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FOUR PROMISING PHARMACOTHERAPIES FOR CYSTIC FIBROSIS

CZTERY OBIECUJĄCE METODY FARMAKOLOGICZNEGO LECZENIA MUKOWISCYDOZY

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ABSTRACT

People with cystic fibrosis are living longer than ever before, often to their 40s and beyond. However, as longevity increases, so does the disease's treatment burden. People with cystic fibrosis (CF) utilize, on average, seven therapies per day. The interventions currently available primarily ameliorate consequences of the disease after the damage is done. In the absence of a cure for CF, a better approach to disease management is to develop therapies that modify the course of the disease by proactively altering the primary effects of this ultimately fatal disorder. A number of next-generation drugs that are in late-stage clinical trials target the basic pathophysiology of CF in various ways; four of them are discussed in this review. All four have demonstrated clinical activity to potentially change the course of the disease by not only arresting damage but also improving surrogate makers for pulmonary outcomes in CF. Ataluren promotes ribosomal read-through of premature stop codons during CFTR synthesis; VX-770 and VX-809 act upon CFTR's ability to regulate chloride secretion. Denufosol stimulates an alternate chloride channel, inhibits sodium absorption, enhances mucin secretion, and increases ciliary beat frequency. Denufosol is an inhalant; the other three drugs are oral preparations, which should minimize any additional treatment burden for people affected by this progressive disease.

Key words: cystic fibrosis, CFTR, chloride channel, denufosol, VX-770, VX-809, ataluren, PCT124

STRESZCZENIE

Chorzy na mukowiscydozę żyją obecnie dłużej niż kiedykolwiek wcześniej, często do 40 lat, a nawet dłużej. Jednak wraz z dłuższym przeżyciem zwiększa się również obciążenie leczeniem. Chorzy na mukowiscydozę wymagają średnio 7 różnych terapii dziennie. Aktualnie dostępne metody leczenia skierowane są przede wszystkim na łagodzenie szkód dokonanych przez chorobę. Wobec niemożności wyleczenia mukowiscydozy lepszym podejściem do jej leczenia jest opracowanie terapii, które pozwolą na zmianę jej przebiegu poprzez aktywne modyfikowanie pierwotnych zaburzeń wywołujących tę, ostatecznie śmiertelną, chorobę. W końcowej fazie badań klinicznych znajduje się obecnie kilka leków nowej generacji. Ich działanie skierowane jest na modyfikację, na różne sposoby, pierwotnych patofizjologicznych zaburzeń stwierdzanych w mukowiscydozie; 4 z nich zostały omówione w niniejszym artykule. Wszystkie wykazały aktywność kliniczną, mogącą potencjalnie zmienić przebieg choroby, nie tylko poprzez zahamowanie jej postępu, ale również poprzez poprawę wyników zastępczych wskaźników czynności płuc u chorych na mukowiscydozę. Ataluren ułatwia rybosomalny odczyt poprzez przedwczesne kodony terminacyjne podczas syntezy CFTR; VX-770 i VX-809 wpływają na zdolność CFTR do regulowania wydzielania chlorku. Denufosol stymuluje alternatywny kanał chlorkowy, hamuje wchłanianie sodu, zwiększa wydzielanie śluzu, a także zwiększa częstotliwość ruchu rzęsek. Denufosol jest lekiem wziewnym, a pozostałe 3 leki to preparaty doustne. Ta forma stosowania powinna przyczynić się do zminimalizowania obciążenia leczeniem chorych dotkniętych tą postępującą chorobą.

Słowa kluczowe: mukowiscydoza, CFTR, kanał chlorkowy, denufosol, VX-770, VX-809, ataluren, PCT124

Introduction

Cystic fibrosis (CF) is the most common serious autosomal recessive disorder in Caucasians, affecting approximately 1 in 3700 live births in the United States, with comparable figures for most countries in the European Union [1, 2]. This multi-system disease is caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR), a glycoprotein that regulates ion channels located in or near the apical cell surface of epithelia in multiple organs [3]. Reduced CFTR function causes defective adenosine 3':5'-cyclic monophosphate (cyclic AMP)-regulated chloride efflux, altering salt transport and fluid movement. This pathophysiology is manifested in CF's hallmarks of:

1. Increased sweat chloride concentrations.
2. Inhibition of first-line defenses against pathogens, related to dehydration of airway surface liquid (ASL) and impairment of ciliary stroke activity.
3. Bacterial colonization of the airway.
4. Progressive lung dysfunction [4].
5. Malabsorption due to pancreatic dysfunction/obstruction [5].
6. Male infertility [6].

