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МУКОВИСЦИДОЗ: НОВЫЕ ТЕНДЕНЦИИ В МЕТОДАХ ТЕРАПИИ

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Cystic Fibrosis: New Trends in Therapy Methods

Резюме

Несмотря на увеличение продолжительности и заметное улучшение качества жизни больных, на сегодняшний день муковисцидоз остается одним из тяжелых пульмонологических заболеваний, ведущим к инвалидизации. В связи с актуальностью проблемы терапии данного заболевания, ежегодно стартуют разработки новых препаратов для лечения муковисцидоза.

Данный обзор описывает новейшие достижения в лечении муковисцидоза, также представлены промежуточные результаты ведущихся клинических исследований. В процессе подготовки обзора были использованы различные базы научных данных: Scopus, Web of Science, EMBASE.

Описаны результаты исследований новых препаратов, предназначенных для противовоспалительной терапии данного заболевания — ацебилустата, препарата LAU-7b, JBT-101.

Рассмотрены результаты исследования альгината олигосахарида, снижающего вязкость мокроты у больных муковисцидозом. Эффект препарата был продемонстрирован на примере усиления действия антибиотика азтреонама, эффективного против Burkholderia cepacia complex — группы патогенных микроорганизмов, часто поражающих дыхательную систему больных муковисцидозом.

Описаны исследования различных препаратов генной терапии муковисцидоза — вещества ABO401, препарата SP-101, представлены результаты клинических исследований аденоассоциированного вектора 4D-710, липосомных наночастиц, в том числе препаратов MRT5005, RCT2100, таргетной терапии корректора галикафтора, комбинаций ивакафтор+лумакафтор, тезакафтор+ивакафтор, ивакафтор+тезакафтор +элексакафтор и ванзакафтор+тезакафтор+деутивакафтор.

Особенное внимание в обзоре было уделено доставке трансгена при помощи векторов, описаны преимущества и недостатки данного метода. Описаны основные современные методы геномного редактирования, их возможности, преимущества и недостатки.

Показана роль таргетной терапии как фактора, способного значительно уменьшать тяжесть течения заболевания. Препараты таргетной терапии способны частично восстанавливать функцию аномального белка у больных муковисцидозом, а значит снижать степень проявления симптомов и значительно повышать качество жизни пациента. Описана необходимость дальнейшей разработки данного направления.

Ключевые слова: *муковисцидоз, обзор, таргетная терапия, противовоспалительная терапия, генная терапия, геномное редактирование, вирусный вектор, патогенетическая терапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

This review provides information on recent advancements in the treatment of cystic fibrosis and presents interim results from ongoing clinical trials. Various scientific databases, including Scopus, Web of Science, and EMBASE, were utilized during the preparation of this review.

The results of studies on new drugs such as acebilustat, LAU-7b, JBT-101 designed for anti-inflammatory therapy of this disease are also presented.

The review describes various approaches to cystic fibrosis therapy — substance ABO401, SP-101. It includes clinical trial results for the adeno-associated vector 4D-710, liposomal nanoparticles, including the drugs MRT5005, RCT2100, the corrector galicaftor, as well as the drugs lumacaftor+ivacaftor, tezacaftor+ivacaftor, tezacaftor+ivacaftor+elexacaftor и tezacaftor+vanzacaftor+deutivacaftor.

Special attention is given to transgene delivery using vectors with a detailed discussion of the advantages and disadvantages of this method. The main modern genome editing techniques, their capabilities, advantages and disadvantages are also described.

The results of the study on the oligosaccharide structures, which reduces sputum viscosity in patients with cystic fibrosis, are presented. This reduction in viscosity enhances the effectiveness of the antibiotic aztreonam, which is active against the Burkholderia cepacia complex — a group of pathogens, which is often responsible for inflammation in cystic fibrosis patients.

The role of targeted therapy as a factor capable of significantly reducing disease severity was highlighted. Targeted therapy drugs can partially restore the function of the abnormal protein in cystic fibrosis patients, thereby reducing symptom severity and significantly improving the patient's quality of life. The necessity of further development in this field was emphasized.

