

Systematic Review



Efficacy of Trikafta (ELX/TEZ/IVA) & Symdeko (TEZ/IVA) in Treating Cystic Fibrosis with F508del Allele: A Systematic Review and Meta-analysis

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Abstract

The objective of the study was to assess and compare the efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) treatment with TEZ/IVA treatment in individuals diagnosed with cystic fibrosis (CF) and carrying the F508del allele. An extensive search of relevant literature was conducted using online resources, namely, PubMed, ScienceDirect, and Google Scholar. The initial search identified 248 articles, and after a careful examination of the full text of 18 articles, 7 met the inclusion and exclusion criteria. These selected reports were then thoroughly examined to perform a comparative analysis of the effectiveness of TEZ/IVA versus ELX/TEZ/IVA in CF patients with the F508del allele. The quality of the selected reports was evaluated using the Cochrane risk-of-bias tool for randomized studies, known as RoB 2. ELX/TEZ/IVA has shown significant improvements in key indicators of CF treatment. It has demonstrated a significant increase in forced expiratory volume in one second levels, indicating improved respiratory capacity and airflow. Additionally, ELX/TEZ/IVA successfully reduced sweat chloride levels and positively impacted Cystic Fibrosis Questionnaire-Revised Respiratory Domain scores, reflecting enhanced respiratory function and improved quality of life for patients. Overall, the study concluded that ELX/TEZ/IVA provided a clinically robust benefit compared to TEZ/IVA alone while maintaining a favourable safety profile.

KEYWORDS: Cystic fibrosis, Phe508del, Symdeko, Trikafta, ivacaftor, tezacaftor, elexacaftor, safety, systematic review

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INTRODUCTION

Cystic fibrosis (CF) is a hereditary disorder characterized by malfunctioning of the CF transmembrane conductance regulator (CFTR) protein.¹ CFTR is found on the apical membrane of epithelial cells, and its absence results in decreased chloride secretion and insufficient fluid transport.² A significant reduction in chloride secretion results in mucus impaction in exocrine organs, airways, and gastrointestinal tracts, which progressively leads to pulmonary exacerbations, nutritional deficits, and respiratory failure.³ It is estimated that more than 70,000 people worldwide are affected by CF.⁴

CFTR mutations are categorized into six groups based on their effect on CFTR protein synthesis, processing, and function. These classes help explain the underlying mechanisms that lead to CF symptoms. Class 2 mutations, which include the most common variant, F508del, result in defective protein folding. This misfolding prevents the CFTR protein from reaching the cell surface, where it would normally regulate chloride ion transport. As a consequence, chloride secretion is impaired, leading to thick mucus buildup in various organs, particularly the lungs and pancreas.^{5,6} Approximately 2000 CFTR gene variations have been identified so far,⁷ and F508del accounts for the majority of CFTR alleles in individuals with CF.⁸

In recent years, advances in CF research and medical treatments, such as CFTR modulator therapies, have significantly improved outcomes for individuals with CF. These therapies target specific CFTR mutations and aim to correct the underlying defect in CFTR protein function. Ivacaftor (IVA) is a CFTR modulator that is authorized for the treatment

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of people who have CF and at least one of the 33 CF-causing mutations.⁹ By enhancing the function of defective CFTR channels at the cell surface, IVA, improves chloride ion transport, leading to improved lung function and reduced respiratory symptoms in CF patients.¹⁰ In individuals with gating mutations, IVA has lowered mortality, lung transplantation rates, and other consequences of CF.¹¹ Tezacaftor (TEZ) is a broad-acting CFTR corrector that promotes the cellular processing and trafficking of normal CFTR and numerous mutant CFTR forms, including F508del, increasing the quantity of CFTR protein at the cell surface and thereby enhancing chloride transport. It assists in restoring proper folding and trafficking of CFTR protein to the cell surface.¹² When used in combination with IVA, TEZ can significantly enhance CFTR function and clinical outcomes. TEZ in combination with IVA has the potential to address an important unmet need for CFTR modulators, by improving the benefit-to-risk profile of CFTR modulation in patients homozygous for F508del and enhancing the benefit of CFTR modulation in patients with IVA-responsive mutations.¹³ Elexacaftor (ELX) is a CFTR corrector that improve CFTR protein processing, stability, and trafficking to the cell surface.¹⁴ By targeting the misfolding issue caused by class 2 mutations, ELX enables the CFTR protein to reach its intended location and function properly as an ion channel.¹⁵ When used in combination with IVA, TEZ and ELX form a novel triple combination therapy.

The gold standard spirometric test for diagnosing and treating CF lung disease involves measuring forced expiratory volume in one second (FEV1).¹⁶ FEV1 measures the volume of air forcibly exhaled in the first second of a forced expiratory maneuver.¹⁷ The percent predicted forced expiratory volume in one second (ppFEV1) compares an individual's FEV1 value to the average FEV1 value of a healthy population of the same age, height, sex, and ethnicity, providing a percentage value. Monitoring ppFEV1 over time helps clinicians evaluate lung function and

track disease progression in CF. A decline in ppFEV1 suggests worsening lung disease, while stable or improved ppFEV1 values indicate better respiratory health.¹⁸ Sweat chloride levels are another important diagnostic tool for CF. The sweat test measures the concentration of chloride ions in sweat. CFTR protein dysfunction leads to increased chloride ion levels in sweat, which is the basis for the sweat chloride test.¹⁹ Elevated sweat chloride levels confirm the diagnosis of CF. To gain insights into the respiratory symptoms and quality of life experienced by individuals with CF, the Cystic Fibrosis Questionnaire-Revised Respiratory Domain (CFQ-R RD) is commonly used. It is a validated questionnaire that assesses various aspects of respiratory health, including symptoms, physical functioning, emotional well-being, and social interactions. The CFQ-R RD helps evaluate the impact of CF on a person's daily life, assess treatment efficacy, and identify areas where intervention may be required to improve overall respiratory health and quality of life.²⁰

In this systematic review, we assessed and compared the efficacy and safety of TEZ/IVA and ELX/TEZ/IVA as therapies for CF patients and their impact on the quality of life of patients. We evaluated studies reporting ppFEV1, sweat chloride levels, and the CFQ-R RD score, for the assessment of TEZ/IVA / ELX/TEZ/IVA treatment regimens in F508del CF patients.

MATERIAL AND METHODS

The main objective of the systematic review was to formulate a comparative analysis between ELX/TEZ/IVA and TEZ/IVA treatment among CF patients with F508del allele. It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines (Figure 1). The review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) against the registration ID: 444643 (Supplementary Table 1).

