

Chojęta Dariusz, Mierzwa Monika, Wróblewski Hubert, Zimna Aleksandra, Zygmunt Ewelina, Kozłowska Anna, Łysiak Katarzyna. Modulators of CFTR protein function in the treatment of cystic fibrosis - a literature review. *Journal of Education, Health and Sport*. 2022;12(8):358-365. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2022.12.08.037> <https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.08.037> <https://zenodo.org/record/6976132>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 01.08.2022. Revised: 07.09.2022. Accepted: 09.08.2022.

Modulators of CFTR protein function in the treatment of cystic fibrosis - a literature review

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Abstract

Cystic fibrosis (CF) is a multi-system genetic disease with an autosomal recessive inheritance mechanism. The breakthroughs in the therapy of patients with CF turned out to be modulators of CFTR protein function. These small-molecule substances, influencing the basic pathogenetic defect, became a model example of precise targeted therapy, thus showing a significant advantage over symptomatic treatment. For modulators of CFTR protein function, numerous therapeutic benefits have been demonstrated with an acceptable safety profile - improved lung function and reduced frequency of pulmonary exacerbations, reduced hospitalization rate, and disease-related improvement in quality of life. The use of these drugs changes the perception of CF from a fatal pediatric disease significantly shortening the life expectancy of patients into a chronic disease in young adults. The subject of further research interest is the development of alternative therapeutic strategies based on new modulators and gene therapy. The publication is a review of the literature and summarizes the current scientific reports on the effectiveness of the use of modulators of CFTR protein function in the treatment of cystic fibrosis.

Key words: cystic fibrosis, modulators of CFTR protein function, targeted therapy, gene therapy

1. Introduction

Cystic fibrosis (CF) is a multi-system disease with a wide symptomatology. The symptoms of the disease most often concern the respiratory and digestive systems. Due to its chronicity and mortality, CF is a serious public health problem. It causes a significant deterioration in the quality of life, and patients have a significantly shorter life expectancy compared to the healthy population [1]. The pathogenesis of cystic fibrosis relates to the CFTR (cystic fibrosis transmembrane conductance regulator) membrane protein. Mutations in the protein coding gene lead to the dysfunction of its work. The latest therapeutic options in the treatment of CF aim to improve the function of CFTR protein [2].

The aim of the study was to present the efficacy and safety of new therapeutic strategies in the treatment of CF - modulators of CFTR protein function. The article was created as a review of the literature available in the Google Scholar and PubMed databases. The search terms included: "cystic fibrosis treatment", "cystic fibrosis modulators of CFTR protein function", "cystic fibrosis ivacaftor / tezacaftor / lumacaftor", "cystic fibrosis gene therapy".

2. CFTR protein

CF is a genetically determined disease with autosomal recessive inheritance. The CFTR protein is a chloride channel and modulator of the functions of other transport proteins (indirectly influencing the transport of sodium ions and bicarbonates through cell membranes). As a result of the dysfunction, the transport of chlorine is disturbed at the cellular level (high chloride concentration in sweat is used in the diagnosis of CF) and the hydration of gland secretions in the respiratory tract or the gastrointestinal tract is reduced [3]. The most common mutation in the CFTR gene is Phe508del (deletion of phenylalanine at position 508), and there are over 2000 mutations described at the moment [4,5]. The degree of preservation of the CFTR protein function depends on the type of mutation (genotype), which in turn translates into the severity of disease symptoms (phenotype) [6]. CFTR gene mutations have been grouped into 6 main classes depending on the type of defect they cause [7]:

- Class I - defective synthesis resulting in the formation of a truncated, immature protein; examples of mutations are G542X, R553X and W1282X;
- Class II - defective process of maturation and post-translational processing of the protein with its subsequent rapid degradation; mutations Phe508del, N1303K and G85E;
- Class III - chloride channel gate opening defect in response to cAMP stimulation; mutations G551D, V530F and S549R;
- Class IV - defect in the pore structure of the channel and the conductivity of chloride ions through the open pores; mutations R117H, R334W and S1235R;
- Class V - errors during transcription and assembly in the cell nucleus, affecting mRNA stability; mutations A455E, c.1680-886A>G and c.2657+5G>A;
- Class VI - instability of the fully functional CFTR protein, faster cell turnover and shortened half-life of protein molecules; mutations Q1412X, rescued Phe508del.