Complications from this multi-system disease are ultimately fatal.

Many clinical improvements have lengthened the survival time for patients with CF. Today, approximately 45% of people with CF are at least 18 years old, and people born this decade with CF can expect to live at least 40 years [3, 7]. This increasing longevity is not due to any single break-through therapy, but rather to the development and widespread adoption of a clinical care structure that includes well-defined but complex treatment regimens [3, 8]. However, longevity poses its own set of problems in terms of an ever-increasing treatment burden, which indicates the need for better therapies for CF [9].

Problems/challenges

The development of new medications to treat CF must surmount four major hurdles. First, as the cumulative gains from the multitude of existing CF therapeutics increase, the challenges become greater for finding new treatments that can demonstrate objective, measurable, clinically significant effects above and beyond existing regimens. For example, forced expiratory volume at one second (FEV_1) has been, and continues to be, the outcome measure of choice in this regard. It is clinically relevant, statistically sensitive, and is widely accepted as the best predictor of CF mortality. However, quantifying clinical improvement in additional ways has predicated the use of other measurements, and some of these surrogate markers of disease still need standardization. Second, CF's status as an orphan disease inherently presents challenges in finding enough participants for clinical trials [3]. Third, new treatments must be not only effective but also easy to administer so that adherence to treatment regimens is maintained. On average, CF patients typically utilize seven therapies each day, the sum of which takes almost an hour and a half to complete [8]. Therapies that add more time or more medications to an existing regimen increase patients' perceived treatment burden, multiplying the probability of non-adherence; thus, this burden needs to be minimized with convenient delivery systems [8]. Finally, as life expectancy increases for people with CF, unstudied complications are arising, such as low bone mineral density. Such circumstances will require new treatment strategies for these conditions; those interventions and their optimal timing and delivery are as yet unknown [3]. A related issue is the paucity of data that exists regarding specific factors that influence longevity; large-scale epidemiological studies are needed to help ensure the best interventions for an aging CF population (fig. 1) [10].

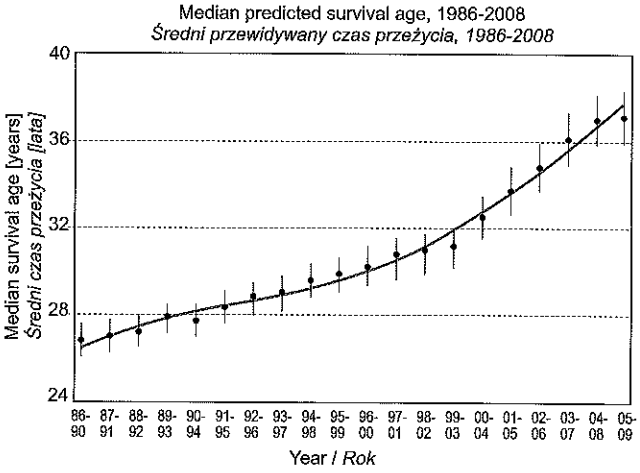

Figure 1. Increase in longevity by birth year for people with cystic fibrosis

Rycina 1. Poprawa wskaźników przeżycia chorych na mukowiscydozę w zależności od roku urodzenia

Cystic Fibrosis Foundation Patient Registry 2009 Annual Report, Bethesda, Maryland, USA. © 2010 Cystic Fibrosis Foundation (reprinted with permission) / *Rejestr Pacjentów z Mukowiscydozą (Cystic Fibrosis Foundation), Raport roczny 2009, Bethesda, Maryland, USA. © 2010 Cystic Fibrosis Foundation (przedruk za zgodą)*

The promise of a "cure" for CF remains elusive, as early trials with gene therapy have not yet lived up to initial expectations. Lung transplantation also has inherent limitations. It is considered a rescue treatment – which constitutively "replaces" part of one disease with a second condition that poses equal, if not greater challenges [12]. Moreover, surgical outcomes from transplants are complex, dependent upon many variables [13]. Lung transplantation also does not ameliorate the nonpulmonary complications of CF that persist, such as pancreatic insufficiency and risk of bowel obstruction [12].