Key words: *cystic fibrosis, review, targeted therapy, genetic therapy, gene editing, genetic vector*

Conflict of interests

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DNA — deoxyribonucleic acid, CFTR — cystic fibrosis transmembrane conductance regulator

Introduction

One of the most common genetic diseases globally is cystic fibrosis; its manifestations deteriorate the quality of patients' lives, forcing them to fight for preservation of their usual functions. The therapy of cystic fibrosis is currently one of the burning topics in healthcare. The importance of this problem for the healthcare system is that, despite early diagnosis of cystic fibrosis, this disease is associated with short patient life and results in early disablement. This article discusses the key areas of therapy development for the treatment of cystic fibrosis and presents results of recent studies in this area. This literature review analyses articles from Scopus, PubMed, Free Medical Journals, eJournals for the past five years.

Cystic fibrosis is a systemic, genetically determined disease

Cystic fibrosis is a genetically determined, autosomal-recessive disease, which is characterised by the involvement of all exocrine glands [1]. An initial defect in the cystic fibrosis transmembrane conductance regulator (CFTR) causes dysfunction of a number of organs and systems, including pathologies of the respiratory system, intestine and reproductive system. This is a systemic disorder, requiring a specific therapeutic approach [2]. On the average, one child in every 4,500–6,000 newborns has cystic fibrosis, and the mean life expectancy in patients with cystic fibrosis varies from 28 to 47.7 years old [3].

This disease is monogenetic: the gene of cystic fibrosis is located on the long arm of the 7th chromosome (the most common mutation in this gene is F508del) and encodes CFTR protein. This protein participates in the active transport of chlorine ions. Currently, mutations in the gene of CFTR protein are divided into seven groups; however, gene therapy can be used for correction of several of them. A mutation results in CFTR protein dysfunction, causing changes in ion transport processes: the number of chlorine ions and water molecules excreted via CFTR protein drops. In turn, it results in changes in the composition and viscosity of exocrine gland secretory product. Thus, one of the most important pathogenetic links in cystic fibrosis development is impaired transportation of a thick secretory product: its movement slows down [4]. A comprehensive therapy of cystic fibrosis should include genetic, pathogenetic (target) and symptomatic therapy.

Genetic therapy of this condition is a subject to wide discussions. Recent studies bring hope that in the future this therapy will contribute to the treatment of cystic fibrosis; however, currently the backbone is targeted therapy [5].

Anti-inflammatory therapy

As of today, anti-inflammatory therapy is one of the most important components in the therapy of cystic fibrosis. This is due to the severity of the intoxication syndrome, which significantly affects the quality of patients' life.

Acebilustat is a synthetic low-molecular leukotriene A4 hydrolase inhibitor; it inhibits leukotriene B4 production, which participates in the pathogenesis of cystic fibrosis as a result of attracting neutrophils to the inflammation site. A randomised, double-blind study of acebilustat demonstrated that, although the drug did not impact the forced expiratory volume over the first second, it delayed and reduced pulmonary exacerbation in subjects [6].

LAU-7b is a synthetic fenretinide analogue of retinol, which targets cell membrane lipids by affecting protein transport and inflammation. LAU-7b can trigger immune-mediated neutrophilic reaction, which blocks bacterial elimination from the site and slows down inflammation. A randomised, double-blind phase II study of LAU-7b demonstrated favourable effect on respiratory function preservation in subjects [7].

JBT-101 is mentioned as an anti-inflammatory drug, which is a type II non-immunosupressive cannabis-receptor agonist, stimulating inflammation elimination due to an increase in the production of special mediators and reduction in inflammatory molecule concentration. The drug demonstrated positive results in the study of its effects in cystic fibrosis patients: inflammation subsided, and patients noted reduction in disease-related pain [8].

One of the most significant factors affecting the quality of life and life expectancy of cystic fibrosis patients is efficient management of bacterial lung damage. One of the most common pathogens observed in cystic fibrosis patients is closely related gram-negative bacteria Burkholderia cepacia [9].

In a randomised, double-blind study, Fischer R., et al. (Journal of Cystic Fibrosis, 2022) evaluated alginate oligosaccharide, which makes mucous in cystic fibrosis patients less viscous. It proved to be efficient in enhancement of the action of aztreonam: the study analysed the reduction rate of microbial load of Burkholderia cepacia complex after the use of a combination of alginate oligosaccharide and aztreonam vs. aztreonam and placebo. The effect was demonstrated with the combined use of alginate oligosaccharide solution for inhalation and aztreonam. Six out of twelve quality criteria in study subjects showed relative improvement after the use of alginate oligosaccharide vs. placebo [10].

