Cochrane Database of Systematic Reviews - - Cochrane Review

Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis

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

Randomised controlled trials (RCTs) of parallel design (published or unpublished).

List of included studies (1)

Kerem 2014

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. They must have at least one PTC (nonsense or stop codon) mutation.

Interventions

Ataluren (or similar compounds for PTC class I mutations) compared with either placebo or another intervention.

Outcome measures

Primary outcomes 1. Quality of life (QoL) (measured using validated quantitative scales or scores (e.g. Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009)) i) total QoL score ii) different sub-domains 2. Respiratory function measures: FEV1, FVC 3. Adverse events i) mild (therapy does not need to be discontinued) ii) moderate (therapy is discontinued, and the adverse effect ceases) iii) severe (life-threatening or debilitating, or which persists even after treatment is discontinued) Secondary outcomes 1. Survival 2. Hospitalisation 3. School or work attendance 4. Extra courses of antibiotics 5. Pulmonary exacerbations 6. Radiological measures of lung disease 7. Acquisition of respiratory pathogens 8. Eradication of respiratory pathogens 9. Nutrition and growth 10. Sweat chloride 11. Cost effectiveness (cost utility assessed as comparison of impact on quality of adjusted life years)

Main results

Our searches identified 56 references to 20 trials; of these, 18 trials were excluded. Both the included parallel RCTs compared ataluren to placebo for 48 weeks in 517 participants (males and females; age range six to 53 years) with CF who had at least one nonsense mutation (a type of class I mutation). The certainty of evidence and risk of bias assessments for the trials were moderate overall. Random sequence generation, allocation concealment and blinding of trial personnel were well documented; participant blinding was less clear. Some participant data were excluded from the analysis in one trial that also had a high risk of bias for selective outcome reporting. PTC Therapeutics Incorporated sponsored both trials with grant support from the Cystic Fibrosis Foundation, the US Food and Drug Administration's Office of Orphan Products Development and the National Institutes of Health. The trials reported no difference between treatment groups in terms of quality of life, and no improvement in respiratory function measures. Ataluren was associated with a higher rate of episodes of renal impairment (risk ratio 12.81, 95% confidence interval 2.46 to 66.65; P = 0.002; I2 = 0%; 2 trials, 517 participants). The trials reported no treatment effect for ataluren for the review's secondary outcomes of pulmonary exacerbation, computed tomography score, weight, body mass index and sweat chloride. No deaths were reported in the trials. The earlier trial performed a post hoc subgroup analysis of participants not receiving concomitant chronic inhaled tobramycin (n = 146). This analysis demonstrated favourable results for ataluren (n = 72) for the relative change in forced expiratory volume in one second (FEV1) per cent (%) predicted and pulmonary exacerbation rate. The later trial aimed to prospectively assess the efficacy of ataluren in participants not concomitantly receiving inhaled aminoglycosides, and found no difference between ataluren and placebo in FEV1 % predicted and pulmonary exacerbation rate.

Authors' conclusions

There is currently insufficient evidence to determine the effect of ataluren as a therapy for people with CF with class I mutations. One trial reported favourable results for ataluren in a post hoc subgroup analysis of participants not receiving chronic inhaled aminoglycosides, but these were not reproduced in the later trial, suggesting that the earlier results may have occurred by chance. Future trials should carefully assess for adverse events, notably renal impairment, and consider the possibility of drug interactions. Crossâ€•over trials should be avoided, given the potential for the treatment to change the natural history of CF.

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See also

Aslam AA, Higgins C, Sinha IP, Southern KW. Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD012040. DOI: 10.1002/14651858.CD012040.pub3.

Keywords

PTC124; Ataluren; CFTR Modulators; pharmacological_intervention;