Efficacy and Safety of Triple Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Patients With Cystic Fibrosis: A Meta-Analysis of Randomized Controlled Trials

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Background: Cystic fibrosis is a rare, recessive, progressive genetic disease caused by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Small molecules have recently been developed to treat the molecular consequences of CFTR mutations and restore CFTR protein function. However, the data on triple combination therapy (mainly from Vertex Pharmaceuticals, which is most tested in clinical trials) are limited. This meta-analysis was aimed to assess the efficacy and safety of this therapy according to different mutation genotypes and comparators.

Methods: Relevant publications were identified through searching several medical databases before 31 December 2021. The primary outcomes of ppFEV₁, sweat chloride concentration and Cystic Fibrosis Questionnaire-Revised (CFQ-R) score were pooled and analyzed. The secondary outcomes were adverse events in triple combination therapy.

Results: Six randomized controlled trials were eligible for analysis. The total outcome of the ppFEV₁ change was higher with triple combination therapy than triple placebo or active control (mean difference, MD, 13.6% and 8.74%, respectively). The pooled result of sweat chloride concentrations with triple combination therapy was lower than that of triple placebo or active control (MD, −44.13 and −39.26, respectively). The pooled estimate of the CFQ-R score was higher with triple combination therapy than triple placebo or active control (MD, 19.8% and 14.63%, respectively). No clear differences in adverse events were found between triple combination therapy and the control (placebo or active control).

Conclusion: CFTR modulators in triple combination achieve better clinical results than placebo and active control, and result in comparable adverse events.

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INTRODUCTION

Cystic fibrosis (CF) is a rare autosomal recessive, progressive genetic disease caused by dysfunction of the CF transmembrane conductance regulator (CFTR) protein. CFTR is responsible for transporting anions, such as chloride and bicarbonate, and is located at the apical surfaces of epithelial cells. If the quantity and/or function of CFTR is diminished, loss of chloride secretion and deficient fluid transport result (Habib et al., 2019), thus ultimately inducing abnormal mucus secretion and multiorgan dysfunction, including pancreatic insufficiency and airway infection and obstruction (Elborn, 2016). The chronic airway impairment leads to progressive lung damage and respiratory failure, and eventually premature death (Heijerman et al., 2019).

Biallelic mutations in CFTR genes cause CF, and more than 2000 genetic variants have been found. The most common mutation is the p.Phe508del CFTR mutation, which is found in 90% of caucasian population (Habib et al., 2019). The p.Phe508del CFTR mutation causes severe dysfunction in CFTR processing and trafficking, thus limiting the quantity and function of CFTR at the cell surface (Dalemans et al., 1991). Nearly 50% of patients have homozygous p.Phe508del CFTR mutations (p.Phe508del-p.Phe508del genotype, F/F), and almost 33% have heterozygous minimal-function CFTR mutations (p.Phe508del minimal-function, F/MP). Another category of CFTR mutations resulting in lesser impairment of CFTR protein activity is residual function mutations (RF), including some genetic mutations associated with the CFTR protein channel-gating defects, denoted gating mutations (Barry et al., 2021). Most patients with these residual function (F/RF) or gating (F-gating) CFTR mutations are heterozygous for the p.Phe508del mutation (Barry et al., 2021).

Recently, small molecules have been developed to treat the molecular consequences of CFTR mutations and restore CFTR protein function (Davies et al., 2018; Keating et al., 2018; Heijerman et al., 2019; Middleton et al., 2019; Barry et al., 2021). Generally, the modulators can be classified as CFTR potentiators (e.g., ivacaftor), which augment the gating of mutant CFTR protein, or first-generation CFTR correctors (e.g., lumacaftor and tezacaftor), which aid in processing and trafficking of the protein to the cell surface (Heijerman et al., 2019; Barry et al., 2021). A single modulator regimen (CFTR potentiator) (Ramsey et al., 2011; De Boeck et al., 2014) or a combination of two modulator regimens (Boyle et al., 2014; Rowe et al., 2017) (CFTR potentiator and CFTR corrector) has been found to ameliorate sweat chloride, lung function, respiratory-related quality of life, bodyweight, and pulmonary exacerbation. However, neither of these treatments fully restores function to the p.Phe508del CFTR protein. Therefore, more effective CFTR modulations are needed to treat the underlying cause of CF (Davies et al., 2018).