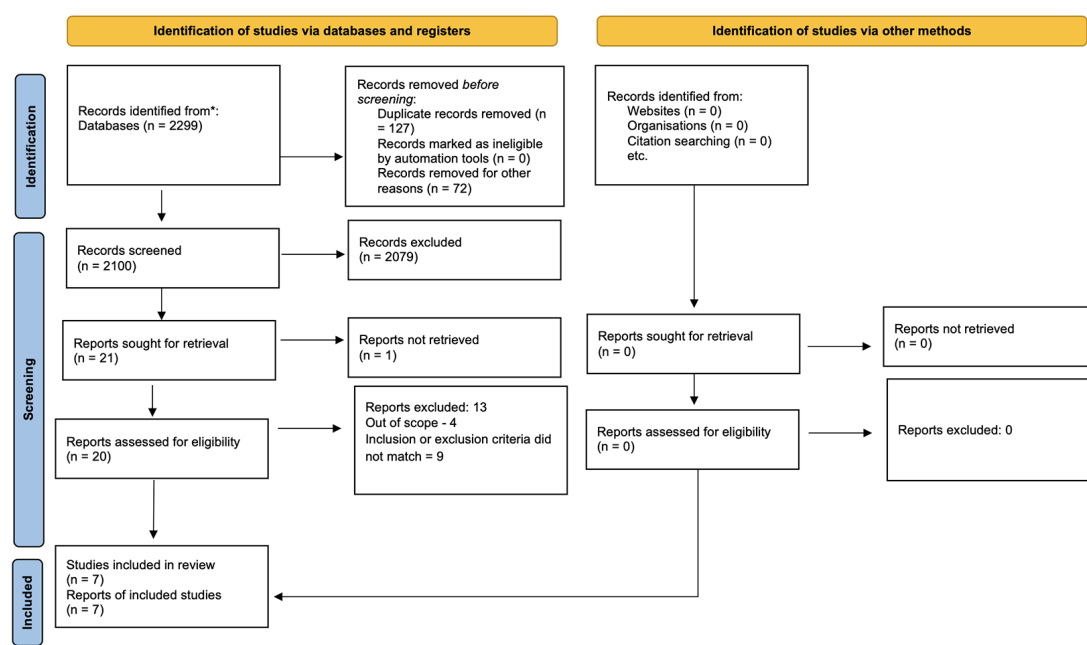


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020-flow diagram for inclusion and exclusion criteria

*PubMed, ScienceDirect, Google Scholar, Cochrane

Data Sources

Internet databases were searched using key terms to locate randomised controlled trials. Online databases searched included Cochrane Central Register for Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, PubMed, NCBI, ScienceDirect, Google Scholar. We utilized the following key terms to increase sensitivity for discovering CF therapeutic trials: “cystic fibrosis” OR “CFTR”, CFTR corrector, CFTR modulator, forced expiratory volume, sweat chloride.

Selection Criteria

Our title-specific search was followed by an abstract-specific screening to exclude extraneous publications. Furthermore, for full-text evaluation, we used the following conditions for inclusion: (1) randomized control trials (2) reports that included patients with CF with the F508del mutation (homozygous or heterozygous), (3) studies reporting predicted FEV1, sweat chloride levels, and CFQ-R RD scores, (4) studies reporting the adverse events of TEZ/IVA / ELX/TEZ/IVA, (5) studies with more than 100 patients recruited, and (6) phase 2 or above randomized studies. We also applied the following exclusion criteria: (1) articles including any CF mutations other than F508del, (2) reports of phase 1 clinical trials, and (3) articles in a language other than English. The whole text was then evaluated using the established qualifying criteria. After several rounds of debate, the authors reached a mutual agreement, with final approval from the principal investigator.

Data Extraction

For data extraction, an authorised tracking sheet (Excel) from the principal investigator, with the mutual agreement of the authors, was utilised. The main outcomes were percentage of predicted FEV1 mean value, sweat chloride levels, CFQ-R RD score, and adverse events. The authors extracted entered the data into the tracking sheet (Excel) for each study's baseline characteristics, clinical data, therapies administered, and findings. The

primary investigator double-checked the spreadsheets for any irregularities.

Risk of Bias Assessment

The chosen research papers underwent an evaluation process to determine their quality using the RoB 2 tool, which is designed for assessing bias in randomized studies (Figure 2). The RoB 2 tool evaluates six areas related to bias, including the randomization process, the impact of assigning participants to interventions, adherence to the intervention, handling of missing outcome data, measurement of outcomes, and selection of reported results. The authors individually assessed the data and then discussed and agreed upon their judgments regarding the risk of bias (Supplementary Table 2).

Statistical Analysis

The statistical analysis for the meta-analysis was performed using RStudio software. Heterogeneity was estimated using the I^2 index. Considering the low heterogeneity of the studies, a fixed effect model was used. The confidence interval of 95% was evaluated for the forest plot. $P < 0.05$ was considered statistically significant.

RESULTS

The studies included in the meta-analysis consisted of seven RCTs with each study recruiting more than 100 patients. The studies were phase 2 and above, which included both heterozygous and homozygous states for the Phe508del mutation. Every study included patients prescribed TEZ 100 mg once daily / IVA 150 mg every 12 hours (TEZ/IVA) or TEZ 100 mg once daily / IVA 150 mg every 12 hours / ELX 200 mg once daily (ELX/TEZ/IVA).

FEV1 Levels

In the case of patients with heterozygous F508 del CF, three studies compared TEZ/IVA with placebo, while one study reported ELX/TEZ/IVA versus placebo. In the phase 3 randomized controlled trial conducted by Taylor-Cousar et al.²¹ for evaluating the combination of IVA and TEZ in patients above the age of 12 years, the TEZ/IVA treatment resulted in a mean absolute change in FEV1 level of 3.4 ± 0.7 percentage points as compared to -0.6 ± 0.7 . Munck et al.²² reported a mean FEV1 level of 1 ± 1.2 percentage points and -0.1 ± 1.2 percentage points for placebo. Similarly, the phase 3 crossover study by Rowe et al.¹² giving a combination therapy of TEZ/IVA resulted in a mean change in FEV1 level of 11.1 ± 2.4 percentage points as compared to 4.7 ± 1 in case of placebo.

In the study conducted by Middleton et al.,²³ for evaluating the ELX/TEZ/IVA treatment for a period of 24 weeks, the mean change in FEV1 from baseline was 13.9 ± 1.1 , which is higher than the aforementioned values obtained from TEZ/IVA treatment. These findings suggest that both treatments have a positive impact on lung function, but ELX/TEZ/IVA may be slightly more effective.

