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THE FIRST RESULTS OF TARGETED THERAPY IN CHILDREN WITH CYSTIC FIBROSIS IN KAZAKHSTAN

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Abstract

Introduction. Cystic fibrosis (CF) is an inherited, autosomal recessive disease caused by mutations in the CFTR gene. In the last decade, the effectiveness of CF treatment has increased significantly due to the development of targeted drugs aimed at restoring the function of the CFTR protein. The highest efficacy is observed in the triple combination elexacaftor/tezacaftor/ivacaftor (Trikafta® (Vertex Pharmaceuticals, USA). In Kazakhstan, it has been used since 2023 (generic elexacaftor/tezacaftor/ivacaftor Trilexa®, Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina). There have been no previous reports on the results of using targeted therapy in patients with CF in Kazakhstan. There is very little information about the effectiveness and safety of generic forms of CFTR modulators.

Aim: to evaluate the effectiveness and safety of the generic targeted drug elexacaftor/tezacaftor/ivacaftor Trilexa® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina) in children and adolescents with CF in real clinical practice

Materials and methods. An observational study included five children with CF aged 11 to 17 years who were treated with the three-component targeted drug elexacaftor/tezacaftor/ivacaftor. The safety of the drug was monitored by recording adverse events and the dynamics of the levels of biochemical blood parameters. The effectiveness of elexacaftor/tezacaftor/ivacaftor was assessed after 12 months based on the results of a sweat test, anthropometric characteristics, respiratory function (FEV1), number of exacerbations and courses of antibacterial therapy.

Conclusion. Within 12 months of therapy with the combination of elexacaftor/tezacaftor/ivacaftor, positive dynamics of clinical and functional parameters and the safety of three-component targeted therapy were shown. It is necessary to expand the circle of children with CF receiving three-component targeted therapy and continue research to assess its effectiveness in Kazakhstan.

Keywords: *cystic fibrosis, CFTR gene, three-component targeted therapy, sweat test, pulmonary function.*

Резюме

ПЕРВЫЙ ОПЫТ ПРИМЕНЕНИЯ ТАРГЕТНОЙ ТЕРАПИИ У ДЕТЕЙ С МУКОВИСЦИДОЗОМ В КАЗАХСТАНЕ

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Актуальность Муковисцидоз (МВ) - наследственное, аутосомно-рецессивное заболевание, вызванное мутациями в гене CFTR. В последнее десятилетие эффективность лечения МВ значительно возросла благодаря разработке таргетных препаратов, направленных на восстановление функции белка CFTR. Наибольшая эффективность наблюдается у тройной комбинации элексакафтор/тезакафтор/ивакафтор (Трикафта® (Vertex Pharmaceuticals, США,). В Казахстане применяется с 2023г. (генерический препарат elexacaftor/tezacaftor/ivacaftor Trilexa®, Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina). Ранее

сообщений о результатах применения таргетной терапии у пациентов с МВ в Казахстане не было. Информации об эффективности и безопасности генерических форм препаратов крайне мало.

Цель: оценка эффективности и безопасности генерического таргетного препарата elexacaftor/tezacaftor/ivacaftor Trilexa® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina) у детей и подростков с МВ в реальной клинической практике

Материалы и методы. Проведено наблюдательное исследование, включены пять детей с МВ в возрасте от 11 до 17 лет, которым проводилось лечение трехкомпонентным таргетным препаратом элексакафтор/тезакафтор/ивакафтор. Безопасность препарата контролировали путем регистрации нежелательных явлений и динамики биохимических показателей крови. Эффективность элексакафтора/тезакафтора/ивакафтора оценивали через 12 месяцев по результатам потовой пробы, антропометрических характеристик, дыхательной функции (ОФВ1), количеству респираторных обострений и курсов антибактериальной терапии.

Результаты: применение трехкомпонентной таргетной терапии элексакафтора/тезакафтора/ивакафтора (генерический препарат Трилекса®,Tuteur S.A.S.I.F.I.A., Буэнос-Айрес, Аргентина) у детей с МВ позволило улучшить показатели дыхательной функции, нутритивного статуса, потового теста, также отмечено снижение частоты легочных обострений и курсов системных антибиотиков после 12 месяцев лечения. Профиль безопасности был удовлетворительным с минимальными нежелательными явлениями.

Заключение. В течение 12 месяцев терапии комбинацией элексакафтор/тезакафтор/ивакафтор показана положительная динамика клинико-функциональных показателей и безопасность трехкомпонентной таргетной терапии. Необходимо расширить круг детей с МВ, получающих трехкомпонентную таргетную терапию и продолжить исследование по оценке ее эффективности в Казахстане.

