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Original Article

A SYSTEMATIC REVIEW ON THE EFFICACY AND SAFETY OF THE COMBINATION OF ELEXACAFTOR, TEZACAFTOR, AND IVACAFTOR IN PATIENTS WITH CYSTIC FIBROSIS

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Abstract:

Introduction: *Elexacaftor/Tezacaftor/Ivacaftor is a new combination of Cystic fibrosis transmembrane conductance regulator (CFTR)-based treatment, which modulates and corrects the CFTR protein. Several recent clinical trials reported promising responses to this combination of treatment among cystic fibrosis patients.*

Aim: *This systematic review aims to evaluate the safety and efficacy of the combination of Elexacaftor, Tezacaftor, Ivacaftor in cystic fibrosis patients.*

Methods: Three healthcare-related databases were searched, namely, PubMed, Cochrane registry for clinical trials, cumulative index of nursing and allied healthcare literature (CINAHL). Search was conducted based on the relevant keywords and medical subject headings (MeSH). These search results were searched for duplications and removed if any, thereafter, these studies underwent superficial (based on title and abstract) screening and thorough screening (based on the full-text study) according to the inclusion and exclusion criteria. Finally, six clinical trials were selected from which the efficacy and safety data were collected. Furthermore, risk of bias data was collected based on the JADAD scale.

Results: *Six clinical trials were included with total with 994 cystic fibrosis patients, 542 were recipients of combination of Elexacaftor, Tezacaftor and Ivacaftor and 452 cystic fibrosis patients received placebo in the control arm, including one single-arm study with 66 patients, who received only triple combination therapy. Three studies included F508del homozygous while three studies included heterozygous patients. Four clinical trials were conducted among adult (>20 years) and two were conducted among child patients. All six trials reported higher ppFEV1 among the triple combination therapy recipients ranging from 9.5% to 13.6%. Furthermore, reduced sweat chloride concentration was reported by 5 out 6 clinical trials, ranging from -33.3 to -60.9 point. Moreover, health-related quality of life improvement was reported by higher CFQ-R RD (cystic fibrosis questionnaire-revised respiratory domain) ranging from 5.9 to 21.9 points. Regarding safety, better nutritional status was reported with BMI change ranging from 0.58 to 1.24, however, there were no difference in pulmonary exacerbations and adverse effect in these two arms. Pulmonary exacerbations ranged from 1.7% to 65% while adverse effects ranged from 28.9% to 93.4%. The clinical trials with child patients reported similar to ppFEV1, higher reductions in sweat chloride concentration, lower CFQ-R RD values, and much higher rates of adverse effects compared adult cystic fibrosis patients.*

Conclusion: *This systematic review showed that combination of Elexacaftor, Tezacaftor, and Ivacaftor is more efficacious than placebo in cystic fibrosis patients. This review also reported that there was no difference in adverse effect or pulmonary exacerbations between these two arms, however, there is different trend in efficacy and safety of child and adult cystic fibrosis patients.*

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Keywords:
Elexacaftor, Tezacaftor, Ivacaftor, Elexacaftor, Cystic fibrosis, Cystic fibrosis transmembrane conductance regulator (CFTR) protein, CFTR Modulators, Trikafta.

Introduction

Cystic fibrosis (CF), an autosomal recessive genetic disease principally affecting the lung, occurred by a genetic mutation, leading to the altered structural and functional status of Cystic fibrosis transmembrane conductance regulator (CFTR) protein[1]. CFTR,

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structurally present at the pulmonary epithelial cell surface, is responsible for chloride and bicarbonate secretion and fluid transport across the cell, therefore, the mutated and non-functional CFTR leads to reduced chloride and fluid secretion[2]. In addition to this, decreased bicarbonate secretion reduces the alkalinization process, which diminishes the anti-microbial effect of the fluid, increasing the potential for infection. This affects the function of wide range of epithelial cells such as the respiratory airways and pancreatic ducts, leading to pulmonary infection and inflammation, progressing to bronchiectasis and declined lung function status along with pancreatic impairment, hepatobiliary insufficiency, and gastrointestinal disease[3].

Recent research reported noteworthy progress in different mutations in CFTR gene and role of these mutations in pathobiology of the disease, which revealed CFTR gene mutation leads to alteration of protein structure with reduction of function [4]. Among the 2000 known mutations, F508del mutation is responsible for majority (around 90%) of the cystic fibrosis cases, which affects the CFTR trafficking and misfolding and delivers the CFTR protein to wrong location inside the cell, suppressing the function of the CFTR protein[5] (Figure 1). CFTR mutations are divided into six separate varieties as per the molecular expression: class I being diminished expression of CFTR protein while class II is due to misfolding of CFTR protein, class III includes non-functional protein, class IV-VI inadequate quantities of CFTR protein[6].

