Remodelling of cystic fibrosis respiratory microbiota in response to extended Elexacaftor–Tezacaftor–Ivacaftor therapy

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Background: The introduction of the highly effective CFTR modulator Elexacaftor/Tezacaftor/Ivacaftor (ETI) has revolutionised clinical outcomes for adults with CF (awCF) eligible for treatment. Despite this little is understood about the long-term impact of ETI on the respiratory microbiota in awCF.

Aims: In this multi-centre study, we investigated changes to the respiratory microbiota of awCF from before onset of ETI therapy to on-ETI therapy of up to 3 years.

Methods: Respiratory samples were collected from 303 awCF from 6 centres in the UK (Cardiff, Manchester, & Southampton), Canada (Calgary), and USA (Dartmouth & Vermont). This consisted of pre-ETI samples stratified to severe, moderate, and mild disease groups based on $\%FEV_1$, and on-ETI samples taken at approximately 6 months, 1, 2, & 3 years. Samples from 11 non-CF healthy participants were included as a comparator group. Microbiota sequencing was performed on all samples.

Results: Microbiota diversity increased with therapy duration. With diversity at years 2 and 3 being comparable ($P>0.05$) to that observed in the mild disease pre-ETI and healthy groups. Microbiota composition became increasingly similar to mild CF/healthy groups with increasing therapy duration but was still significantly different ($P<0.05$) at 3 years. Dominance of CF pathogens reduced with therapy duration, with a shift to microbiota characterised by strict anaerobes associated with better clinical outcomes. Despite the reduction in abundance many CF pathogens still persisted.

Conclusions: Long-term ETI therapy resulted in positive changes in the respiratory microbiota, typically associated with better clinical outcomes and microbiota more closely resembling mild CF/healthy microbiota. Despite a positive trajectory towards a healthy-like microbiota, we posit that progression in awCF is impeded by the cumulative effects of progressive airway and lung parenchymal damage, along with the impacts of long-term and continued antibiotic therapy.