Ключевые слова: *муковисцидоз, ген CFTR, трехкомпонентная таргетная терапия, потовый тест, функция внешнего дыхания.*

Түйіндеме

ҚАЗАҚСТАНДА МУКОВИСЦИДОЗЫ БАР БАЛАЛАРДА ТАРГЕТТІ ТЕРАПИЯНЫ ҚОЛДАНУДЫҢ АЛҒАШҚЫ ТӘЖІРИБЕСІ

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Өзектілігі. Муковисцидоз (МВ) - CFTR геніндегі мутациялардан туындаған тұқым қуалайтын, аутосомды-рецессивті ауру. Соңғы онжылдықта CFTR ақуызының қызметін қалпына келтіруге бағытталған мақсатты препараттарды әзірлеу арқылы МВ емдеу тиімділігі айтарлықтай өсті. Ең жоғары тиімділік элексакафтор/тезакафтор/ ивакафтордың үштік комбинациясында байқалады (Трикафта®, Vertex Pharmaceuticals, АҚШ). Қазақстанда 2023 жылдан бастап қолданылады (генерикалық препарат elexacaftor/tezacaftor/ivacaftor trilexa®, Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina). Бұған дейін Қазақстанда МВ бар пациенттерде мақсатты терапияны қолдану нәтижелері туралы хабарламалар болған жоқ. Препараттардың жалпы түрлерінің тиімділігі мен қауіпсіздігі туралы ақпарат өте аз.

Мақсаты: нақты клиникалық тәжірибеде МВ бар балалар мен жасөспірімдерде elexacaftor/tezacaftor/ivacaftor trilexa® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina) жалпы мақсатты препаратының тиімділігі мен қауіпсіздігін бағалау.

Материалдар мен әдістері: Байқау зерттеуі жүргізілді, 11-17 жас аралығындағы МВ бар бес бала енгізілді, олар үш компонентті мақсатты препаратпен ем жүргізді элексакафтор/тезакафтор/ивакафтор. Препараттың қауіпсіздігі жағымсыз құбылыстарды тіркеу және қанның биохимиялық көрсеткіштері деңгейінің динамикасы арқылы бақыланды. Элексакафтордың/тезакафтордың/ивакафтордың тиімділігі 12 айдан кейін тер сынамасы, антропометриялық өлшемдер, тыныс алу функциясы (Бірінші секундта мәжбүрлі дем шығару көлемі), өршу саны және бактерияға қарсы терапия курстары бойынша бағаланды.

Нәтижесі: МВ бар балаларда электрокафтор/тезакафтор/ивакафтордың үш компонентті мақсатты терапиясын (Трилекс®жалпы препараты, Tuteur S.A.S.I.F.I.A., Буэнос-Айрес, Аргентина) қолдану тыныс алу функциясының, тамақтану жағдайының, тер сынағының көрсеткіштерінің жақсарғанын көрсетті, 12 айдан кейін өкпенің өршу жиілігінің және жүйелі антибиотиктер курстарының төмендеуі байқалды емдеу. Қауіпсіздік профилі ең аз жағымсыз құбылыстармен қанағаттанарлық болды.

Қорытынды. Элексакафтор/тезакафтор/ивакафтор комбинациясымен терапияның 12 айында клиникалық-функционалдық көрсеткіштердің оң динамикасы және үш компонентті мақсатты терапияның қауіпсіздігі

көрсетілген. Үш компонентті мақсатты терапия алатын МВ бар балалар тобын кеңейту және оның Қазақстандағы тиімділігін бағалау бойынша зерттеуді жалғастыру қажет.

Түйінді сөздер: *муковисцидоз, CFTR гені, үш компонентті таргетті терапиясы, тер сынағы, сыртқы тыныс алу функциясы.*

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Introduction

Cystic fibrosis (CF) is a hereditary, autosomal recessive disorder caused by mutations in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene, which leads to the dysfunction of chloride channel and the formation of viscous mucus in exocrine glands [4]. Main features of CF include rapid decrease in the quality of life of the patients due to progressive respiratory disease and pancreatic insufficiency that leads to high disability and mortality. Advances in understanding and treatment strategies have greatly extended the lifespan for CF patients. Currently, the proportion of adults with CF in many European countries exceeds 50% [20], while in Kazakhstan the same figure is 10% [9], which is associated with late diagnosis and untimely initiation of multi-component therapy.

The effectiveness of the CF treatment has increased significantly in recent decades due to an improved understanding of the CF pathophysiology and genetics and the development of novel therapies. Treatment of CF is a complex and personalized process. Basic therapy for CF is aimed at relieving symptoms and preventing complications and includes antibacterial, mucolytic, enzyme replacement therapy, nutritional support, rehabilitation, etc. This treatment gives significant clinical results, improves quality of life and increases life expectancy [13].