Gene therapy

Since the *CFTR* gene was discovered, over 2,000 genetic variants of the gene have been identified. This finding brought hope for possible correction of this erroneous variant and insertion of a normal copy of the gene. However, CFTR sensibility to modulators is far from 100%. Approximately 10% of cystic fibrosis patients have mutations, where CFTR protein either is not synthesised at all or is synthesised in insufficient amounts, making patients insensitive to CFTR modifiers. Also, there are reports on individual intolerance of these products, which is observed in 10–20% of cystic fibrosis patients [11].

One gene therapy involves transgene delivery by adenovirus-associated vectors. Studies of this therapy report absence of any favourable or side effects. Later, studies in this field aimed to boost tropism of adenovirus-associated vectors; find unknown vector serotypes; search for new promotors; enhance expression levels of a required protein; and find it in the lungs. Also, an important component of studies was attempts to lower the immunological potency of these vectors [12].

Studies in this area are conducted by several large companies. Abeona Therapeutics has completed preclinical trials of ABO401. This product is a capsid of an adenovirus-associated vector, serotype 204, and contains a functional copy of human *mini-CFTR gene*. Its potential benefits include high specificity as regards the lung epithelium and possible transduction of bronchial cells and nasal epithelial cells [13].

Spirovant Sciences is developing SP-101. It uses an adenovirus-associated vector capsid with high tropism towards lung epithelium cells. In 2020, the US Food and Drug Administration (FDA) assigned this product the status of an orphan medicinal product [12].

4D Molecular Therapeutics is conducting phase 1/2 clinical trials of 4D-710. The results of lung biopsy material of subjects sampled on week 4–8 after therapy initiation show absence of any signs of pulmonary inflammation, as well as approx. 400% increase in CFTR protein expression vs. materials sampled from healthy subjects. Also, there were no reports of safety concerns of the product [14].

Another gene therapy is transgene delivery by lentivirus vectors. The benefits of these vectors include relatively long duration of expression and possible preservation of the required transgene in cells even if they divide. It is achieved due to low immunological potency, possible integration of various populations in cells, and their integration in their genome. Drawbacks of these genes are potential potentiation of insertion mutagenesis and higher risks of neoplastic aberration of cells. Currently, trials in this area are in the pre-clinical phase [12].

A separate group of gene therapies of cystic fibrosis includes non-virus transgene delivery using liposomes and polymer nanoparticles. The benefits of using liposomes to deliver transgene are simplicity of scaling and high informational capacity, making them safe and efficient, as demonstrated by clinical trials [15].

When comparing liposome nanoparticles for the packing and delivery of chemically modified messenger RNA of CFTR protein to ivacaftor, both these products demonstrate comparable efficiency, evidencing the possibility of using the former in the therapy of cystic fibrosis [16].

Currently, an inhalation product, which could deliver intact messenger RNA of CFTR protein to the lung tissue, has been actively developed. The first clinical study of the inhalation delivery by liposome nanoparticles in cystic fibrosis patients was conducted using MRT5005. The study show that the forced expiratory volume per 1 second remained stable, with no improvements for the patients; however, the product demonstrated safety and relatively good tolerability [17]. Despite completed phase 1 and 2 clinical trials of MRT5005, there is no official information on the transition to phase 3, or project completion.

ReCode Therapeutics has been conducting phase 1b clinical trials to evaluate the safety of RCT2100, an inhalation gene therapy using liposome nanoparticles [18].

In pre-clinical studies, CFTR messenger RNA delivered by a liposome nanoparticle, selectively targeting the organs, restored CFTR protein function in the lung cells, sampled from cystic fibrosis patients. These results demonstrate potential efficacy of the product in cystic fibrosis patients, who do not respond to the existing target therapy [19].

Results of studies of the use of polymers have been published. One study demonstrated the possibility to improve the quantity of liposome nanoparticles penetrating mucous layers due to particle covering with polyethylene glycol at the molecular level. This approach allowed boosting the efficacy of nucleic acid administered to murine lung cells in vivo [12].

Of note, one of the crucial tasks of the gene therapy is improving the method of gene structure delivery to epithelial cells because of mucous present on the epithelial surface, mucociliary clearance, and deeper location of the epithelial stem cells. Due to the constant cellular turnover, this therapy faces the need for repeated gene structure delivery, and it is associated with a higher risk of spontaneous cell mutagenesis. Also, there is a risk of immune response to the vector protein. In addition, currently, there is no comprehensive information regarding the types of cells, which should be the primary target of the therapy in order to ensure the highest treatment efficacy; and there are no reports on the possible action of the product on several target cells at a time [20–22].

