ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΠΜΣ «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική
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# ΝΕΕΣ ΠΡΟΟΠΤΙΚΕΣ ΣΤΗ ΘΕΡΑΠΕΙΑ ΤΗΣ ΚΥΣΤΙΚΗΣ ΙΝΩΣΗΣ ΣΤΑ ΠΑΙΔΙΑ: ΜΙΑ ΣΥΣΤΗΜΑΤΙΚΗ ΒΙΒΛΙΟΓΡΑΦΙΚΗ ΑΝΑΣΚΟΠΗΣΗ

# CURRENT PERSPECTIVES OF CHILDHOOD CYSTIC FIBROSIS: A SYSTEMATIC REVIEW

**ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ**

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Σεπτέμβριος 2020

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## A. Abstract

Introduction

Cystic Fibrosis (CF) is a multisystem, inherited disease caused by defects of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The last decade, CFTR modulators have radically changed CF treatment.

Aim

The aim of this review is a systematic research of current evidence on efficacy and safety of CFTR modulators in children with different mutations of the CFTR protein.

Methods

Literature search was conducted in the PubMed, Cochrane Library and ClinicalTrials.gov in order to identify randomized clinical trials (RCTs) assessing the efficacy and safety of CFTR modulators in children that were published until 31 August 2020. References from the extracted studies were also manually scanned for relevant articles.

Results

A final pool of 17 studies was included in the systematic review. Ivacaftor (IVA) proved generally effective in children carrying a gating CFTR mutation, but ineffective in homozygous for the Phe508del mutation and carriers of the Arg117His allele. Lumacaftor (LUM) combined with ivacaftor have disputable effectiveness in homozygous for the Phe508del mutation. Tezacaftor (TEZ) together with IVA benefit children homozygous for the same mutation, but not carriers of one Phe508del allele and one of a residual mutation. The most effective combinations are VX-659/TEZ/IVA and elexacaftor(ELX)/TEZ/IVA in children with at least one Phe508del mutation. All CFTR modulators proved well-tolerated in children older than 12 months of age.

Conclusion

CFTR modulators are a promising treatment for children with CF. More research is essential to assess the efficacy of the existing CFTR modulators in




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children younger than 6 years and develop new modulators that would be effective in children with rare mutations.

## Α. Περίληψη


### Εισαγωγή

Η κυστική ίνωση είναι μία πολυσυστηματική κληρονομική νόσος που οφείλεται σε διαταραχή της λειτουργίας της πρωτεΐνης ρυθμιστή της διαμεμβρανικής αγωγιμότητας της κυστικής ίνωση (CFTR protein). Την τελευταία δεκαετία, οι ρυθμιστές της CFTR πρωτεΐνης (CFTR modulators) άλλαξαν δραστικά τη θεραπεία της κυστικής ίνωσης.

### Στόχος

Ο στόχος αυτής της βιβλιογραφικής ανασκόπησης είναι η συστηματική έρευνα της αποτελεσματικότητας και ασφάλειας των CFTR modulators στα παιδιά με διαφορετικές μεταλλάξεις της πρωτεΐνης CFTR.

### Μέθοδος

Πραγματοποιήθηκε βιβλιογραφική έρευνα στις βάσεις δεδομένων PubMed, Cochrane Library and ClinicalTrials.gov, με σκοπό την ταυτοποίηση τυχαιοποιημένων κλινικών μελετών που αξιολογούν την αποτελεσματικότητα και την ασφάλεια των CFTR modulators και δημοσιεύτηκαν έως τις 31 Αυγούστου 2020. Οι βιβλιογραφικές αναφορές των επιλεγμένων μελετών αξιολογήθηκαν επίσης για σχετικά άρθρα.

### Αποτελέσματα

Ένας τελικός αριθμός 17 μελετών συμπεριελήφθησαν στη βιβλιογραφική ανασκόπηση. Το ivacaftor αποδείχθηκε γενικά αποτελεσματικό σε παιδιά φορείς μεταλλάξεων που επηρεάζουν τη δράση της πρωτεΐνης ως κανάλι, αλλά αναποτελεσματικό σε ομόζυγους για τη Phe508del μετάλλαξη και φορείς του αλληλίου Arg117His. Το lumacaftor σε συνδυασμό με το ivacaftor έχουν αμφισβητήσιμη αποτελεσματικότητα σε ομόζυγους για τη Phe508del μετάλλαξη. Το tezacaftor χορηγούμενο με ivacaftor ωφελεί τα παιδιά που είναι ομόζυγα στην προαναφερθείσα μετάλλαξη, αλλά όχι τα παιδιά φορείς ενός




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αλληλίου Phe508del και ενός υπεύθυνου για υπολειπόμενη λειτουργία της πρωτεΐνης. Οι πιο αποτελεσματικοί συνδυασμοί είναι αυτοί των VX-659/TEZ/IVA και elexacaftor(ELX)/TEZ/IVA με τουλάχιστον μία μετάλλαξη Phe508del. Όλοι οι CFTR modulators αποδείχθηκαν καλά ανεκτοί σε παιδιά ηλικίας άνω των 12 μηνών.

Συμπεράσματα

Οι CFTR modulators είναι μία υποσχόμενη θεραπεία για τα παιδιά που πάσχουν από κυστική ίνωση. Περαιτέρω έρευνα απαιτείται για να αξιολογηθεί η αποτελεσματικότητα των κυκλοφορούντων CFTR modulators σε παιδιά μικρότερα των 6 ετών, αλλά και να αναπτυχθούν νέοι modulators αποτελεσματικοί σε παιδιά μου φέρουν σπάνιες μεταλλάξεις.



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## B. Introduction

Cystic fibrosis (CF) is a multisystem disorder affecting children and adults. It is the most common disease that follows autosomal recessive inheritance in Caucasian populations and it is caused by numerous mutations of the CF gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein.(1) This protein is an anion channel regulated by cyclic adenosine monophosphate (cAMP) which is responsible for transportation of chloride across the cellular membrane. CF gene is located on Chromosome 7.