The major advancement in CF treatment has been the discovery of small molecules and the creation of targeted drugs that are aimed at restoring the function of the CFTR protein, providing pathogenetic treatment for CF patients. The action of CFTR modulators is based on the ability of molecules to increase the amount of CFTR protein on the surface of the epithelial cell and / or enhance its function. According to the mechanism of action, two main groups of CFTR modulators can be distinguished - correctors and potentiators [8]

Potentiators are CFTR modulators that act on the mutant CFTR protein that is already located in the apical membrane of the epithelial cell. The action of potentiators is aimed at restoring the function of the ion channel formed by this CFTR protein. Correctors ensure the delivery of the mutant CFTR protein to the apical membrane and allow it to occupy the correct position on the membrane. In 2019, the FDA registered the triple combination Elexacaftor/Tezacaftor/Ivacaftor Trikafta® (Vertex Pharmaceuticals, USA) - a combination of the potentiator Ivacaftor and 2 correctors - Elexacaftor and Tezacaftor [14]. The triple combination of modulators is intended for the treatment of CF patients carrying one or two F508del variants or another genetic variant of CFTR sensitive to this drug [19]. Currently, the drug is approved by the FDA for patients 2 years and older with CF [5]. According to numerous clinical studies, the triple combination Elexacaftor/Tezacaftor/Ivacaftor have demonstrated a significant improvement in nutritional status, an increase in respiratory function indicators, a decrease in the number of exacerbations and, as a result, the number of courses of oral and intravenous antibacterial therapy in adults and children with cystic fibrosis [1, 3, 5, 6, 7, 11, 16, 19].

The first group of CF patients in Kazakhstan began triple CFTR modulator therapy in 2023. The medical panel of the Scientific Center of Pediatrics and Pediatric Surgery (Almaty) recommended the use of triple targeted therapy in children with the corresponding CFTR genotype. The treatment is provided by the Public Fund «Kazakhstan Halkyna». CF patients are provided with a generic formulation of Trilexa (Tuteur S.A.S.I.F.I.A., Argentina).

We present the first clinical cases of five children who received triple targeted therapy over a one-year period.

Aim of the study

To evaluate the safety and efficacy of the generic drug Elexacaftor/Tezacaftor/Ivacaftor Trilexa® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina) used in children and adolescents with CF in routine clinical practice.

Materials and Methods

Patients

We present an observational study in clinical practice, participans: five children (three males, Table 1), aged 11 – 17 years, diagnosed with Cystic Fibrosis (CF) who were under the care of The Scientific Center of Pediatrics and Pediatric Surgery (Almaty). Before the start of the therapy, parents/guardians of all patients signed informed consent for targeted therapy, collection and processing of relevant medical information. Patient 4, upon reaching the age of 18, receives medical care at the Astana Medical University. The diagnosis of CF in all participants was established in childhood (min 4 months - max 6 years), in all cases confirmed by a positive sweat test and two pathogenic mutations in the CFTR gene (table 2).

Table 1.

Safety parameters.

	Patient 1 (female)			Patient 2 (female)			Patient 3 (male)			Patient 4 (male)			Patient 5 (male)		
	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ
Total bilirubin (μmol/L)	8.40	7.59	-9.64	4.70	10.90	+131.91	8.10	10.56	+30.37	11.40	20.10	+76.32	**21.40**	**47.29**	+120.98
Direct bilirubin (μmol/L)	4.00	3.93	-1.75	1.90	4.70	+147.37	4.10	4.71	+14.88	N/A	N/A	N/A	6.63	5.00	-24.59
ALT (U/L)	N/A	13.60	N/A	11.60	16.00	+37.93	12.80	13.40	+4.69	28.00	21.20	-24.29	26.00	**38.30**	+47.31
AST (U/L)	N/A	16.80	N/A	15.20	17.40	+14.47	21.80	24.04	+10.28	23.00	16.80	-26.96	25.60	**34.31**	+34.02
Adverse events	No			Severe cough excess sputum – first 3 days of treatment; skin rash, resolved with antihistamines			Skin rash – first day of treatment, resolved spontaneously; decreased blood pressure – first 2 months of treatment, resolved spontaneously			Severe cough excess sputum – first 2 days of treatment			Increased bilirubin and transaminase levels < 2 × the upper limit of normal		

ALT – alanine aminotransferase; AST – aspartate aminotransferase; N/A – not available.