Recently, a next-generation corrector [VX-659 or elexacaftor (previously known as VX-445)] with a different structure and mechanism of action, has been found to increase CFTR processing, trafficking and function in vitro (Veit et al., 2020; Becq et al., 2022). The combination of a next-generation corrector and tezacaftor increases the efficacy of CFTR function to a greater extent than either compound alone (Davies et al., 2018); moreover, ivacaftor further potentiates chloride transport. However, the data on triple combination therapy (next-generation corrector plus corrector plus potentiator) are limited. This meta-analysis examines current studies on triple combination therapy and assesses the available data in terms of efficacy and safety, according to different mutation genotypes and comparators.

METHODS

Study Search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Vrabel, 2009). The checklist is presented in Supplementary Table S1. The literature search was performed through PubMed, Web of Science and Cochrane Library on 31 Dec 2021. The search terms and queries are presented in Supplementary Table S2. This meta-analysis was registered at PROSPERO (CRD42021293402).

Study Selection and Eligibility Criteria

Relevant studies were collected, and duplicates were removed (identification). According to the titles and abstracts, we selected the studies relevant to our analysis for full-text review (screening). Studies were screened according to the inclusion and exclusion criteria. If multiple studies reported the same outcomes based on the same patient population or cases with any overlapping information, we included only the most informative study. An additional search was performed on the references of the included studies to further identify potentially eligible studies.

The inclusion criteria were as follows: 1) population: patients diagnosed with CF with at least one p.Phe508del CFTR mutation; 2) intervention: patients who underwent triple combination therapy (next-generation corrector plus corrector plus potentiator) for CF; 3) comparison: patients who underwent placebo treatment or active-control therapy; 4) outcomes: primary outcomes included the absolute change from baseline in predicted forced expiratory volume in 1 s (ppFEV₁), absolute change from baseline in sweat chloride concentration and absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score; secondary outcomes included adverse events; and 5) study design: randomized controlled trials (RCTs).

The exclusion criteria were as follows: 1) case reports or reviews; 2) single arm studies; 3) no reporting of outcomes of interest; 4) studies published in languages other than English; 5) preclinical studies or experiments in vitro.

Data Collection

A formalized table was independently used by Y.Z.W. and P.W.L to extract data from each paper. The following information was included: 1) authors; 2) publication year; 3) study design; 4)
setting (single center/multicenter); 5) enrollment period; 6) number of patients; 7) components of triple combination therapy; 8) components of active control therapy; 9) absolute change in ppFEV₁ (if dose differed, only data from the highest dose was collected); 10) absolute change in sweat chloride concentration (if dose differed, only data from the highest dose was collected); 11) absolute change in CFQ-R score (if dose differed, only data from the highest dose was collected); 12) any adverse events; and 13) p.Phe508del mutation type.

Assessment of the Risk of Bias in the Included Studies
Cochrane analysis was conducted to assess the risk of bias in the RCTs (Higgins and Green, 2013). Five aspects of bias (selection bias, performance bias, detection bias, attrition bias and reporting bias) were evaluated.

Statistical Analysis
RevMan 5.3 (Cochrane) was used for statistical analysis. The Mantel-Haenszel random effects model and risk ratio (RR) were used for binary results, and the inverse variance method was used for continuous outcomes (Higgins et al., 2003). I² was used to evaluate heterogeneity, and I² > 50% and p < 0.05 were considered thresholds for significant heterogeneity. All statistical values are reported with 95% confidence intervals (CIs). Subgroup analysis was conducted if the heterogeneity was significant.

RESULTS
Search Results
A total of 361 studies were found by searching the PubMed, Cochrane Library and Web of Science databases. The study flowchart is shown in Figure 1. A total of 133 duplicate studies were excluded, and an additional 196 studies were removed for reasons associated with the title, abstract and language. Thirty-two records were eligible for full text review. Two cases series or reports studies were excluded. Sixteen studies were excluded for being reviews or meeting abstracts. Four studies were excluded for overlapping patients or being single arm studies, and four studies were excluded for being preclinical studies or experiments. Finally, six RCTs were included in the final analysis (Davies et al., 2018; Keating et al., 2018; Heijerman et al., 2019; Middleton et al., 2019; Barry et al., 2021; Sutharsan et al., 2021), all of which were multicenter RCTs. The main characteristics of the included studies are shown in Table 1. Five included studies used the same triple combination therapy (Keating et al., 2018; Heijerman et al., 2019; Middleton et al., 2019; Barry et al., 2021; Sutharsan et al., 2021) (elexacaftor-tezacaftor-ivacaftor, ELX-TEZ-IVA), and one study (Davies et al., 2018) used VX659-TEZ-IVA as the triple combination therapy. Two studies (Davies et al., 2018; Keating et al., 2018) used triple placebo or active-control as the comparator, three studies used only active control as the comparator (Heijerman et al., 2019; Barry et al., 2021; Sutharsan et al., 2021), and one study used only triple placebo as the comparator (Middleton et al., 2019).
Methodological Quality of the Included Studies (Risk of Bias)

