant, 0.39 [7% saline] vs 0.89 [0.9% saline]); difference, 0.5; 95% CI, 0.14-0.86; P = .02).65 In a randomized clinical trial of 185 patients chronically infected with *P aeruginosa*, azithromycin, compared with placebo, significantly improved lung function from baseline (ppFEV1, 4.4% vs −1.8%; mean difference, 6.2%; 95%CI, 2.6%-9.8%) at end of 168 days of treatment.

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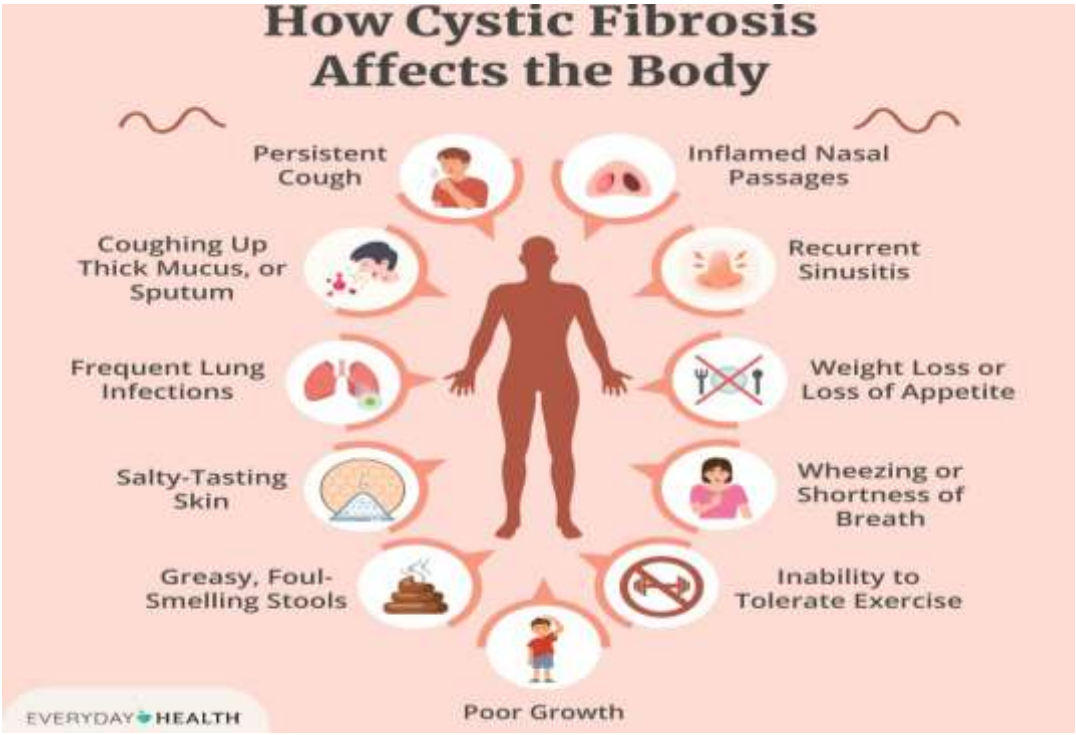

Figure 3: How cystic fibrosis affects the body

CFTR Modulator Therapies

CFTR modulator therapies act by 2 mechanisms to enhance CFTR function. Potentiators, like ivacaftor, increase the probability that the protein channel is open, so chloride or bicarbonate can flow more easily through the cell membrane. Correctors, like lumacaftor, Tezacaftor and elexacaftor, improve channel quantity at the cell surface by helping the protein fold properly, enable transport to the cell surface. Severe variants such as F508del need both potentiators and correctors to improve channel quantity and function. Four modulators are currently approved by US and European drug regulatory agencies, and eligibility for each treatment depends on the specific CFTR genetic variants present.