Previous approaches

Today's approved treatments address the many facets of CF in response to the disease's manifestations and its complications. As such, they are a "reactionary" approach to targeting specific secondary effects of CFTR dysfunction, primarily seeking to minimize damage after it occurs (tab. I). Furthermore, no medication currently on the market addresses the disease's basic pathophysiology, which is insidious in its early stages. Even asymptomatic children with CF still exhibit decreased lung function in their first six years of life and pulmonary function in people with CF do not return to baseline values after pulmonary exacerbations, thus progressively reducing lung capacity on a percent predicted basis [14-16]. This underscores the need to develop treatments that address CF in a systemic manner – that is, by tackling the disease's pathophysiology.

Table I: Categories of treatments for cystic fibrosis
Tabela I: Rodzaje metod leczenia mukowiscydozy

Category *Rodzaj*	Type *Typ*	Available now *Obecnie dostępne*	In clinical trials *W badaniach klinicznych*
Anti-infectives *Przeciwzakaźne*	oral macrolides *doustne makrolidy* non-systemic *niesystemowe*	azithromycin *azytromycyna* nebulized: colistin, tobramycin *w nebulizacji: kolistyna, tobramycyna*	dry-powder inhaled *inhalatory proszkowe:* tobramycin, tobramycin-fosfomycin, ciprofloxacin, levofloxacin, liposomal amikacin, colistin, aztreonam lysine
Anti-inflammatories *Przeciwzapalne*	inhaled *wziewne* oral *doustne*		glutathione, phosphodiesterase-5 inhibitors (e.g., sildenafil) ibuprofen, acetylcysteine, simvastatin, methotrexate, docosahexaenoic acid, hydroxychloroquine, pioglitazone, α1-antitrypsin
Mucolytics *Mukolityki*		dornase alfa (recombinant human DNase) *(rekombinowana ludzka DNasa)*	acetylcysteine
Pancreatic enzymes *Enzymy trzustkowe*		porcine-derived exocrine pancreatic enzymes *egzokrynne hormony trzustkowe pochodzenia wieprzowego*	meripase, trizytek (porcine-free) *(nie wieprzowe)*
Airway hydrators *Nawilżacze dróg oddechowych*	osmotic agents *środki osmotyczne* ion channel modifiers *modyfikatory kanału jonowego*	hypertonic saline *hipertoniczny roztwór soli fizjologicznej*	inhaled mannitol* *wziewny mannitol* denufosol, lancovutide, GS9411, cobiprostone (SP1-8811)
CFTR regulators *Regulatory CFTR*			VX-700, VX-809, ataluren (formerly / *poprzednio*) PCT124)
Vaccines *Szczepionki*			for *pseudomonas* spp. *przeciwko pseudomonas*
Gene therapy *Terapia genowa*			using cationic liposomes as vectors *przy użyciu liposomów kationowych jako wektorów*

* carries risk of exacerbating *Burkholderia cepacia* / *niesie ryzyko zaostrzenia przebiegu zakażenia Burkholderia cepacia*

If we cannot correct CF's actual gene defect(s), then the next best approach is to modify the gene *effect* – that is, to modulate the fundamental underlying problem. Proactively changing the course of the disease with treatments that can prevent, arrest, or minimize functional damage and reduce the treatment burden for people with CF is the subject of intense research efforts (tab. I). This paper discusses four such pharmacotherapeutics that are in late-stage clinical trials (fig. 2).

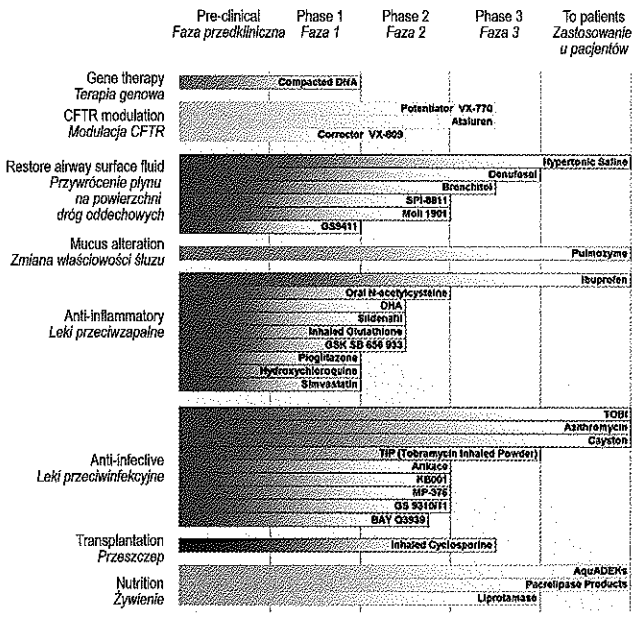

Figure 2. Cystic fibrosis drug development pipeline as of November 1, 2010
Rycina 2. Program przygotowania leków na mukowiscydozę, stan na dzień 1 listopada 2010 r.