There are six classes of mutations of CFTR protein which affect the structure or function of the protein in different ways, first described in 1989.(2, 3) Class I mutations are responsible for complete lack of production of the CFTR protein. Class II mutations include the most common one (Phe508del) and cause problems in protein maturation, misfolded forms of the protein and early degradation. Nearly 90% of the patients carry at least one copy of the Phe508del mutation, which originates from the absence of one phenylalanine in 508$^{th}$ position of the CF protein. (4) Class III mutations are called gating mutations because they cause defective regulation and problems with the opening of the ion channel and the most prevalent gating mutation is G551D. About 4% of patients suffering from CF carry this mutation.(5) Class IV mutations result in reduced conductance of chloride ions through the apical membrane, as they affect the stability of the ion channel and one common example of this category is Arg117His . Class V mutations are related with reduced production of normal CFTR protein. Finally, the last class of mutations (IV) accelerates channel turnover from the surface of the epithelial cells.(6)

CFTR protein is responsible for the conductance of chloride through the upper membrane of epithelial cells of airways and exocrine glands, such as the sweat glands, the pancreas and the biliary system. Defects of the CFTR protein cause problems in secretion of chloride and reabsorption of sodium and water through the upper membrane of the epithelial cells, resulting in viscous secretions in the respiratory tract, gastrointestinal (GI) tract and exocrine glands that cannot be easily cleared. Inability to clear secretions from the respiratory tract leads to recurrent infections of the airway which result in progressive lung



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disease. Early clinical manifestations in young children are bronchiolitis and bronchitis. It is common to be infected from Staphylococcus Aureus, Haemophilus Influenza or even Pseudomonada Aeruginosa from a very young age (within the first month of life).(1) Recurrent infections from young age lead to destruction of the airway and creation of bronchiectasis.

Other clinical manifestations are associated with the GI tract and may be obvious from neonatal age. In 15-20% of infants, obstruction of the ileum with meconium can be seen (meconium ileus).(1) An uncommon clinical condition is meconium peritonitis in infants with CF. Approximately 85% of children with CF have pancreatic insufficiency, resulting in malabsorption and failure to thrive, which is treated with pancreatic enzyme replacement.(1) Viscous bile may also lead to obstruction of the biliary ductules and finally obstructive cirrhosis.

In addition, although male patients may be considered azzoospermic due to failure of development of Wolffman duct structures, sexual function is not affected. Furthermore, female patients usually face fertility issues associated with chronic lung disease and malabsorption.(1)

The diagnosis of CF is based on specific criteria, which are the presence of clinical manifestations from the respiratory, GI or genitourinary tract or a family history of a sibling who has CF or a positive newborn screening test in conjunction with positive result in one of the following laboratory tests: increased chloride concentration of sweat in two measurements who have taken place in separate days, identification of two CF gene mutations or abnormal measurement of nasal potential difference.

For many years, symptomatic treatment has been used in children suffering from CF, aiming at clearing viscous secretions from the airways and controlling pulmonary infections in order to prevent gradual airway destruction. Classic treatments included human recombinant deoxyribonuclease (DNase) and nebulized hypertonic saline combined with airway clearance therapy. An integral part of the treatment is also the administration of antibiotics in order to control progression of lung infection. Antibiotic therapy varies from some courses of oral antibiotic therapy during pulmonary exacerbations to continuous



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prophylactic treatment with antibiotics. Patients colonized by Pseudomonada aeruginosa may need aerosolised antibiotic therapy with tobramycin inhalation solution.

The last few years an innovation in the treatment of CF has emerged with the introduction of CFTR modulators. They consist a new category of medical agents including correctors, which are small molecules capable of improving processing and trafficking of CFTR to the cell membrane, and potentiators that increase channel gating.(4) Nowadays there are four agents, the correctors lumacaftor (LUM), tezacaftor (TEZ) and elexacaftor (ELX) and the potentiator ivacaftor (IVA), which are approved by the Food and Drug Administration (FDA).(7)

## C. Methods

Selection criteria

The following inclusion criteria have been used:

- Publication date was before 31 August 2020
- Clinical Trials assessing the use of CFTR modulators
- They were designed as randomized control trials (RCT) or randomized, placebo controlled, crossover trials
- The population under study was children suffering from CF

Studies were excluded from this review if they present one of the following exclusion criteria:

- Reports in languages other than English
- In vitro trials
- Phase 1 trials
- Studies in animals
- Conference abstracts
- Pilot trials
- Retracted papers



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### Search Methodology

This systematic review is performed in compliance with the guidelines of the Cochrane Handbook for Systematic reviews(8) and reported in accordance with the PRISMA statement.(9) Literature search was conducted on Pubmed and Cochrane Library in order to find studies compatible with the inclusion criteria. The search terms included ‘cystic fibrosis’, ‘CF’, ‘CFTR Modulators’, ‘cystic fibrosis treatment’, ‘pediatrics’ and ‘children’. Titles and abstracts were reviewed for eligibility by a single independent author. In possibly relative studies, full texts were screened. The references of the retrieved papers were manually scanned in order to find relevant studies.

### Data Extraction

The full texts from the selected papers were manually scanned and data retrieved. The following data were extracted Author’s name, Date of Publication, Population, Intervention, Duration, Primary and secondary endpoints and Report of Adverse Events (AEs).

## D. Results

### Study selection

The flow diagram of the systematic review is presented in Table 1. Last literature search was conducted on 31 August 2020. Initially, 319 studies were retrieved from database search and 33 from manually searching the relevant references. Sixteen studies were removed as duplicates and 336 were scanned to identify which were compliant with the inclusion criteria. Finally, 42 studies met those criteria and full-text articles were assessed for eligibility. Through meticulous search, 26 of these were excluded as some of them included adults, some were in vitro trials or had design other than RCT. Sixteen articles meeting the inclusion criteria were identified, including seventeen relevant studies.