3. Modulators of CFTR protein function

Targeted therapy in the treatment of CF aims to improve the function of the CFTR protein. This is possible thanks to the use of small-molecule substances that interact at the molecular and cellular level, which translates into an effect in the form of therapeutic benefits

and reducing the symptoms of the disease. The basic classification of modulators of CFTR protein function includes:

- Potentiators (ivacaftor) - increase the level of activity and transport of chlorides through the CFTR protein [3,8], improves the defect of class III and IV mutations [7];
- Correctors (lumacaftor, tezacaftor, elexacaftor) - affect the structure and increase the transport of CFTR protein molecules to the cell membrane surface [3,8], improve the class II mutation defect [7].

Many substances and their combinations are still under research, and drugs approved for clinical use by the US Food and Drug Administration (FDA) are summarized in Table 1.

	Date of approval for clinical use by the FDA	Patient's age qualifying for therapy	Typ modulatora funkcji białka CFTR	Types of mutations qualifying for therapy
Ivacaftor	2012	4 months and older	Potentiator	At least one class III mutation (G551D or other less frequent mutation) or class IV mutation (R117H)
Ivacaftor + Lumacaftor	2015	2 years and older	Combination (potentiator + corrector)	Homozygous for Phe508del
Ivacaftor + Tezacaftor	2018	6 years and older	Combination (potentiator + corrector)	Homozygous Phe508del or heterozygous Phe508del and at least one of the other specific mutations
Ivacaftor + Tezavaftor + Elexacaftor	2019	6 years and older	Combination (potentiator + 2 correctors)	At least one copy of the Phe508del mutation (homozygotes and heterozygotes) or at least one of the other specific mutations

Table 1. Modulators of CFTR protein function [based on: 3,9-13]

It is worth noting that drugs have indicated specific types of CFTR gene mutations qualifying for therapy. Therefore, before starting targeted therapy, genotyping is necessary [9, 14]. Due to the mutation frequency, it is estimated that the carriers of the G551D mutation constitute about 5% of patients population, 90% of patients have at least one mutation in the Phe508del gene (homozygotes + heterozygotes), while Phe508del homozygotes constitute 50% of patients [6]. It is estimated that the percentage of people with CF who do not currently qualify for targeted treatment due to the type of mutation they have is about 10% [15]. In this group of patients, alternative therapeutic strategies are sought: new modulators of the CFTR protein function, gene therapies modifying the function of other genes influencing the expression of the CFTR gene [15-19], genetic material vectors that can supply the cells with the correct CFTR

gene [20] or modulators of the functions of alternative ion channels indirectly influencing the function of the chloride channel of the CFTR protein [3,16,19].

4. Results of CF treatment with modulators of CFTR protein function

The therapeutic benefits of using targeted therapies based on modulators of CFTR protein function in the treatment of CF are summarized in Table 2. It is worth noting that due to the frequent manifestation of CF from the respiratory system, scientists notice a particularly positive effect of modulators on lung function and improving the quality of life of patients. On the other hand, the scientific evidence for the effect on weight gain or the improvement of pancreatic function seems to be of low quality, due to the small amount of research and the small size of the groups of patients studied. It is emphasized that modulators of CFTR protein function show the most therapeutic benefit if therapy is started early enough in patients without advanced lung disease. It is predicted that this approach may inhibit the progression of pulmonary disease, reduce the rate of pulmonary exacerbations, reduce mortality and extend the median age of life [21,22].