The results of the assessment of the included RCTs are provided in Supplementary Table S3. All studies reported five aspects of bias (selection bias, performance bias, detection bias, attrition bias and reporting bias). All risks of bias in the included studies were low; therefore, the overall quality of included studies was considered high.

Pooled Analysis of Primary Outcomes (ppFEV₁, Sweat Chloride Concentration and CFQ-R Score) With Triple Placebo Comparator and F/MF Mutation

The pooled estimate of the absolute change in sweat chloride concentration in the triple combination therapy group was significantly lower than that in the triple placebo group (MD, −44.13; 95% CI, −53.92 to −34.34); however, the heterogeneity was significantly high (I² = 97%, p < 0.001) (Figure 2B). Moreover, the pooled outcome of CFQ-R was much higher in the triple combination therapy group than the triple placebo group (MD, 19.8; 95% CI, 17.31–22.29), with relatively unclear heterogeneity (I² = 26%) (Figure 2C).

Pooled Analysis of Primary Outcomes (ppFEV₁, Sweat Chloride Concentration and CFQ-R Score) With Active Control Comparator and all Mutations and Subgroup Analysis of F/F Mutations

The pooled estimate of the absolute change in ppFEV₁ in the triple combination therapy group was significantly higher than that in the active group (MD, 8.74; 95% CI, 5.56–11.92), but the heterogeneity was significant (I² = 94%, p < 0.001) (Figure 3A). After the data from Barry et al. (Barry et al., 2021), containing F-gating or RF mutations, were omitted, subgroup analysis was conducted in patients with F/F mutations. The pooled estimate of ppFEV₁ in the triple combination therapy group was still higher than that in the active group (MD, 10.00; 95% CI, 9.09–10.92). Moreover, the heterogeneity became non-significant (I² = 0%) (Figure 3A).

The pooled estimate of the absolute change in sweat chloride concentration in the triple combination therapy group was clearly higher than that in the active group (MD, 10.00; 95% CI, 9.09–10.92). However, the heterogeneity became non-significant (I² = 0%) (Figure 3A).

| Author    | Year | Setting | Treatment duration | Triple therapy | Placebo/Active placebo | No. of patients included in analysis | Genotypes               |
|-----------|------|---------|-------------------|----------------|------------------------|-------------------------------------|-------------------------|
| Davies    | 2018 | Multicenter | 4 weeks           | VX-659(400 mg) | TEZ(100 mg) + IVA(300 mg) | 40                                  | F/MF and F/F            |
| Keating   | 2018 | Multicenter | 4 weeks           | VX-445(ELX)    | TEZ(100 mg) + IVA(300 mg) | 42                                  | F/MF and F/F            |
| Heijerman | 2019 | Multicenter | 4 weeks           | ELX(200 mg)    | TEZ(100 mg) + IVA(300 mg) | 55                                  | F/F                     |
| Middleton | 2019 | Multicenter | 24 weeks          | ELX(200 mg)    | TEZ(100 mg) + IVA(300 mg) | 200                                 | F/MF                    |
| Barry     | 2021 | Multicenter | 8 weeks           | ELX(200 mg)    | TEZ(100 mg) + IVA(300 mg) | 132                                 | F-gating/RF             |
| Sutharsan | 2021 | Multicenter | 24 weeks          | ELX(200 mg)    | TEZ(100 mg) + IVA(300 mg) | 87                                  | F/F                     |

aTEZ: tezacaftor.
bIVA: ivacaftor.
cF/MF: p.Phe508del-minimal function.
dF/F: p.Phe508del-p.Phe508del.
eELX: elexacaftor (VX-445)
fF-gating: p.Phe508del-gating.
gRF: p.Phe508del-residual function.

