CFTR MODULATOR THERAPY FOR CYSTIC FIBROSIS

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ABSTRACT

Introduction: *Cystic fibrosis (CF) is the most common life-limiting autosomal recessive condition in Caucasians, affecting the respiratory system, digestive tract and all exocrine glands. It is caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The genetic analysis, in addition to diagnosis, serves to create a modern individual CFTR modulator therapy.*

Aim: *The aim of this article is to do a presentation of products for CFTR modulator therapy, which are available worldwide; introduction to their pharmacokinetic and pharmacodynamic properties; evaluation of the effect of their application.*

Materials: *We have conducted a study of medical literature related to the products for CFTR modulator therapy and review of information on the topic.*

Results: *The use of approved CFTR modulator therapy products in patients suitable for their use (specific genotype) results in an improvement in FEV1 values and body mass index and a reduction in the incidence of exacerbations in these patients.*

Conclusion: *CFTR modulator therapy significantly improves the prognosis and quality of life of cystic fibrosis patients as a result of certain mutations in the CFTR gene. Quality care for other patients with other mutations is especially important so that they can benefit from personalized treatment in the future.*

Keywords: *cystic fibrosis, CFTR, therapy, genetics, products*

INTRODUCTION

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive condition in Caucasians. It is caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein is a chloride channel expressed in the apical membrane of epithelial cells. It primarily regulates the movement of chloride, but is also involved in sodium, bicarbonate and water transport. Mutations in both copies of the gene result in clinical disease (1). Dysfunction of CFTR leads to the accumulation of mucus in all tubular structures. Narrowing and obstruction of their lumen damages the relevant organs and maintains a process of chronic infection (2).

Cystic fibrosis is a complex multisystem disorder with a wide and variable spectrum of manifestations. The phenotypic alterations are primarily identified in the epithelial cells of airways, sinuses, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system (3).

Genetic Knowledge

A great progress in the genetic knowledge of cystic fibrosis was made in the late 20th century. In 1985, CFTR was mapped. It belongs to the group of ATP-binding cassette (ABC) proteins. CFTR follows the same domain structure as other ABC transporters: it has two nucleotide-binding domains (NBDs) in tandem with two transmembrane domains (TMDs). What differentiates it from the other transporters (apart from its channel activity) is its regulatory domain or 'R' region (4). Each TMD is by 6 transmembrane helices (TM1–TM6 and TM7–TM12). Every membrane spanning domain followed by a nucleotide binding domain (NBD). A distinctive characteristic of CFTR is the presence of an intrinsically disordered region, the regulatory domain (RD), located between NBD1 and TMD2. In most ABC-proteins the ATPase activity of the NBDs utilize the energy of ATP binding and hydrolysis to energize the translocation of various substrates across membranes. Conversely, CFTR is a unique case of an ABC-protein that forms an ATP-gated ion channel. CFTR is ex-

pressed in a variety of organs and tissues including gut smooth muscle, tubular kidney cells and mucosal and secretory epithelia (5).

CFTR Mutation Classes

There are currently 2088 mutations listed in CFTR mutation database (6). These mutations can be grouped according to their functional defect into seven classes.

Class I mutations affect protein production and include mostly nonsense mutations (i.e., those with premature stop codons), thus often causing degradation of mRNA by nonsense-mediated decay. G542X, W1282X are examples of mutations causing the defect.

Class II mutations include Phe508del and affect CFTR protein traffic as a result of protein misfolding and retention at the endoplasmic reticulum (ER) by the ER quality control mechanism. Such retention is followed by premature degradation, which prevents the protein from trafficking to the cell surface, thus severely reducing CFTR function. F508del, N1303K, S945L, H949Y, D979A are examples of mutations causing the defect.

Class III mutations impair gating of the CFTR channel. G551D is examples of mutation causing the defect.

Class IV mutations cause a substantial decrease in CFTR channel conductance (i.e., flow) of chloride and bicarbonate ions. R117H, G622D, M1137V, I1139V, D1152H, D1154G, R347P

are examples of mutations causing the defect.

Class V mutations lead to a major reduction in the levels of normal CFTR protein, often

because of alternative splicing that generates both aberrant and normal mRNA species, the proportion between which might vary among patients and in different organs of each patient. A455E, D565G are examples of mutations causing the defect.

Class VI mutations destabilise CFTR at the cell surface, either by increasing CFTR endocytosis or by decreasing its recycling back to the cell surface. Q1412X, 432delTC, 4279insA are examples of mutations causing the defect.

Class VII mutations have the same outcome as class I mutations – i.e., absence of the CFTR protein—but cannot be rescued by corrective therapy (7,8).