Before starting targeted therapy, all participants had elevated sweat test measurements (above 60 mmol/l) - from 61 mmol/l in patient 2 to 139 mmol/l in patient 3 (table 2). Four of the five participants (Patients 1, 3, 4 and 5) had pancreatic insufficiency and got enzyme replacement therapy. All patients received basic CF therapy [20]; all were prescribed regular nebulized rhDNase. The respiratory tract of patients 1, 2, 3 and 5 were infected with Pseudomonas aeruginosa and they received inhaled antibiotics.

Methods

The prescription of elexacaftor/tezacaftor/ivacaftor was recommended to the patients by medical panel. In accordance with the age and body weight of the patients, the drug was administered in the form of tablets at a dose of elexacaftor/tezacaftor/ivacaftor 100 mg/50 mg/75 mg + ivacaftor 150 mg. Patients received the generic medication Trilexa ® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina).

The safety of the drug was monitored by recording adverse events during treatment and the dynamics of transaminase and bilirubin levels (table 1).

The efficacy of elexacaftor/tezacaftor/ivacaftor + ivacaftor was assessed after 12 months using the following parameters: sweat test results, anthropometric characteristics (weight, height, BMI), respiratory function tests (FEV1), number of exacerbations, and number of courses of antibacterial therapy (table 2).

Table 2.

Efficacy parameters.

	Patient 1 (female)			Patient 2 (female)			Patient 3 (male)			Patient 4 (male)			Patient 5 (male)		
Genotype	F508del/3667ins4			E92K/E92K			F508del/3667ins4			F508del/R553X			F508del/S1196X		
Age at the start of therapy (years)	15			16			11			17			15		
	Pre	**Post**	**%Δ**	**Pre**	**Post**	**%Δ**	**Pre**	**Post**	**%Δ**	**Pre**	**Post**	**%Δ**	**Pre**	**Post**	**%Δ**
Weight (kg)	58.00	59.00	+1.72	49.00	50.00	+2.04	34.00	40.00	+17.65	55.00	68.00	+23.64	68.00	80.00	+17.65
Height (cm)	169.00	178.00	+5.33	163.00	163.00	0	138.00	155.00	+12.32	178.00	180.00	+1.12	179.00	183.00	+2.23
BMI (kg/m^2)	20.31	18.62	-8.32	18.44	18.82	+2.06	17.85	16.65	-6.72	17.36	20.99	+20.91	21.22	23.89	+12.58
Sweat chloride (mmol/L)	129.00	87.00	-32.56	61.00	46.00	-24.59	139.00	99.00	-28.78	136.00	76.00	-44.12	102.00	52.00	-49.02
FEV1 (%pred)	101.00	105.00	+3.96	71.76	73.19	+1.99	78.00	92.00	+17.95	74.40	89.00	+20.27	76.44	99.73	+30.47

BMI – body mass index; FEV1 – forced expiratory volume in the first second.

Data analysis

The data collected from patients prior to and following treatment were tabulated. Changes in parameter values were calculated as the ratio of the difference between pre- and post-treatment measurements to the pre-treatment values. The results were presented as percentages, with the sign of the difference maintained. In order to reduce the potential confounding effects of heterogeneity among patients, we chose to exclude sample characteristics, such as the median, mean and standard deviation, from the analysis.

The data processing and visualization were conducted using Python (version 3.9.16) with the NumPy, pandas, matplotlib, and seaborn packages. The data regarding the frequency of respiratory exacerbations and the administration of antibiotics within a year before therapy and during treatment were represented as a heatmap, while the changes in the key quantitative parameters were illustrated in the form of line plots.

Results

The administration of elexacaftor/tezacaftor/ivacaftor + ivacaftor resulted in a notable reduction in the incidence of respiratory exacerbations. Consequently, the necessity for intravenous and oral antibiotic therapy was also lower during treatment than a year before its initiation (Figure 1).

Serum transaminase levels in patients 1,2,3,4 remained within normal limits during a year of targeted therapy. A minor, less than 2-fold increase in AST and ALT levels (38.30 U/L and 34.31 U/L, respectively) was noted in patient 5.