Genome editing

This method allows correcting a gene mutation and, basically, saving the individual from their disease, i.e. cystic fibrosis in this case. Several techniques can be used for genome editing.

CRISPR/Cas9: this method is based on generation of a breakage defect in deoxyribonucleic acid (DNA) using CRISPR-associated endonucleases (proteins Cas), which are specifically programmed. The accuracy of this method is a result of the action of a specific directing ribonucleic acid, which is complementary to the target chain of the DNA section. The method is highly efficient, since a specific target gene can be selected, and several aberrant genes can be edited at once. Gene correction with the CRISPR/Cas9 system is possible using only one protein; and ribonucleic acid, which directs the gene editing process, can be purchased or synthesised in the laboratory over a short period of time, making this technique not only an accurate, but also an inexpensive method. The drawback of the method is the large size of protein Cas9, which cannot fit in the adenovirus-associated vector [23].

ZFN — zinc finger nucleases. These are protein domains, the composition of which includes zinc and the structure of which resembles a finger. Each domain can form a unique link only with its specific three-nucleotide DNA section. The benefit of the method is its low immunological potency and small protein size; however, drawbacks are superior: the method can cause numerous damages to the integrity of DNA strands, which are initially not a target of a specific ZFN complex. Also, the costs of reproducing a specific ZFN type in laboratory settings are high, and this process is technologically challenging [24].

TALEN is a technology based on the operation of domain structures, which are complementary not to the three-, but one-nucleotide sequence. This method is associated with fewer cytotoxic effects, but it is sensitive to DNA methylation and is less efficient [25].

Base editing is a method of genome editing based on transformation of a specific letter in the DNA text. Base editors can edit only specific types of single base change (C→T, G→A, A→G, T→C), but cannot correct other specific mutations (e.g., C→A or G→T). At the same time, unlike CRISPR/Cas9, no double-stranded breakages are created. The efficacy of this method is high, since there are no random insertions and deletions because DNK remains intact. Still, this system is too large to be delivered by adenovirus-associated vectors, and it is quite challenging to edit a DNA sequence, where several A or C residues are close to one another [26].

Prime editing is a genome editing, using a modified enzyme Cas9, which cuts a non-complementary DNA chain and builds a new chain with the help of reverse transcriptase and specific pgRNA (prime editing guide RNA). The method is quite efficient as it can correct various types of mutations (insertions, deletions, single base changes); however, the system is still too big for adenovirus-associated vectors and bears a risk of adverse effects for a non-target DNA sequence, as well as mutagenesis for the target sequence [27].

At the moment, the outlooks of wide application of this genome editing method are quite vague, because the number of successfully corrected mutations is low. However, genome editing using the prime editing method in cystic fibrosis patients is promising for the future genetic engineering studies.

Target therapy

There are molecules, which can partially restore the function of abnormal CFTR protein, making its structure close to normal. A therapeutic approach depends on the class of mutation.

At the moment, the most current therapy is the use of CFTR modifiers, i.e. products, which directly restore protein functions. These products include potentiators, correctors, amplifiers, stabilisers [28].

Potentiators target class III mutations, where regulatory CFTR domains function incorrectly, causing production of a normal amount of non-functional CFTR protein on the cell membrane; and class IV mutations, where chloride transport via the ion channel decreases due to its very fast closure. Potentiators, including ivacaftor (VX-770) and genistin, affect the mutated CFRT protein located in the apical cell membrane, triggering the ion channel and promoting its opening.

Lumacaftor (VX-809), curcumin, 4-phenylbutyrate/genistin, sildenafil analogue (KM11060), tezacaftor (VX-661) are correctors. They target class II mutations, since correctors create conditions, where mutant CFTR protein moves to the apical membrane, where the protein takes the correct configuration [28].

At the moment, patients with class I mutations are treated with products, which stimulate stop codon reading in messenger RNA, ensuring continued translation of CFTR protein. They include, for instance, ataluren, a product used for the treatment of Duchenne muscular dystrophy. Currently, there is not enough evidence to determine the efficacy of ataluren in the therapy of cystic fibrosis patients with class I mutations. An earlier study reported favourable results of the use of ataluren in a post hoc analysis in subgroups of subjects, who were not treated with inhalation aminoglycosides for a long time; however, these results were not reproduced in a later study, suggesting that the earlier results could have been random [29].