Ivacaftor is available as a monotherapy, and lumacaftor-ivacaftor, tezacaftor-ivacaftor, and elexacaftortezacaftor- ivacaftor are available as combination therapies. Ivacaftor (formerlyVX-770) was the first CFTR modulator tested in randomized clinical trials of patients with cystic fibrosis in 2006. Ivacaftor was tested first for patients with cystic fibrosis who have a G551D-CFTR variant where the CFTR protein is transported to the cell membrane, but the CFTR channel does not open properly. In a randomized clinical trial of 161 patients with at least 1 copy of G551D, compared with placebo, patients at 24 weeks' follow-up had improved ppFEV1 (10.1%vs −0.4%; mean difference, 10.5%; 95%CI, 8.5%-12.5%), a 55% reduction in pulmonary exacerbations (28 vs 44; rate ratio, 0.43; 95% CI, 0.27-0.68), and increased weight (3.1 kg vs 0.4 kg; mean difference, 2.7 kg; 95% CI, 1.3-4.1 kg).68 Respiratory symptoms were scored on a 100-point scale on the respiratory domain of the Cystic Fibrosis Questionnaire revised (CFQ-R), for which higher numbers indicate a lower effect of these symptoms on quality of life (minimal clinically important difference, 4 points). Ivacaftor improved respiratory symptom scores by 8.6 points relative to placebo (5.9 vs −2.7; mean difference, 8.6; $P < .001$). Ivacaftor is approved for patients 4 months or older. For people with 2 copies of the F508del variant, ivacaftor alone did not improve CFTR activity or demonstrate clinical efficacy.

These patients required the combination of corrector and potentiator medications. Randomized, placebo-controlled clinical trials of first-generation correctors, lumacaftor or tezacaftor, in combination with ivacaftor demonstrated modest improvements in ppFEV1 and reduction in pulmonary exacerbations in patients homozygous for the F508del variant. When the 2 correctors were combined with the potentiator, ivacaftor, in phase 3 randomized trials, this triple combination was effective and had similar clinical responses for people with cystic fibrosis who were either homozygous for the F508del variant or who had 1 copy of the F508del

variant and 1 copy of a minimal function variant on the second allele. In a randomized clinical trial of 107 patients who were homozygous for the F508del variant, the elexacaftor-tezacaftorivacaftor combination compared with tezacaftor-ivacaftor alone increased ppFEV1 (10.4%vs0.4%;difference, 10.0%;95%CI, 7.4%to 12.6%), decreased sweat chloride concentration (−43.4vs 1.7mEq/L; difference, −45.1; 95%CI, −50.1 to −40.1 mEq/L), and improved respiratory symptom scores above the 4-point minimally important clinical difference for CFQ-R (16 vs −1.4; difference, 17.4; 95%CI, 11.8 to 23) at 4 weeks' follow-up. Elexacaftor-tezacaftor-ivacaftor is approved for patients aged 2 years or older; approximately 90% of people with cystic fibrosis, including for those with variants that have demonstrated in vitro culture response to treatment.80,90-92 This technique known as the typing has increased access to therapy with modulator drugs among people with rare (<1%) CFTR variants.

Ivacaftor and its combination CFTR modulator were generally well tolerated and had similar safety profiles in phase 3 studies involving younger age groups. 69-71,74,75,80,90,91,93,94 Compared with placebo, elexacaftor-tezacaftor-ivacaftor had a similar incidence of adverse events (93.1% vs 96.1%) including headache (17%), upper respiratory tract infection (16%), abdominal pain (14%), diarrhea (13%), exanthem (10%), increased alanine transaminase (10%), or aspartate transaminase (9%). Serious adverse events were less common in the treatment group (13.9% vs 20.9%). For all CFTR modulator therapies, liver function monitoring is recommended quarterly for the first year of treatment and then annually.67,72,76,78 Ophthalmologic examinations for children are recommended annually based on toxicology studies of ivacaftor that identified cataracts in juvenile rats, although this adverse effect was not observed in human trials. Drug interactions are important considerations because ivacaftor and combination therapies are both substrates and inducers inthecytochromeP450(CYP3A) pathway.[3]

V. CONCLUSION

Cystic fibrosis affects approximately 89000 identified people worldwide and is associated with a spectrum of disease related to exocrine dysfunction, including chronic respiratory bacterial infections and reduced life expectancy. First-line pulmonary therapies consist of mucolytics, anti-inflammatories, and antibiotics, and approximately90% of people with cystic fibrosis2yearsandolder benefit from a combination of ivacaftor, tezacaftor, and elexacaftor.

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