Managing Hepatotoxicity in CF Patients on Elexacaftor/Tezacaftor/Ivacaftor: Efficacy of Dose Reduction and Insights into Delayed Toxicity

Marissa Angelich (ma91960@usc.edu), Soumar Haddad (soumarha@usc.edu), Amin Khudari (zakkourk@usc.edu), Sarkis Sislyan (ssislyan@usc.edu), Paul Beringer, PharmD(beringer@usc.edu)

Background: Treatment with Elexacaftor/Tezacaftor/Ivacaftor (ETI) is associated with significant lung function and nutritional status improvements in individuals with cystic fibrosis (CF). However, adverse effects (AEs) including clinically significant hepatotoxicity have been reported.[1] Abrupt discontinuation of ETI is associated with pulmonary exacerbations.[2-4] the purpose of this study is to (1) evaluate the effect of dose reduction on managing AEs such as hepatotoxicity, and (2) evaluate the prevalence and risk factors for delayed hepatotoxicity (DH) beyond one year of ETI therapy.

Methods: Retrospective analysis was conducted using electronic medical record data. Adult CF patients with documentation of ETI therapy were included and underwent comprehensive review of transaminase levels and ETI dose. Those with dose reductions due to AEs underwent further assessment of pulmonary function tests (PFTs) before and after ETI dose reduction. Individuals who experienced transaminase elevations beyond one year of therapy were deemed to have DH, and comparison of groups was conducted regarding demographics, prevalence of CF liver disease (CFLD), and other risk factors.

Results: Fifteen patients underwent ETI dose reduction due to AEs within the first year of therapy. Clinical stability without significant changes in PFTs after dose reduction was observed in all patients. 13 of these 15 cases saw resolution or improvement of AEs. DH was observed in 36 out of 124 patients who had at least one year of documented ETI use. Those with DH had a higher percent prevalence of CFLD, prior hepatotoxicity or cholestasis, pulmonary or viral infections, and acetaminophen use. Three cases of significant delayed transaminase elevations were determined to have “probable” or “possible” ETI causality. Median onset was 21 months after ETI initiation. Dose reduction led to resolution in all 3 cases.

Conclusion: This study provides evidence that ETI dose reduction improves hepatotoxicity without evidence of clinical deterioration. While most transaminase elevations occur within the first year of ETI therapy, some cases emerge later with varied severity. Factors beyond ETI, including but not limited to pre-existing liver conditions and acetaminophen use, also contribute to these delayed reactions. Despite these complex causes, our findings emphasize the need for continued vigilance by clinicians for liver injuries after one year of ETI therapy.

References:

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