*TABLE 1 | The main characteristics of included studies.*
lower than that in the active group (MD, −39.26; 95% CI, −48.17 to −30.36), with clear heterogeneity ($I^2 = 97\%$, $p < 0.001$) (Figure 3B).

Subgroup analysis indicated that the pooled estimate of the sweat chloride concentration in the triple combination therapy group was lower than that in the active group in patients with F/F mutations (MD, −43.58; 95% CI, −45.84 to −41.32), and the heterogeneity was not clear ($I^2 = 46\%$) (Figure 3B).

The pooled outcome of the absolute change in CFQ-R in the triple combination therapy group was significantly higher than that in the active group in patients with F/F mutations (MD, 27.9%; 95% CI, 17.10 to 21.25), and the heterogeneity was significant ($I^2 = 73\%$, $p = 0.005$) (Figure 3C). Subgroup analysis was conducted in patients with F/F mutations, and the pooled estimate of CFQ-R in the triple combination therapy group was still clearly higher than that in the active group (MD, 27.9%; 95% CI, 17.10 to 21.25). In addition, the heterogeneity became non-significant ($I^2 = 0\%$) (Figure 3C).

### Adverse Events Between the Triple Combination Therapy Group and Placebo/Active Control Group

The pooled incidence of any adverse events in the triple combination therapy group was nearly the same as that in the placebo group (RR, 0.96; 95% CI, 0.92 to 1.01), with insignificant heterogeneity ($I^2 = 0\%$) (Figure 4A). Similarly, the pooled incidence of any adverse events in the triple combination therapy group was equivalent to that in the active group (RR, 0.98; 95% CI, 0.90 to 1.06), without clear heterogeneity ($I^2 = 0\%$) (Figure 4B).

Most of these adverse events were considered mild or moderate in the triple combination therapy group and placebo/active control group (Tables 2, 3). Furthermore, no clear differences were observed in adverse events leading to discontinuation of the trial regimen among the patients in the triple combination therapy group and placebo/active control group.
FIGURE 3 | Forest plots of the included studies evaluating the efficacy of triple combination therapy vs. active control with all mutations and subgroup analysis of F/F mutations. (A) ppFEV₁. (B) Sweat chloride concentration. (C) CFQ-R respiratory domain score.
The most common adverse events were cough, infective pulmonary exacerbation of CF, headache, oropharyngeal pain, sputum increased and hemoptysis, which showed no clear difference between the triple combination therapy group and placebo/active control group (Tables 2, 3).
TABLE 3 | Adverse event for active control with all mutation genotype.

| Adverse event | Davies (N = 18) | Keating (N = 21) | Heijerman (N = 7) | Barry (N = 55) | Sutharsan (N = 68) |
|---------------|-----------------|-----------------|------------------|---------------|-------------------|
| Number of patients (percent) | Triple therapy | Active control | Triple therapy | Active control | Triple therapy | Active control | Triple therapy | Active control | Triple therapy | Active control |
| Any adverse event | 15 (83) | 9 (82) | 19 (90) | 5 (71) | 32 (58) | 33 (63) | 88 (66.7) | 83 (65.9) | 77 (89) | 81 (92) |
| Maximum severity of adverse event | Mild | 7 (47) | 2 (22) | 10 (53) | 2 (40) | 21 (40) | 58 (43.9) | 50 (39.7) | 48 (55) | 46 (52) |
| | Moderate | 6 (40) | 4 (44) | 8 (42) | 2 (40) | 11 (21) | 25 (18.9) | 29 (23.0) | 22 (25) | 28 (32) |
| | Severe | 2 (13) | 3 (23) | 1 (5) | 1 (20) | 0 | 1 (2) | 5 (3.8) | 4 (3.2) | 7 (8) | 7 (8) |
| Serious adverse event | 1 (6) | 2 (18) | 0 | 1 (14) | 2 (4) | 1 (2) | 5 (3.8) | 11 (8.7) | 5 (6) | 14 (18) |
| Adverse event leading to discontinuation of the trial regimen | 0 | 0 | 1 (5) | 1 (14) | 0 | 0 | 1 (0.8) | 2 (1.8) | 2 (2) | 1 (1) |
| Most common adverse events | Cough | 4 (22) | 2 (18) | 7 (33) | 1 (14) | 8 (15) | 4 (8) | 3 (2.3) | 18 (14.3) | 11 (13) | 23 (26) |
| | Infective pulmonary exacerbation of cystic fibrosis | 5 (28) | 3 (27) | 5 (24) | 1 (14) | 1 (2) | 6 (12) | 3 (2.3) | 13 (10.3) | 10 (11) | 36 (41) |
| | Headache | 3 (17) | 0 | NA | NA | 3 (5) | 4 (8) | 11 (8.3) | 19 (15.1) | 25 (29) | 18 (20) |
| | Oropharyngeal pain | 2 (11) | 0 | NA | NA | 4 (7) | 0 | NA | NA | 11 (13) | 7 (8) |
| | Sputum increased | 3 (17) | 1 (9) | 8 (38) | 0 | NA | NA | NA | 10 (11) | 16 (18) |
| | Hemoptysis | NA | NA | 3 (14) | 0 | 2 (4) | 5 (10) | NA | NA | NA | NA |

