Recent outline of Treatment lines of Cystic Fibrosis in Children

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Conflict of interest: None declared.

Funding: No funding sources

Abstract

Background: In cystic fibrosis (CF), respiratory disease is the main factor that influences the outcome and the prognosis of patients. Bacterial infections being responsible for severe exacerbations. The etiology is often multi-microbial with resistant strains. Recently, CFTR modulator therapy showed promising results in slowing the disease or even stopping the damaging effects. However, until the discovery of a specific targeted therapy for every pathogenic mutation, the lung must be treated, and its function carefully preserved. Therefore, besides clearance techniques and mucolytic therapy, the antibiotic therapy plays a crucial role in CF lung disease management and life expectancy improvement. The main goals of antibiotic therapy in CF are the prevention, eradication, and control of CF-associated respiratory infections. General principles of antibiotic therapy are to introduce aggressive treatment from the beginning, in higher doses than usual, with prolonged duration of therapy (2–4 weeks), and association of nebulized antibiotics.

Keywords: Treatment lines, Cystic Fibrosis

Tob Regul Sci.™ 2023;9(1): 7038 - 7048

DOI: doi.org/10.18001/TRS.9.1.498

Introduction:

Cystic fibrosis (CF) is the most common fatal genetic disease among Caucasians, occurring in 1 in 3,000 live births. According to the international registries, ~150,000 patients have a diagnosis of CF worldwide Based on the improvement in the nutritional and clinical care of the patients and setting CF centers with a multi-disciplined approach, general characteristics and the survival rates of CF patients have been changed remarkably. After the contribution of cystic fibrosis transmembrane conductance regulator protein (CFTR) modulator therapies, these changes will be more prominent in especially high-income countries. However, other factors in the diagnosis and treatment of patients in developing countries, even patients receiving CFTR modulators in high-income countries should be taken into account. Increased life expectancy, higher costs of new

treatment modalities and a better understanding of genetics, call for a more sophisticated approach to these patients.

Treatment

I.Respiratory system:

A. Antibiotics are prescribed for Preventing and controlling lung infections, mainly consist of inhaled forms of azithromycin, tobramycin, aztreonam and levofloxacin. Other antibiotics recommended are ciprofloxacin, cephalexin, amoxicillin, and doxycycline depending on the sensitivity patterns. The 2013 CF pulmonary guidelines recommend oral azithromycin only for patients with persistent P. aeruginosa cultures but not for patients with nontuberculosis mycobacteria, as there is evidence of resistance. Additionally, the anti-infl ammatory effects of azithromycin are beneficial in patients with CF ***(1).***

- ***New antimicrobials and methods of delivery:***

1. Inhaled aztreonam:

Inhaled aztreonam, for the treatment of P. *aeruginosa* infections in CF patients. It is an aerosolized formulation of the monobactam antibiotic aztreonam and lysine. In contrast, the intravenous formulation of aztreonam contains arginine which can cause airway inflammation ***(2).***

2. Levofloxacin inhalation solution

Aerosolized levofloxacin is another new pharmaceutical agent developed for the treatment of P. aeruginosa pulmonary infections in patients with CF. Levofloxacin is a second generation fluoroquinolone that causes cell death by inhibiting topoisomerase, an enzyme required for DNA synthesis. It has properties that render it particularly effective against bacterial infections in the CF lung. Thickened mucus layers in the lung of CF patients have been shown to contain areas of low oxygen tension, for example. In vitro studies of the effect of oxygen limitation on antimicrobial activity against *P.aeruginosa* demonstrate that,unlike tobramycin, amikacin and aztreonam, *P.aeruginosa* minimum inhibitory concentrations (MICs) and time–kill curves for levofloxacin are similar under aerobic and anaerobic conditions ***(3).***

The same investigators have confirmed that, in comparison to aztreonam and aminoglycosides, levofloxacin has the most rapid rate of killing among P. aeruginosa isolates and its bactericidal activity is not affected by sputum ***(3).*** It is also may also have anti-inflammatory effect ***(4).***

Levofloxacin produced a dose-dependent reduction of both TNF-α and *P. aeruginosa* lipopolysaccharide-induced IL-6 and IL-8 levels in cultured human airway epithelial cells. Phase I studies of safety, tolerability and pharmacokinetic parameters of inhaled levofloxacin in stable CF patients showed the drug to be safe, resulting in low serum levels. This should result in a very low risk of systemic toxicities such as tendinopathy or arthropathy. A subsequent phase II randomized, placebo controlled study of 151 CF patients with *P.aeruginosa* infection demonstrated that inhaled levofloxacin 240 mg twice daily for 28 days resulted in an 8.7% increase in FEV1 percent predicted compared to placebo ***(5).***