In the case of homozygous F508del CF patients, Heijerman et al.²⁴ assessed the effects of TEZ/IVA and ELX/TEZ/IVA on various parameters. The mean change in percentage of predicted FEV1

Main Points

- The study aimed to evaluate Trikafta (elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and Symdeko (TEZ/IVA) in cystic fibrosis (CF) patients with the F508del allele. A comprehensive literature search was conducted using PubMed, ScienceDirect, and Google Scholar until April 2023. Out of the 248 articles reviewed, 8 met the inclusion criteria and were assessed using the Cochrane risk-of-bias tool.
- Trikafta (ELX/TEZ/IVA) has emerged as a promising treatment option for CF patients carrying the F508del allele. Its efficacy, as demonstrated by significant improvements in FEV1 levels, reduction in sweat chloride levels, and enhanced Cystic Fibrosis Questionnaire-Revised Respiratory Domain scores, suggests superior therapeutic outcomes compared to Symdeko (TEZ/IVA).
- With its favourable safety profile and consistent performance across heterozygous and homozygous F508del patients, Trikafta emerges as a promising and preferred treatment option for enhancing respiratory function and quality of life in CF management.

Table 1. Summary of baseline characteristics, dosage, and associated adverse events in reviewed studies

Author, year	Phase of the study	Type of study	Sample size	F508del (homozygous/heterozygous)	Treatment group (dose)	Comparator	Adverse events
Taylor-Cousar et al. ²¹ (2017)	Phase 3	Randomized, double-blind, multicenter, placebo-controlled, parallel group trial	510	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Infective pulmonary exacerbation of CF Cough Headache Nasopharyngitis Increased sputum production Pyrexia Hemoptysis Oropharyngeal pain Fatigue
Rowe et al. ¹² (2017)	Phase 3	Randomized, double-blind, placebo-controlled	248	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Infective pulmonary exacerbation of CF Cough Fatigue Hemoptysis Headache Pyrexia Dyspnea Sputum increased Diarrhea Nausea Oropharyngeal pain Nasal congestion Nasopharyngitis Blood CPK increased
Donaldson et al., ⁹ (2018)	Phase 2	Randomized, placebo-controlled, double-blind, multicenter	172	Both	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Infective pulmonary exacerbation of CF Cough Headache Increased sputum Fatigue Nausea Diarrhea
Munck et al., ²² (2020)	Phase 3	Randomized, double-blind, placebo-controlled, multicenter study	168	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Cough Fatigue Hemoptysis Sputum increased
Middleton et al., ²³ (2019)	Phase 3	Randomized, double-blind, placebo-controlled	403	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours/ elexacaftor 200 mg once daily	Placebo	Sputum increased Headache Cough Diarrhea Upper respiratory tract infection Nasopharyngitis Oropharyngeal pain Hemoptysis Fatigue
Heijerman et al., ²⁴ (2019)	Phase 3	Multi-centre, randomised, double-blind, active-controlled trial	113	Homozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours/ elexacaftor 200 mg once daily	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Cough Nasopharyngitis Oropharyngeal pain Upper respiratory tract infection Headache Hemoptysis
Sutharsan et al. ²⁵ (2022)	Phase 3	Randomized, phase3b controlled trials	176	Homozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours/ elexacaftor 200 mg once daily	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Headache, nazopharyngitis, cough, oropharyngeal pain

CF: cystic fibrosis, CPK: creatine phosphokinase

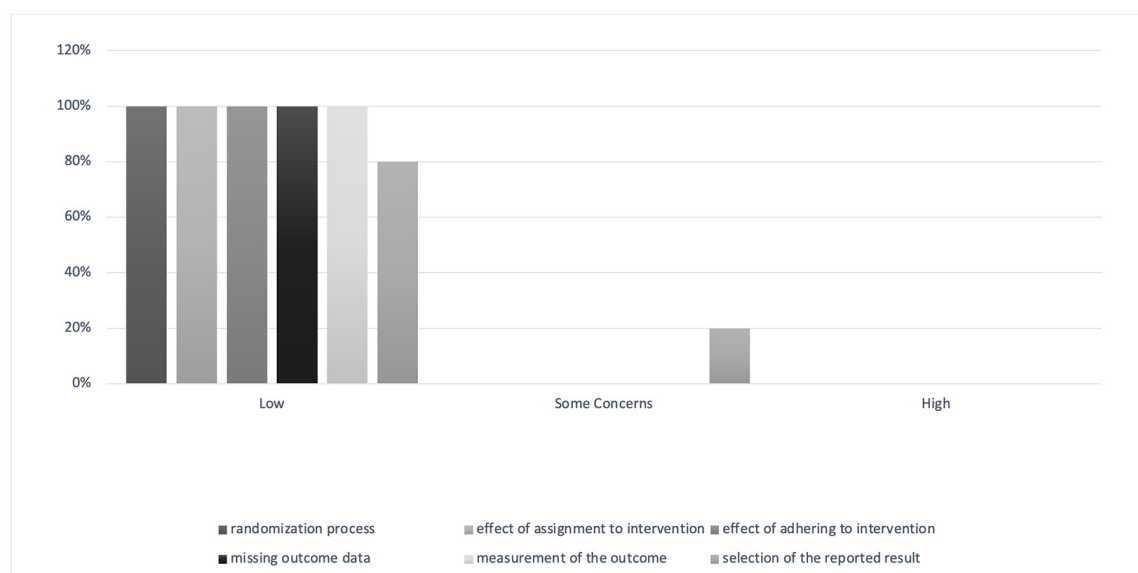


Figure 2. Risk of bias judgement of five included randomized studies by using RoB 2; a revised Cochrane risk-of-bias tool for randomized trials
RoB 2: Risk of Bias 2

was found to be 0.4 ± 1.9 for TEZ/IVA and 10.4 ± 1.8 for ELX/TEZ/IVA. A significant difference in FEV1 levels was observed, with a least square mean change of 10 units from baseline. Similarly, Sutharsan et al.,²⁵ investigated the effects of TEZ/IVA and ELX/TEZ/IVA on homozygous F508del CF patients at week 24. The change in the percentage of the predicted FEV1 mean value was $1.2 \pm 3\%$ for TEZ/IVA and $11.2 \pm 1.4\%$ for ELX/TEZ/IVA. The least squares mean change in FEV1 from baseline was 10.2. In the study by Donaldson et al.,⁹ homozygous F508del CF patients were assessed at week 4. The TEZ/IVA group showed a change in the mean percentage of predicted FEV1 value of 3.61 ± 1.39 .

Sweat Chloride Concentration

For heterozygous F508 del CF patients, Taylor-Cousar et al.²¹ reported, at a time point of 24 weeks, the mean sweat chloride level was 101.3 ± 10.9 and the least mean square change was reported to be -10.1 for TEZ/IVA. At a time point of 8 weeks, Rowe et al.¹² reported the mean sweat chloride level was 64.1 (28.9) mmol/litre with a least squares mean change of -9.5 for TEZ/IVA treatment. At a time point of 12 weeks, Donaldson et al.⁹ reported that the mean sweat chloride levels were 100.6 (13.0) mmol/litre for TEZ/IVA and the least square mean change was -3.5 for TEZ/IVA. For the ELX/TEZ/IVA treatment, Middleton et al.²³ reported a least square mean change from baseline of -41.8 for a period of 24 weeks. The findings from these studies indicate that while both TEZ/IVA and ELX/TEZ/IVA treatments have shown improvements in sweat chloride levels, ELX/TEZ/IVA demonstrated significant improvement over TEZ/IVA.

