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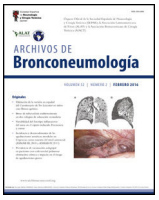

Clinical Letter

Immune-Mediated Hepatocellular Injury Induced by Elexacaftor/Tezacaftor/Ivacaftor Therapy

For years, cystic fibrosis (CF) treatment has relied on symptomatic management. The development of CFTR modulators, has significantly improved quality of life and life expectancy, especially since the approval of elexacaftor/tezacaftor/ivacaftor (ETI), indicated for patients with at least one F508del gene mutation. Phase 2 and 3 clinical trials have demonstrated the efficacy and safety of ETI, with few adverse effects, including, elevated transaminases (10.9%) and transaminitis (3–8%). These hepatic effects vary in severity, involving cases of drug-induced liver injury (DILI), acute liver failure, and hepatic necrosis, occasionally requiring drug discontinuation [1,2].

We report a rare case of idiosyncratic hepatocellular injury induced by ETI, with an immune-mediated mechanism demonstrated through the lymphocyte transformation test (LTT). The patient, a 43-year-old male with a significant allergic history to iodinated contrast, paracetamol, metamizole, quinolones, linezolid and trimethoprim/sulfamethoxazole. Diagnosed with CF F508del/Q98R, severe pulmonary involvement (ppFEV1 prior to desensitization protocol: 27%), exocrine pancreatic insufficiency and osteoporosis. ETI and Ivacaftor therapy was initiated, but nine days later, the patient developed a maculopapular rash and eosinophilia (1020/μL), prompting drug withdrawal. Based on a positive LTT for ETI and Ivacaftor, a desensitization protocol was initiated, and the subject gradually was able to tolerate full therapeutic dosing of both treatments after approximately three months [3]. Ten months after starting the full dose, signs of altered liver markers were detected (without coagulopathy or clinical signs of hepatitis), reaching peak values of AST (294 U/L; normal range 0–40 U/L), ALT (519 U/L; normal range 0–35 U/L), GGT (210 U/L; normal range 0–73 U/L) and total bilirubin (2.84 mg/dL; normal range 0.3–1.2 mg/dL) five months later, which led to the discontinuation of treatment. Despite symptomatic and functional improvement (best ppFEV1: 37%), due to data of mixed hepatitis ETI was discontinued. Concurrently, evaluation by the clinical pharmacology team was initiated, ruling out viral infection and other liver diseases, and also excluding the possibility that the symptoms were related to concomitant medication. The team determined the drug-related causality of DILI, using the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM 2016), resulting in a score of +7 (probable). In vitro re-exposure to the drug via LTT was again positive, adding 1 point to the scale and demonstrating an immune mediated mechanism. ETI was therefore definitively contraindicated.

As ETI use becomes more widespread, previously uncommon adverse effects reported in clinical trials are emerging. The diagnosis of DILI is challenging when the reaction is dose-independent or idiosyncratic, caused by unpredictable events due to immunologic or metabolic mechanisms. The diagnosis is based on exclusion of alternative causes and the use of causality algorithms. The RUCAM remains the only clinically validated liver-specific scale for DILI, nevertheless it has limitations when there are different risk factors for DILI than those listed in the algorithm, delayed-onset toxicity, or concurrent hepatotoxic drug exposure [4]. We investigated the immunologic mechanism using LTT, which our group has validated for DILI diagnosis, demonstrating a sensitivity of 77%, specificity of 100%, and 92% sensitivity for hepatocellular phenotypes. Accordingly, we have interpreted the in vitro re-exposure (positive LTT) as equivalent to RUCAM's item "Response to re-exposure" (+1) [5]. Although other cases of ETI-induced hepatotoxicity have been published [1,2], this is the first case of hepatocellular DILI induced by ETI with a demonstrated immune-mediated mechanism via LTT. This case offers immunological insight that complements RUCAM scale and set a precedent for future research for potential solutions in a problem that currently leaves CF patients without a viable long-term treatment option.

Contribution of each author

We are aware that the maximum number of authors for a clinical letter is three. However, we respectfully request that both Cindy Stephania Aponte Guevara and Sara Navarro Carrera be acknowledged as co-first authors, having equally contributed to the conception, design, and writing of the manuscript. Their contributions have been fundamental and equivalent throughout all stages of the preparation of this work.

Ester Zamarrón De Lucas and María Concepción Prados Sánchez have equally contributed as senior supervisors, participating in the critical review, content refinement, and final editing of the manuscript.

Artificial intelligence involvement

Artificial intelligence software was used exclusively for grammatical corrections and linguistic polishing of the manuscript. The scientific content and conclusions were entirely generated by the authors.

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Conflicts of interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

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