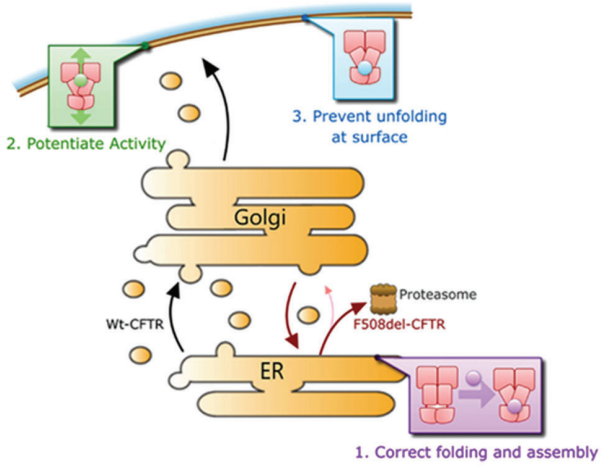

Figure 1: *This figure shows how correct CFTR gene leads to the production of proper protein, which was produced in the Endoplasmic reticulum, matured in the Golgi apparatus, and localized in the appropriate site of the cell surface. However, F508del causes misfolding, preventing unfolding at the cell surface with deficient functionality[7].*

Management of the cystic fibrosis has been the symptomatic management, for example, nutritional supplementation, antibiotic and other supportive treatment, for decades[8]. However, the treatment paradigm for cystic fibrosis has changed dramatically with the advent of newer drugs targeting the non-functioning CFTR proteins[9]. None of these newer drugs are gene therapy and do not make any change of the gene, rather binds to the protein and makes structural correction of the protein, which falls into one of the two major categories: CFTR modulator and CFTR corrector[10]. While CFTR modulators helps the CFTR protein to localize to the cell surface and function properly, CFTR correctors, on the other hand, are small molecules which upon binding to the CFTR protein helps to fold in to appropriate 3-D shape and function properly[11].

Ivacaftor, a CFTR modulator, binds to the CFTR protein, potentiating the protein with improved localization, and better functional capacity in chloride and bicarbonate transport[12]. Several clinical trials reported improved pulmonary function and quality of life in cystic fibrosis patients who received Ivacaftor alone or in combination with other CFTR correctors like Tezacaftor or Lumecaftor[13-17]. Ivacaftor can be administered orally with Tmax of 3-5 hours with streamlined pharmacokinetics and pharmacodynamics with limited interaction with other drugs[18].

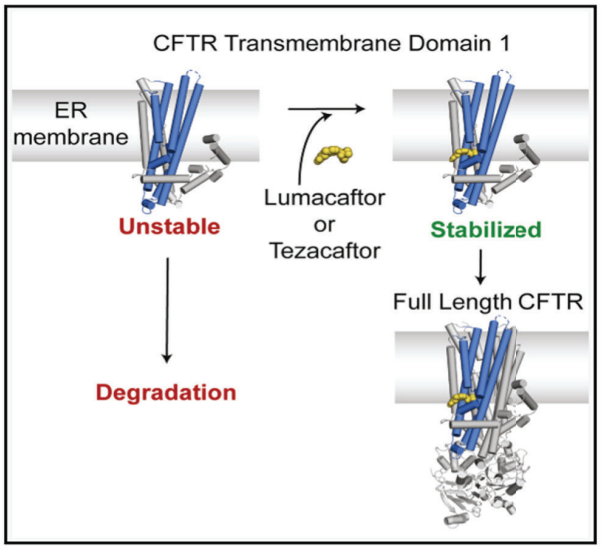

Figure 2: *Mechanism of action of combination treatment of Elexacaftor and Tezacaftor; ensuring proper processing of the protein followed by improved localization, resulting in better chloride and fluid transport through the channel protein[12,19].*

Elexacaftor and Tezacaftor are CFTR correctors, binds to the CFTR protein, which makes structural alteration, these structural changes stabilizes the CFTR protein, which then moves to the cell surface and function as a Chloride channel[19]. Furthermore, Tezacaftor modulates the sequence of CFTR protein to ensure the correct positioning of the CFTR on the cell surface, leading to the proper functioning of the ion channel, resulting in increased passage of chloride and bicarbonate, ensuring the lubrication with the removal of symptoms originating from the disease[20]. Several clinical trials reported superior efficacy in controlling symptoms when Tezacaftor is administered along with Ivacaftor[21]. Furthermore, pharmacodynamic studies have shown minimum drug-drug interaction of Tezacaftor with other relevant drugs[22]. Elexacaftor works by binding different structural site than Tezacaftor, which has synergistic effects on each other's function[23].

Flume et al., (2012) reported clinical improvement in Phe508del mutated cystic fibrosis patients, who were treated with triple combination therapy (Elexacaftor, Ivacaftor, Tezacaftor) in the form of decreased pulmonary exacerbations, increased ppFEV1, increased chloride concentration in the sweat[16]. Taylor-Cousar et al., (2017) reported higher BMI, higher ppFEV1, increased chloride concentration in the Phe508del mutated cystic patients who were treated with triple therapy compared to treatment with Tezacaftor and Ivacaftor[13]. However, Ratjen et al., (2017) reported no change in ppFEV1 and BMI, while higher rates of adverse effects among the double combination (Lumecaftor and Ivacaftor) recipients, which was different from other clinical trials[24].