In the study conducted by Heijerman et al.²⁴ homozygous F508del CF patients were assessed at week 4; sweat chloride levels showed an average of 90.0 ± 12.3 mmol/litre for TEZ/IVA, while ELX/TEZ/IVA exhibited 91.4 ± 11.0 mmol/litre. The least

square mean change in sweat chloride levels was found to be -45.1 . Similarly, Sutharsan et al.²⁵ reported that sweat chloride levels were 89.8 ± 11.7 mmol/litre for TEZ/IVA and 89.0 ± 12.2 mmol/litre for ELX/TEZ/IVA, with a least square mean change of -42.8 . In the study conducted by Donaldson et al.⁹, sweat chloride levels for TEZ/IVA were 52.9 ± 19.6 mmol/litre, with a least squares mean change value of -7.02 . This also suggests that treatment with ELX/TEZ/IVA shows clinically better results in the case of homozygous F508del CF patients.

CFQ-R RD Score

For heterozygous F508 del CF patients, Taylor-Cousar et al.²¹ reported that the CFQ-R RD score for TEZ/IVA was 70.1 ± 16.8 and the least square mean change in the CFQ-R RD score for TEZ/IVA was 5.1 , indicating an improvement from baseline for TEZ/IVA treatment. Similar results were reported by Rowe et al.,¹² and Donaldson et al.,⁹ who showed that the least square mean change in the CFQ-R RD score for TEZ/IVA was 11.1 and 2.1 , respectively. Both studies reported that the TEZ/IVA treatment proved to be efficacious. Notably, Middleton et al.²³ reported a CFQ-R RD score of 68.3 ± 16.9 and a least squares mean of 20.1 for the ELX/TEZ/IVA treatment, which demonstrated better results than TEZ/IVA.

For homozygous F508del CF patients, Heijerman et al.²⁴ reported that the CFQ-R RD scores were 72.6 ± 17.9 and 70.6 ± 16.2 for TEZ/IVA and ELX/TEZ/IVA, respectively, with a least square mean change of 17.4 . Sutharsan et al.²⁵ showed that TEZ/IVA exhibited a mean score of 73.1 ± 17.6 , while ELX/TEZ/IVA had a score of 71.2 ± 19.6 . The least square mean change in CFQ-R RD score was 17.1 . Donaldson et al.⁹ reported that the least-squares mean change for CFQ-R RD scores was 3.79 . Collectively, the results show that the ELX/TEZ/IVA regimen is a better alternative to TEZ/IVA regimen.

Table 2. Comparative analysis of FEV1 levels, sweat chloride levels, CFQ-R RD and their respective changes from baseline in heterozygous F508 del CF patients

Author, year	Time of assessment (week)	Absolute change from baseline in percentage of predicted FEV1- (Symdeko)	Absolute change from baseline in percentage of predicted FEV1- points. (Placebo)	Absolute change from baseline in percentage of predicted FEV1 mean value treatment (Trikafta)	Least square mean change (95% CI) in FEV1 (difference from baseline)	Absolute change from baseline in sweat chloride (mmol/liter) treatment (Symdeko)	Absolute change from baseline in sweat chloride (mmol/liter) treatment (Placebo)	Absolute change from baseline in sweat chloride (mmol/liter) treatment (Trikafta)	Least square mean change (95% CI) in sweat chloride (difference)	Absolute change from baseline in CFQ-R RD score (Symdeko)	Absolute change from baseline in CFQ-R RD score (Placebo)	Absolute change from baseline in CFQ-R RD score (Trikafta)	Least square mean change (95% CI) in CFQ-R RD score (difference)	Conclusion
Taylor-Cousar et al., ²¹ (2017)	24	3.4±0.7	-0.6±0.7	NA	4	-9.9±1	0.2±1	NA	-10.1	5±1.5	-0.1±1.5	NA	5.1	The combination of TEZ/IVA was efficacious and safe
Rowe et al., ¹² (2017)	8	11.1±2.4	4.7±1	NA	6.8	-9.5±2.2	-4.5±2.2	NA	-9.5	11.1±2.4	9.7±2.5	NA	11.1	TEZ/IVA therapy was efficacious
Mundk et al., ²² (2020)	12	1±1.2	-0.1±1.2	NA	1.2	-4.7±1.9	-1.2±1.9	NA	-3.5	5.9±1.2	-0.1±1.2	NA	2.1	TEZ/IVA was efficacious and safe
Middleton et al., ²³ (2019)	24	NA	-0.4±1.1	13.9±1.1	14.3	NA	-0.4±1.8	-42.2±1.8	-41.8	NA	-2.7±1.9	17.5±1.9	20.1	ELX/TEZ/IVA was efficacious in patients with CF

CI: confidence interval, ELX/TEZ/IVA: elxacaftor/tezacaftor/ivacaftor, CF: cystic fibrosis, NA: not applicable, FEV1: forced expiratory volume in one second, CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain

Meta-analysis for FEV1, Sweat Chloride and CFQ-R RD Score

Results showed that the mean change from the baseline level of FEV1 in patients who were heterozygous for the F508 deletion was significantly greater ($P = 0.0123$) in the Symdeko treated group, compared to the placebo treated group, with an overall effect size, $Z=2.5040$, and a pooled mean difference of 3.83 [95% confidence interval (CI): 0.83; 6.82] (Figure 3). The data were found to be significantly heterogeneous ($I^2=99\%$; $P < 0.01$) with overall effect size, $Z=-0.6479$; $P = 0.517$. On the other hand, a significant increase in the mean absolute change from baseline value of FEV1 was observed in patients heterozygous for the F508 deletion treated with Trikafta, as compared to placebo-treated patients, with overall effect size $Z=130.483$, $P < 0.001$ (Figure 4).

In patients homozygous for the F508 deletion, the mean change from baseline value of FEV1 was found to be significantly increased in patients treated with Symdeko as compared to the placebo-treated group (Figure 5) with overall effect size, $Z=11.2006$; $P < 0.0001$. Furthermore, a significantly lower mean difference from baseline in the value of FEV1 level was observed in patients homozygous for the F508 deletion after treatment with Symdeko, compared to Trikafta, with an overall effect size of $Z=-39.7555$, $P < 0.0001$. The data was found to be homogeneous ($I^2=0\%$; $P = 1.00$), with a pooled mean difference of -10.00 (95% CI: -10.49; -9.51) (Figure 6).

