

Combination Correctors and Potentiators for Cystic Fibrosis: A Systematic Review and Meta-analysis

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Background:

The most common cause of cystic fibrosis (CF) is the Phe508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, resulting in CFTR's reduced trafficking, targeted by correctors, and reduced functioning, targeted by potentiators. For the majority of CF patients, the combination correctors and potentiators (CCPs) lumacaftor/ivacaftor and tezacaftor/ivacaftor, are the only treatments licensed to target the disease origin.

Objectives:

To assess the effects of CCPs on clinical efficacy outcomes, adverse events (AEs) and quality of life in CF patients. Methods: Electronic databases and clinical trial registries were searched before March 31st for randomised controlled trials comparing CCPs to placebo in CF patients. Bias assessments were conducted and data extracted for primary outcomes; change in percentage predicted forced expiratory volume in 1 second (ppFEV1), pulmonary exacerbations (PEX) and change in the respiratory domain of the cystic fibrosis revised questionnaire (CFQ-R-RD). AEs and discontinuations were analysed as secondary outcomes. Meta-analyses were conducted with subgroup stratification by CF mutation type and CCP drug.

Results:

9 studies were included (n=2543) lasting 4-24weeks. Overall CCPs compared to placebo decreased PEX, relative risk (RR)=0.69 [95%CI=0.60,0.80], increased ppFEV1, mean difference (MD)=3.03 [95%CI=1.61,4.45] and increased CFQ-R-RD scores, MD=5.07 [95%CI=2.30,7.83]. All efficacy outcomes were significant in Phe508del homozygotes, whilst only CFQ-R-RD increases were significant in Phe508del heterozygotes. In Phe508del heterozygotes with a residual function mutation increases in CFQ-R-RD scores and ppFEV1 were significant. Overall participant completion was >95% but discontinuations due to AEs were higher with CCPs, RR=1.87[95%CI=1.10, 3.19]. This was significant with lumacaftor/ivacaftor but not with tezacaftor/ivacaftor.

Conclusion:

Overall CCPs are safe and well tolerated. High quality evidence shows CCPs lead to modest improvements in ppFEV1 and reduce PEx in the short term for Phe508del homozygous patients. The clinical significance of these effects on long term outcomes for CF needs further research.