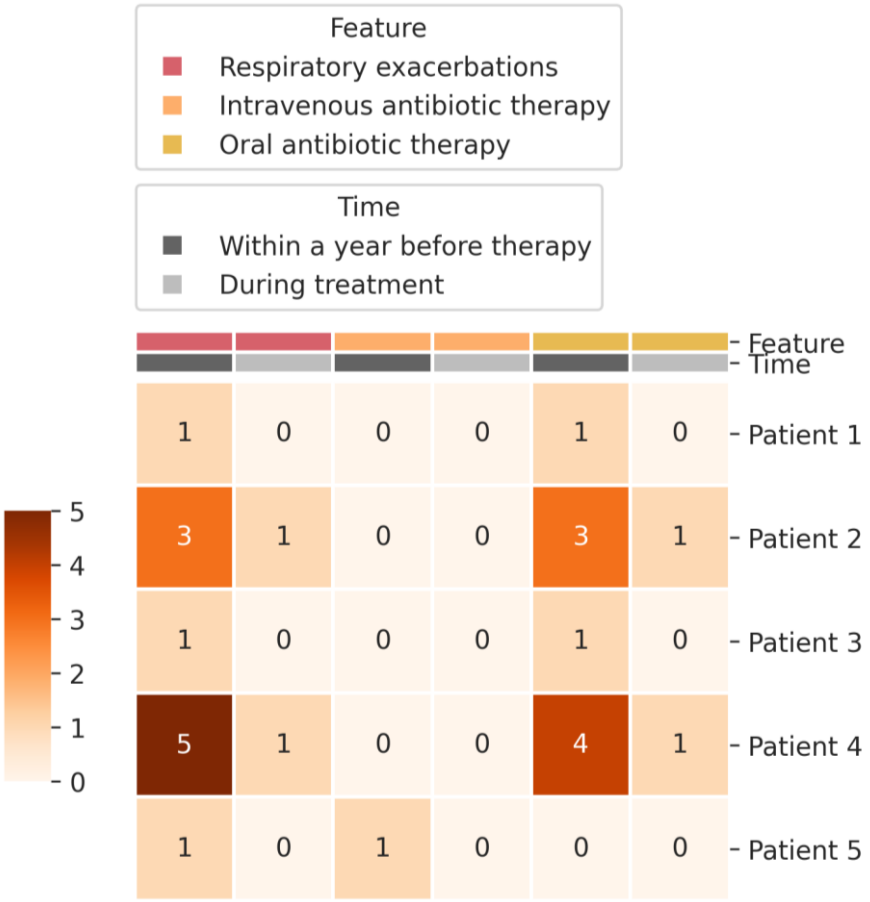

Figure 1. Heatmap of the frequency of respiratory exacerbations and the administration of antibiotics.

The same patient had an increase in total bilirubin before the start of targeted therapy (21.40 μmol/L), after 12 months it was 47.29 μmol/L, direct bilirubin level was within normal limits (table 1). No severe adverse events were observed during 12 months of treatment. There was a severe cough and an increase in the amount of sputum in patients 2 and 4 for 2-3 days, which resolved spontaneously. Patients 2 and 3 had skin rash, which resolved with antihistamines in patient 2 and spontaneously in patient 3 (table1) [10]. None of the patients refused to continue treatment.

The administration of elexacaftor/tezacaftor/ivacaftor+ivacaftor resulted in weight gain, a decrease in sweat chloride concentration, and an increase in FEV1 to some extent in all patients (Table 2, Figures 2, 3, 4). However, the BMI exhibited a divergent trend due to the pronounced growth observed in Patients 1 and 3 during treatment (Table 2, Figure 5).

Discussion

The development and implementation of the drugs that modulate the defective CFTR protein function has opened a fundamentally new era in the treatment of CF [15].

A triple combination containing a potentiator and two correctors elexacaftor/tezacaftor/ivacaftor+ivacaftor demonstrated the best effect on the dynamics of anthropometric data, pulmonary function, reduced the frequency of pulmonary exacerbations, and improved the quality of life of patients [1, 3, 5, 6, 8, 11, 14, 19].

Most of the studies were carried out using the original formulation Trikafta®, (manufactured by Vertex Pharmaceuticals, USA). There are only a few studies on the effectiveness and safety of generic drugs. [16, 18]

The generic drug Trilexa® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina)*, containing a triple fixed dose combination similar to the original drug, demonstrated positive effects on respiratory function indicators, sweat test and nutritional status in patients over 18 years of age. The generic drug was well tolerated, and no serious adverse events (AE) were recorded [7].

Our study demonstrated positive dynamic with the first use of the targeted generic drug elexacaftor/tezacaftor/ivacaftor+ivacaftor in real clinical practice in patients under 18 years of age.

All patients showed regression or complete cessation of respiratory exacerbations. An increase in body weight was also observed in all cases, with a maximum increase of 23.6% from the initial one, although BMI had a different trend, which is explained by a large increase in height in relation to body weight in two cases. An important indicator of the clinical effectiveness of the therapy was a decrease in the need for courses of systemic antibacterial therapy.

A significant decline in the concentration of chlorides in sweat fluid, min 24.6%, max 49.0% of the initial value confirms the effectiveness of this drug in influencing the pathogenetic mechanisms of the disease, in particular restoring the function of the CFTR protein, which ensures the clinical effects of therapy.