The mean change from the baseline value of sweat chloride was found to be significantly ($P = 0.0019$) decreased in patients heterozygous for the F508 deletion receiving Symdeko compared to the group receiving placebo, with an overall effect size, $Z=-3.1003$, and a pooled mean difference of -6.21 (95% CI: -10.14; -2.28). The data were found to be significantly heterogeneous with $I^2=100\%$, $P < 0.01$ (Figure 7). The mean absolute change in sweat chloride from baseline was found to be significantly lower in patients with heterozygous for F508 deletion receiving Trikafta compared to placebo (Figure 8), with overall effect size: $Z=-233.0850$; $P < 0.0001$.

In patients with a homogeneous genotype for F508 deletion, a significant increase in the mean difference from baseline of sweat chloride was observed after treatment with Symdeko compared to placebo (Figure 9), with overall effect size, $Z=26.7201$, $P < 0.0001$. There was a significantly higher mean change from baseline sweat chloride values in patients homozygous for the F508 deletion receiving Symdeko compared to Trikafta, with a pooled mean difference of 43.88 (95% CI: 41.63, 46.13) (Figure 10) and overall effect size, $Z=38$, $P = 0.9673$. The data were found to be homogeneous; $I^2=0\%$; $P = 0.45$.

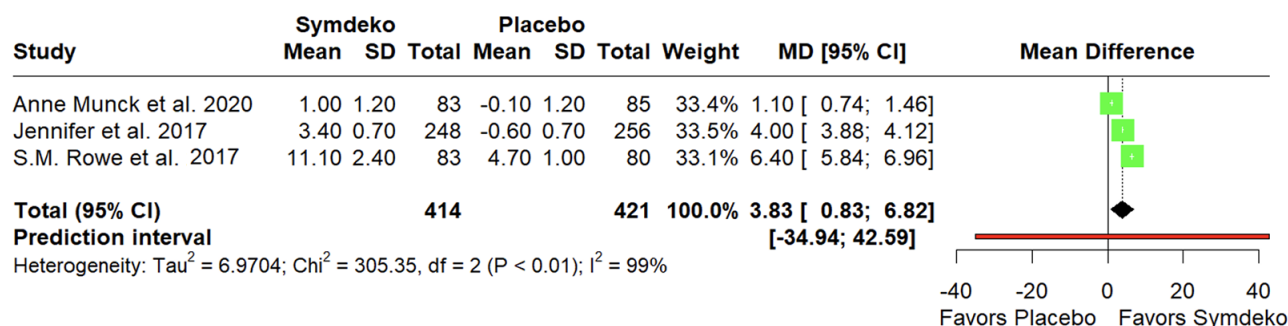


Figure 3. No significant mean difference in FEV1 level was observed in patients with heterogenous for F508 deletion receiving Symdeko or placebo
SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

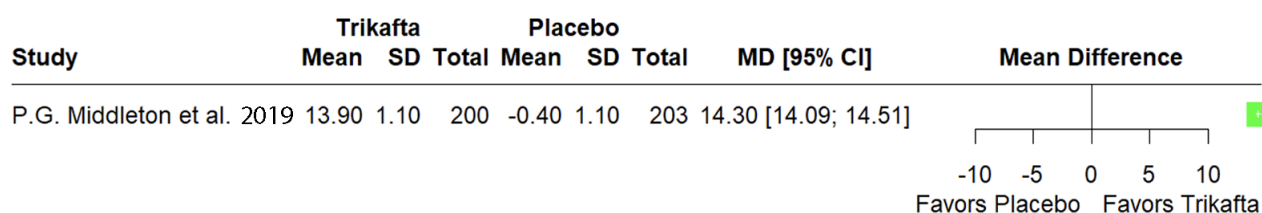


Figure 4. Significant mean difference in absolute change in FEV1 level from baseline was observed in patients with heterogenous for F508 deletion receiving Trikafta compared to placebo

SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

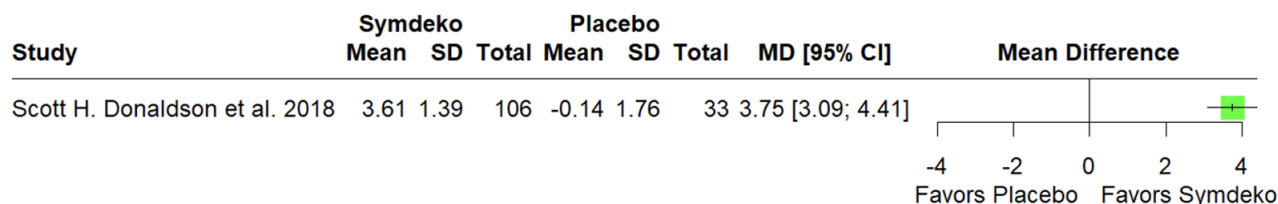


Figure 5. No significant mean difference in FEV1 level was observed in patients with homogenous for F508 deletion receiving Symdeko or placebo
SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

In patients heterozygous for F508 deletion receiving Symdeko, the mean change from baseline in CFQR value was found to be significantly increased compared to placebo, with an overall effect size, $Z=2.9937$, $P = 0.0028$, and a pooled mean difference of 4.19 (95% CI: 1.45; 6.93) (Figure 11). The data was found to be homogeneous ($I^2=0\%$; $P = 0.46$) with overall effect size, $Z=0.4164$; $P = 0.6771$. Furthermore, a significant increase in the mean absolute change of CFQR in patients receiving Trikafta from baseline was observed compared to placebo (Figure 12), with overall effect size, $Z=106.7108$; $P < 0.001$.

In patients homozygous for F508 deletion, the mean change from baseline value of CFQR was found to be significantly increased in patients receiving Trikafta, compared to Symdeko, with pooled mean difference of -16.52 (95% CI: -17.97; -15.07) (Figure 13) and overall effect size $= -22.3503$, $P < 0.0001$. The data was found to be heterogeneous ($I^2=65\%$, $P = 0.09$).