3. *Tobramycin inhalation powder*

Tobramycin inhalation powder (TIP) has the advantages of being able to be delivered very quickly (in approximately 5 min) using a "podhaler™" inhalation device and having good lung delivery *(5).*

Initial pharmacokinetic studies demonstrated that TIP could achieve higher maximal sputum concentrations comparedto TIS *(5).*

4. Colistin inhalation powder

Colistimethate sodium (colistin), a cationic polypeptide antibiotic which functions by disrupting the bacterial cell membrane, can also be delivered as an encapsulated dry powder formulation for inhalation. Colobreathe comes as capsules containing the equivalent of 125 mg colistimethate sodium (1662500 IU) in fine particle form. One inhaled capsule delivers the equivalent of a nebulized dose (≥2 MU) *(6).*

5. *Inhaled liposomal amikacin*

Another novel method of delivery is the packaging of antibiotics within liposomes for aerosolization. Arikace, inhaled liposomal amikacin, contains high concentrations of aqueous, water soluble amikacin, an aminoglycoside, encased within a liposome. Because the liposome is very small and has a neutral charge (shielding the positively charged amikacin from the negatively charged CF sputum), the drug is able to effectively penetrate into CF sputum and bacterial biofilms**.**Once at the site of infection, liposomes release the active drug, amikacin, upon exposure to rhamnolipids, a by-product of the P. aeruginosa bacteria itself *(6).*

B. Control of airway inflammation: NSAIDs, inhaled and systemic steroids and cromolyn *(7).*

- New guidelines released in 2013 show ibuprofen can prevent the loss of lung function in children under age 18 years *(1).* Ibuprofen is the only anti-inflammatory drug recommended for chronic use in patients with CF. High doses are known to inhibit migration and aggregation of neutrophils throughout the body, including the lungs *(8).*

hyperactive inflammatory response with continuous neutrophil influx results in irreversible airway damage in CF *(8).*

Although ibuprofen has a protective effect on the airways, serum levels must be maintained at high doses with a peak plasma concentration of 50 to 100 mcg /mL. Lower doses have been shown to have a proinflammatory effect on mucosa and can lead to disease progression *(8).*

- Corticosteroids are recommended in patients with asthma or in acute exacerbations but are not to be used for prophylaxis *(11).*

C.Reducing viscoelasticity and removing thick, sticky mucus from the lungs and dilating the airways: inhaled β agonists with humidified oxygen; a 3–6% hypertonic saline solution and dornase alfa are recommended *(11).*

- During CF exacerbations, an inhaled beta2-adrenergic agonist is recommended to treat acute hyperresponsiveness *(1).*

D.Airway clearance therapy to clear mucus buildup is recommended for all patients to maintain adequate lung function ***(11).***

There are a variety of airway clearance techniques, including conventional chest physiotherapy, positive expiratory pressure (PEP) therapy, high-pressure PEP therapy, active cycle of breathing techniques, autogenic drainage, airway oscillating devices (e.g., Flutter®, Cornet®, Acapella®, Quake®, Aerobika®, and intrapulmonary percussive ventilation), external high frequency chest compression devices (e.g., The Vest™, ThAIRapy Vest®, SmartVest®, and Hayek Oscillator), and exercise. While these airway clearance techniques may differ in terms of the need for assistance or equipment, they all have the same goal of removing mucus secretions from the lungs. Selecting the most appropriate airway clearance technique is influenced by age, individual preference, adverse events, an individual's airway pathophysiology, and cost ***(8).***

	Properties	Administration	Clinical effect
Dornase alfa	Recombinant human deoxyribonuclease; breaks down polymerised DNA produced by degrading neutrophils	No specific timing with airway clearance; no differences with daily, twice daily, or alternate day regimens	FEV_1 improvement; reduced pulmonary exacerbations; little evidence in less than 6 years
Hypertonic saline (3% or 7%)	Osmotic agent; airway surface liquid hydration	Before or during airway clearance; tolerability testing required for bronchospasm; bronchodilator pretreatment recommended	No change or improvement in FEV_1; reduced pulmonary exacerbations; symptom resolution; quality of life improvement; $FEV_{0.5}$ and $LCI_{2.5}$ improvement
Mannitol	Osmotic agent; airway surface liquid hydration	Available in dry powder; before or during airway clearance techniques; tolerability testing needed for bronchospasm	FEV_1 improvement; reduced pulmonary exacerbations; low efficacy in children

FEV_1=forced expiratory volume in 1 seconds. $FEV_{0.5}$=forced expiratory volume in 0·5 seconds. LCI=lung clearance index.