DISCUSSION

Previous studies have revealed that monotherapy (ivacaftor), compared with placebo, improved the ppFEV₁ in patients with Gly551Asp gating mutations (Ramsay et al., 2011). Subsequent studies have indicated that double combination therapy (corrector and potentiator, such as tezacaftor and ivacaftor), relative to placebo, improved ppFEV₁, sweat chloride concentration and CFQ-R (Taylor-Cousar et al., 2017). However, not all double combination therapies have been found to effectively result in improvements in patients. Lumacaftor and ivacaftor slightly increased the ppFEV₁ in patients with p.Phe508del homozygous mutation (Boyle et al., 2014; Wainwright et al., 2015), whereas no clinical benefits have been observed for patients with p.Phe508del heterozygous mutation (Boyle et al., 2014). A potential treatment rationale is that if the second mutation is responsive to ivacaftor alone, then double combination therapies may provide benefits (Meoli et al., 2021). Because the mechanism of the next-generation corrector differs from that of tezacaftor, the hypothesis that triple combination therapy would restore CFTR protein function has been suggested. In this meta-analysis, triple combination therapy was found to increase ppFEV₁ by 13.6% relative to triple placebo in patients with F/MF mutations, with almost no heterogeneity. In the therapy group, as compared with the active control group, the ppFEV₁ also markedly increased, by 8.74%; however, the heterogeneity was significant across studies. Clearly heterogeneous data came from Barry et al. (2021). After removal of the data from Barry et al., the heterogeneity of the pooled results clearly decreased. The CFTR mutations in Barry’s study were F-gating/RF, which are relatively less responsive to triple combination therapy. Sweat chloride concentration is the standard indicator of CFTR function (Middleton and Taylor-Cousar, 2021). The pooled sweat chloride concentration under triple combination therapy was much lower than that under triple placebo, thus indicating that triple therapy significantly restored the function of CFTR. Although the heterogeneity clearly came from Davies et al. (2018), the sweat chloride concentration in that study was much lower than those in the other two studies (Keating et al., 2018; Middleton et al., 2019). The next-generation corrector used in Davies et al. (2018) was VX659, and the effective data were extracted from the highest dose group (VX659 400 mg + TEZ + IVA), in contrast to Keating et al. (2018) and Middleton et al. (2019) (ELX 200 mg + TEZ + IVA). We attempted to use the data from a similar dose group (VX659 240 mg + TEZ + IVA) to decrease the heterogeneity; however, clear heterogeneity was still observed ($I^2 = 91\%$). Because the baseline demographic characteristics in the three patients were similar, the potential reason for the significant heterogeneity might have been that the structure and mechanism of VX659 differed from those of ELX. Fortunately, the presented effects VX659 were favorable for the patients. More studies are needed in the future to elucidate the specific mechanistic differences between VX659 and ELX. Similarly, triple combination therapy, in contrast to the active control, greatly decreased the pooled concentration of sweat chloride. The heterogeneity among studies might be explained by the data from Barry et al. (2021), which included F-gating/RF mutations. After exclusion of the heterogeneous data, the pooled results for sweat chloride concentration had only slight heterogeneity.