Adverse Events

Each study included in the review evaluated the adverse events experienced by the participants during the respective treatment interventions. In a phase 3 randomized, double-blind, multicenter, placebo-controlled trial conducted by Taylor-Cousar et al.²¹ adverse events were observed in the treatment group of heterozygous F508del patients receiving TEZ 100 mg once daily and IVA 150 mg every 12 hours. The reported adverse events included infective pulmonary exacerbation of CF, cough, headache, nasopharyngitis, increased sputum production, pyrexia, hemoptysis, oropharyngeal pain, and fatigue. Similar adverse events were reported by Rowe et al.¹², who conducted a phase 3 trial involving heterozygous F508del patients receiving TEZ and IVA. In a similar study conducted by Munck et al.,²² with heterozygous F508del patients receiving TEZ and IVA, the reported adverse events included cough, fatigue, hemoptysis, and increased sputum production. Middleton et al.²³ evaluated the triple combination treatment and reported

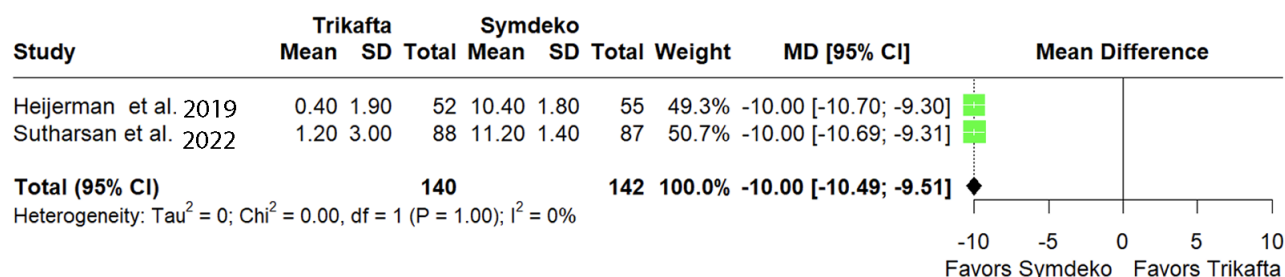


Figure 6. No significant mean difference in FEV1 level was observed in patients with homogenous for F508 deletion receiving Symdeko or Trikafta
SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

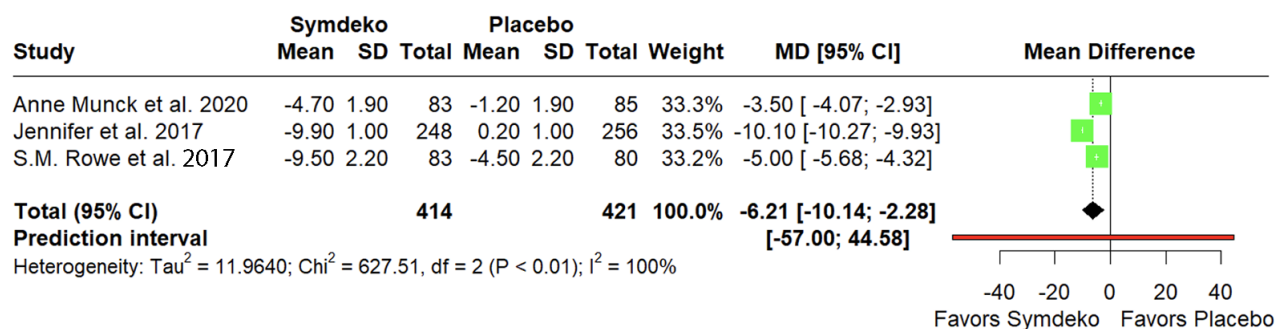


Figure 7. Significant mean difference in sweat chloride level was observed in patients with heterogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, MD: mean difference

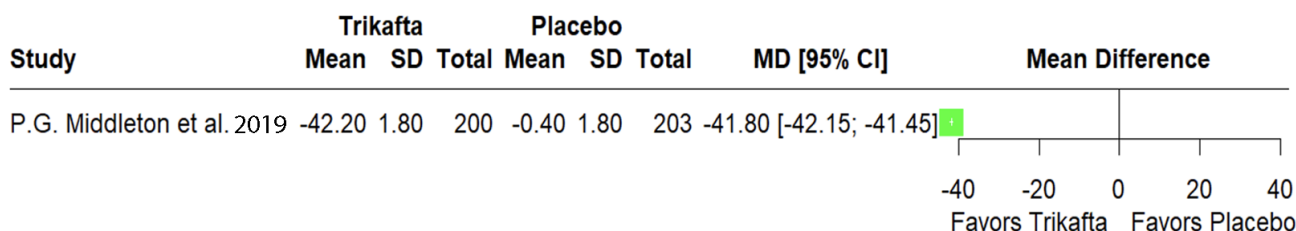


Figure 8. Significant mean difference in absolute change in sweat chloride level from baseline was observed in patients with heterogenous for F508 deletion receiving Trikafta compared to placebo

SD: standard deviation, CI: confidence interval, MD: mean difference

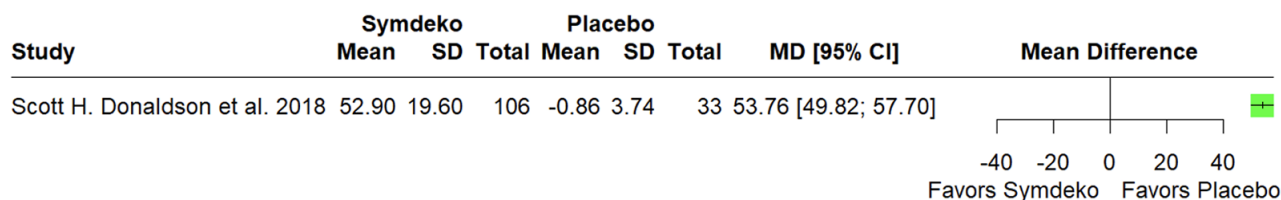


Figure 9. Significant mean difference in sweat chloride level was observed in patients with homogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, MD: mean difference

an increase in sputum production, as well as the occurrence of headache, cough, diarrhea, upper respiratory tract infection, nasopharyngitis, oropharyngeal pain, hemoptysis, and fatigue.

In the phase 2 randomized, placebo-controlled study by Donaldson et al.⁹, adverse events were observed in the homozygous F508del patient group receiving TEZ and IVA. These adverse events included infective pulmonary

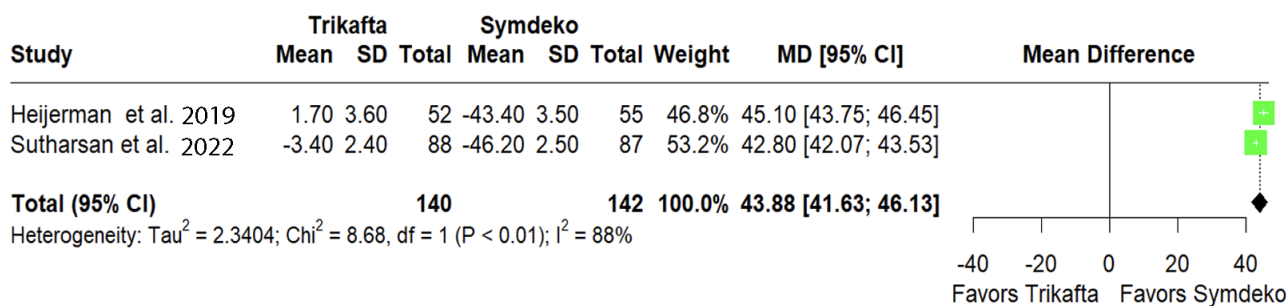


Figure 10. Significant mean difference in sweat chloride level was observed in patients with homogenous for F508 deletion receiving Symdeko or Trikafta