Please note that the effects of the antibiotic azithromycin on inflammation could place it in the anti-inflammatory category rather than anti-infective. Reprinted with permission from the Cystic Fibrosis Foundation / *Warto zauważyć, że działanie antybiotyku azitromycyny na procesy zapalne pozwala zaliczyć lek do kategorii przeciwzapalnych raczej niż przeciwinfekcyjnych. Przedruk za zgodą Cystic Fibrosis Foundation. Przedruk za zgodą Cystic Fibrosis Foundation*

Ataluren (PTC124): gene modulation for protein restoration

Ten percent of all people with CF have a nonsense mutation in their DNA that inserts a premature stop codon (either UGA, UAG, or UAA) into the protein-coding region of mRNA [3, 17]. This genetic alteration halts CFTR synthesis before ribosomal translation is complete, producing a truncated, nonfunctional version of that protein. Such mutations are usually indicative of severe CF phenotypes [18]. An agent that could overcome the effects of this mutation by inducing ribosomal read-through of premature (but not normal) stop codons would have great therapeutic utility in patients with CF and other genetic diseases caused by nonsense stop codons.

Early proof-of-concept trials with aminoglycosides demonstrated the potential for overcoming nonsense mutations. Gentamicin was shown to alter RNA translation and facilitate read-through of the premature stop codon without affecting the normal stop codon. This effect has been demonstrated in multiple disease models, including Duchenne muscular dystrophy (DMD), Hurler's syndrome, cystinosis, and others. Because almost one-third of all inherited diseases contain genetic defects cause by stop (nonsense) mutations, the possibilities for gene modulation are tantalizing [19]. Gentamicin's toxicity raises questions regarding safe, effective dosing and long-term tolerability – as well as its potential effects on translational mechanisms of other genes [19]. Collectively, this has caused researchers to search for more innocuous drugs that can overcome nonsense mutations.

Ataluren (formerly PTC124) is a novel, orally bioavailable small molecule that promotes read-through of premature stop codons in CFTR mRNA, facilitating normal gene translation to its correct stop signal, and thus enabling production of the full-length, functional CFTR protein.

Results of the first Phase 2b trial of ataluren dosing in 30 children age 6 to 18 were released in mid-November 2010. In this trial, the patients served as their own controls, because all study patients had abnormal baseline total chloride transport values and reduced total chloride transport responses. Patients were assessed in two 28-day cycles of treatment and in each 28 day period there were 14 days on and 14 days off drug. In one cycle they received a lower dose (4, 4, and 8 mg/kg) and in the other cycle they received a higher dose (10, 10, and 20 mg/kg) They were randomized with respect to the order of the cycles, but all patients received the same total amount of ataluren during these two separate 28-day cycles. Statistically significant improvements in nasal epithelial chloride transport were seen in the first cycle of the study and were maintained throughout the study's second cycle; some patients achieved chloride transport values in the range of healthy children. Total chloride response was higher at the higher dosage given in both groups (10, 10, 20 mg/kg). Changes in pulmonary function were not statistically significant. Secondary analyses using immunohistochemistry showed an average of 17% improvement in CFTR protein expression. Response rates did not differ based on patient genotype or other variables. All study participants will be followed up for 28 months (from day 1 of this study) [18]. In addition, a 48-week, international Phase 3 study is underway to determine safety and efficacy in people age 6 and older (fig. 3).

This study is notable for its "firsts." It was the first to use immunohistochemistry to document changes in CFTR expression in epithelial cells, and it was the first to use TEPD testing on pediatric patients. Genotypes that responded to ataluren in this study included Q493X, G542X, R553X, W882X, E1104X, R1162X, and W1282X – a tantalizing first glimpse at the potential for widespread application. Furthermore, the responsiveness in children persisted longer than similar results in adults did [18]. Given the poor prognosis that CF patients with this type of mutation have, the possibility of modifying this disease, especially in its early stages in children, is exciting.