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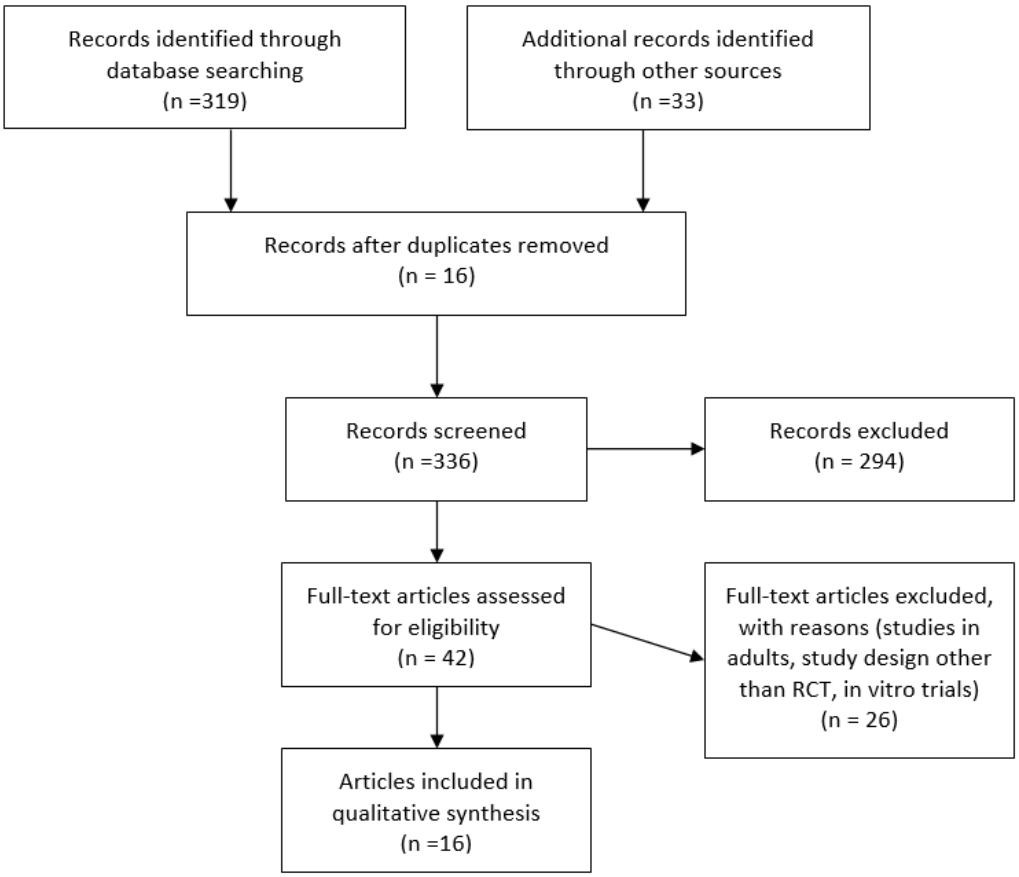


*Table 1 Flow chart of the literature search*

Studies characteristics and outcomes assessed

All the studies are phase 2 and 3 clinical trials assessing the efficacy and safety of CFTR modulators.(4, 5, 10-23) One study provides several treatment arms and performs multiple analyses, thus making it difficult to extract definite conclusions.(14) The patients included in the selected clinical trials are children between 6 and 16 years old. No randomized clinical trials including patients younger than 6 years old were identified through the search of the literature. (Table 2)



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| First Author, year | Participants | Interventions | Results | Design |
|---|---|---|---|---|
| **Ramsey, 2011** | N=161<br>Age ≥ 12 years old<br>Mutation: at least one G551D allele | • IVA 150mg BID<br>• Placebo | • Change in ppFEV1 (week 48): 10.5%, p<0.001<br>• Change in ppFEV1 in patients < 18 years old (week 48): 11.4%, p=0.005<br>• 55% reduction in risk of pulmonary exacerbation (week 48), p=0.001<br>• Change in ST (week 48): -48.1mmol/l, p<0.001<br>• Change in weight (week 48): 2.7kg, p<0.001<br>• Change in CFQ-R score (week 48): 8.6, p<0.001 | Randomized, double-blind placebo-controlled trial |
| **Davies, 2013** | N=52<br>Age 6-11 years old<br>Mutation: at least one G551D allele | • IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 24): 12.5%, (95% CI 6.6, 18.3, p<0.001)<br>• Treatment difference in ppFEV1 (week 48): 10%, (95% CI 4.5, 15.5, p<0.001)<br>• Treatment difference in ST (week 48): -54.3 mmol/l, p<0.0001<br>• Treatment difference in weight (week 48): 2.8kg, p<0.001<br>• Treatment difference in CFQ-R score (week 24): 6.1, p=0.109 >0.05 | Randomized, double-blind placebo-controlled trial |

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| | | | | |
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| **Davies, 2013** | N=21<br>Age ≥ 6 years old<br>Mutation: at least one G551D allele | • Placebo → Washout → IVA 150mg BID<br>• IVA 150 mg BID → Washout → Placebo | • Treatment difference in LCI: -2.16, (95% CI -2.88, 1.44, p<0.0001)<br>• Treatment difference in ppFEV1: 8.67%, (95% CI 2.34, 14.97, p=0.0103)<br>• Treatment difference in ST: -47.51 mmol/l, (95% CI -54.57, -40.44, p<0.0001)<br>• Treatment difference in CFQ-R score: 1.33, p=0.3796 >0.05<br>• Treatment difference in $FEF_{25\%-75\%}$: 16.56%, (95% CI -2.3, 27.71, p=0.0237) | Randomized, double-blind placebo-controlled crossover trial |
| **De Boeck, 2014** | N=39<br>Age ≥ 6 years old<br>Mutation: at least one non-G551D gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) | • IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 8): 10.7%, (95% CI 7.3, 14.1)<br>• Treatment difference in ST (week 8): -49.2 mmol/l, (95% CI -57.0, -41.4, p<0.0001)<br>• Treatment difference in CFQ-R score (week 8): 9.6, (95% CI 4.5, 14.7, p=0.0004)<br>• Change in BMI (week 8): 0.7 $kg/m^2$, (95% CI 0.34, 0.99, p<0.0001) | Randomized, double-blind placebo-controlled trial (8 weeks)/ Open-label extension |
| **Flume, 2012** | N=140<br>Age ≥ 6 years old<br>Mutation: Homozygous for the Phe508del mutation | • IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 16): 1.7%, (95% CI -0.6, 4.1, P=0.15>0.05)<br>• Treatment difference in ST (week 16): -2.9 mmol/l, (95% CI -5.6, -0.2, p=0.04) | Randomized, double-blind placebo-controlled trial (16 weeks)/ open-label extension |