A previous systematic review conducted by Habib et al., (2019) reported the effect of different combinations of different dosage of Lumecaftor, Ivacaftor combination and Tezacaftor-Ivacaftor combination, which led to a confusing result as they could not report a specific combination of drugs[25]. However, Kapouni et al., (2023) conducted systematic review solely on the present combination of triple drugs which reported promising efficacy without the report of disabling toxicity though this systematic review make no notes on the difference in patient population by age[26]. As there was clearly two different population of patient with cystic fibrosis, without mentioning this report seem to be inadequate[26].

Rationale: Although multiple clinical trials reported better efficacy along with variable safety of triple combination (Elexacaftor, Ivacaftor, Tezacaftor) therapy, there were some inconsistencies in the report along with some conflicting reports regarding the mutation status of the participants which should be addressed. Although there is a previous systematic review with the same combination of treatment, there was some inconsistencies regarding the separate patient population depending on the age of the patients [26]. Therefore, a new systematic review with updated data is warranted in this subject where there is potential to improve the quality of life of cystic fibrosis patients.

This systematic review aims to evaluate the efficacy and safety of triple combination of Elexacaftor, Ivacaftor, and Tezacaftor compared to placebo in cystic fibrosis patients. Regarding the efficacy of the ppFEV1, sweat chloride concentration change were compared. Regarding safety, the rate of adverse effects, changes BMI, and pulmonary exacerbations were compared. Furthermore, change of quality-of-life was compared using the cystic fibrosis questionnaire-revised respiratory domain (CFQ-R RD) as a tool.

Methodology

The planning, database search, data extraction, and data reporting of this systematic review were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)- 2020 statements[27].

Search strategy

The search strategy for this systematic review has been developed based on the PICO criteria, where population (P) was the cystic fibrosis patient, intervention (I) was the combination of Elexacaftor, Tezacaftor, and Ivacaftor. Furthermore, comparison(c) was placebo, the outcome (O) was efficacy and safety of the treatment. Efficacy includes forced expiratory volume in 1 second (FEV1), pulmonary exacerbations. Safety outcomes include adverse effects, lung clearance index (LCI). Relevant keywords were searched along with the medical subject headings combined with Boolean operators like AND, NOR, OR, NOT. Three databases focused on healthcare were searched with the search strings.

PubMed search strategy

PubMed was searched with five keywords: Ivacaftor, Tezacaftor, Elexacaftor, "cystic fibrosis", and CFTR in the title and abstract section, which led to 388 articles. This search was further modified with the filters of "randomized controlled trial", "human", "English", which led to 62 articles, when the search was conducted on 25th May 2023 (table 1).

Table I

Search result from PubMed database

Keywords or MeSH	Search string	Results
Ivacaftor, Tezacaftor, Elexacaftor, Cystic fibrosis, CFTR	"ivacaftor"[Title/Abstract] AND "tezacaftor"[Title/Abstract] AND ("cystic fibrosis"[Title/Abstract] OR "CFTR"[All Fields])	388 articles on 25th May 2023
Filters of "Randomized control trial", "human", "english"	(((("ivacaftor"[Title/Abstract] AND "tezacaftor" [Title/ Abstract] AND "cystic fibrosis"[Title/Abstract]) OR "CFTR"[All Fields]) AND ("loattrfree full text"[Filter] AND "randomized controlled trial" [Publication Type] AND "humans"[MeSH Terms] AND "english"[Language])) AND ((ffrft[Filter]) AND (randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (english[Filter]))	62 articles on 25th May 2023

Cochrane search strategy

Cochrane registry for clinical trials was searched using both MeSH and keywords. These keywords were added by Boolean operator AND to form the search string, which led to 76 articles on 25th May 2023 (Table II).

Table II

Search results from Cochrane registry for clinical trials database

Keywords or MeSH	Search string	Result
Ivacaftor	#1: (Ivacaftor): ti,ab,kw	483 articles
Tezacaftor	#2: (Tezacaftor): ti, ab, kw	147 articles
Elexacaftor	#3: (Elexacaftor): ti, ab, kw	121 articles
Cystic fibrosis	#4: (Cystic fibrosis): ti, ab, kw	6738 articles
CFTR	#5: (CFTR): ti, ab, kw	797 articles
Efficacy	#6: (Efficacy): ti, ab, kw	437496
Final string	#1 AND #2 AND #3 AND #4 AND #5 AND #6	76 articles 25th May 25, 2023

Cumulative index for nursing and allied healthcare literature (CINAHL) search strategy

CINAHL database was searched using following phrases: "Ivacaftor", "Tezacaftor", "cystic fibrosis", "CFTR", "Elexacaftor" to search the abstract section, which led to 21 articles, when the database was searched on 25th May 2023 (table III).

Table III

Search results for CINAHL database search

Keywords or MeSH	Search string	Result
Ivacaftor, Tezacaftor, Cystic fibrosis, CFTR, Efficacy	AB (Ivacaftor) AND AB (Tezacaftor) AND AB (Elexacaftor) AND AB (Cystic fibrosis) AND AB (CFTR) AND AB (Efficacy)	21 articles Searched on 25th May 2023

Reviewing process

Articles (citations) from these three databases were downloaded in different folders of EndNote citations software, which were then accumulated in a single folder to search for duplicates, followed by the exclusion of duplicates. Thereafter, the title and abstract of these articles were reviewed and irrelevant and non-related articles were removed from the study. Remaining articles were downloaded in full text format, however, the studies which could not be downloaded in full-text format were discarded from this review. A full text-based study on the preset inclusion and exclusion criteria was done to find out relevant studies. Finally, studies were selected to extract the data.