	Therapeutic benefits common to all drugs	Drug-specific therapeutic benefits
Ivacaftor	<ol style="list-style-type: none"> 1. Improved lung function - an increase in the predicted FEV₁ value: about 3-4 percentage points for ivacaftor [3] and ivacaftor + lumacaftor [11], about 4-6 percentage points for ivacaftor + tezacaftor [12, 23-24], about 10-13 percentage points for ivacaftor + tezacaftor + elexacaftor [25-27], 2. Reduction in the frequency of pulmonary exacerbations [3,11,12,26], 	<ol style="list-style-type: none"> 1. Reducing the frequency of hospitalizations [30,31], 2. Weight gain (BMI increase) [31-33], 3. Reduction in the frequency of recurrent pancreatitis in patients with a history of recurrent pancreatitis [34], 4. Improvement of glucose tolerance in the group of patients with cystic fibrosis-related diabetes [35].
Ivacaftor + Lumacaftor	<ol style="list-style-type: none"> 3. Reduction of chloride ion concentration in sweat [8,9,13,24,26-28], 4. Improvement of the quality of life associated with the symptoms of CF [13,25-27,29]. 	<ol style="list-style-type: none"> 1. Improvement of glucose tolerance assessed by oral glucose tolerance test in a group of patients with impaired glucose tolerance and cystic fibrosis-related diabetes [36].
Ivacaftor + Tezacaftor		
Ivacaftor + Tezacaftor + Elexacaftor		<ol style="list-style-type: none"> 1. Weight gain (BMI increase) [27,33].

Table 2. Results of CF treatment with modulators of CFTR protein function. (CF – cystic fibrosis; FEV₁ - forced expiratory volume in one second; BMI – body mass index)

Current scientific evidence suggests that modulators of CFTR protein function are unable to eliminate airway colonization by pathogens in patients with advanced lung disease [37,38]. This seems to be an important observation considering that patients often have symptoms of infection and chronic inflammation of the airways, and most people with cystic fibrosis die of advanced lung disease [38]. For this reason, the prevention of infections and the use of antimicrobial agents should be a necessary complement to the therapy using modulators of CFTR protein function.

Clinically approved modulators of CFTR protein function have a favorable safety profile. The most frequently reported adverse events are mild to moderate in severity and do not require treatment discontinuation in most cases [39]. The most common pulmonary adverse events reported by patients during treatment were upper respiratory tract infections, cough and expectoration difficulty and pain in the paranasal sinuses. The extrapulmonary adverse events included headache, diarrhea, rash, and increased blood levels of liver enzymes [39].

The relatively recent approval of modulators of CFTR protein function for clinical use (since 2012) makes it difficult to assess their impact on life expectancy of patients [22]. Studies based on simulation methods in patients treated with ivacaftor and lumacaftor predict an increase in the median survival age by 6.1 years [40]. The current trend of reducing mortality and extending the life span results from such interventions as early diagnosis based on common screening of newborns and early initiation of effective symptomatic treatment [4,9,41]. Additionally, it can be assumed that in the next few years this trend will be further strengthened thanks to the use of modulators of CFTR protein function in therapy. At the same time, it is worth noting that prolonged life expectancy may carry the risk of a higher incidence of complications and comorbidities in patients with CF and diseases resulting from the aging process, which have not been a significant problem in this group of patients so far [41,42].

5. Conclusions

The progress of medicine in the diagnosis and treatment of CF since the discovery of the CFTR gene can be described as very significant. CF, from an epidemiological point of view, can therefore be perceived not only as a pediatric disease, but also mainly affecting young adults. Extending the life span of patients in recent years and improving their quality of life in many countries around the world has become possible thanks to screening newborns and the early initiation of symptomatic treatment. Based on the available scientific data, modulators of CFTR protein function can be considered as an effective and safe targeted therapy adapted to the patient's genotype. The therapeutic benefits of these drugs are improved lung function and reduced frequency of pulmonary exacerbations, reduced hospitalization rates, and improved disease-related quality of life. In the group of patients ineligible due to their type of mutation, alternative therapeutic strategies are sought, such as gene therapies or modulators of the functions of other ion channels.

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