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| **Moss, 2015** | N=69<br>Age ≥ 6 years old<br>Mutation: Arg117His | • IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (6-11 years): -6.3%, (95% CI -11.96, -0.71, p=0.03)<br>• Treatment difference in ST (6-11 years): -27.6 mmol/l, (95% CI -37.16, -18.10, p<0.0001)<br>• Treatment difference in CFQ-R score (6-11 years): -6.1, (95% CI -15.68, 3.41, p=0.19)<br>• Treatment difference in BMI (6-11 years): -0.18 kg/m$^2$, (95% CI –2.38, 2.01, p=0.87) | Randomized, double-blind placebo-controlled trial |
| **Wainwright, 2015 (TRAFFIC)** | N=559<br>Age ≥ 12 years old<br>Mutation: Homozygous for the Phe508del mutation | • LUM 600 mg SID/IVA 250mg BID<br>• Placebo<br>• LUM 400 mg BID/IVA 250mg BID | • Treatment difference in ppFEV1 (LUM 600 mg SID/IVA vs placebo): 4.03%, (95% CI 2.62, 5.44, P<0.001)<br>• Treatment difference in ppFEV1 (LUM 400 mg BID/IVA vs placebo): 2.6%, (95% CI 1.18, 4.01, P=0.0003)<br>• Treatment difference in BMI (LUM 600 mg SID/IVA vs placebo): 0.16 kg/m$^2$, (95% CI -0.04, 0.35, P=0.16)<br>• Treatment difference in BMI (LUM 400 mg BID/IVA vs placebo): 0.13 kg/m$^2$ (95% CI -0.07, 0.32, P=0.13) | Two-phase randomized, double-blind placebo-controlled trial |

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| | | | • Treatment difference in CFQ-R score (LUM 600 mg SID/IVA vs placebo): 3.88, (95% CI 0.7, 7.05, p=0.0168)<br>• Treatment difference in CFQ-R score (LUM 400 mg BID/IVA vs placebo): 1.50, (95% CI -1.69, 4.69, p=0.3569) | |
| **Wainwright, 2015 (TRANSPORT)** | N=563<br>Age ≥ 12 years old<br>Mutation: Homozygous for the Phe508del mutation | • LUM 600 mg SID/IVA 250mg BID<br>• Placebo<br>• LUM 400 mg BID/IVA 250mg BID | • Treatment difference in ppFEV1 (LUM 600 mg SID/IVA vs placebo): 2.62%, (95% CI 1.18, 4.06, P=0.0004)<br>• Treatment difference in ppFEV1 (LUM 400 mg BID/IVA vs placebo): 3.00%, (95% CI 1.56, 4.44, P<0.0001)<br>• Treatment difference in BMI (LUM 600 mg SID/IVA vs placebo): 0.41 kg/$m^2$, (95% C(4, 5, 10-23)I 0.23, 0.59, P<0.0001)<br>• Treatment difference in BMI (LUM 400 mg BID/IVA vs placebo): 0.36 kg/$m^2$ (95% CI 0.17, 0.54, P=0.0001)<br>• Treatment difference in CFQ-R score (LUM 600 mg SID/IVA vs placebo): 2.21, (95% CI -0.91, 5.33, p=0.1651)<br>• Treatment difference in CFQ-R score (LUM 400 mg BID/IVA vs placebo): 2.85, (95% CI -0.27, 5.98, p=0.0736) | Two-phase randomized, double-blind placebo-controlled trial |

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| **Ratjen, 2017** | N=206<br>Age 6-11 years old<br>Mutation: Homozygous for the Phe508del mutation | • LUM 200 mg SID/IVA 250mg BID<br>• Placebo | • Treatment difference in LCI: -1.1, (95% CI -1.4, -0.8, p<0.0001)<br>• Treatment difference in ppFEV1 (week 24): 2.4%, (95% CI 0.4, 4.4, p=0.0182)<br>• Treatment difference in ST: -20.8 mmol/l, (95% CI -23.4, -18.2, p<0.0001)<br>• Treatment difference in CFQ-R score (week 24): 2.5, (95% CI -0.1, 5.1, p=0.0628)<br>• Treatment difference in BMI (week 24): 0.1 $kg/m^2$, (95% CI –0.1, 0.3, p=0.2522) | Randomized, double-blind placebo-controlled trial |
| **Rowe, 2017** | N=248<br>Age ≥ 12 years old<br>Mutation: Heterozygous for the Phe508del mutation and a second allele with residual mutation | • TEZ 100 mg SID/IVA 150mg BID<br>• IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (IVA vs placebo): 4.7%, (95% CI 3.7, 5.8, p<0.001)<br>• Treatment difference in ppFEV1 (TEZ/IVA vs placebo): 6.8%, (95% CI 5.7, 7.8, p<0.001)<br>• Treatment difference in ppFEV1 (TEZ/IVA vs IVA): 2.1%, (95% CI 1.2, 2.9, p<0.001)<br>• Treatment difference in CFQ-R score (IVA vs placebo): 9.7, (95% CI 7.2, 12.2, p<0.001) | Randomized, double-blind placebo-controlled crossover trial |

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| | | | • Treatment difference in CFQ-R score (TEZ/IVA vs placebo): 11.1, (95% CI 8.7, 13.6, p<0.001)<br>• Treatment difference in CFQ-R score (TEZ/IVA vs IVA): 1.4, (95% CI -1.0, 3.9, p=0.26)<br>• Treatment difference in ST (IVA vs placebo): -4.5 mmol/l, (95% CI -6.7, -2.3)<br>• Treatment difference in ST (TEZ/IVA vs placebo): -9.5 mmol/l, (95% CI -11.7, -7.3)<br>• Treatment difference in ST (TEZ/IVA vs IVA): -5.1 mmol/l, (95% CI -7.0, -3.1) | |
| **Taylor-Cousar, 2017** | N=510<br>Age ≥ 12 years old<br>Mutation: Homozygous for the Phe508del mutation | • TEZ 100 mg SID/IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 24): 4.0%, (95% CI 3.1, 4.8, p<0.001)<br>• Treatment difference in ST: -10.1 mmol/l, (95% CI -11.4, -8.8)<br>• Treatment difference in CFQ-R score (week 24): 5.1, (95% CI 3.2, 7.0)<br>• Treatment difference in BMI (week 24): 0.06 kg/m$^2$, (95% CI –0.08, 0.19, p=0.41)<br>• 35% lower risk of pulmonary exacerbation in TEZ/IVA group (p=0.005) | Randomized, double-blind placebo-controlled parallel-group trial |

