Cochrane Database of Systematic Reviews - - Cochrane Review

Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis

Code: CD009841 **Year:** 2019 **Date:** 2012 - updated: 21 NOV 2018 **Author:** Skilton M

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

RCTs of parallel design (published or unpublished).

List of included studies (5)

Accurso 2010; Davies 2013; Flume 2011; Ramsey 2015; Strive 2011

Participants

Children or adults with CF, as confirmed either by the presence of two disease-causing mutations, or by a combination of a positive sweat test and recognised clinical features of CF; people with any level of disease severity and any relevant mutation class, where CFTR has been demonstrated to successfully embed within the cell membrane and display defective function

Interventions

Potentiators vs placebo or another intervention. Trials where CFTR potentiators are used in combination with other CFTR function modulators were excluded.

Outcome measures

Primary outcomes 1. Survival 2. Quality of life (QoL) (measured using validated quantitative scales or scores (e.g. Cystic Fibrosis Questionnaire- Revised (CFQ-R) (Quittner 2009)) 3. Forced expiratory flow rate at one second (FEV1) (relative change from baseline) Secondary outcomes 1. Adverse effects 2. Hospitalisation 3. School or work attendance 4. Other physiological measures of lung function 5. Extra courses of antibiotics 6. Radiological measures of lung disease 7. Acquisition of respiratory pathogens 8. Eradication of respiratory pathogens 9. Nutrition and growth 10. Sweat chloride (change from baseline) 11. Cost of treatment

Main results

We included five RCTs (447 participants with different mutations) lasting from 28 days to 48 weeks, all assessing the CFTR potentiator ivacaftor. The quality of the evidence was moderate to low, mainly due to risk of bias (incomplete outcome data and selective reporting) and imprecision of results, particularly where few individuals experienced adverse events. Trial design was generally wellâ€•documented. All trials were industryâ€•sponsored and supported by other nonâ€•pharmaceutical funding bodies. F508del (class II) (140 participants): one 16â€•week trial reported no deaths, or changes in quality of life (QoL) or lung function (either relative or absolute change in forced expiratory volume in one second (FEV1) (moderateâ€•quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in ivacaftor and placebo groups, but there was no difference between groups (lowâ€•quality evidence); there was also no difference between groups in participants interrupting or discontinuing treatment (lowâ€•quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. There was also no difference in weight. Sweat chloride concentration decreased, mean difference (MD) â€•2.90 mmol/L (95% confidence interval (CI) â€•5.60 to â€•0.20). G551D (class III) (238 participants): the 28â€•day phase 2 trial (19 participants) and two 48â€•week phase 3 trials (adult trial (167 adults), paediatric trial (52 children)) reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor in the adult trial at 24 weeks, MD 8.10 (95% CI 4.77 to 11.43) and 48 weeks, MD 8.60 (95% CI 5.27 to 11.93 (moderateâ€•quality evidence). The adult trial reported a higher relative change in FEV1 with ivacaftor at 24 weeks, MD 16.90% (95% CI 13.60 to 20.20) and 48 weeks, MD 16.80% (95% CI 13.50 to 20.10); the paediatric trial reported this at 24 weeks, MD 17.4% (P

Authors' conclusions

There is no evidence supporting the use of ivacaftor in people with the F508del mutation. Both G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in adults and children (over six years of age) with CF. The R117H trial demonstrated an improvement in the respiratory QoL score, but no improvement in respiratory function. As new mutationâ€•specific therapies emerge, it is important that trials examine outcomes relevant to people with CF and their families and that adverse events are reported robustly and consistently. Postâ€•market surveillance is essential and ongoing health economic evaluations are required.

https://doi.org//10.1002/14651858.CD009841.pub3

See also

Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD009841. DOI: 10.1002/14651858.CD009841.pub3

Keywords

Adult; CFTR Modulators; pharmacological_intervention;