Data extraction

Data extraction was done on a previously generated Excel datasheet in three different segments: background data, efficacy and safety data, risk of bias data. Data were extracted on the background variables, efficacy outcomes, safety outcomes, and risk of bias variables. Background variables included: name of the first author, year and the journal of publication, country where the study was conducted, number of patients in the experimental and the control arm, characteristics of the participants, treatment given in the experimental arm and in the control arm with dose. Furthermore, regarding background data, mean age of the patients along with follow-up duration were collected. Regarding the efficacy following data were collected: percent-predicted forced expiratory volume in one second (ppFEV1), pulmonary exacerbations (PEx), nutritional status, and hospitalization due to PEx. Regarding the safety of the drugs following data were collected: elevated liver function tests (LFTs), adverse effects due to the drug, Cystic fibrosis questionnaire-Revised (CFQ-R) based respiratory symptoms. Finally, regarding the quality of evidence data were collected on the presence of randomization, appropriateness of randomization, presence of blinding, type of blinding, percentage of patient continued the follow-up etc.

Risk of bias analysis

Risk of bias assessment was done using both the JADAD scale [28, 29]. JADAD scale is calculated based on three principles: Randomization, Allocation concealment (blinding), and Withdrawal or attrition [30]. JADAD scale is a five-point scale which reserves one point for the presence of the randomization, another point for following any of the approved methods of randomization. One point for allocation concealment from the patients and two points for the allocation concealment from both the patients and the physicians. Finally, one point if the withdrawal or attrition was less than 20%.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were selected before starting the data collection and database searching to prevent bias. To create these criteria previous systematic reviews on similar topics were consulted (table IV).

Table IV

Inclusion and exclusion criteria for the study selection

Serial	Inclusion criteria	Exclusion criteria
1	Clinical trials on CFTR mutated cystic fibrosis patients	Non-human studies
2	Participants received combination of Ivacaftor and Tezacaftor in the experimental arm.	Retrospective studies
3	Article supposed to be published in an English language journal	Case series, case report, clinical audit, review article, systematic review with meta-analysis
4	Articles published from the beginning of the PubMed, Cochrane, CINAHL to 2023	No report on Glycated hemoglobin, FPG, adverse effects, weight gain, hypoglycemia.

Outcomes

Several efficacy and safety outcomes were used with ppFEV1 is the primary efficacy outcome, which indicates the predicted percentage of FEV1 in both baseline and 24 weeks after the treatment. Any positive increase of the ppFEV1 indicates better response of the drug. Sweat chloride concentration is another efficacy variable which is measured at the baseline and after 24 weeks of treatment, and decreased chloride concentration indicates clinical improvement of the patient. Cystic fibrosis questionnaire-revised respiratory domain (CFQ-R RD) is calculated score based on the CFQ-R with score ranging from 1-100 with higher scores indicating improved health-related quality of life (HRQoL) [31]. Regarding the safety of the combination drug, both BMI and adverse effects were utilized where higher BMI indicates safer drug and lower rate of adverse effects indicates safer drug. However, higher pulmonary exacerbations indicate lower safety of the drug with higher exacerbated events of cystic fibrosis.

Results

This systematic review data presentation and reporting was in line with the PRISMA 2020 statement to maintain conformity with other systematic reviews [27]. The PRISMA flow chart in figure 3 depicts the process in three stages. In identification stage, 159 articles were collected from three databases: PubMed (62 articles), Cochrane library (76 articles), and CINAHL (21 articles). These articles were collected and accumulated in a single folder of EndNote software to scrutinize these articles to find out any duplicate entries. 39 duplications were found, and these were removed from the review (figure 3). Remaining 120 articles entered the screening stage and, in this stage, primarily these articles were screened based on the content of the title and the abstract, which suggested 70 articles which were irrelevant to the objectives of