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| **Munck, 2020** | N=165<br>Age ≥ 12 years old<br>Mutation: Heterozygous for the Phe508del mutation and a minimal function mutation | • TEZ 100 mg SID/IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 12): 1.2%, (95% CI -0.3, 2.6, p=0.12)<br>• Treatment difference in ST: -3.5 mmol/l, (95% CI -5.9, -1.2, p=0.0034)<br>• Treatment difference in CFQ-R score: 2.1, (95% CI -1.2, 5.4, p=0.21)<br>• Treatment difference in BMI: -0.08 $kg/m^2$, (95% CI –0.27, 0.11, p=0.38) | |
| **NCT03447249, 2020** | N=385<br>Age ≥ 12 years old<br>Mutation: Heterozygous for the Phe508del mutation and a minimal function mutation | • VX-659 240 mg SID/TEZ 100 mg SID/IVA 150 mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 24): 14.0%, (95% CI 12.4, 15.7, p<0.001)<br>• RR (placebo: VX-659/TEZ/IVA) =0.14 (p<0.001)<br>• Treatment difference in ST (week 24): -44.6 mmol/l, (95% CI -47.2, -41.9, p<0.0001)<br>• Treatment difference in CFQ-R score (week 24): 20.1, (95% CI 17.2, 23.0, p<0.0001)<br>• Treatment difference in BMI (week 24): 1.11 $kg/m^2$, (95% CI 0.91, 1.31, p<0.0001) | Randomized, double-blind placebo-controlled trial |
| **NCT03460990, 2019** | N=116<br>Age ≥ 12 years old<br>Mutation: Homozygous for the Phe508del mutation | • VX-659 240mg SID/TEZ 100mg | • Treatment difference in ppFEV1: 10.0%, (95% CI 7.4, 12.5, p<0.0001) | Randomized, double-blind active-controlled trial |

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| | | SID/IVA 150 mg BID<br>• TEZ 100mg SID/IVA 150mg BID | • Treatment difference in ST: -48.7 mmol/l, (95% CI -53.9, -43.5, p<0.0001)<br>• Treatment difference in CFQ-R score: 13.5, (95% CI 8.8, 18.3, p<0.0001) | |
| **Donaldson, 2017** | N=131<br>Age ≥ 12 years old<br>Mutation: Heterozygous for the Phe508del mutation or Phe508del/G551D | • TEZ 10-50 mg SID/IVA 150 mg BID<br>• TEZ 10-50 mg SID<br>• Placebo | • Treatment difference in ppFEV1 in patients Phe508del/Phe508del (TEZ 100mg SID/IVA 150mg BID vs placebo): 3.75%, (95% CI 0.94, 683, p<0.05)<br>• Change in ST in patients Phe508del/Phe508del (TEZ 100mg SID /IVA 150 mg BID): -6.04 mmol/l (p<0.05)<br>• Change in ST in patients Phe508del/G551D (TEZ 100mg ID /IVA 150 mg BID): - 7.02 mmol/l (p<0.05) | Randomized, double-blind placebo-controlled trial |
| **Middleton, 2019** | N=403<br>Age ≥ 12 years old<br>Mutation: Heterozygous for the Phe508del mutation and a minimal function mutation | • ELX 200 mg SID/TEZ 100 mg SID/IVA 150mg BID<br>• Placebo | • Treatment difference in ppFEV1 (week 4): 13.8%, (95% CI 12.1, 15.4, p<0.001)<br>• Treatment difference in pulmonary exacerbations (week 24): 0.37 (95% CI 0.25, 0.55, p<0.001)<br>• Treatment difference in ST (week 24): -41.8 mmol/l, (95% CI -44.4, -39.3, p<0.001) | Randomized, double-blind placebo-controlled trial |

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| | | | • Treatment difference in CFQ-R score (week 24): 20.2, (95% CI 17.5, 23.0, p<0.001)<br>• Treatment difference in BMI (week 24): 1.04 kg/$m^2$, (95% CI 0.85, 1.23, p<0.001) | |
| **Heijerman, 2019** | N=113<br>Age ≥ 12 years old<br>Mutation: Homozygous for the Phe508del mutation | • TEZ 100 mg SID/IVA 150mg BID<br>• ELX 200 mg SID/TEZ 100 mg SID/IVA 150mg BID | • Treatment difference in ppFEV1: 10.0%, (95% CI 7.4, 12.6, p<0.0001)<br>• Treatment difference in ST: -45.1 mmol/l, (95% CI -50.1, -40.1, p<0.0001)<br>• Treatment difference in CFQ-R score: 17.4, (95% CI 11.8, 23.0, p<0.0001) | Randomized, double-blind active-controlled trial |

*Table 2 Studies characteristics*

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The absolute change in percent predicted forced expiratory volume in one second (ppFEV1) is evaluated in all the selected studies. Two studies assess as primary outcome the absolute change in Lung Clearance Index (LCI).(5, 20) As secondary endpoints in the extracted studies are evaluated: absolute change in sweat chloride concentration, risk of pulmonary exacerbation, change in anthropometric parameters and patient-reported outcomes (PROs). PROs are evaluated using the revised cystic fibrosis questionnaire (CFQ-R) Respiratory domain score.

The dose of CFTR modulators in the studies is age and weight depended. Interventions included in the studies are IVA, tezacaftor with ivacaftor (TEZ/IVA), lumacaftor with ivacaftor (LUM/IVA), elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), VX-659/TEZ/IVA and placebo.