Fig .1: Licensed mucoactive agents as adjuncts to airway clearance (10).

II.Pancreatic insufficiency:

Pancrelipase and vitamin supplements are beneficial for CF patients with digestion issues, malnutrition, and malabsorption ***(11).***

Currently, there are three FDA-approved pancreatic enzyme preparations available in the USA: CREON® in April 2009, Zenpep® in August 2009, and Pancreaze® in April 2010.These products are the initial enteric-coated pancrelipase preparations since crude extracts were first introduced over 50 years ago, and they all come from pigs. With the approval of new dosage forms, certain companies have used the chance to make changes to their formulations in terms of excipients, enhanced packaging, and stability to achieve a more reliable administration of pancreatic enzymes.and the degree of steatorrhea and are adjusted for dietary fat consumed. It is important to swallow CREON capsules whole, without crushing or chewing them. Capsules may be opened, and the contents can be mixed with soft acidic foods like apple sauce on a spoon until children can swallow capsules whole. This mixture should be taken during meals, right after mixing. In case capsules are opened, mix the contents only with foods with pH ≤4.5 to prevent

damage to the protective enteric coating and early release of enzymes. Since CREON is enteric-coated and protected from gastric acid, there is no need for a proton pump inhibitor or H2 receptor antagonist ***(12).***

In the medical field, certain patients may not have a sufficient response to PERT due to reasons like poor patient adherence, inadequate PERT dosage, inaccurate fat intake estimation, pancreatic bicarbonate secretion deficiency, atypical bile salt composition, abnormal intestinal ion transport, gut inflammation, changed gut motility, excessive bacterial growth, and hindered long chain fatty acid absorption. High-fiber diets have been linked to a slight yet notable rise in fecal fat elimination in individuals with CP with EPI. Furthermore, antacids containing calcium and magnesium are linked to the creation of soaps and the deposit of glycine-conjugated bile salts in the intestine, potentially worsening steatorrhea in patients with EPI ***(13)***

Characteristics of the PERT preparation, such as enzyme particle size, dissolution properties, stomach emptying rate, and timing of intake with meals, can influence its effectiveness. Individuals with EPI often experience decreased secretion of pancreatic bicarbonate, which can lead to inadequate pH levels in the duodenum and small intestine, affecting the dissolution of the PERT enteric coating. Although it is challenging to treat bicarbonate transport issues, one way to improve the dissolution of PERT is by elevating the pH of the gastric fluids that enter the duodenum to enhance the treatment. Moreover, raising the pH in the duodenum could decrease the formation of bile salt precipitates. Therefore, if signs of poor digestion continue, it may be helpful to include an H2 receptor antagonist or a proton pump inhibitor to enhance the effectiveness of pancreatic enzyme replacement therapy, as is commonly recommended for CF patients ***(14).***

If all the above unsuccessful, gastrointestinal disorders that could disrupt the absorption of nutrients in the intestines should be considered, including bacterial overgrowth, giardiasis, celiac disease, or blind loop syndrome post surgery in the gastrointestinal tract ***(14).*** A full medical evaluation is needed if there is no improvement.

PERT can result in a rare complication that is only observed in CF patients taking extremely high enzyme doses. Certain aspects of CF, such as dense intestinal secretions, the amount of PERT given, and the components in the enteric coating of pancrelipase medications, could be contributing factors. So, it is advised to keep the daily dose under 2500 lipase units/kg of body weight per meal or 10000 lipase units/kg of body weight per day for both children and adults with CF ***(14).*** In a recent Egyptian study, most of the studied cases had severe fecal elastase deficiency, only 4 cases (26.7%) in the age group (1-4 years) had moderate deficiency with no statistically significant difference in the mean FE-1 level between the 3 age groups and none of the cases was considered exocrine pancreatic sufficient regarding FE-1 level***(17).***The recommended dose for adult and pediatric patients greater than 12 months initial starting dosage is 500 lipase units/kg/meal for adult and pediatric patients 4 years and older and 1,000 lipase units/kg/meal for pediatric patients greater than 12 months to less than 4 years. Titrate the dosage to either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day. Higher dosages may be administered if documented effective by fecal fat measures or improvement of malabsorption. Pediatric Patients Birth to 12 Months: The recommended dosage is 3,000lipase units (one capsule) per 120 mL of formula or per breastfeeding ***(16).***

III. Urogenital system:

There are currently no remedies available for azoospermia or male infertility in individuals with CBAVD; yet, if sperm is being produced, it can be extracted from the testes or epididymis for reproductive purposes ***(16).***