SD: standard deviation, CI: confidence interval

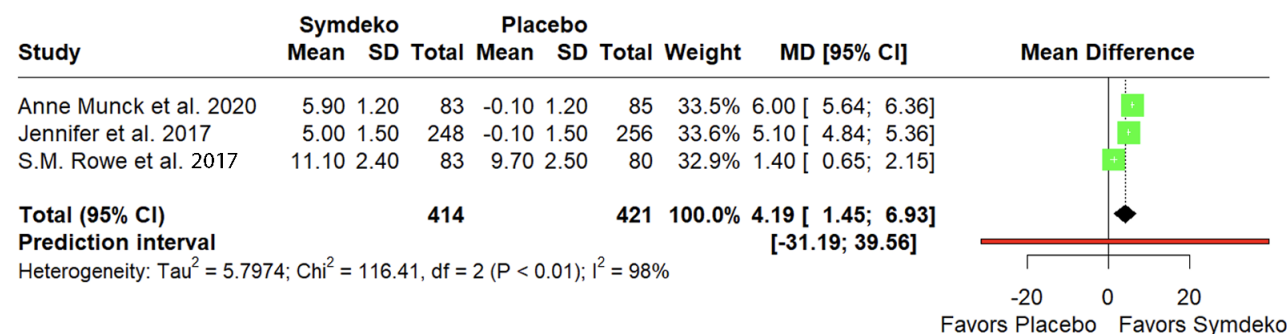


Figure 11. Significant mean difference in CFQ-R level was observed in patients with heterogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, MD: mean difference

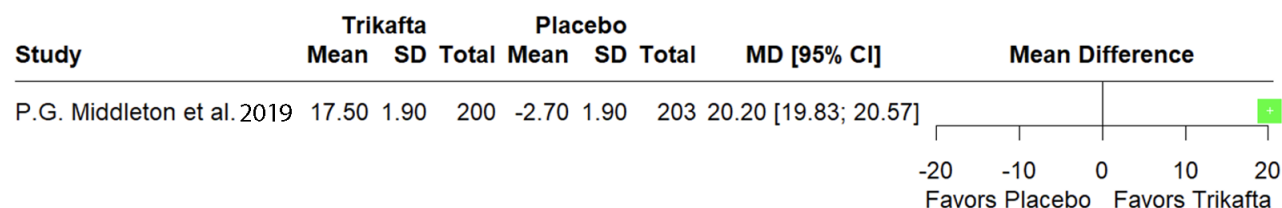


Figure 12. Significant mean difference in absolute change in CFQ-R level from baseline was observed in patients with heterogenous for F508 deletion receiving Trikafta compared to placebo

SD: standard deviation, CI: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised

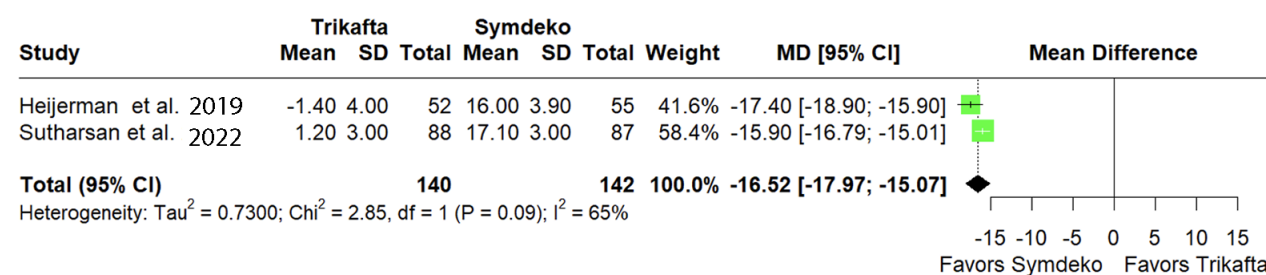


Figure 13. Significant mean difference in CFQ-R level was observed in patients with homogenous for F508 deletion receiving Symdeko or Trikafta

SD: standard deviation, CI: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, MD: mean difference

exacerbation of CF, cough, headache, increased sputum, fatigue, nausea, and diarrhea. Heijerman et al.²⁴ conducted a phase 3 multicentre trial to test triple combination therapy of TEZ, IVA, and ELX. The adverse events included cough, nasopharyngitis,

oropharyngeal pain, upper respiratory tract infection, headache, and hemoptysis. Similarly, Sutharsan et al.²⁵ reported headache, nasopharyngitis, cough, oropharyngeal pain.

Table 3. Comparative analysis of FEV1 levels, sweat chloride levels, CFQ-R RD and their respective changes from baseline in homozygous F508 del cystic fibrosis patients

Author, year	Time of assessment (week)	Absolute change from baseline in percentage of predicted FEV1 mean value treatment (Symdeko)	Absolute change from baseline in percentage of predicted FEV1 mean value treatment (Trikafta)	Least square mean change (95% CI) in FEV1 (difference from baseline)	Absolute change from baseline in sweat chloride (mmol/litre) treatment (Symdeko)	Absolute change from baseline in sweat chloride (mmol/litre) treatment (Trikafta)	Least square mean change (95% CI) in sweat chloride (difference)	Absolute change from baseline in CFQ-R RD score (Symdeko)	Absolute change from baseline in CFQ-R RD score (Trikafta)	Least square mean change (95% CI) in CFQ-R RD score (difference)	Conclusion
Heijerman et al., ²⁴ (2019)	4	0.4±1.9	10.4±1.8	10	1.7±3.6	-43.4±3.5	-45.1	-1.4±4	16±3.9	17.4	ELX/TEZ/IVA provided clinically robust benefit vs. TEZ/IVA alone with a favourable safety profile
Sutharsan et al., ²⁵ (2022)	24	1.2±3	11.2±1.4	10.2	-3.4±2.4	-46.2±2.5	-42.8	1.2±3	17.1±3	17.1	ELX/TEZ/IVA improved lung function and quality of life
Donaldson et al., ⁹ (2018)	4	3.61±1.39	NA	3.61	52.9±19.6	NA	-2.63	NA	NA	3.79	Improved lung function in TEZ/IVA regimen

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain, CI: confidence interval, NA: not applicable, ELX/TEZ/IVA: elxacaftor/tezacaftor/ivacaftor, FEV1: forced expiratory volume in one second

Table 1 summarizes baseline characteristics, dosage, and adverse events reported in the included studies. Table 2 shows comparative analysis of FEV1 levels, sweat chloride levels, CFQ-R RD scores and their respective changes from baseline in heterozygous F508 del CF patients, while Table 3 depicts the same for homozygous F508 del CF patients.