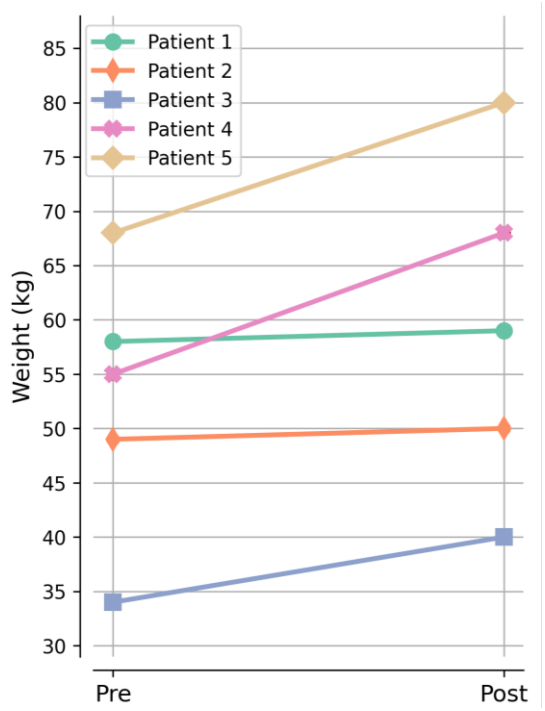

Figure 2. Line plot of pre- and post-treatment weight.

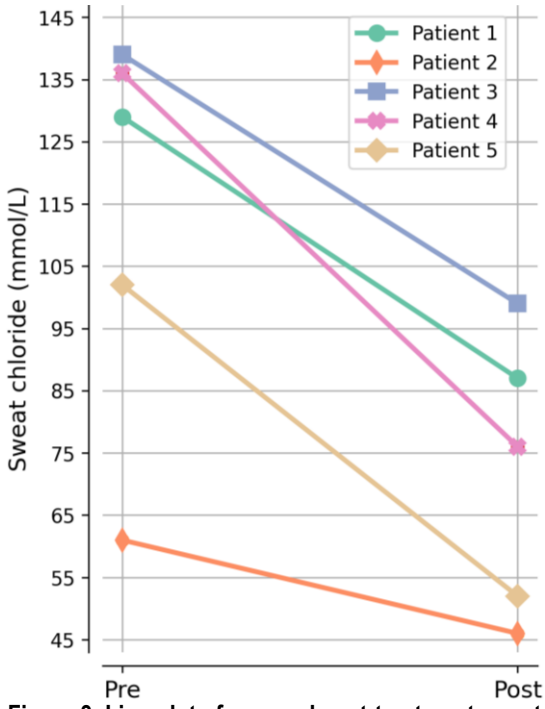

Figure 3. Line plot of pre- and post-treatment sweat chloride concentration.

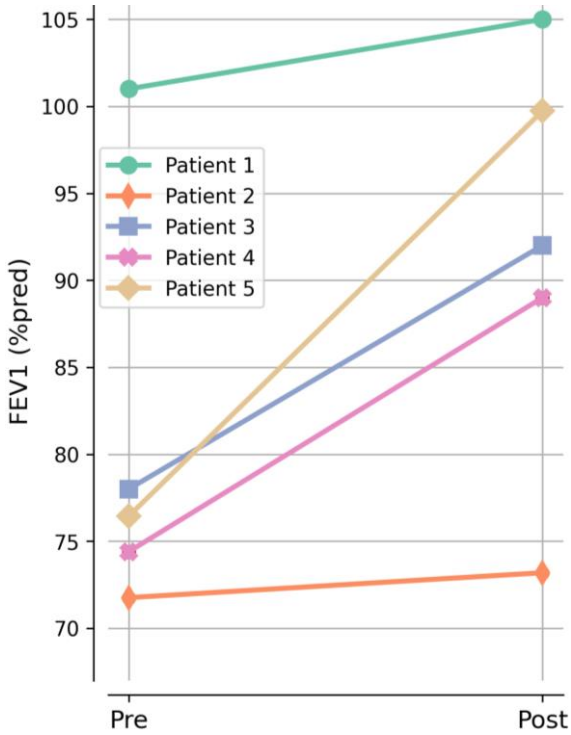

Figure 4. Line plot of pre- and post-treatment forced expiratory volume in the first second (FEV1).

