Cochrane Database of Systematic Reviews - - Cochrane Review

Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del)

Code: CD010966 **Year:** 2023 **Date:** 2014 - updated 3 DEC 2022 **Author:** Southern KW

Study design (if review, criteria of inclusion for studies)

RCTs of parallel design. Excl: quasi-randomised studies; cross-over studies.

List of included studies (34)

Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; McCarty 2002; PROGRESS 2017; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002;

Participants

Children or adults with CF, as confirmed either by the presence of two disease-causing mutations, or by a combination of positive sweat test and recognised clinical features of CF. Participants should have at least one class II mutation.

Interventions

CFTR correctors (drugs which aims to increase the amount of CFTR expressed at the epithelial cell apical membrane, by reducing or preventing degradation of CFTR by normal intracellular mechanisms) compared with either placebo or another intervention.

Outcome measures

Primary outcomes 1. Survival 2. Quality of life (QoL) measured using validated quantitative scales or scores 3. Physiological measures of lung function: FEV1, FVC. Secondary outcomes 1. Adverse effects 2. Hospitalisation 3. School or work attendance 4. Extra courses of antibiotics 5. Sweat chloride 6. Radiological measures 7. Acquisition of respiratory pathogens 8. Eradication of respiratory pathogens 9. Nutrition and growth (weight, BMI, height)

Main results

Authors included 34 RCTs (4781 participants), lasting between 1 day and 48 weeks; an extension of two lumacaftorâ€•ivacaftor studies provided additional 96â€•week safety data (1029 participants). Assessed eight monotherapy RCTs (344 participants) (4PBA, CPX, lumacaftor, cavosonstat and FDL169), 16 dualâ€•therapy RCTs (2627 participants) (lumacaftorâ€•ivacaftor or tezacaftorâ€•ivacaftor) and 11 tripleâ€•therapy RCTs (1804 participants) (elexacaftorâ€•tezacaftorâ€•ivacaftor/deutivacaftor; VXâ€•659â€•tezacaftorâ€•ivacaftor/deutivacaftor; VXâ€•440â€•tezacaftorâ€•ivacaftor; VXâ€•152â€•tezacaftorâ€•ivacaftor). Participants in 21 RCTs had the genotype F508del/F508del, in seven RCTs they had F508del/minimal function (MF), in one RCT F508del/gating genotypes, in one RCT either F508del/F508del genotypes or F508del/residual function genotypes, in one RCT either F508del/gating or F508del/residual function genotypes, and in three RCTs either F508del/F508del genotypes or F508del/MF genotypes. Risk of bias judgements varied across different comparisons. Results from 16 RCTs may not be applicable to all pwCF due to age limits (e.g. adults only) or nonâ€•standard designs (converting from monotherapy to combination therapy). Monotherapy - Investigators reported no deaths or clinically relevant improvements in quality of life (QoL). There was insufficient evidence to determine effects on lung function. No placeboâ€•controlled monotherapy RCT demonstrated differences in mild, moderate or severe adverse effects (AEs); the clinical relevance of these events is difficult to assess due to their variety and few participants (all F508del/F508del). Dual therapy - In a tezacaftorâ€•ivacaftor group there was one death (deemed unrelated to the study drug). QoL scores (respiratory domain) favoured both lumacaftorâ€•ivacaftor and tezacaftorâ€•ivacaftor therapy compared to placebo at all time points (moderateâ€•certainty evidence). At six months, relative change in forced expiratory volume in one second (FEV1) % predicted improved with all dual combination therapies compared to placebo (highâ€• to moderateâ€•certainty evidence). More pwCF reported early transient breathlessness with lumacaftorâ€•ivacaftor (odds ratio (OR) 2.05, 99% confidence interval (CI) 1.10 to 3.83; I2 = 0%; 2 studies, 739 participants; highâ€•certainty evidence). Over 120 weeks (initial study period and followâ€•up), systolic blood pressure rose by 5.1 mmHg and diastolic blood pressure by 4.1 mmHg with twiceâ€•daily 400 mg lumacaftorâ€•ivacaftor (80 participants). The tezacaftorâ€•ivacaftor RCTs did not report these adverse effects. Pulmonary exacerbation rates decreased in pwCF receiving additional therapies to ivacaftor compared to placebo (all moderateâ€•certainty evidence): lumacaftor 600 mg (hazard ratio (HR) 0.70, 95% CI 0.57 to 0.87; I2 = 0%; 2 studies, 739 participants); lumacaftor 400 mg (HR 0.61, 95% CI 0.49 to 0.76; I2 = 0%; 2 studies, 740 participants); and tezacaftor (HR 0.64, 95% CI 0.46 to 0.89; 1 study, 506 participants). Triple therapy - No study reported any deaths (highâ€•certainty evidence). All

