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CO4

A systematic review (SR) and network meta-analysis (NMA) of cystic fibrosis transmembrane conductance receptor (CFTR) modulator therapies and established clinical management (ECM) using per cent predicted forced expiratory volume in one second ($ppFEV_1$) as a measure of lung function

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Introduction

- Cystic fibrosis is a life-limiting disease, characterised by progressive loss of lung function and severe respiratory infections.
- CFTR modulators are the first treatments to address the underlying cause of CF.
- When treated with CFTR modulators, people with CF often experience an acute increase in lung function, commonly measured using per cent predicted forced expiratory volume in one second ($ppFEV_1$).
- However, the magnitude of the acute $ppFEV_1$ increase may vary between different CFTR modulator treatments and patient subgroups (age and genotype).

Objective

Assess the effectiveness of elexacafor/tezacaftor/ivacaftor (ELX/TEZ/IVA), lumacaftor/ivacaftor (LUM/IVA) and tezacaftor/ivacaftor (TEZ/IVA) compared to each other and ECM, across different genotypes (F/F, F/MF, F/RF and F/gating)

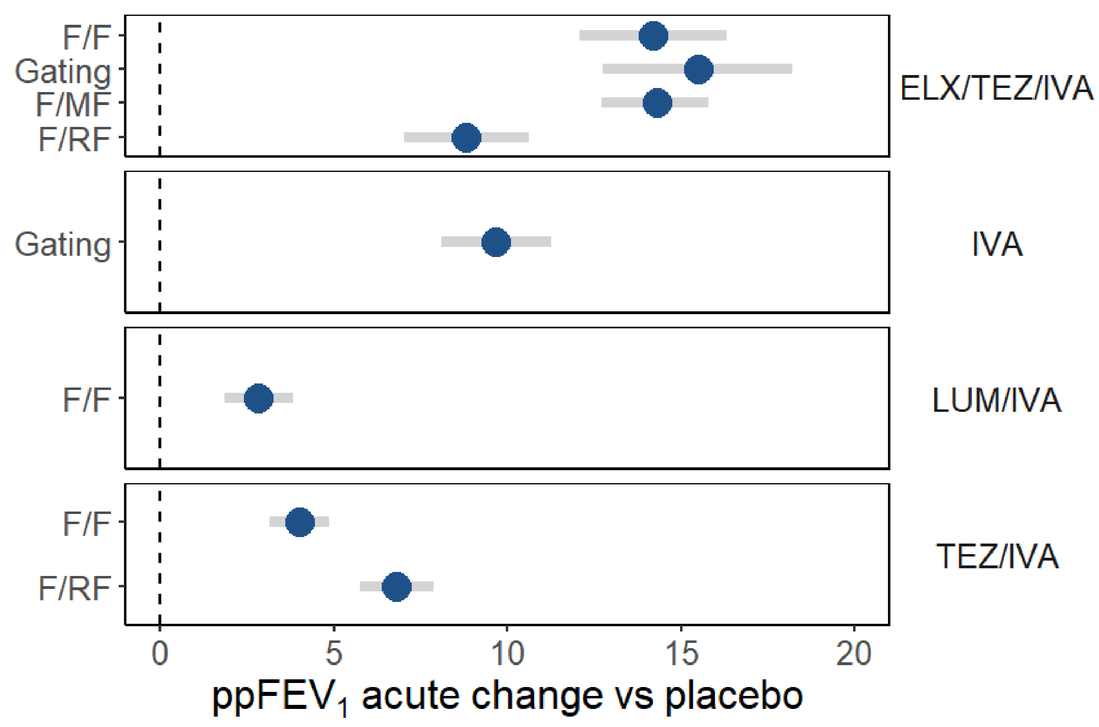
Methods

- Systematic review (PROSPERO: CRD42023399583) of MEDLINE, Embase, CENTRAL (from inception to 2023), health technology assessment body websites, conference proceedings and clinical trial registries searched (grey literature searched from 2018 to 2023). Two reviewers agreed on studies for inclusion and performed quality assessment with the Cochrane Risk of Bias 2 tool (outcome level) for randomised clinical trials (RCTs) and an adapted ROBINS-I checklist for non-randomised pre-post studies.
- Bayesian NMAs were performed when direct comparisons in RCTs were unavailable, using fixed effect (FE) and random effects (RE) → final model chosen based on the lowest deviance information criterion (DIC).

Results

- Nineteen RCTs and seven associated open-label extension studies were included from the SR.
- In all analyses, ELX/TEZ/IVA was associated with a large increase in $ppFEV_1$ compared to placebo and compared to LUM/IVA and TEZ/IVA in the F/F genotype, with 95% credible intervals excluding 0.
- ELX/TEZ/IVA effect sizes were attenuated compared to TEZ/IVA in the F/RF analysis, and IVA in the Gating analysis.

Results of the NMAs (F/F, Gating, F/RF) and Middleton 2019[1] RCT data for F/MF



N.B. The Gating analysis for ELX/TEZ/IVA includes F/Gating population only whereas for IVA monotherapy, data from all patients with at least one gating mutation were included

Abbreviations: ELX/TEZ/IVA, elexacafor/tezacaftor/ivacaftor; F/F; homogenous F508del mutation; F/MF, minimal function mutation; F/RF, residual function mutation; IVA, ivacaftor; LUM/IVA, lumacaftor/ivacaftor, NMA, network meta-analysis; $ppFEV_1$, per cent predicted forced expiratory volume in one second; RCT, randomised controlled trial; TEZ/IVA, tezacaftor/ivacaftor

Conclusions

- CFTR modulators lead to acute improvements in $ppFEV_1$ for people with CF. The magnitude of this improvement is considerably larger for ELX/TEZ/IVA.
- Our results are consistent with real-world registry-based studies, which have reported an acute increase in $ppFEV_1$ two-year post initiation of ELX/TEZ/IVA of 10.2% (UK)[2] and 8.9% (USA).[3]

References

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2. Vega-Hernandez G, MacGregor G, Wilfin A, Adams F, Haugh C, Baxter CA, *et al.* LONGITUDE: An observational study of the long-term effectiveness of elexacaftor/tezacaftor/ivacaftor in people aged >12 years with cystic fibrosis using data from the United Kingdom Cystic Fibrosis Registry - 2-year analysis. *Journal of Cystic Fibrosis* 2025; **24**: 716-23.
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