Lumacaftor/Ivacaftor (LI) for Treatment of Cystic Fibrosis: A Contemporary Approach

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Received: May 20, 2018; Published: July 20, 2018

Abstract

Cystic fibrosis has been treated by many conventional regimens including Antibiotics, mucolytics etc. Lumacaftor/Ivacaftor (LI) is a new drug for treating Cystic fibrosis. Our study is based on a detailed analysis and review of the trials using Lumacaftor/Ivacaftor as the treatment drug for Cystic Fibrosis. The study trials with these drugs showed an improvement in the lung functions of the patients treated with this drug with no considerable improvement in pancreatic function. Some side effects such as chest tightness, dyspnea also appeared but the benefits of the drug outweighed the risks. LI being a new drug is very costly compared to other treatment options for Cystic Fibrosis. With more extensive trials and research, LI can be a potential alternate for other regimens in treating Cystic fibrosis.

Keywords: Lumacaftor/Ivacaftor (LI); Cystic Fibrosis

Introduction

Among the many diseases affecting lungs, digestive tract and other organs of the body, Cystic fibrosis is a common disorder affecting both digestive tract and lungs simultaneously. It basically affects the mucus producing cells of the body’s organs and as a result the secretions produced by these cells are thick and sticky rather than thin and slippery. As a result of the abnormal functions of these organs, six pulmonary symptoms are recognized as central to cystic fibrosis which include cough, sputum production, wheeze, chest tightness, difficulty breathing/shortness of breath, and fever [1]. As for digestive tract abnormality, patients present with gastro-esophageal reflux and there is a greater risk of aspiration of gastric contents in these patients. Thus GER, symptomatic and silent, is a significant problem in CF [2]. There has also been an association and presence of bile acids in the saliva of children with cystic fibrosis which also displays an increased risk of aspiration in these patients [3]. In a survey, data from 26 regional and national cystic fibrosis programs across Europe showed that 400 out of 1,600,000 infants were having cystic fibrosis [4]. The incidence and prevalence of Cystic fibrosis varies but an estimate of prevalence of 0.737/10,000 in the 27 European countries, which is similar to the value of 0.797 has been established [5]. Our review provides an insight to the effects of conventional treatment modalities and Lumacaftor/Ivacaftor in treating the patients of Cystic Fibrosis.

Pathophysiology of Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutation in a single large gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein [6]. CFTR protein is an ATP-gated chloride channel, which secretes chloride in lungs and GI tract, and reabsorbs chloride in sweat glands. ΔF508 - CFTR, is the most common mutation which creates a misfolded protein that is not appropriately transported to the cell membrane, causing its degradation [7]. Chloride accumulation results in compensatory Na+ reabsorption via Na+ channels which in turn leads to increased water reabsorption. Consequently, abnormally thick mucus is secreted into the bronchi, biliary tract, pancreas, intestines, and reproductive system. This secretion forms mucous plugs and plaques resulting in chronic respiratory infections, pancreatic enzyme insufficiency, and associated complications in untreated patients [8]. Pulmonary involvement in most of the patients is the principal cause of death [9].

Conventional Treatment Options

The main goals of Cystic Fibrosis management are prevention of exacerbations, enzyme supplementation to facilitate adequate growth of individuals and treatment and prevention of pulmonary infections which are a leading cause of morbidity and mortality in cystic fibrosis patients [10]. Antibiotics along with mucous clearing therapies are the cornerstone of treatment, as they help maintain the pulmonary function to a baseline level. Azithromycin is the mainstay of treatment due to its anti-inflammatory and anti-microbial effects [11]. Other antibiotics used for treatment and prevention of pulmonary infections include drugs with good pseudomonal coverage, which is the most common organism causing pulmonary infections in cystic fibrosis patients. These include nebulized tobramycin and aztreonam. Bronchodilators such as albuterol and mucolytics (dornasealfa breaks down DNA in the sputum, thus making it less viscous.) are used to keep the airways clear and hence prevent infections [12]. Hypertonic saline can also be used to keep the surface of airways hydrated and helps prevent acute exacerbations. Denufosol liquefy the mucus by opening chloride channels is useful in some patients [13]. Nutritional supplements (pancreatic enzymes and multivitamins) are vital for patients with suboptimal pancreatic function [14].