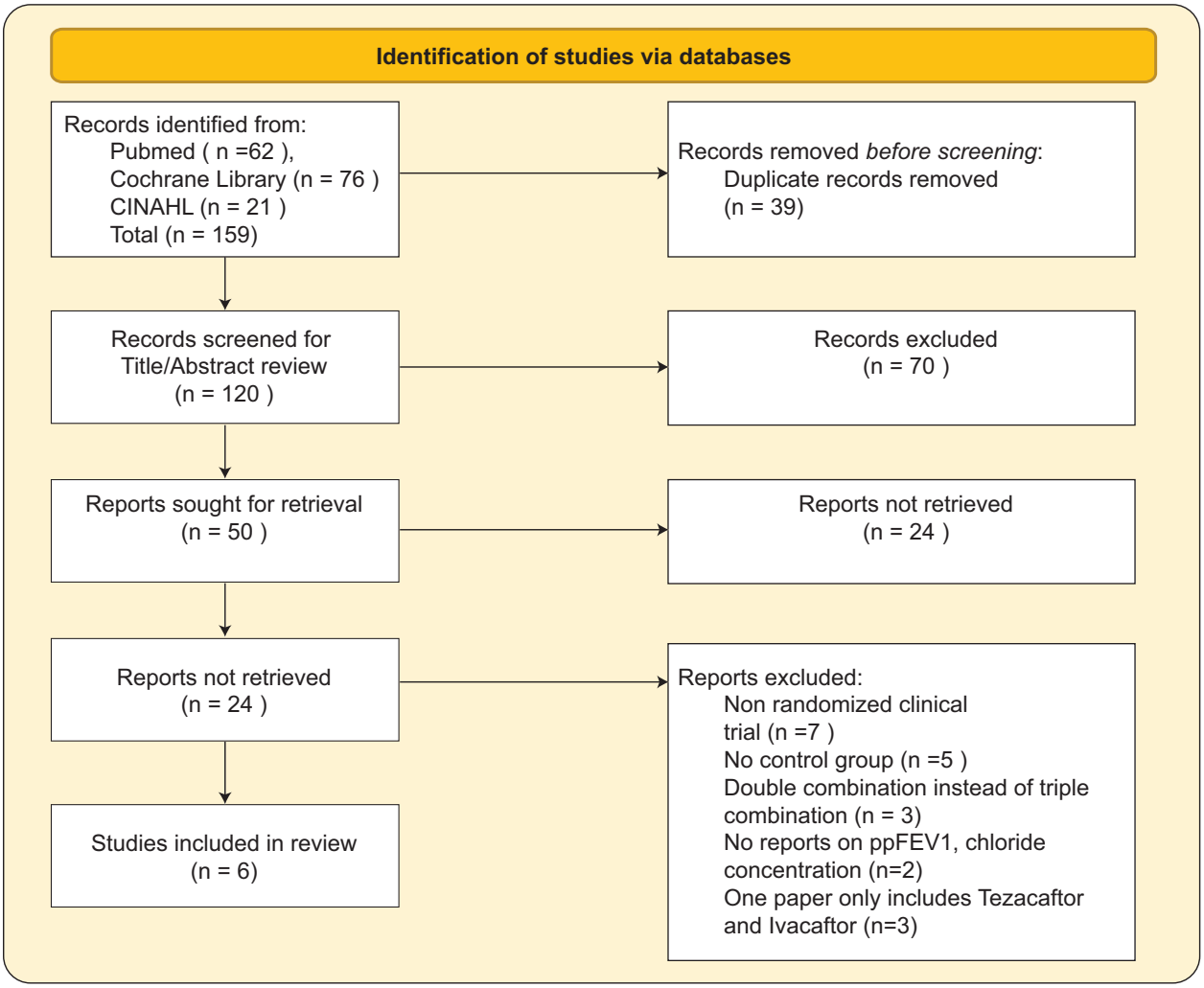

Figure 1: *Flow-diagram with three stages (Identification, screening, and included) revealing the work-flow during the article search and screening based on the PRISMA statement released on 2020*[27].

this study, and these articles were removed from the study. The remaining 50 articles were sought to be retrieved in full-text version to screen thoroughly; however, 24 articles could not be retrieved in full-text version from any source, therefore, therefore these articles were excluded from the study (figure 3). The remaining 26 articles were downloaded full-text and studied thoroughly and based on the previously determined inclusion and exclusion criteria 8 non-randomized articles were rejected from the review. Furthermore, six articles were rejected due to the absence of any control group. Moreover, two trials were removed as these trials administered combination of Lumecaftor & Ivacaftor or combination of Tezacaftor and Ivacaftor instead of triple combination. Another two clinical trials were removed as these did not report ppFEV1, chloride concentration in sweat, or CFQ-R as efficacy variables. Two clinical trials were excluded as these included only Tezacaftor and Ivacaftor without including Elexacaftor[13, 17]. Finally, six articles were included in the systematic review, from which data on background variables, efficacy & safety variables and risk of bias were collected (figure 3).

Study characteristics of the included clinical trials

Six clinical trials were included in this systematic review with 994 cystic fibrosis patients, 542 cystic fibrosis patients received triple combination therapy while 452 cystic fibrosis patients were in the control arm, including one single arm study with 66 patients (table V). One of these clinical trials was phase II and three were phase III randomized controlled clinical trials, and two trials were phase 3b. Five of the clinical trials were conducted in multiple countries and one was conducted in the USA (table V). While all six clinical trials enrolled cystic fibrosis patients, three clinical trials recruited Phe508del homozygous patients while three recruited Phe508del heterozygous or F508 minimal function patients (table V). All six clinical trials administered triple combination therapy (Elexacaftor, Tezacaftor, and Ivacaftor) in the experimental arm and the control arm participants received placebo, however, Zemanick et al., reported a single arm trial[15,32-36]. Mean age of the participants ranged from 9 years to 28.8 years while follow-up duration ranged from 24 weeks to 36 weeks (table V).