DISCUSSION

The present systematic review aimed to evaluate the comparative effects of TEZ/IVA and ELX/TEZ/IVA on FEV1 levels, sweat chloride concentration, and CFQ-R RD scores, in patients with heterozygous and homozygous F508del CF.

Recent studies comparing the new ELX/TEZ/IVA regimen with older regimens have reported significantly better efficacy of ELX/TEZ/IVA therapy. A recent study on the assessment of blood proteome in patients treated with lumacaftor/IVA (LUM/IVA) vs. ELX/TEZ/IVA therapy reported that ELX/TEZ/IVA is more effective in regulating innate-immune responses, resulting in decreased inflammation both in the airways and throughout the body. This decrease in systemic and airway inflammation is crucial because chronic inflammation contributes significantly to disease progression in CF, exacerbating tissue damage and promoting recurrent infections. By attenuating inflammation more effectively than LUM/IVA or TEZ/IVA, ELX/TEZ/IVA presents a dual benefit in both correcting CFTR function and reducing the inflammatory burden.²⁶

The studies included in the present meta-analysis have shown that ELX/TEZ/IVA produces improvements in FEV1 (typically 10-14% increases from baseline), which is greater than the FEV1 improvements achieved with TEZ/IVA alone (approximately 4-6% increases from baseline).²³ This improvement in lung function reflects not only enhanced chloride ion transport but also a likely reduction in mucus viscosity and an overall improvement in airway clearance. Additionally, ELX/TEZ/IVA has been linked to notable reductions in pulmonary exacerbations, hospitalizations, and antibiotic use, highlighting its efficacy in mitigating respiratory complications commonly experienced by CF patients.²⁴

Another critical measure in CF therapy efficacy is the reduction in sweat chloride levels, which serves as a direct indicator of CFTR function. ELX/TEZ/IVA achieves an average decrease in sweat chloride levels of around 40-45 mmol/L, considerably greater than the 30 mmol/L reduction typically observed with TEZ/IVA therapy.²¹ This larger absolute decrease in sweat chloride corroborates the higher efficacy of ELX/TEZ/IVA in addressing the underlying CFTR defect and aligns with its broader clinical benefits.

In the current study, ELX/TEZ/IVA appears to have a greater impact on sweat chloride reduction and FEV1 levels compared to TEZ/IVA, as indicated by the larger absolute changes reported in the studies. The observed improvements in CFQ-R scores with TEZ/IVA and ELX/TEZ/IVA treatments indicate the beneficial impact of these treatments on the patients' respiratory well-being. While both treatments showed improvements, ELX/TEZ/IVA demonstrated slightly better results in the studies reviewed.

The findings from these clinical trials indicate that the combination therapies of TEZ, IVA, and ELX are generally well-tolerated across diverse patient populations, including those homozygous and heterozygous for the F508del mutation. While adverse events such as cough, nasopharyngitis, fatigue, and headache were frequently reported, they were largely manageable and consistent with the underlying respiratory manifestations of CF. General symptoms like fatigue and headache were consistently noted across trials, alongside occasional reports of pyrexia, which were also manageable. Hemoptysis, a serious but less frequent event, was reported in several studies, along with oropharyngeal pain and nasal congestion. While most trials showed similar profiles of adverse events, variations in their frequency were observed depending on the phase of the study, sample size, and whether the patients were homozygous or heterozygous for the F508del mutation. Three studies reported the incidence of infective pulmonary exacerbation of CF for which the physicians should prescribe necessary medications. The similarity in adverse event profiles across study phases and populations suggests that both therapies have a predictable and manageable safety profile. However, the presence of gastrointestinal symptoms like nausea and diarrhea in some trials highlights the need to further explore strategies to mitigate these effects. Overall, the results support the use of these therapies as an effective treatment option for CF.

The observed differences in the effects of TEZ/IVA and ELX/TEZ/IVA on FEV1 levels in heterozygous F508del CF patients may be attributed to variations in the mechanisms of action and drug compositions. TEZ/IVA, which combines IVA and TEZ, has shown consistent improvements in FEV1 levels across multiple studies. This may be due to the dual action of IVA on the gating defect caused by the G551D mutation and the residual function mutation caused by the F508del allele.²⁷ TEZ, on the other hand, acts as a corrector by improving CFTR protein processing and trafficking. ELX/TEZ/IVA, a combination therapy containing ELX, TEZ, and IVA, has demonstrated superior efficacy in improving FEV1 levels compared to TEZ/IVA. This may be attributed to the additional action of ELX, which is a potent corrector that enhances the processing and trafficking of CFTR proteins. The presence of ELX in ELX/TEZ/IVA may provide a more comprehensive and effective treatment approach, leading to greater improvements in lung function.

The observed differences in the effects of TEZ/IVA and ELX/TEZ/IVA on FEV1 levels, sweat chloride concentration, and CFQ-R RD scores in patients with F508del CF may be attributed to variations in their compositions, mechanisms of action, and the presence of additional components in ELX/TEZ/IVA. ELX/TEZ/IVA with its triple combination therapy provides greater improvements in lung function and sweat chloride reduction compared to TEZ/IVA, particularly in heterozygous F508del CF patients. However, both treatments demonstrate positive effects in improving the respiratory symptoms and quality of life of CF patients.

The present systematic review has some limitations that should be considered when drawing conclusions. The effects of ELX/TEZ/IVA were not fully reported in all studies. Further studies on ELX/TEZ/IVA regimens are needed to ensure concrete results.

Moreover, the duration of treatment varied among the included studies, ranging from short-term evaluations to longer-term assessments. The limited availability of long-term data restricts our understanding of the sustained benefits or potential adverse effects associated with the different treatment options. The number of trials comparing head-to-head ELX/TEZ/IVA to TEZ/IVA is few. Some aspects such as emotional adverse effects should be further studied as this aspect was not compared between the two drugs. Further research with extended follow-up periods is necessary to better evaluate the long-term efficacy and safety profiles of these treatments.

CONCLUSION

The systematic review demonstrates that both TEZ/IVA and ELX/TEZ/IVA have shown improvements in FEV1 levels, sweat chloride levels, and CFQ-R RD scores in homozygous F508del CF patients. ELX/TEZ/IVA consistently exhibited significant improvements across all measured parameters. For both heterozygous and homozygous F508del CF patients, TEZ/IVA and ELX/TEZ/IVA demonstrated positive impacts on lung function, with ELX/TEZ/IVA showing slightly better results. Further research with larger sample sizes, standardized study designs, and longer-term follow-up is needed to confirm these findings and gain a more comprehensive understanding of the comparative effectiveness and safety profiles of these treatments.

Ethics

Footnotes

Authorship Contributions

Concept: M.A.K., Design: M.A.K., Data Collection or Processing: K.H., Analysis or Interpretation: S.K., A.G., Literature Search: K.H., Writing: S.K., A.G.

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