Two other groups of products — amplifiers and stabilisers — are currently studied and are not used in clinical settings. Amplifiers reconstruct protein translation during ribosome movement along the messenger RNA; this is how PTI-428 works. Stabilisers prolong the period, during which CFTR remains in membrane plasma.

First generation CFTR modifiers should be discussed separately. The first potentiator, which was used in clinical settings, is ivacaftor (VX-770). Ivacaftor is used mostly for patients with mutation G551D. This pathological mutation causes delayed CFTR channel opening. Therefore, its efficacy in patients with the most common CFTR mutation — F508del — increases if it is used in a combination with a corrector (lumacaftor or tezacaftor) [30, 31].

These conclusions underlie the development of a new product — lumacaftor+ivacaftor, a second CFTR modifier, which has dual action on the pathogenetic target. This product is the first CFTR modifier registered in the Russian Federation in December 2020. Lumacaftor+ivacaftor combination is associated with the following side effects: high blood pressure, worsening of short-term respiratory symptoms [32, 33]. However, despite the correlation with the identified side effects, the product is very efficient regarding the bronchopulmonary system and the rate of exacerbations. This combination is safe, and the majority of side effects are not side reactions, but complications of the disease, and resolve within two weeks with therapy. Also, if the starter dose is reduced for the first two weeks of the therapy, the rate and severity of side effects can be corrected [34].

The third first generation CFTR modifier (tezacaftor+ivacaftor) is used in children over six years of age, who have heterozygous mutation F508del or homozygotic mutation F508del/F508del; this combination has demonstrated better results and safety in clinical settings vs. lumacaftor+ivacaftor [35].

Galicaftor (ABBV-2222, previously known as GLPG2222) is a new corrector developed by AbbVie. The use of this product in a study resulted in significantly reduced chloride levels in sweat. While the product was well tolerated, it did not demonstrate any clinically significant increase in forced vital capacity values in cystic fibrosis patients. At the same time, high doses of galicaftor, used as a monotherapy in heterozygous patients with mutation F508del, as well as galicaftor+ivacaftor, used in homozygotic patients with mutation F508del, demonstrated a higher percent of estimated forced expiratory volume over the first second and reduced sweat chloride levels [36, 37].

Let's discuss second generation CFTR modifiers. Iva caftor+tezacaftor+elexacaftor is the first second generation modifier for the therapy of patients over six years of age. This product, developed by Vertex Pharmaceuticals and combining triple therapy, which can be used in children with cystic fibrosis, has proven safety. A one-year follow-up of children treated with this product showed positive dynamics in functional capacities and functional resistance [38].

Ivacaftor+tezacaftor+elexacaftor, combining a CFTR corrector and CFTR potentiator, demonstrates high efficacy among target therapy products for the therapy of cystic fibrosis. This combination makes it possible to boost CFTR functions on the cell surface, resulting in higher CFTR activity, i.e. the genetic defect is corrected, if the patient has a respective mutation in their genome. Study results show weight and height gain, better body mass index, and normal sweat test results in cystic fibrosis patients (in 28.5% of subjects). Also, there are reports on significantly improved pulmonary functions: higher forced vital capacity and forced expiratory volume over the first second [39].

It is known that the product is efficient not only for its primary objectives, it has favourable effects on

chronic rhinosinusitis progression in cystic fibrosis patients: nasal polyps disappear, and paranasal sinus pneumatisation significantly improves [40].

Vertex Pharmaceuticals is currently developing a product with a novel triple combination as a next generation successor of ivacaftor+tezacaftor+elexacaftor. The product contains tezacaftor, one of the three modifiers, used in ivacaftor+tezacaftor+elexacaftor, together with two novel modifiers — vanzacaftor (VX-121) and deutivacaftor (VX-561). Deutivacaftor is an ivacaftor analogue, where one of tert-butyl groups was substituted with a deuterated group. This modified version of ivacaftor demonstrated comparable pharmacological activity in pilot studies. Also, deutivacaftor is more stable in the body, so it could be taken once daily. That is why tezacaftor+vanzacaftor+deutivacaftor was initially developed to improve compliance of patients with cystic fibrosis therapy, because, unlike ivacaftor+tezacaftor+elexacaftor, it would be taken once instead of twice daily [36].