Table V

Background characteristics of the included trials

Author and date	Study design	Country	Number of Subjects		Patients Characteristics	treatment	Control	Age (years)	Follow up (weeks)
			E	C					
(Keating et al., 2018) [15]	Double blind, phase 2 RCT	Multiple countries	74	48	F508del homozygous Cystic fibrosis patients	Iva 150 mg bid + Teza 100 mg OD + Elexa 200 mg bid	Placebo	27.1 ± 7.4	36 weeks
(Heijerman et al., 2019) [32]	Phase 3, RCT	Multiple countries	55	52	F508del homozygous Cystic fibrosis patients	Iva 150 mg bid + Teza 100 mg OD + Elexa 200 mg bid	Placebo	28·8 ±11·5)	32 weeks
(Middleton et al., 2019) [33]	Phase 3, Randomized controlled trial	Multiple countries	200	203	F508del heterozygous Cystic fibrosis patients	Iva 150 mg bid + Teza 100 mg OD + Elexa 200 mg bid	Placebo	Mean 25.6 ± 9.7	24 weeks
(Zemanick et al., 2021) [34]	Phase 3, open-label, single arm study	Multiple (5) countries	66		F508del-minimal function or F508del-F508del genotypes	Iva 150 mg bid + Teza 100 mg OD + Elexa 200 mg bid	Placebo	9.3 ± 1.9	24 weeks
(Mall et al., 2022) [35]	Phase 3b, RCT	Multiple countries	60	61	F508del heterozygous and MF Cystic fibrosis	Iva 150 mg bid + Teza 100 mg OD + Elexa 200 mg bid	Placebo	9 (6-11) years	24 weeks
(Sutharsan et al., 2022) [36]	Double blind, phase 3b, RCT	USA (multiple centers)	87	88	F508del homozygous Cystic fibrosis patients	Iva 150 mg bid + Teza 100 mg OD + Elexa 200 mg bid	Tezacaftor + Ivacaftor	Mean 21 (18-42)	24 weeks

Abbreviation: E: Experimental, C: Control, Iva: Ivacaftor, Teza: Tezacaftor, Elexa: Elexacaftor, OD: Once daily, BID: twice daily, MF: Minimal function

Outcomes of the triple combination treatment

Efficacy outcomes:

ppFEV1

All six clinical trials reported ppFEV1 as an efficacy parameter and all these clinical trials reported higher ppFEV1 in the experimental arm (triple combination drug recipients)[15, 32-36]. Change of ppFEV1 in the experimental arm ranged from 9.5% to 13.6% whereas it ranged from -0.3 to +0.4 in the control arm (table 6).

Sweat chloride concentration

Five out of six clinical trials reported chloride concentration in the sweat as an efficacy parameter and all five clinical trials reported lower sweat chloride concentration in the experimental arm participants, who were the recipients of triple combination therapy [15, 32-35]. Sweat chloride concentration in the experimental arm ranged from -33.2 to -60.9 while it ranged from -0.9 to 1.7 in the control arm (table VI).

CFQ-R RD (Cystic fibrosis questionnaire-revised respiratory domain)

All six clinical trials reported CFQ-R RD and all six clinical trials reported higher CFQ-R RD values in the triple combination drug recipients of experimental arm [15, 32-36]. Mean CFQ-R RD value in the experimental arm ranged from 5.9 to 21.9 while it ranged from -2.7 to 5.9 in the control arm (table VI).

Table VI

Efficacy of the triple combination CFTR modulator compared to placebo.

	Author and date					
	ppFEV1		Sweat chloride concentration		CFQ-R RD	
	E	C	E	C	E	C
(Keating et al., 2018) [15]	11.1 ± 2.1	0.4 ± 2.8	39.1±2.3	1.2±3.6	17.5 (15.6 – 19.5)	-2.7 (-4.6 - -0.8)
(Heijerman et al., 2019) [32]	10·4 (8·6, 12·2)	0·4 (1·4, 2·3)	43·4 (46·9, 40·0)	1·7 (1·9, 5·3)	16·0 (12·1, 19·9)	1·4 (5·4, 2·6)
(Middleton et al., 2019) [33]	13.6 (12.4 to 14.8)	0.2 (1.3 to 1.0)	33.2±2.8	0.8±4.9	20.8±5.4	5.2±7.1
(Zemanick et al., 2021) [34]	10.2 (7.9 to 12.6)		60.9 (63.7 to “58.2)		7.0 (4.7 – 9.2)	
(Mall et al., 2022) [35]	9.5 (6.6 to 12.4) -0.9 (-3.8 to 2.0)		-1.5 (4.4 to 1.4) 5.9 (2.8 to 9.1)		-52.1 (55.0 to “49.2) 0.5 (-2.7 to 3.6)	
(Sutharsan et al., 2022) [36]	9.89 ± 1.7	-0.3 ± 1.7	NR	NR	21.9±5.7	5.9±3.7

Abbreviation: ppFEV1: Predicted percentage of forced expiratory volume in 1 second, CFQ-R RD: Cystic fibrosis questionnaire-revised respiratory domain, E: Experimental, C: Control

Safety outcomes of the combination of Elexacaftor, Tezacaftor, and Ivacaftor

Body mass index (BMI)

Five out of six clinical trials reported BMI as a safety outcome and three out of these four clinical trials reported higher BMI in the experimental arm while another reported no significant differences between these two arms and one study was single arm[15,32, 33,35,36]. BMI in the experimental arm ranged from 0.58 to 1.24 whereas BMI in the control arm ranged from 0.09 to 0.56 (table VI).