VX-770 and VX-809: correcting and potentiating CFTR's effect

VX-770 and VX-809 individually and collectively represent two novel, potentially complementary approaches to increase CFTR function at the cell membrane surface. VX-770 is a *potentiator*; it increases the gating activity of the CFTR protein to open the chloride channel so that chloride ions can flow through it. VX-809 is a *corrector*; it helps position CFTR in the correct place at the apical surfaces of epithelial cell membranes, thus improving CFTR's functionality as a chloride channel.

Several characteristics of these compounds make them attractive as potential pharmacotherapies for CF. In addition to addressing the underlying gene effect, they work on the most prevalent CF mutations. VX-770 has demonstrated the ability to work on multiple CFTR forms *in vitro* – positively affecting ion channel function of the G551D CFTR mutation (present in 5% of people with CF) as well as the F508del CFTR mutation (present in 70% of people with CF) [20]. VX-809 has significantly reduced sweat chloride levels in people homozygous for the F508-del mutation [21]. Another plus is that both VX-770 and VX-809 are oral preparations: VX-770 is taken twice a day; VX-809 is taken once a day [9, 21-23]. VX-770 is in later-stage clinical trials, with three long-term Phase 3 trials underway (tab. II). At the time of this manuscript's submission date, no final results from Phase 2 trials of VX-809 had been published.

A recent clinical trial of VX-770 showed promising results with 39 patients who had at least one G551D-CFTR allele. Within-subject changes showed clinically significant improvements in nasal potential difference and reduction in sweat chloride levels; after treatment with VX-770, sweat chloride levels in some subjects were lower than the diagnostic range for CF. Modest but significant improvements in lung function were also seen. Of the six doses tested, the most significant improvements were seen with 75- and 150-mg doses [9]. Although this trial did not investigate how VX-770 affected airway surface liquid, studies on cultures of human bronchial cells showed that VX-770 reduced surface liquid absorption (fig. 4) [20].

We wait with anticipation for the results of the Phase 2 trial that tests the potential synergistic effect of giving VX-770 and VX-809 concomitantly [22, 23]. Further testing is needed to see if these compounds singly or in combination have an effect on other types of CF mutations (fig. 5).

Denufosol: a novel ion channel modulator

In humans, at least two types of chloride channels exist in the airway lumen: 1. CFTR, which responds to cyclic AMP agonists, and 2. a calcium-activated chloride channel (CaCC), which is stimulated by P_{2U} purinoceptors ($P2Y_2$). In the early and mid-1990s, proof-of-concept studies showed that uridine-5' triphosphate (UTP) could activate alternate chloride conductance *via* $P2Y_2$ binding when CFTR was non-functional [24].