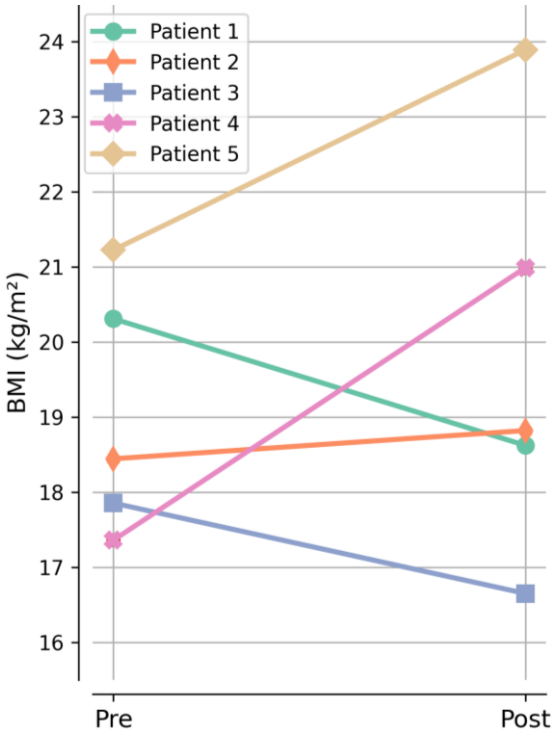

Figure 5. Line plot of pre- and post-treatment body mass index (BMI).

A positive trend was also noted in functional indicators: FEV1 increased in all patients with the greatest increase in 2 cases, by 20.37% and 30.47% respectively. Similar dynamics in spirometry indicators were noted by other researchers [15].

The use of a triple-targeted generic formulation did not lead to the development of severe adverse events. Only two patients experienced a skin rash that did not require discontinuation of therapy. Similar effects were previously described by researchers when taking the original drug [10].

One of the known side effects of CFTR modulators is drug-induced liver damage with an increase in the content of liver transaminases and bilirubin, and impaired metabolism of bile acids [17, 12]. In our study, one patient

showed a slight increase in the levels of transaminases and total bilirubin (Table 1).

It should be noted that our study results are limited to a small sample of patients; expanding the cohort of patients will provide more significant data on the effectiveness and safety of the targeted generic drug.

Conclusion

The first clinical experience with CF targeted therapy in children in the Republic of Kazakhstan has been demonstrated.

The use of a generic formulation of Elexacaftor/ Tezacaftor/Ivacaftor, Trilexa® (Tuteur S.A.S.I.F.I.A., Buenos Aires, Argentina) in target naïve children with Cystic Fibrosis with responsive CFTR variants demonstrated significant improvement in respiratory function, nutritional status and sweat test parameters after 12 months of treatment as well as reduction in pulmonary exacerbations and systemic antibiotics courses incidence.

The safety profile was also quite satisfactory with minimal adverse events and no significant increase in serum transaminase levels.

It is necessary to expand the circle of people with CF receiving pathogenetic therapy in Kazakhstan and continue research to assess the effectiveness of this treatment.

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References:

1. *Bell S.C., Mall M.A., Gutierrez H. et al.* The future of cystic fibrosis care: a global perspective. *Lancet Respir. Med.* 2020; 8 (1): 65–124. DOI: 10.1016/S2213-2600(19)30337-6.

2. Castellani C, Duff AJA, Bell SC et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros. 2018 Mar;17(2):153-178. doi: 10.1016/j.jcf.2018.02.006. Epub 2018 Mar 3. PMID: 29506920

3. *Dawood S.N., Rabih A.M., Niaj A., Raman A., Uprety M., Calero M.J., Villanueva M.R.B., Joshaghani N., Villa N., Badla O., Goit R., Saddik S.E., Mohammed L.* Newly Discovered Cutting-Edge Triple Combination Cystic Fibrosis Therapy: A Systematic Review. Cureus. 2022 Sep 20;14(9):e29359. doi: 10.7759/cureus.29359. PMID: 36284811; PMCID: PMC9583755.

4. *Derichs N.* Targeting a genetic defect: cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. Eur Respir Rev. 2013 Mar 1.22(127):58-65. DOI: 10.1183/09059180.00008412. PMID: 23457166; PMCID: PMC9487424.

5. Elexacaftor-Tezacaftor-Ivacaftor and Ivacaftor (Trikafta): CADTH Reimbursement Recommendation: Indication: For the treatment of cystic fibrosis in patients aged 2 and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Dec. Available from: https://www.ncbi.nlm.nih.gov/books/NBK599836/

6. *Graeber S.Y., Vitzthum C., Pallenberg S.T., Naehrlich L., Stahl M., Rohrbach A., Drescher M., Minso R., Ringshausen F.C., Rueckes-Nilges C., Klajda J., Berges J., Yu Y., Scheuermann H., Hirtz S., Sommerburg O., Dittrich A.M., Tümmler B., Mall M.A.* Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on CFTR Function in Patients with Cystic Fibrosis and One or Two *F508del* Alleles. Am J Respir Crit Care Med. 2022 Mar 1.205(5):540-549. doi: 10.1164/rccm.202110-2249OC. PMID: 34936849.