In 2025, Vertex reported results of three phase 3 clinical trials, where itezacaftor+vanzacaftor+deutivacaftor was studied vs. ivacaftor+tezacaftor+elexacaftor in cystic fibrosis patients with responsive mutations: SKYLINE 102 and SKYLINE 103 studies, evaluating over 1,000 adults and young people over 12 years of age [41].

At the same time, a third study, RIDGELINE 105, was conducted, where vanzacaftor+tezacaftor+deutivacaftor was tested in children between 6 and 11 years of age. Results demonstrated that patients had stable respiratory function both with ivacaftor+tezacaftor+elexacaftor and the novel therapy; however, the novel therapy turned out to be more efficient in reduction of sweat chloride ion levels, indirectly proving higher CFTR protein levels [42].

Conclusion

Cystic fibrosis is a genetic condition, where exocrine glands and body systems function incorrectly. The main cause of the disease is *CFTR* gene mutation, resulting in dysfunction of the protein responsible for chloride ion and water transport. As a consequence, secret viscosity increases, and its transport slows down. The main therapy as of today is target therapy.

Anti-inflammatory therapy is essential for the management of cystic fibrosis. Acebilustat allowed delaying and mitigating pulmonary exacerbations in patients, despite no effect for the forced expiratory volume over the first second. LAU-7b preserved pulmonary function in subjects in a randomised, double-blind study. JBT-101 demonstrated inflammation reduction, and patients reported improvement in their pain syndrome. Unlike the mentioned products, alginate oligosaccharide demonstrated efficiency due to reduced mucous viscosity.

Gene therapy of cystic fibrosis is very promising. Adenovirus and adenovirus-associated vectors are being actively studied in order to reduce their immunological potency and boost CFTR protein expression. Adenovirus-associated products ABO401 and SP-101 have promising benefits of high specificity in relation to epithelial cells, while 4D-710 significantly increases CFTR protein production. The benefits of lentivirus vectors are long-term gene expression, but there is also a risk of oncogenic cell transformation. Non-viral methods of transgene delivery using liposomes demonstrated their efficacy and safety. Unlike MRT5005, RCT2100 restored CFTR protein function in pulmonary cells of patients. Currently, studies are ongoing to evaluate promising delivery methods using polymer nanoparticles, and possible solutions to the objectives of the gene therapy are studied.

Genome editing methods make it possible to target *CFTR* gene mutations. CRISPR/Cas9 is the most precise technique; however, it requires modifications because of the protein Cas9 size. ZFN and TALEN are less efficient and more expensive methods. Base editing and prime editing allow editing DNA without two-strand breakages, but they have limitations due to the system size and side effects. Genome editing cannot be used in clinical settings, but is being actively studied.

Target therapy is the main therapy for cystic fibrosis; its objective is partial restoration of CFTR protein function. At the moment, the most common therapy is the use of CFTR modifiers. These are potentiators, correctors, amplifiers, and stabilisers. Potentiators (ivacaftor) facilitate ion channel opening and are usually used in a combination with other classes of modulators. Correctors assist CFTR protein in reaching the apical cell membrane and are used in combinations with other products Two other groups of products (amplifiers and stabilisers) are being studied.

Despite good tolerability of galicaftor, it did not demonstrate any efficacy in improving the forced vital capacity. Nevertheless, a combination of galicaftor and ivacaftor in homozygotics carriers of mutation 508del resulted in a higher percent of estimated forced expiratory volume over the first second and reduced sweat chloride levels.

Lumacaftor+ivacaftor, a combined CFTR modifier, demonstrated efficacy and is the first CFTR modifier registered in the Russian Federation. Associated side effects are merely a complication of the underlying disease and are corrected with the starter dose reduction. Tezacaftor+ivacaftor, another first generation CFTR modifier, demonstrated even better results and safety. Ivacaftor+tezacaftor+elexacaftor demonstrates high efficacy among target therapy products in patients with cystic fibrosis. The product boosts patients' functions and improves their quality of life. Ivacaftor+tezacaftor+elexacaftor has favourable effects for the associated otorhinolaryngologic pathology. Modified tezacaf

tor+vanzacaftor+deutivacaftor combination gives high hopes. This product has been studied, and results show reduced sweat chloride levels, indirectly pointing out to higher CFTR protein levels. Also, the product is more efficient as compared to ivacaftor+tezacaftor+elexacaft or; it is associated with better compliance as it is taken only once daily.

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