IV. Gastrointestinal tract (GIT):

To avoid or treat intestinal blockages, oral rehydration and osmotic laxatives can be used for incomplete blockages, while hyperosmolar contrast enemas are recommended for treating complete DIOS. A well-balanced enema or intestinal lavage solution with certain electrolytes, , can be used depending on whether the patient is vomiting. To avoid repetition, oral polyethylene glycol can be regularly administered for a period of 6 months to 1 year. Histamine-2 receptor blockers and proton pump inhibitors are utilized for reducing gastric acidity. Prokinetics (such as domperidone, metoclopramide, and macrolide antibiotics) are frequently used in conjunction to improve gastric emptying**.** Yet, recent pediatric guidelines regarding treatment of GERD state that there isn't enough proof of effectiveness to support regular use of prokinetic therapy ***(16).***

Azithromycin, a macrolide antibiotic, modifies esophageal and gastric motility and is frequently used in the treatment of CF**,** As it accelerates gastric emptying in patients with gastroparesis. Also, has less side effects and has a longer duration of action than erythromycinIf GERD worsens and lung disease becomes severe, a Nissen fundoplication may help by reducing pulmonary exacerbations and improving FEV1% and weight significantly ***(17).***

V. Nutrition and electrolyte:

It is advised to ensure proper nutrition, prevent dehydration, and follow a high-calorie, high-fat diet. Additionally, supplement with vitamins ADEK and minerals like fluoride and zinc. Moreover, sodium chloride supplementation is adjusted based on the patient's age and the surrounding conditions**.** Improvement in overall health, immune system, and breathing is seen when malnutrition is addressed. Because the patient needs more nutrients and has a higher metabolism, their diet should be easy to digest and contain 20-50% more proteins and calories compared to healthy children of the same weight ***(18).***

Breastfeeding is important during the first year postpartum and its significance continues beyond that time frame. Infants who are not breastfed, especially if they are malnourished, should be given milk formulas that contain protein hydrolysates and a mix of medium-chain triglycerides that are easier to digest and more effectively used than long-chain triglycerides ***(19).***

By consuming medium-chain triglycerides instead of long-chain triglycerides, caloric needs are met to a significant extent. Adding 1 ml/kg of corn or sunflower oil to daily nutrition can provide the ideal amount of key fatty acids, linoleic and alpha linolenic. Fat-soluble vitamins also need extra consumption, but the requirements for water-soluble vitamins and minerals are not fundamentally different from those of normal children ***(19).***

Because patients with CF are prone to dehydration, they need to increase their intake of table salt. This aspect should be carefully considered, particularly in situations of higher perspiration, like during summer and fever. Treating hypovolemia, hyponatremia, hypokalemia,

and metabolic alkalosis with low chloride levels in cases of hyponatremic dehydration is done by giving 10-20 ml/kg 0.9% NaCl intravenously as a quick injection for 15-30 minutes ***(19).***

VI.Current and future medicinal products:

The current and future therapeutic targets are mainly focused on correcting structural and functional abnormalities of CFTR protein. Additionally, some agents for symptomatic improvement are also in pipeline

1. CFTR modulators:

A new group of drugs called CFTR modulators are available which are able to correct the basic defect in CF, i.e. CFTR protein itself though the exact mechanism is not fully elucidated.

a. Ivacaftor:

After entering the clinic as the first CFTR modulator, ivacaftor has been approved for use as an oral preparation for a number of years. Ivacaftor is used as a potentiator in monotherapy for mutations involving cell surface proteins. These mutations may result in low concentrations of CFTR, conductance mutations, or gating (failing to open) mutations. ***(20).***

Developed by vertex pharmaceuticals and approved by FDA in 2012 for children ≥6 years having rare mutation, G551D (class III). was the first successful medicine to repair the defective protein and has proven to be very effective in two large multicentric trials, STRIVE and ENVISION ***(20).***

A decrease of around 50 mmol/L in sweat chloride was observed, acting as a valuable biomarker on a group basis but not reflecting lung function changes in individuals. Young kids have demonstrated the recovery of pancreatic exocrine function,indicating that pancreatic illness may not be entirely irreversible.Longer term registry data has shown that the clinical benefits transplantation and mortality***(21).***

Marked improvement in FEV1, body weight and quality of life were observed. Now FDA has broadened its use in other mutations and also children aged 2–5 years based on the results of KIWI trial. Same finding also reported in a phase IV study (GOAL) in patients carrying at least one G551D allele and more than 72% patients in this trial also carried F508del as second allele. Ivacaftor prolongs the duration of the channel being in an open state in G551D mutation, However, the primary drawback of this treatment is that only 2.3% of patients have this mutation. Its effectiveness in the most common mutation, F508del (class II), is limited due to reduced protein availability. Also, the expensive nature of therapy could act as a barr***ier (22).***

b. Lumacaftor:

Another CFTR modulator, lumacaftor has demonstrated promising outcomes in individuals with the F508del mutation. There was an increase in the transportation of protein to the cel surface when studying cultured human bronchial epithelium in vitro ***(23).***

Despite increased protein transportation to the correct site, there was no improvement in the underlying functional deficiency. Additionally, a different in vitro experiment showed conflicting

adverse outcomes that were confirmed by a clinical study. There was no notable enhancement in FEV1, CFQR scores, and rates of respiratory exacerbations detected ***(24).***

c. Orkambi

A mixture of lumacaftor and ivacaftor,Orkambi, was suggested to address protein trafficking and channel gating issues based on specific mechanisms of each drug. In the beginning, phase II trials included both homozygous and heterozygous F508del patients over the age of 12, but only homozygous patients demonstrated medically important outcomes. Two large phase III trials, TRAFFIC and TRANSPORT tested the combination therapy (600 + 250 and 400 + 250 mg versus placebo) in patients ≥12 years with main goal of FEV1 improvement at 24 weeks. Patients finishing the study were proceeded to 48 weeks PROGRESS trial. Both individual and combined findings demonstrated a notable enhancement in factors such as FEV1, fewer exacerbations, decreased hospital stays, higher BMI, and improved CFQR scores. This trend was observed consistently among various dosage schedules and patient demographics ***(20).***

Furthermore, promising results were observed in a phase I trial conducted on homozygous children ≤ 12 years, but additional advancement in phase studies is needed**.** But, in a different study, the combination therapy showed much less improvement in pulmonary function compared to ivacaftor monotherapy in patients with the G551D mutation ***(20).***

- ***Possible limitations of CFTR modulators include (25):***

(a)non-significant response in F508del mutation heterozygotes by ivacaftor.

(b) Need to continue other daily symptomatic treatment.

(c) Interaction with CYP3A inducers and inhibitors.

(d) Side effects including elevated transaminases, cataract, oropharyngeal pain and URTI.

(e) Insignificant benefit in <12 years old.

(f) Need of higher dose up to 600 mg (in case of lumacaftor).

(g) Mutual interaction of lumacaftor and ivacaftor leading to increased metabolism of ivacaftor and need of a higher dose combination.

Furthermore, due to the complex structure of CFTR, one single "corrector drug" is unable to correct all misfolding across various domains, making a combination of drugs necessary. Additionally, in terms of conducting clinical trials, there is a challenge with determining sample sizes due to the specific criteria (primary and secondary end points) that need to be met. This becomes even more complex when working with a population that has already been narrowed down by specific mutations, requiring unique adaptive trial designs.

2. Corrector/modifier therapeutic agents in clinical development pipeline:

Many other compounds depicting corrector/potentiator activity besides read-through and gene transfer agents and are undergoing various phases of studies.

3. Newer therapeutic agents for symptomatic improvement CF management not only requires CFTR correction and modification but intensive symptomatic treatment targeting inflammation, infection, bronchial hydration and nutrition: ( )

4. Gene Therapy:

Gene therapy for CF lung disease has undergone a longer process since the first clinical trials commenced in the early 1990s following the cloning of the CFTR gene ***(26).***

Advancements in gene and cell therapy approaches for CF in addition to CFTR modulators, gene therapy offers a solution to fix the defective gene. While promising in its early days, various challenges hindering the effective utilization of this therapeutic approach, such as vector design, in vivo delivery to epithelial cells (mucus and glycocalix) and off-target effects (random integration). Yet, new gene delivery vectors (lentiviral and non-viral vectors), advancements in gene-editing methods such as zinc-finger nucleases, TALENs, and CRISPR/Cas9, the use of mRNA in lung treatment, and the ability to turn patient-specific pluripotent stem cells into airway epithelial cells have brought new life to the field and hold promise for innovative gene therapy in CF patients ***(26).***

Given that CFTR modulators serve as a systemic therapy for various diseased organs, the implementation of gene therapy in CF patients utilizing effective CFTR modulator choices may be delayed until there is progress in the field's capacity to genetically address multiple impacted organs in CF, such as the lung, pancreas, and intestine. Consequently, ongoing gene therapy research focuses on addressing the life-threatening lung conditions in a specific group of CF patients who lack viable treatment alternatives ***(26).***

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