- Lung Function

IVA was the first CFTR modulator to be used in patients with CF.(24) In a study comparing IVA with placebo in children aged 6-11 years old suffering from CF and having at least one allele G551D, Davies et al. postulated that the administration of IVA 150mg two times daily (BID) increases ppFEV1 by 10 points [95% Confidence Interval (CI)=(4.5, 15.5), $p<0.001$].(12) Another parameter also improved with IVA 150 mg BID in patients older than 6 years with at least one allele G551D and predicted FEV1>90% was LCI.(5) In the study of Ramsey et al., patients 12-18 years old also increased ppFEV1 by 11.4 points ($p=0.005<0.05$).(19) In addition, Boeck et al. proved that IVA 150mg BID compared to placebo increased ppFEV1 by 10.7%, 95% CI=(7.3, 14.1) in patients older than 6 years with at least one non-G551D gating mutation.(13) On the other hand, one study published by Moss et al. reports that IVA 150mg BID does not improve ppFEV1 in patients 6-11 years old with Arg117His-CFTR mutation, a residual mutation, compared to placebo [treatment difference through week 24: -6.3 points [95% CI=(-11.96, -0.71), $p=0.03 <0.05$] (17). Lastly, in a placebo-controlled trial involving patients older than 12 years old homozygous for the most common CFTR-mutation, Phe508del, IVA alone



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shows no statistically significant improvement in ppFEV1 (absolute change in ppFEV1: 1,7%, p=0.15>0.05).(15)

LUM 200mg once daily (SID)/IVA 250 mg BID has also been tested in patients older than 12 and 6-11 years old homozygous for the Phe508del mutation. In the first group Wainwright et al. reported statistically significant improvement in ppFEV1.(23) In another phase 3 placebo-controlled clinical trial in children 6-11 years old with the same genetic mutations, the improvement in ppFEV1 with LUM/IVA was 2.4 points [95% CI=(0.4,4.4), p=0.0182<0.05] and the absolute change in LCI was -1.1 [95% CI=(-1.4,-0.8), p=0.0001<0.05].(20)

Another treatment evaluated in patients with at least one allele of the Phe508del mutation is TEZ/IVA. A placebo-controlled clinical trial assessing the efficacy of TEZ 100mg SID and IVA 150mg BID in patients over 12, heterozygous for the Phe508del mutation and a minimal function mutation, reported no statistically significant improvement in ppFEV1.(18) A three-arm placebo-controlled, two period, crossover trial comparing IVA and TEZ/IVA with placebo in patients older than 12 years heterozygous for the same CFTR-mutation and a residual function mutation reported that TEZ/IVA increases ppFEV1 6.8 points[95% CI=(5.7,7.8), p<0.001].(21) Taylor-Cousar et al. also reported significant improvement in FEV1 in patients older than 12 years homozygous for the Phe508del mutation with the administration of TEZ/IVA.(22) Donaldson et al. by conducting multiple comparisons between groups receiving different doses of TEZ and IVA concluded that in patients with two Phe508del alleles, TEZ 100mg SID/IVA 150mg BID increased ppFEV1 by 3.75% (p<0.05).(14)

Lastly, the triple combination ELX/TEZ/IVA in two studies was reported to be effective in patients with at least one allele of Phe508del mutation. A placebo-controlled trial in patients heterozygous for the Phe508del older than 12 years conducted by Middleton et al. reported significant improvement in FEV1 at week 4 [+13.8 points, 95% CI=(12.1,15.4), p<0.001].(4) Heijerman et al. suggested an improvement by 10 points [95% CI=(7.4,12.6), p<0.0001] with ELX/TEZ/IVA compared with TEZ/IVA in patients older than 12 years of age homozygous for the Phe508del.(16) In two clinical trials including children



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homozygous for the Phe508del mutation older than 12 years of age, the combination of VX-659/TEZ/IVA was reported to increase ppFEV1 significantly compared with TEZ/IVA and placebo.(10, 11)

- Pulmonary exacerbations

Limited data have been retrieved regarding pulmonary exacerbations in children with CF. Patients over 12 years old suffering from CF that have the G551D mutation were in 55% lower risk of having a pulmonary exacerbation when receiving IVA 150 mg BID compared to placebo (p=0.001).(19) Wainwright et al. suggested 30-39% lower risk of pulmonary exacerbation in patients homozygous for the Phe508del older than 12 years.(23) Children homozygous for the Phe508del and older than 12 years had 63% lower rate of pulmonary exacerbations with the triple therapy (ELX/TEZ/IVA) compared with placebo (p<0.001).(4)

- Sweat chloride concentration

*Ivacaftor*

Sweat chloride concentration constitutes a relatively common secondary outcome in clinical trials assessing the efficacy of CFTR modulators. IVA BID administered in weight- and age-based dose significantly reduced sweat chloride concentration in children older than 6 years with at least one allele of Class III gating mutations.(5, 12, 19) Respectively, in a placebo-controlled trial in patients older than 6 years with at least one allele of non-G551D gating mutation, IVA 150 mg bid reduced sweat chloride by -49.2 mmol/L [95% CI=(-57.0,-41.4), p<0.0001].(13)

In three clinical trials involving children 6-11 years and older than 12 years homozygous for the Phe508del mutation LUM/IVA at a dose adjusted by age and weight was reported to reduce sweat chloride concentration by a significant amount.(20, 23)

In two placebo-controlled clinical trials in patients older than 12 years with one allele Phe508del and one of a minimal function mutation, TEZ 100mg SID/IVA 150mg BID reduced sweat chloride by 3.5 mmol/L[95% CI=(-5.9, -1.2),



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p=0.0034<0.05] and 9.5 mmol/L[95% CI=(-11.7, -7.3)] respectively.(18, 21) In children of the same age homozygous for the Phe508del allele the combination of TEZ and IVA also reduced sweat chloride concentration significantly. (22)

The administration of ELX/TEZ/IVA significantly reduced sweat chloride compared with both placebo and TEZ/IVA in heterozygous for the Phe508del and a minimal function mutation older than 12 years.(4, 16)

- Anthropometric parameters

CF is associated with abnormal growth and weight gain in children. As a result, it is important to examine the effect of CFTR modulators on body mass index (BMI) and weight changes and their contribution to the improvement of patients' nutritional status.

