# Elexacaftor/tezacaftor/ivacaftor Treatment Reduces Airway Inflammation in Cystic Fibrosis

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**Abstract**

ETI treatment reduces inflammatory markers and positive bacterial cultures on BAL in PwCF. These findings suggest that ETI has a greater impact on chronic infection and inflammation than ivacaftor alone. However, airway inflammation persists in a fraction of treated individuals, indicating an ongoing need to optimize other treatments in a subset of patients.

To the editor,

Airway mucus dehydration from loss of cystic fibrosis transmembrane conductance regulator (CFTR) activity leads to excessive airway muco-inflammation that drives the onset and progression of lung disease in cystic fibrosis (CF.)[1,2] Previous studies with the highly effective modulator therapy (HEMT) ivacaftor have demonstrated improvement in CFTR function and substantial clinical benefits. However, clinical studies of ivacaftor therapy in people with CF (PwCF) with eligible genotypes have not consistently demonstrated a significant reduction in markers of airway inflammation.[3,4] This somewhat unanticipated result suggests that airway inflammation may persist in PwCF on HEMT and could benefit from anti-inflammatory therapies.

Recently, elexacaftor-tezacaftor-ivacaftor (ETI, Trikafta) was approved as a HEMT available to a larger fraction of PwCF. While *in vitro*evidence suggests that ETI treatment may alter inflammatory pathways in CF[5], there is little information regarding the impact of ETI on airway inflammation in treated individuals. To address this issue, we identified PwCF who underwent bronchoscopy with bronchoalveolar lavage (BAL) after starting ETI therapy. To avoid confounding by indication, the study population was limited to those who had surveillance procedures before and after starting ETI therapy. BAL markers of inflammation and infection obtained during these procedures were then compared.

**Methods**

A database of all PwCF on ETI therapy was cross-referenced to a bronchoscopy database to identify individuals who underwent bronchoscopy with BAL while on ETI therapy. Procedures performed while the individual was on intravenous antibiotics were excluded, as were procedures where pulmonary exacerbation was the indication. Individuals were excluded from further analysis if they did not have at least one bronchoscopy performed while not on ETI therapy within 5 years of the index procedure. Clinical information including demographics and CFTR genotype, indication for bronchoscopy, as well as BAL findings including culture data, cell count, neutrophil count and neutrophil percentage were abstracted from the medical record. Pathogen positive cultures were defined as growth of any potentially pathogenic organism on culture. Statistical analysis was performed using GraphPad Prism using paired T-tests (continuous data) or Fisher exact test (dichotomous data). Neutrophil cells counts were log transformed prior to analysis. The study was approved by the UNC IRB (#21-1137).

## Results

To assess whether ETI therapy affected lower airway inflammation, we identified 16 patients who had bronchoscopy and BAL performed while on ETI therapy. Two individuals were excluded who did not have comparison bronchoscopies performed while not on ETI therapy within five years, and a further 6 were excluded due to pre or post ETI bronchoscopy being performed for suspected bronchopneumonia. The study population consisted of 8 subjects, all white, and was 75% male with an average age of 12.7±5.3 years at the time of the bronchoscopy on ETI therapy. The locations of bronchoalveolar lavage were determined clinically. In 42% of subjects lavage was performed in different lobes in the matched procedures.

BAL markers of neutrophilic inflammation were significantly reduced in the samples obtained from PwCF while on ETI, including both % neutrophils and neutrophil counts (**Fig. 1A-B** ). While pathogens were recovered from 5 of 8 PwCF not on ETI, no pathogens were recovered from any procedure performed on an individual on ETI (**Fig. 1D** ).

## Discussion

The Use of ETI in eligible PwCF was associated with a marked decrease in markers of inflammation in BAL and fewer positive cultures from BAL fluid. While consistent with the known pathophysiology of CF, this result differs from prior studies of ivacaftor alone that have not shown a clear impact on airway inflammation or infection despite substantial clinical benefit.[4] It is possible that ETI results in greater restoration of CFTR activity than ivacaftor alone in eligible genotypes, and clinical studies have suggested a clinical benefit of ETI in patients previously treated with ivacaftor.[6]However, further investigation will be necessary to confirm these findings and better understand the differences between ETI therapy and ivacaftor alone.

The failure of ivacaftor alone to substantially reduce airway inflammation in treated patients has suggested that individuals on HEMT may still benefit from anti-inflammatory therapies. Our findings suggest that anti-inflammatory therapies may be less effective for many treated with ETI, although substantial levels of airway inflammation remained in some PwCF on ETI. It is not clear if this reflects therapeutic failure of ETI to effectively improve CFTR activity or the presence of established structural lung disease that led to continued inflammation and infection despite normal levels of CFTR. Regardless, the findings indicate that individualized strategies will be needed to optimize efficacy of ETI and/or identify those who continue to need anti-inflammatory or other treatments despite HEMT.

Strengths of this study include use of bronchoscopy with BAL as the gold standard measure of airway inflammation. Limitations include the small size and reliance on clinically indicated procedures and findings for analysis. Therefore, measures such as neutrophil elastase or cytokines that are not routinely performed clinically were not available.

In conclusion, ETI treatment reduces inflammatory markers and positive bacterial cultures on BAL in PwCF. These findings suggest that ETI has a greater impact on chronic infection and inflammation than ivacaftor alone. However, airway inflammation persists in a fraction of treated individuals, indicating an ongoing need to optimize other treatments in a subset of patients.

## Conflict of interest statement

The authors have no conflicts of interest to report.

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