The detection of genetic defects in patients with cystic fibrosis makes it possible to develop increasingly effective treatment approaches focusing on the main classes of mutations, looking for ways to correct or circumvent the problem in an alternative way.

CFTR Modulator Therapy for Cystic Fibrosis

The currently available products for CFTR modulator therapy are Kalydeco (ivacaftor) approved in 2012, Orkambi (ivacaftor / lumikaftor) approved in 2015, Symdeco / Symkevi (ivacaftor / tezakaftor) approved in 2018 and Trikafta (elexacaftor / tezacaftor / ivacaftor) approved in 2019.The four listed products are from the company Vertex.

They modulate CFTR by acting as potentiators (increasing the time during which the CFTR channel is open, which leads to greater movement of ions) or correctors (facilitating the maturation of CFTR-protein, which leads to its improved transport to the cell membrane) (9).

Ivacaftor (Kalydeco)

Ivacaftor was approved for the treatment of CF in patients ≥2 years of age and the presence of one of the following CFTR mutations G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H. The use of potentiator ivacaftor resulted in significant improvement in percent predicted FEV1 (10-15%), BMI, sweat chlorine and is generally well tolerated. The dosage is 2x150 mg (2x1 tablet every 12 hours) for patients over 6 years, 2x50 mg (2x1 sachet) for patients under 6 years and under 14 kg and 2x75 mg (2x1 sachet) for patients under 6 years and over 14 kg. From the summer of 2017 the FDA in the USA expands the readings with new mutations of 4th and 5th class: 2789 + 5G-> A, 3849 + 10kbC-> T, 3272-26A-> G, 711 + 3A-> G, E56K, P67L, R74W, D110E, D110H, R117C, L206W, R347H, R352Q, A455E, D579G, E831X, S945L, S977F, F1052V, R1070W, F1074L, D1152H and D1270N. The possibility of developing cataract has been reported as a serious side effect (9,10,11).

Orkambi (Ivacaftor / Lumikaftor)

Ivacaftor / lumikaftor is used for patients homozygous for delF508 - class 2 mutation.

It is a combination of ivacaftor with the corrector lumacaftor. The use of ivacaftor/lumikaftor resulted in a less extent improvement (compared to ivacaftor) in FEV1 and sweat test values, but there is proven reductions in exacerbations and improvement in body mass index indicators. The dosage is 2x1 tablet, with two types of tablets available - lumacaftor 100 mg / ivacaftor 125 mg for children 6 to 11 years of age and lumacaftor 200 mg / ivacaftor 125 mg for patients over 12 years of age. Heaviness in the chest and metrorrhagia have been reported as serious side effects (9,12).

Symdeco/Symkevi (Ivacaftor/Tezakaftor)

Ivacaftor/tezakaftor is used for heterozygous patients with delF508 and another mutation of the following: P67L, R117C, L206W, R352Q, A455E, D579G,

711 + 3A-> G, S945L, S977F, R1070W, D1152H, 2789 + 5G-> A, 3272-26A-> Gi 3849 + 10kbC-> T. It is a combination of Ivacaftor with the corrector tezacaftor. It shows better results than Orkambi. The dosage is 1 tablet Symkevi® in the morning (tezacaftor 100 mg / ivacaftor 150 mg) and 1 tablet Kalydeko® in the evening (ivacaftor 150 mg). No serious side effects have been reported 9,13).

Trikafta (Elexacaftor/Tezacaftor/Ivacaftor)

In 2019 FDA approved Trikafta (elexacaftor/ tezacaftor/ivacaftor and ivacaftor) to treat the underlying cause of cystic fibrosis in people ages 12 and older who have at least one F508del mutation. It is a combination of Ivacaftor and the correctors elexacaftor and tezacaftor. In NEJM Middleton et al. published the results of 3-phase, randomized, double-blind, and placebo-controlled study of 403 patients showing the effectiveness of Trikafta. The dosage is two elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg tablets in the morning and one ivacaftor 150 mg tablet in the evening. Liver damage and cataract have been reported as serious side effects (14).

CONCLUSION

CFTR modulator therapy significantly improves the prognosis and quality of life of cystic fibrosis patients as a result of certain mutations in the CFTR gene. Quality care for other patients with other mutations is especially important so that they can benefit from personalized treatment in the future.

In Bulgaria, the drugs that are reimbursed at 100% of the national health insurance fund are Kreon, Pulmozyme (dormase alfa), Colobreathe (Colistin) and Tobi (Tobramycin). They are given free of charge to any patient with a genetically proven cystic fibrosis, but there are certain indication for their use. For now, the CFTR modulator therapy is difficult to access and very expensive for patients in our country, but we hope that this will change soon.

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