other evidence was lowâ€• to moderateâ€•certainty. QoL respiratory domain scores probably improved with triple therapy compared to control at six months (six studies). There was probably a greater relative and absolute change in FEV1 % predicted with triple therapy (four studies each across all combinations). The absolute change in FEV1 % predicted was probably greater for F508del/MF participants taking elexacaftorâ€•tezacaftorâ€•ivacaftor compared to placebo (mean difference 14.30, 95% CI 12.76 to 15.84; 1 study, 403 participants; moderateâ€•certainty evidence), with similar results for other drug combinations and genotypes. There was little or no difference in adverse events between triple therapy and control (10 studies). No study reported time to next pulmonary exacerbation, but fewer F508del/F508del participants experienced a pulmonary exacerbation with elexacaftorâ€•tezacaftorâ€•ivacaftor at four weeks (OR 0.17, 99% CI 0.06 to 0.45; 1 study, 175 participants) and 24 weeks (OR 0.29, 95% CI 0.14 to 0.60; 1 study, 405 participants); similar results were seen across other triple therapy and genotype combinations.

Authors' conclusions

There is insufficient evidence of clinically important effects from corrector monotherapy in pwCF with F508del/F508del. Additional data in this review reduced the evidence for efficacy of dual therapy; these agents can no longer be considered as standard therapy. Their use may be appropriate in exceptional circumstances (e.g. if triple therapy is not tolerated or due to age). Both dual therapies (lumacaftorâ€•ivacaftor, tezacaftorâ€•ivacaftor) result in similar small improvements in QoL and respiratory function with lower pulmonary exacerbation rates. While the effect sizes for QoL and FEV1 still favour treatment, they have reduced compared to our previous findings. Lumacaftorâ€•ivacaftor was associated with an increase in early transient shortness of breath and longerâ€•term increases in blood pressure (not observed for tezacaftorâ€•ivacaftor). Tezacaftorâ€•ivacaftor has a better safety profile, although data are lacking in children under 12 years. In this population, lumacaftorâ€•ivacaftor had an important impact on respiratory function with no apparent immediate safety concerns, but this should be balanced against the blood pressure increase and shortness of breath seen in longerâ€•term adult data when considering lumacaftorâ€•ivacaftor. Data from triple therapy trials demonstrate improvements in several key outcomes, including FEV1 and QoL. There is probably little or no difference in adverse events for triple therapy (elexacaftorâ€•tezacaftorâ€•ivacaftor/deutivacaftor; VXâ€•659â€•tezacaftorâ€•ivacaftor/deutivacaftor; VXâ€•440â€•tezacaftorâ€•ivacaftor; VXâ€•152â€•tezacaftorâ€•ivacaftor) in pwCF with one or two F508del variants aged 12 years or older (moderateâ€•certainty evidence). Further RCTs are required in children under 12 years and those with more severe lung disease.

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See also

Heneghan M, Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database of Systematic Reviews 2023, Issue 11. Art. No.: CD010966. DOI: 10.1002/14651858.CD010966.pub4. Accessed 16 December 2023.

Keywords

Child; Adult; Adolescent; Aminophenols; CFTR Modulators; Genetic Predisposition to Disease; pharmacological_intervention; VX-770; ivacaftor;