7. *Kracowckij C.A., Kagasezhew R.U.* Experience with generic drug use elekcakavtor / tesakavtor / iwakavtor + iwakavtor u pazientow. Pul'monology. 2023;33(6):781-791. https://doi.org/10.18093/0869-0189-2023-33-6-781-791

8. *Middleton P.G., Mall M.A., Dřevínek P. et al.* Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. N. Engl. J. Med. 2019; 381 (19): 1809–1819. DOI: 10.1056/NEJMoa1908639

9. *Mukatova I., Amelina E., Syzdykova A., Kim S., Ramankul A., Mukanov A.* P137 Clinical characteristics of adult cystic fibrosis (CF) patients in Kazakhstan. Journal of Cystic Fibrosis. Volume 23, Supplement 1. June 2024, Pages S127-S128. DOI: 10.1016/S1569-1993(24)00495-8

10. *Okroglic L., Sohier P., Martin C. et al.* Acneiform eruption following elexacaftor–tezacaftor–ivacaftor treatment in patients with cystic fibrosis. JAMA Dermatol. 2023; 159 (1): 68–72. DOI: 10.1001/jamadermatol.2022.5208

11. *Patel S.D., Bono T.R., Rowe S. M., Solomon G.M.* CFTR targeted therapies: recent advances in cystic fibrosis and possibilities in other diseases of the airways. *Eur. Respir. Rev.* 2020; 29 (156): 190068. DOI:10.1183/16000617.0068-2019.

12. *Schnell A., Jüngert J., Klett D. et al.* Increase of liver stiffness and altered bile acid metabolism after triple CFTR modulator initiation in children and young adults with cystic fibrosis. Liver Int. 2023; 43 (4): 878–887. DOI: 10.1111/liv.15544

13. *Shteinberg M., Haq I.J., Polineni D., Davies J.C.*. Cystic fibrosis. Lancet. 2021 Jun 5;397(10290):2195-2211. DOI: 10.1016/S0140-6736(20)32542-3. PMID: 34090606.

14. *Southern K.W., Murphy J., Sinha I.P., Nevitt S.J.* Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database Syst Rev. 2020 Dec 17;12(12):CD010966. doi: 10.1002/14651858.CD010966.pub3. Update in: Cochrane Database Syst Rev. 2023 Nov 20;11:CD010966. doi:10.1002/14651858.CD010966.pub4. PMID:33331662; PMCID: PMC8094390.

15. *Taylor-Cousar J.L., Mall M.A., Ramsey B.W. et al.* Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles. ERJ Open Res. 2019; 5 (2): 00082–02019. DOI: 10.1183/23120541.00082-2019.

16. *Teper A., Lubovich S., Rodríguez V., Zaragoza S., Rodríguez E., Bournissen F.G.* Real-life experience with a

generic formulation of lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for the Phe508del CFTR mutation. Pediatr Pulmonol. 2023 Dec;58(12):3560-3565. doi: 10.1002/ppul.26690. Epub 2023 Sep 15. PMID: 37712606

17. *Tewkesbury D.H., Athwal V., Bright-Thomas R.J. et al.* Longitudinal effects of elexacaftor/tezacaftor/ivacaftor on liver tests at a large single adult cystic fibrosis centre. J. Cyst. Fibros. 2023; 22 (2): 256–262. DOI: 10.1016/j.jcf.2023.01.007

18. *Zampoli M., Verstraete J., Baird C., Calligaro G., Morrow B.* Affordable Cystic Fibrosis (CF) Transmembrane Conductance Regulator Modulator Drugs for CF: All CF Lives Worldwide Matter! Am J Respir Crit Care Med. 2023 Nov 1. 208(9):915-916. doi: 10.1164/rccm.202307-1200VP. PMID: 37549229. PMCID: PMC10870869

19. *Zemanick E.T., Taylor-Cousar J.L., Davies J., Gibson R.L., Mall M.A., McKone E.F., McNally P., et al.* A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One *F508del* Allele. Am J Respir Crit Care Med. 2021 Jun 15;203(12):1522-1532. doi: 10.1164/rccm.202102-0509OC. PMID: 33734030; PMCID: PMC8483230.

20. Zolin A., Adamoli A., Bakkeheim E., van Rens J. et al. ECFSPR Annual Report 2022, 2024 https://www.ecfs.eu/sites/default/files/Annual%20Report_2022_ECFSPR_20240603.pdf. https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports

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