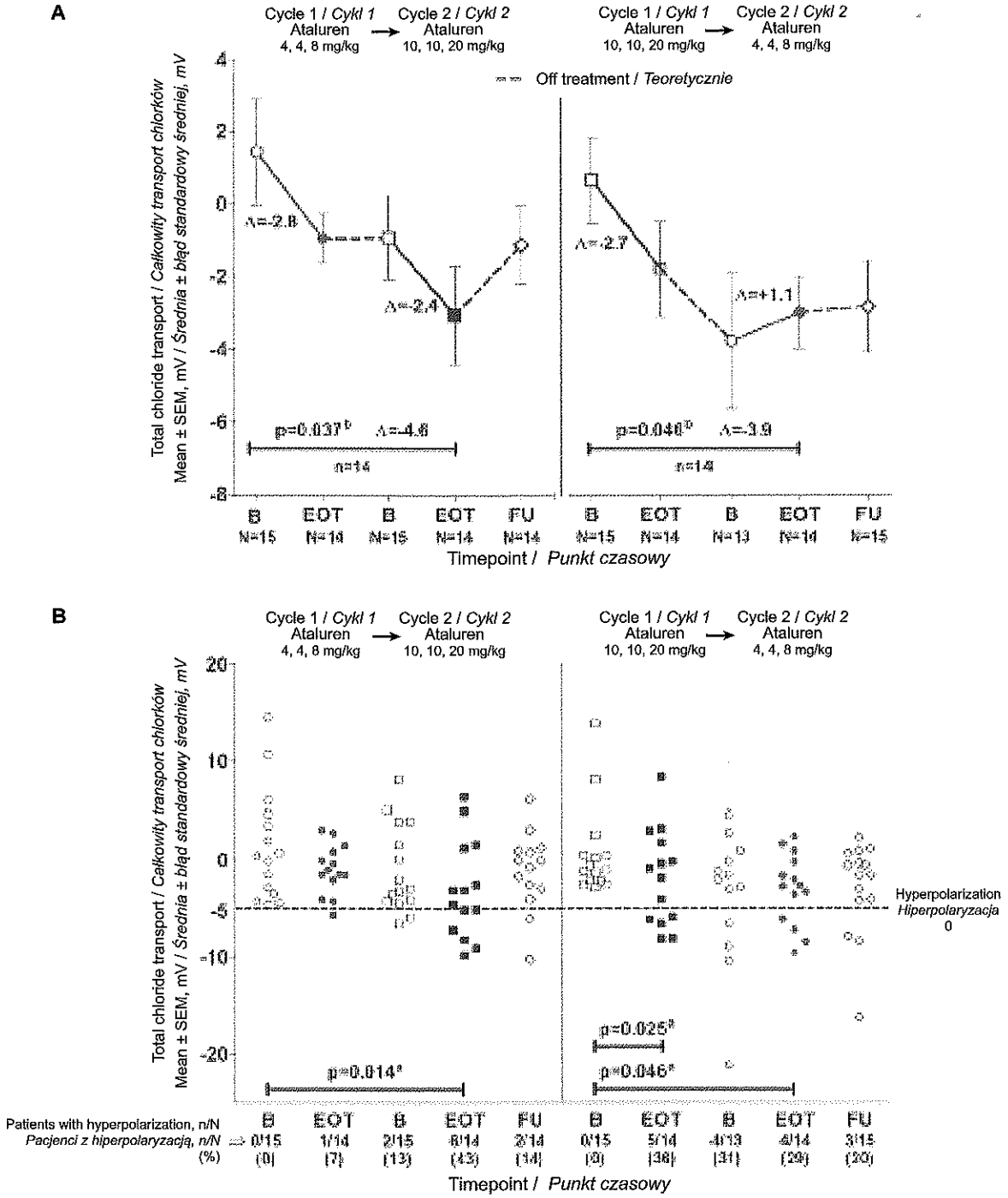

Figure 3. Individual and mean total chloride transport values in Phase 2b trial of ataluren
Rycina 3. Pojedyncze i średnie wartości całkowitego transportu chlorków w fazie 2b badania atulurenu
A: Hyperpolarization at end of treatment *vs.* at baseline. EOT – end of treatment, FU – follow-up / *Hiperpolaryzacja na końcu leczenia w porównaniu do danych wyjściowych. EOT – koniec leczenia, FU – obserwacja*
B: Paired T-test (end of treatment *vs.* at baseline) / *Sparowany test T (koniec leczenia w porównaniu do danych wyjściowych)*

Denufosol is a novel ion channel regulating agent that activates this alternate (non-CFTR) chloride channel by stimulating $P2Y_2$ receptors on the apical surface of airway epithelia. This stimulation involves two steps: hyperpolarization of the apical membrane, and activation of the apical chloride channels [25]. Denufosol enables both by:

1. Stimulating the calcium-activated chloride channel (CaCC) to increase chloride secretion.
2. Inhibiting sodium absorption via the epithelial sodium channel (ENaC).
3. Enhancing mucin secretion.
4. Stimulating ciliary beat frequency.

TABLE II: Summary of characteristics of VX-770 and VX-809 [22, 23]
TABELA II: Podsumowanie charakterystyki VX-770 and VX-809 [22, 23]

Drug *Lek*	Preparation *Sposób użycia*	Mutations influenced *Wpływ na mutacje*	Recent clinical trials *Ostatnie badania kliniczne*
VX-770	oral, 2×/day *doustnie,* *2× dziennie*	G551D, F508del	three Phase 3 trials in progress for people with the G551D mutation: – two 48-week trials – one for children aged 6 to 11, and one for adults – one 96-week trial for people aged 6 and older *w toku trzy badania kliniczne fazy 3 u chorych z mutacją G551D:* *– dwa badania 48-tygodniowe – jedno u dzieci w wieku 6-11 lat i jedno u dorosłych* *– jedno badanie 96-tygodniowe dla chorych od 6 roku życia*
VX-809	oral, once×/day *doustnie* *1× dziennie*	F508del	one Phase 2 study complete onother Phase 2 study in progress *ukończone 1 badanie fazy 2 inne badanie w fazie 2 w toku*
VX-770+VX-809	oral *doustnie*		recruiting for Phase 2 trial underway to test efficacy of giving singly and together *rekrutacja do fazy 2 w toku w celu zbadania skuteczności podawania pojedynczych preparatów oraz obu razem*