Adverse event

All six clinical trials reported adverse events such as pulmonary toxicities like cough, abnormal respiration, dyspnea, and increased sputum production, a safety outcome with two clinical trials reporting higher rate of adverse events in the experimental arm while another three trials reported higher rates in the control arm[15, 32-36]. The rate of adverse events in the experimental arm ranged from 37.1% to 80% while it ranged from 28.9% to 93.4% in the control arm, however, the highest adverse effects were reported by Zemanick et al., at 98.5% (table VII).

Pulmonary exacerbations

Five out of six clinical trials reported rate of pulmonary exacerbations as a safety outcome and two out of five clinical trials reported higher rates of pulmonary exacerbations in the experimental arm while two out of five clinical trials reported higher rates of adverse event in the control arm, however, Mall et al., only reported pulmonary exacerbations due to infection. [15, 32, 33, 35, 36]. Rate of pulmonary exacerbations in the experimental arm ranged from 1.7% to 65% while it ranged from 26.2% to 98.0% in the control arm (table VII).

Risk of bias

JADAD scale reported low risk of bias for four out of six clinical trials as 4 clinical trials scored 4 or more out of 5 in JADAD scale[32, 33, 35, 36]. However, three clinical trials failed in follow-up as >20% withdrawal were reported, moreover, three clinical trials lack in double blinding and two clinical trials did not mention enough detail regarding the appropriateness of randomization (table VIII)[15, 32-36].

Table VII

Safety outcomes of the triple combination drug versus placebo in cystic fibrosis patients

Author and date	BMI		Adverse event		PEx	
	E	C	E	C	E	C
(Keating et al., 2018) [15]	0.58 (0.29 – 0.73)	0.56 (0.31 – 0.71)	71.2%	56.7%	65%	45%
(Heijerman et al., 2019) [32]	1.01 (0.89 – 1.21)	0.28 (0.11 – 0.41)	58%	63%	53%	43%
(Middleton et al., 2019) [33]	1.13 (0.99 to 1.26)	0.09 (“0.05 to 0.22)	37.1%	28.9%	37%	98%
(Zemanick et al., 2021) [34]	1.0		98.5% (pulmonary toxicities like cough, abnormal respiration, dyspnea, and increased sputum production)		NR	NR
(Mall et al., 2022) [35]	NR	NR	80.0%	93.4%	1.7% (infective)	26.2% (infective)
(Sutharsan et al., 2022) [36]	1.24 (1.12 to 1.39)	0.17 (“0.09 to 0.29)	59.4%	69.7%	49%	50%

BMI: Body mass index, PEx: Pulmonary exacerbations, BMI: Body mass index, E: Experimental, C: Control, %: Mean percentage of patients suffering from this adverse event.

Table VIII

JADAD score of the included clinical trials

Author and Date	Randomization	Appropriateness of randomization	Blinding	Double blinding	Withdrawal	Score
(Keating et al., 2018) [15]	1	1	1	0	0	3/5
(Heijerman et al., 2019) [32]	1	1	1	1	0	4/5
(Middleton et al., 2019) [33]	1	1	1	0	1	4/5
(Zemanick et al., 2021) [34]	0	0	1	0	1	2/5
(Mall et al., 2022) [35]	1	1	1	0	1	4/5
(Sutharsan et al., 2022) [36]	1	1	1	1	0	4/5

Discussion

This systematic review was conducted to assess the efficacy and safety of the combination of Elexacaftor, Tezacaftor, Ivacaftor compared to placebo in Cystic fibrosis patients with non-functional or minimal function CFTR protein. This systematic review provided up-to-date and concise synthesis on triple drug combination on the cystic fibrosis patients, which was attempted by previous systematic review conducted by Kapouni et al., (2023), however, this systematic review did not comment on the difference in age among different studies[26].

As the current systematic review highlights, Phe508del mutated patients were benefit the most when triple drug was given as shown by more than 10% increase in majority of the clinical trials included in this review[15, 32-36]. Lower rates of improvement were seen by real world data on the effect of Ivacaftor alone in cystic fibrosis patients[37]. This was supported by the in vitro study on bronchial epithelial cell line, which showed that combination of CFTR potentiator, CFTR corrector, and CFTR modulator augments the CFTR function[38].

Current systematic review also reported significantly decrease in chloride concentration in the sweat which was 30 points down from the baseline value in all trials and 37 points down from the baseline value compared to the negligible improvement in the control arm patients who received placebo. The significance of this cannot be overstated as among all other characteristics of Cystic fibrosis, raised Chloride concentration is used as the diagnostic test to detect the disease[39]. Which was also supported by pharmacokinetic modeling study as it shows that the sustained CFTR modulation in cystic fibrosis patients older than 12 years[40].

