A_{lumen}/A (all $p < 0.001$), but not in A_{wt}/A ($p = 0.35$). Between 64% and 66% of AA pairs were defined as bronchiectasis and 59% as AWT.
Conclusions: Progressive bronchiectasis can be observed in CwCF during late childhood into adolescence. AA analysis results agree with PRAGMA-CF results to monitor disease progression in CwCF.
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Reference

[1] Wijker NE, Vidmar S, Grimwood K, Sly PD, Byrnes CA, Carlin JB, *et al.* Early markers of cystic fibrosis structural lung disease: Follow-up of the ACFBAL cohort. *Eur Respir J* 2020;55(4).

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Effects of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in patients with cystic fibrosis and one or two F508del alleles

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Background: We recently demonstrated that triple combination cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) improves CFTR function in airway and intestinal epithelia to 40% to 50% of normal in patients with CF with one or two F508del alleles. In previous studies, this improvement in CFTR function was shown to improve clinical outcomes, but effects on the lung clearance index (LCI) determined using multiple-breath washout and abnormalities in lung morphology and perfusion detected using magnetic resonance imaging (MRI) have not been studied. The aim of this study was to examine the effect of ELX/TEZ/IVA on LCI and lung MRI scores in people with CF and one or two F508del alleles aged 12 and older.
Methods: This prospective, observational, multicenter, postapproval study assessed LCI and lung MRI scores before and 8 to 16 weeks after initiation of ELX/TEZ/IVA.
Results: Ninety-one people with CF, including 45 heterozygous for F508del and a minimal function mutation (MF) and 46 homozygous for F508del, were enrolled. Treatment with ELX/TEZ/IVA improved LCI in F508del/MF (−2.4, interquartile range (IQR) −3.7 to −1.1; $p < 0.001$) and F508del homozygous (−1.4, IQR −2.4 to −0.4; $p < 0.001$) patients. ELX/TEZ/IVA also improved the MRI global score in F508del/MF (−6.0, IQR −11.0 to −1.3; $p < 0.001$) and F508del homozygous (−6.5, IQR −11.0 to −1.3; $p < 0.001$) patients.
Conclusions: Our data demonstrate that improvement in CFTR function with ELX/TEZ/IVA improves lung ventilation and abnormalities in lung morphology, including airway mucus plugging and wall thickening in adolescents and adults with CF and one or two F508del alleles in a real-world postapproval setting.
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Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for *F508del-CFTR* and a gating or residual function mutation

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Background: The triple combination regimen of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in people with CF aged 12 years and older with cystic fibrosis (CF) and heterozygous for *F508del-CFTR* and either a *CFTR* gating mutation (*F508del*-gating genotypes) or a residual function mutation (*F508del*-residual function genotypes). A 96-week, Phase 3, open-label extension study was conducted to assess long-term safety and efficacy in these participants.
Methods: Participants received ELX 200 mg once daily/TEZ 100 mg once daily/IVA 150 mg every 12 hours. The primary endpoint was safety and tolerability; secondary endpoints included absolute changes in percent predicted FEV_1 ($ppFEV_1$), sweat chloride concentration, body mass index (BMI), body weight, and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score.
Results: 251 participants (*F508del*-gating genotypes, n = 92; *F508del*-residual function genotypes, n = 159) were enrolled and dosed. Mean (SD) exposure to ELX/TEZ/IVA was 89.3 (20.0) weeks. Overall, 241 participants (96.0%) had an adverse event (AE), which for most were mild (32.3%) or moderate (55.0%) in severity. The exposure-adjusted rates of AEs and serious AEs (589.36 and 13.38 events per 100 patient years) were lower than in the 8-week parent study (1033.98 and 26.74 events per 100 patient years). Thirteen patients (5.2%) had AEs that led to treatment discontinuation (increased liver function tests [n = 6], psychiatric events [n = 4], other events [n = 3]), and there was one death due to an operative complication during resection of a cecal mass, which was not considered related to ELX/TEZ/IVA. Following a 4-week run-in period with either IVA or TEZ/IVA, participants who received ELX/TEZ/IVA in the parent study had improvements in $ppFEV_1$, sweat chloride concentration, and CFQ-R respiratory domain score that were maintained to Week 96 of this extension study, while participants who started ELX/TEZ/IVA in the extension study had similar improvements from parent study baseline at Week 96 (Table 1).