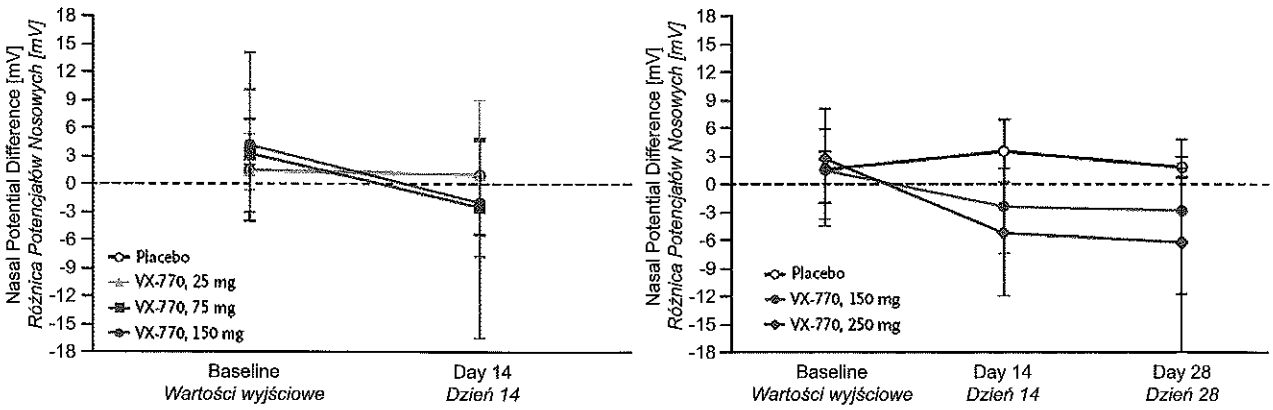

Figure 4. Phase 2 trial results – nasal potential differences for all VX-770 doses tested [9]
Rycina 4. Wyniki fazy 2 – różnice w potencjałach nosowych dla wszystkich testowanych dawek VX-770 [9]

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These integrated actions collectively enhance airway hydration and mucociliary clearance – which should help preserve lung function.

Phase 1 and 2 trials established denufosol's safety and tolerability in people age 2 and older. The first large Phase 3 trial to be completed, the TIGER-1 study (transport of ions to generate epithelial rehydration), tested denufosol on patients with "mild" cystic fibrosis; i.e., those who had at least 75% of predicted FEV_1. The goal was to determine whether patients with little or no measurable baseline pulmonary function impairment could benefit from early intervention with denufosol, and the expectation was that use of this therapeutic could help prevent, retard, or arrest pulmonary dysfunction [26].

The study, which followed 352 patients at least 5 years of age for 48 weeks, had its primary endpoint as the mean change in FEV_1 measured between weeks 1 and 24. Three pulmonary function measurements were assessed: FEV_1, forced vital capacity (FVC), and forced expiratory flow (FEF) at 25% to 75% of FVC. The large sample size had greater than 95% power to detect a treatment difference of a change from baseline FEV1 of 0.075 L [26]. Even with this statistical strength, demonstrating a benefit that would reach this primary endpoint would be challenging – as noted in a recent trial of azithromycin that failed to show improvement in patients with significantly greater impairment of lung function than the cohort in the TIGER-1 trial [27].

Surprisingly, denufosol did more than demonstrate its superiority over placebo – the use of this inhalant not only arrested deterioration of lung function, but it also improved it. Patients who received denufosol the entire 48 weeks had an average increase of 115 ml (4.9%) in FEV_1 over baseline; after being switched to the active drug, patients who received denufosol in the 24-week open-label portion of the study had a mean gain of 78 ml (3.4%) in FEV_1 [26]. In addition, even though denufosol did not decrease the incidence of pulmonary exacerbations (PEs) during the trial, results suggest that denufosol may also function as a pulmonary protectant or cause qualitative difference in PEs when they occur (fig. 6).