This systematic review also reported improvement of the quality of life of cystic fibrosis patients, which was shown by increase in the CFQ-R RD of more than 17 points. CFQ-R RD is a subjective scoring which indicates how patients feel better after treating with the triple combination drug compared to placebo[31]. This was supported by previous systematic reviews on the effect of CFTR modulators on cystic fibrosis patients, reporting similar benefits in CFQ-R RD scores with mean difference of 8.5[41].

Furthermore, four included articles of this systematic review reported improving BMI among the cystic fibrosis patients who were treated with triple drug regimen compared to placebo, indicating these patients are getting healthier by this treatment[15,32, 33,36]. Similar improvement in nutritional status was reported by other CFTR modulator combination (Lumecaftor & Ivacaftor) in cystic fibrosis patients with 0.8 kg/m^2 BMI improvement[42]. Increased BMI indicates the potential of Elexacaftor-Tezacaftor-Ivacaftor in treating the growth retardation in CFTR mutated patients, which was reported by case reports and clinical trials[43].

No significant difference was reported regarding the pulmonary exacerbations between the triple drug recipients in the experimental arm compared to the placebo recipients in the control arm. Which is contrary to the previous finding reporting higher rates of adverse effects due to the triple combination therapy in cystic fibrosis patients[20]. Previous study on adolescent cystic fibrosis patients with G85E mutations reported lower rates of pulmonary exacerbations among the triple drug recipients[44]. The difference might be due to the definition of pulmonary exacerbations as Mall et al., (2022) reported only pulmonary exacerbations due to infection and the study reported only 1.7% pulmonary exacerbations[35].

Although there was no significant difference in the rate of adverse effects between these two arms as three clinical trials reported higher adverse effect in the control arm and three clinical trials reported higher adverse effects in the experimental arm, however, there was a trend of higher adverse effects among the recipients of placebo[15, 32-36]. Most common adverse effects were originating from pulmonary toxicities like cough, abnormal respiration, dyspnea, and increased sputum production, however, these trials also reported non-pulmonary adverse effects like headache, generalized weakness, oropharyngeal pain[15, 32-36]. Previous systematic review on the effect of Elexacaftor-Tezacaftor-Ivacaftor on the cystic fibrosis patients also reported favorable safety profile[45]. However, there was report of drug-induced hepatic inflammation, pancreatitis, and intestinal obstruction among the triple drug recipients which should be further evaluated[26].

This systematic review included papers from two different age groups: children and adults. Zemanick et al., (2021) and Mall et al., (2022) reported the effect on the children, however, rest of the four clinical trials reported trial on adult cystic fibrosis patients[34, 35]. Regarding ppFEV1 there was no difference between the child and adult cystic fibrosis patients. However, child cystic fibrosis patients benefitted significantly more than adult patients regarding sweat chloride concentration[15, 32-36]. However, regarding the CFQ-R RD, the trial with the children reported the least benefit from triple combination treatment. There was no reportable benefit in BMI from children, however, trials with children reported the highest adverse effects as high as 80% to 98.5% whereas adult's trials reported 72% or lower adverse effects[15, 32-36].

Limitations: This systematic review made no effort to compare combination of dual therapy to triple therapy, limiting the role of this review in the decision-making

process of dual versus triple therapy. This systematic review did not add any quantitative analysis (meta-analysis), leading to the absence of the numerical comparison of the data. Furthermore, this systematic review only searched three databases, leaving a place for improvement of the review by searching additional healthcare-related databases, conference proceedings and not to mention personal communication with the scientist conducted these clinical trials. Moreover, a good number of citations could not be retrieved for the full-text analysis due to unavailability or lack of paid subscriptions, which could be improved by securing funding for relevant expenses. Finally, a single scientist was dedicated to this systematic review, which might have reduced the comprehensiveness in the search and introduced the possibility of individual bias. Several data were not found on several studies, which limited the analysis. Furthermore, none of the studies followed up the patients more than 36 weeks, which limited the scope on long-term results of the drugs.

Conclusion

This systematic review reported higher efficacy of Elexacaftor-Tezacaftor-Ivacaftor combination in cystic fibrosis patients compared to placebo. Efficacy was demonstrated by higher ppFEV1 value and lower sweat chloride concentrations. This review also reported better wellbeing and quality of life among the triple drug recipient cystic fibrosis patients, which was shown by higher CFQ-R RD points. This systematic review ensured the safety of the drug with higher BMI indicating nutritional improvement. This also showed similar pulmonary exacerbations and adverse effects between these two treatment recipients. So, it can be stated that this systematic demonstrated the potential clinical benefit of the triple combination treatment without increasing toxicity of the treatment, rather increasing the nutritional status of the patients. More importantly, this systematic review showed that there is a different trend in efficacy and safety between the child and adult patient population.

Future studies should be conducted with lower follow-up duration to find out the effect of the drug on the development of the patient. Furthermore, future studies should be done after conducting genetic studies to subclassify the patient population based on the genetic mutation. Future systematic reviews should be done with a meta-analysis to report the quantitative analysis along with the qualitative analysis.

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