In two placebo-controlled clinical trials involving patients with at least one G551D mutation, children receiving IVA 150 mg BID gained statistically significant weight during the treatment period.(12, 19) In a study published by De Boeck et al., BMI increased by 0.7 $kg/m^2$ [95% CI=(0.34, 0.99), p<0.0001] in children over 6 years with at least one non-G551D mutation receiving IVA 150mg BID compared to the placebo group.(13) On the contrary, children older than 6 years carrying the Arg117His mutation did not show statistically significant increase in BMI with IVA compared with placebo.(17)

In children 6-12 years old homozygous for the Phe508del mutation, results about the change of BMI with LUM/IVA are controversial. Two clinical trials reported not statistically significant increase and one a subtle but statistically significant improvement.(20, 23)

TEZ/IVA in two placebo-controlled trials in patients heterozygous for the Phe508del and a minimal function mutation and others homozygous for the Phe508del, over 12 years of age, was reported not to increase BMI significantly.(18, 22) On the other hand, the combination of VX-659/TEZ/IVA was reported to improve BMI in children older than 12 years carrying one Phe508del allele and one with a residual mutation.(11)



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Finally, triple therapy (ELX/TEZ/IVA) significantly increases BMI in patients over 12 years with at least one allele Phe508del by 1.04 kg/m$^2$ [95% CI= (0.85, 1.23), p<0.0001].(4)

- CFQ-R Respiratory domain score

The CFQ-R score consists a secondary outcome calculated in trials involving children older than 6 years of age. IVA 150 mg BID compared with placebo in patients older than 12 years with at least one allele G551D improves CFQ-R score by 8.6 points (p<0.001).(19) Patients with the same genetic profile aged from 6 to 11 years old did not benefit from IVA.(5, 12) On the other hand, children older than 6 years, with at least one non-G551D mutation present statistically significant improvement in CFQ-R score with IVA.(13) Children carrying one Arg117His allele did not report significant improvement of CFQ-R score while taking IVA.(17)

LUM/IVA in children homozygous for the Phe508del mutation, between 6 and -11 years old, did not increase CFQ-R score compared to placebo.(20) In older children with the same mutation results are controversial.(23)

Rowe et al. reported statistically significant improvement in CFQ-R score comparing both IVA and TEZ/IVA with placebo in patients older than 12 years baring one allele of Phe508del and one second allele with a CFTR mutation with residual function. (21) In the same study, TEZ/IVA showed no statistically significant increase in CFQ-R score versus IVA alone. Munck et al., in contrast, reported no statistically significant change in CFQ-R score with TEZ/IVA compared to placebo in another sample with same age and mutation.(18) In a another placebo-controlled clinical trial, Taylor-Cousar et al. reported significant improvement of this score in patients homozygous for the Phe508del allele at least 12 years of age.(22)

The most significant improvement of CFQ-R score was observed with ELX/TEZ/IVA in two studies involving patients older than 12 years homozygous for the Phe508del mutation. The first reported an absolute change by 17.4 points [95% CI= (11.8, 23.0), p<0.0001] with the triple therapy compared with TEZ/IVA.(16) The second one is a placebo-controlled trial that reported an absolute increase of 20.2 points at week 24 [95% CI= (17.5, 23.0),



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p<0.0001].(4) In addition, the combination of VX-659/TEZ/IVA in children older than 12 years carrying one allele of the Phe508del mutation and one with a residual mutation was reported to increase CFQ-R score by 20.1 points [95% CI= (17.2, 23.0), p<0.0001].(11)

- Safety and reported Adverse events (AEs)

IVA is generally safe and improves lung function in children with at least one allele of gating mutations. The most common adverse events (AE) are mild to moderate and related with the primary disease (CF).(5, 12, 13, 19)

The proportion of patients reporting AEs was similar in LUM/IVA and placebo groups.(20) Serious adverse events leading to treatment discontinuation were infective pulmonary exacerbations, elevation of AST and ALT, gastroenteritis and ileus.(20) (23)

The most common AEs in clinical trials comparing TEZ/IVA with placebo were infective pulmonary exacerbations, cough, fatigue, hemoptysis. These clinical manifestations are associated with CF. There was no clinically meaningful elevation in transaminase concentration. Moreover, no statistically significant decrease in FEV1 within 2 to 4 hours after administration of TEZ/IVA was observed.(18, 21, 25)

The discontinuation rate in trials with ELX/TEZ/IVA due to adverse events was ≤1%.(4, 16) The triple therapy was related both with elevated aminotransferase levels in 10.9% of the participants compared with placebo (4.0%) and rash in 10.9% versus 6.5% in the placebo group. (4) Heijerman et al. reported only two serious AEs (4%), which were rash and pulmonary exacerbation.(16)

## E. Discussion

IVA is generally effective in children with CF having at least one allele of a gating mutation.(5, 12, 13, 19) On the contrary, it was not proved beneficial in patients homozygous for the Phe508del mutation or a mutation with residual



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function, such as Arg117His.(15, 17) Ivacaftor is a potentiator that binds to the CFTR protein and increases the transportation of chloride and water across the cellular membrane.(12) The mechanism of its action justifies the need of functioning CFTR protein production. As a result, it is not effective for patients homozygous for the Phe508del mutation and other classes of mutations that completely prevent CFTR protein's production.

In patients with these genetic mutations, combination therapies have been evaluated, including a potentiator (IVA) and a corrector (LUM or TEZ). In patients older than 12 years homozygous for the Phe508del LUM/IVA was reported to be effective.(23) Moreover, in children 6-11 years old with the same mutation it reduced significantly LCI and ppFEV1.(20) On the contrary, an observational study including patients over 10 years with Phe508del/Phe508del genotype, suggested no improvement of ppFEV1 and BMI with LUM/IVA.(26) However, significant reduction of pulmonary exacerbations and duration of intravenous antibiotic therapy was observed.