History of Lumacaftor/Ivacaftor

Lumacaftor/ivacaftor (LI) combination drug is a new treatment modality devised to potentially reverse the abnormalities in chloride transport in cystic fibrosis patients who have two copies of the F508del mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Ivacaftor works by increasing the activity of the CFTR protein at epithelial cell surface, while lumacaftor increases the number of CFTR proteins that are trafficked to the cell surface, acting as a chaperone during protein folding [15]. The drug combination is available as a single pill containing 200 mg of lumacaftor and 125 mg of ivacaftor. It was approved by the US FDA in July 2015 [16]. However, excessively high price of over 260,000 per patient per annum has limited the use of this drug combination [17]. The combination treatment improves pulmonary function by approximately 3% and reduces hospitalization events by over 30% [18].

Outcomes and Interpretation of Clinical Trials

LI is not a very old regimen and the efficacy trials are still not extensively validated. Although, the studies have assured that it serves the purpose in managing the pulmonary symptoms of the disease; pancreatic insufficiency still requires the administration of the enzymes. Clinical studies and trials have yet not been on a large scale and there are limited numbers of published data from the trials. PubMed National Library of Medicine, US shows a total of seven trials for LI or Lumacaftor alone.

The first trial was published in 2014 and funded by Vertex Pharma, conducted by investigators at Johns Hopkins University and the results were quite promising. Boyle et al. trial was phase 2 controlled investigations that comprised of data from 24 countries and included multiple cohorts, with homozygous and heterozygous mutations of CFTR mutation. It was concluded that sweat chloride did not decrease significantly although with Lumacaftor alone chest tightness and dyspnea were reported. Overall, the trial states that LI can improve FEV1 for patients with homozygous CFTR mutation [19]. Soon after this trial, Vertex worked closely with other clinical researchers and facilities to push this medication for a phase 3 trial, which was published one year later in 2015. They are popularly referred as TRAFFIC and TRANSPORT trials, which were more efficient than previously done trial and were divided into these aforementioned trials. These two adjoined trials suggested that LI should be in a combined therapy and can benefit homozygous CFTR mutations. Not much beneficial effects or outcomes were mentioned for heterozygous CFTR mutation [18].

Third trial was again funded by the same source and previously done trials were brought in further evaluation into another singular cohort of PROGRESS. This trial suggested additional side effects of pulmonary exacerbations, increased sputum and hemoptysis. Again, betterment in FEV1 was found, with slower debilitation than the other registered cases, this showed an encouraging outcome for considering it a major stay for treatment. The homozygosity or heterozygosity of mutations in CFTR gene was not commented in this third trial [20]. LI was again trialed by Rowe et al. and the first age specific trial was done in patients of 18 years or older. The side effects were similar as stated in previous trials, but it was seen that changes from baseline sweat chloride at day 56 showed that chloride levels and respiratory symptoms have improved, although no effect was seen in heterozygous mutation patients [21].

In 2017, second age specific trial (6 - 11 years) was evaluated that stated nearly similar results than the older patients and the percent predicted FEV1 had no significant difference than predicted from previous trials. Although, this trial specified that 24 - week treatment with LI can improve lung clearance, quality of life and most importantly the sweat chloride level which was reported in the last trial, but not corrected in previously done investigations [22].

**Success Rates**

Cystic fibrosis patients have reportedly improved Forced Expiratory Volume by using Ivacaftor and Lumacaftor. 1000 patients of cystic fibrosis with Phe508del mutation in CFTR protein, under phase III randomized controlled multicenter trials, with drug delivered in two different dose combinations improved predicted forced expiratory volume by 2.6% to 4.0% compared with a placebo without drastic increases in serious adverse events. Significant improvement in lung function and weight gain is seen with the combination of lumacaftor and ivacaftor but with deterioration of respiratory and pulmonary symptoms. Ivacaftor alone produced better results in treatment of patients with the Gly551Asp mutation. Forced Expiratory Volume improvement was much remarkable with ivacaftor compared with other inhalants (DNase and Tobramycin) [23].