The promising results from the TIGER-1 study make this inhaled medication a potential treatment for preserving lung function in patients with CF, particularly when administered early in the disease process. The TIGER-2 trial has been in progress to study denufosol's effects over a one-year period, to be followed by three-year open-label extension study [28]. Unfortunately, at the time of writing, an interim analysis of the study showed the trial did not achieve statistical significance for its primary efficacy endpoint, which was a change from baseline in FEV1 at

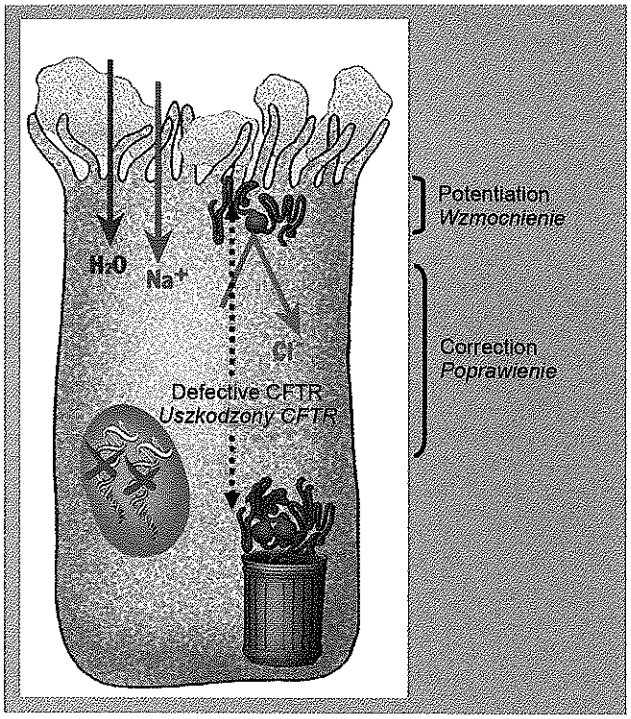

Figure 5. CFTR modulation with VX-770 and VX-809
Rycina 5. Modulacja CFTR przy użyciu VX-770 i VX-809

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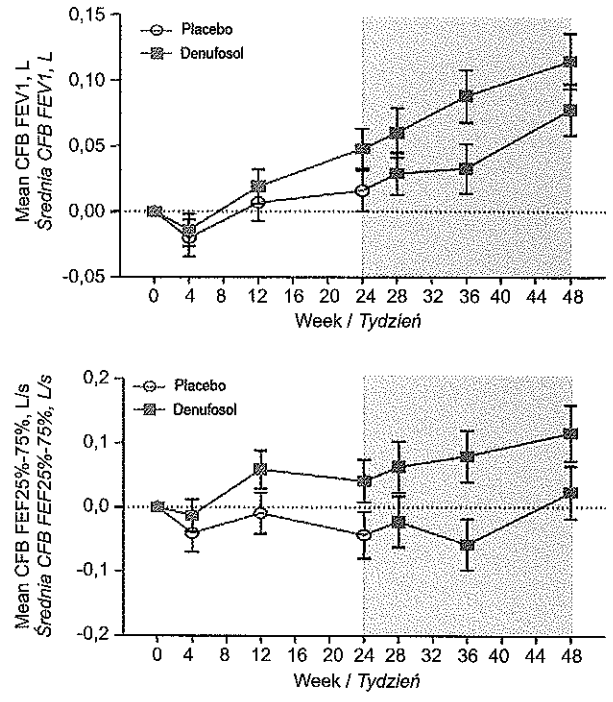

Figure 6. Mean CFB FEV_1 and FEF results from TIGER-1 study
Rycina 6. Średnie wyników CFB FEV_1 i FEF w badaniu TIGER-1

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week 48. Interim results also did not meet any of the secondary endpoints. These results and the study design will be reviewed in detail over the next few months as the promise of denufosol as a first-in-class chloride ion channel modulator hangs in the balance.

Conclusions

A large number of potential disease-modifying treatments for CF are in development. The ones discussed in this paper have promising potential to effectively treat the basic gene effect of nonfunctional CFTR without significantly increasing patients' perceived treatment burden, as three of these four pharmacotherapeutics are oral; denufosol is inhaled. Late-stage clinical trials are in progress for all four drugs to determine their long-term safety and adverse event profiles.

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