The second combination of TEZ/IVA was reported ineffective in patients heterozygous for the Phe508del mutation and a residual function mutation in one placebo-controlled clinical trial, but effective in a second one.(18, 21) In patients with two alleles of the Phe508del mutation has shown significant effectiveness.(22)

Two combinations including three CFTR modulators have been under research. Both VX-659/TEZ/IVA and ELX/TEZ/IVA were reported to be effective in patients over 12 years with at least one allele of the Phe508del mutation.(4, 10, 11, 16) Further research is essential to evaluate the efficacy and safety of triple combinations in younger children that carry at least one Phe508del allele.

CFTR modulators can also benefit other aspects of CF clinical manifestations. Recently, a case report suggested the beneficial effect of IVA in regaining pancreatic function, after long-term administration in a 10-year-old child with pancreatic exocrine insufficiency.(27) The ARRIVAL study reported significant improvements in biomarkers related with the pancreatic function (lipase and amylase concentration) in children 12-24 months with a CFTR



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gating mutation.(28) IVA has been associated with improvements in several growth variables, including linear growth, in prepubertal children carrying the G551D mutation.(29)

Moreover, in a retrospective observational study of the United States CF Foundation Patient Registry, IVA monotherapy was proved to increase hemoglobin levels in carriers of the G551D-CFTR mutation, while the combination LUM/IVA was correlated with increased hemoglobin levels in carriers of the Phe508del allele.(30) Furthermore, CFTR modulators have an impact on pathogen virulence, thus altering airway microbiology and protecting patients against infections.(31, 32) In a retrospective cohort conducted by Singh et al., it was postulated that patients taking LUM/IVA for CF or IVA alone had significantly delayed colonization from Pseudomonas Aeruginosa and Staphylococcus Aureus.(33) On the contrary, CFTR modulators do not interfere with the core airway epithelium response in infections from rhinovirus.(34)

Additionally, some patients with residual function CFTR mutations have a reduction in sweat chloride concentration with IVA. Among patients with decreased sweat chloride, increased chloride in current human nasal epithelium (HNE) cultures may be evident of clinical response to IVA.(35) On top of that, female patients were proved to have larger reduction in sweat chloride concentration with LUM/IVA compared with male patients.(36)

In three open-label single-arm clinical trials IVA was proved generally safe and effective in children from 12 months to 5 years with at least one allele of a gating mutation.(28, 37, 38) In one them published by Davies et al., IVA administered in children 2-5 years old, with a gating mutation, at a dose adjusted by age and weight, reported to be safe. However, raised concentration of alanine transaminase (ALT) and aspartate transaminase (AST) was the only serious AE, leading to study discontinuation. Five children (15%) had a rise in AST and ALT greater than eight times the upper normal limit. All had a history of elevated AST and ALT before study enrollment. Four of them discontinued study treatment according to the protocol and transaminase concentrations returned to normal.(37) Moreover, the ARRIVAL study suggested that 28% of the patients 12-24 months old receiving IVA, demonstrated elevated AST, ALT



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or both.(28) For this reason, close follow-up is essential in young children receiving this treatment.

An open-label phase III study, published by Milla et al., in children 6-11 years old with two Phe508del alleles, reported improvement of lung function, sweat chloride and nutritional status with the combination of lumacaftor and ivacaftor, but not significant improvement in ppFEV1. (39) LUM/IVA was proved by the same clinical trial to be associated with an increase of the aminotransferase concentration by 19.3% and 15% by a second one involving children 2-5 years.(39, 40) Another manifestation observed in children receiving LUM/IVA was a significant drop of FEV1 after the first dose, which was only partially restored after salbutamol inhalation.(41)

Two observational studies in patients older than 6 years with one G551D allele and older than 10 years with an non-G551, confirmed long-term effectiveness and safety of IVA in these groups.(42, 43) Data extracted from United Kingdom and United States registries from 2011 to 2015 are consistent with RCTs supporting the efficacy of IVA in patients with a G551D mutation.(44) A retrospective cohort study of John Hopkins CF Center showed not significant change in ppFEV1 with LUM/IVA during a surveillance period of 11months post initiation and a relatively high rate of drug intolerance.(45) Evaluation of open-label extended studies and retrospective observational studies involving existing CFTR modulators is essential to assess the long-term benefits, efficacy and safety in different age groups, races, genders and other characteristics.

Next-generation treatments are now under research. A triple combination of a new corrector, VX-445, with TEZ and IVA demonstrated significant improvement of the CFTR function in vitro in patients with one or two Phe508del alleles.(46) This is a promising alternative treatment whose safety and efficacy should be assessed in adults and children suffering from CF. Moreover, another corrector, VX-659 combined with TEZ and IVA proved to be effective in a randomized, controlled, double-blind in vitro clinical trial, using human bronchial epithelial cells of patients with at least one Phe508del allele.(47)



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Despite the radical change of CFTR treatment with the development of CFTR modulators, there are very rare mutations that still cannot be treated. R560S is one of those and belongs to class II mutations. LUM and TEZ alone or in combination proved to be ineffective in carriers of this mutation.(48) As a result, further research is necessary in order to develop new modulators that would be effective in rare mutations producing CFTR channels with complete lack of function.

This systematic review has several limitations. It was conducted by a single author that performed literature scan. History of CFTR modulators is not long. The first one to be approved by FDA was ivacaftor in January 2012.(24) RCTs evaluating the safety and efficacy of CFTR modulators in children are limited and include children older than 6 years. There are no RCTs in the literature including children younger than 6 years. Moreover, many of the studies assessing safety and efficacy of the CFTR modulators in patients with CF older than 12 years, do not stratify the population by age. As a result, the age may turn up as a confounder, because results about children and adults cannot be discriminated. Another limitation is that only three electronic databases were scanned to collect studies relative to the subject. However, it is not possible that important high-quality studies have not been evaluated.

The triple therapy has not been tested in children younger than 12 years, which should be the one of the next research targets. There are patients with nonsense mutations that cannot be benefited from the existing interventions. As a result, the development of new treatments is necessary.

In conclusion, CFTR modulators have radically changed treatment of patients with CF. Further research is necessary to confirm long-term safety and efficacy of existing modulators. Additionally, more RCTs including children younger than 6 years of age are necessary. To sum up, the development of new CFTR modulators for patients carrying mutation that produce CFTR protein with complete absence of normal function should be an area of future research.



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