The CFQ-R respiratory domain score was used to evaluate the quality of life of patients with CF. The pooled results of the CFQ-R respiratory domain scores in the triple therapy combination were more satisfactory than those in the triple placebo group. Moreover, the consistency across studies was acceptable. The pooled estimate was also higher in the triple therapy combination group than the active control group; however, the data from Barry et al. (2021)
clearly differed because of the inclusion of patients with F-gating/RF mutations. The heterogeneity decreased to insignificance in patients with only F/F mutations, and the pooled results were also elevated slightly.

Beyond the prominent benefits of the triple therapy combination, the safety was also favorable, as compared with that of placebo or active control, regardless of gene mutation type. The adverse events in the triple therapy combination group were nearly the same as those in the placebo or active control groups, with almost no heterogeneity. The specific adverse events (cough, infective pulmonary exacerbation, oropharyngeal pain, headache and increased sputum) were also similar between the triple therapy combination group and triple placebo or active control groups. Moreover, no dose-responsive relationship in adverse events was seen with the triple therapy combination (Davies et al., 2018; Keating et al., 2018). Overall, the safety of the triple therapy combination was similar to that in previous studies of CFTR modulators (Wainwright et al., 2015; Rowe et al., 2017; Taylor-Cousar et al., 2017). Hence, triple therapy combination appeared to achieve efficacy and safety simultaneously.

A recent systematic review about the efficacy and safety of CFTR modulators was conducted by Gramegna et al. (2020). The authors provided a comprehensive review of clinical results for monotherapy, dual combination and triple combination in CF patients with various genotypic mutations. They concluded that CF patients with one gating mutation receiving IVA can benefit mostly in lung function, moreover, CF patients with homozygous or heterozygous p.Phe508del receiving ELX/TEZ/IVA can benefit in lung function, pulmonary exacerbation decrease and symptom improvement (Gramegna et al., 2020). Due to the multiple mixed comparisons in Gramegna’s research, they only made qualitative synthesis. By contrast, a quantitative synthesis (meta-analysis) is conducted in this research, which could manifest a pooled estimate for efficacy and safety of triple therapy combination compared with placebo and active-control group. Moreover, the result of NCT04058353 (which was ongoing when Gramegna’s article published) is included in our meta-analysis, confirming triple combination could offer additional benefit relative to previous CFTR modulators (Barry et al., 2021).

To our knowledge, this study is the first meta-analysis evaluating the efficacy and safety of the triple therapy combination in treating CF. The strengths of this meta-analysis were as follows. First, all included studies were multicenter RCTs, thus minimizing bias within the studies. Second, the comparison was conducted according to the type of control group (triple placebo or active control) and the type of mutation (F/MF or F/F); hence, the heterogeneity among the studies was as low as possible. Third, no clear adverse events were found in the triple therapy combination group, thus providing a basis for larger RCTs in the future.

Despite the advantages of triple combination therapy, some limitations of this study should also be considered: First, all patients included in the studies were 12 years or older, and data on the safety and efficacy of triple therapy combination in patients younger than 12 years were limited. However, a recent phase 3 open-label study has indicated that the treatment was safe and efficacious in children 6–11 years of age with at least one F508del-CFTR allele, thus supporting its use in this patient population (Zemanick et al., 2021). Furthermore, if the triple therapy combination does not have any significant safety issues in younger patients, the therapy is likely to be commenced in children after newborn screening, before the development of clinical disease (Middleton and Taylor-Cousar, 2021). Second, the mutation types differed in the included studies with an active control group, thus resulting in clear heterogeneity. However, the final effects were consistent across the included studies, and the difference was only in the extent of response to the triple therapy combination. In fact, researchers expect highly effective therapeutics to be available for all patients with CF, regardless of their variants, in the near future (Middleton and Taylor-Cousar, 2021). Third, the results from the included studies were mostly short-term; however, two included studies (Middleton et al., 2019; Sutharsan et al., 2021) used triple therapy for a relatively long period (24 weeks). Additional long-term results remain necessary to confirm the results.

In conclusion, the triple therapy combination had highly significant efficacy and safety in treating CF, as compared with placebo or active control, for patients with F/F, F/MF, F/RF or F-gating mutations. More well-designed RCTs are needed to support the efficacy and safety, and extend the indications for younger patients diagnosed with CF, to achieve radical treatment for CF before the development of the disease.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

YW is responsible for writing manuscript BM is responsible for statistics WL is responsible for submission and data collection PL is responsible for the idea and data collection.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.863280/full#supplementary-material