The approval of ORKAMBI was based on data from people aged 12 and above under two Phase 3 studies (TRAFFIC and TRANSPORT). They have shown remarkable improvement in lung function with reduced pulmonary exacerbation and improved BMI. Lumacaftor increases the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the F508del CFTR protein, and Ivacaftor, improves the function of the CFTR protein once it reaches the cell surface [24].

**Cost effectiveness**

In view of its high cost, combination treatment lumacaftor/ivacaftor has not been recommended for use in the NHS in England and Wales for cystic fibrosis (CF). National Institute for Health and Care Excellence (NICE) says the product’s price of over hundred thousand pounds per patient per annum is not justified by the therapeutic benefits. A number of studies conducted to compare the efficacy and cost effectiveness of other available therapies (inhaled hypertonic saline, dornasealfa, azithromycin, inhaled tobramycin) to LI found these drugs to be equally effective in the management of cystic fibrosis and cost only fraction the price of LI combination. LI combination decreases the incidence of pulmonary exacerbation significantly and hence decrease the cost of inpatient hospital stays which are about 1000$/day [25]. However, this can be achieved by alternative drugs like dornasealfa and tobramycin as well at one-tenth the price of LI. Even the highest reported mean or median total annual cost of care is still only a fraction of the annual cost of lumacaftor-ivacaftor alone [26]. Overall, LI combination produces significant gains in QALYs (quality-adjusted life years) albeit at an extremely high cost and hence did not prove to be a breakthrough product for CF patients.

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Side effects

Lumacaftor/Ivacaftor has overall positively impacted the treatment plan for cystic fibrosis and it is evident that the side effects were limited. Although like all the pharmacological surveys, LI regimens also have been reported with symptoms. One survey showed that this combined drug can present with pulmonary symptoms. Also, the patients with already FEV1 lower than 40% were more prone towards these symptoms [27]. Another similar survey to evaluate the efficacy of the drug, cough, dyspnea and abnormal breathing were the main side effects of this medication among the patients with a low FEV1 groups [28]. An article published in November 2017, thoroughly reviewed the literature to find the side effects of LI in published trials and stated that it can cause: Transaminitis, non-congenital cataracts in children, increased activity of CYP3A leading to decreased therapeutic effects of the medications that require this substrate and can be directly hepatotoxic. Apart from this, literature provides an evidence that the administration of this drug can cause dyspnea, especially in initial administration [29]. Overall, the drug can cause liver and pulmonary problems, along with ocular symptoms, but the risk benefit ratio supports the treatment plan and have successfully passed the trials to be efficaciously treating CF, which otherwise can affect the quality of life of patients and can cause pulmonary failure progressing to death.

Conclusion

A detailed analysis of Cystic fibrosis treatment with Lumacaftor/Ivacaftor shows considerable improvement in the functions of lungs in aforementioned study trials. This improvement was shown by Patients with Homozygosity and patients with heterozygous alleles did not show considerable improvement. Apart from the therapeutic effects, adverse effects such as Chest Tightness, dyspnea and other symptoms appeared in the study trials. Pancreatic Enzyme still needs replacement as Lumacaftor/Ivacaftor did not show any improvement in Pancreatic function. Compared to other Treatment regimens of Cystic Fibrosis, similar therapeutic effects can be achieved and at a lower cost. Lumacaftor/Ivacaftor being a new treatment regimen is costly than the other regimens. However, the side effects of Lumacaftor/Ivacaftor have greatly outnumbered the therapeutic effects of the drug and thus can be considered as a potential alternate for other regimens in treating Cystic Fibrosis. However, the efficacy and benefits of Lumacaftor/Ivacaftor still need further research and analysis as it being a new drug.

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