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Predictive pharmacogenetic risk of pancreatitis in Inflammatory Bowel Disease patients treated with thiopurines: a case-control study from the ENEIDA registry

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Background: Treatment with thiopurines may be associated with different adverse effects, including acute pancreatitis. Risk factors for developing pancreatitis due to thiopurines in patients with Inflammatory Bowel Disease (IBD) are not clearly identified, with underlying genetic predisposition being a possible cause. Our aim was to evaluate predictive pharmacogenetic risk of pancreatitis in IBD patients treated with thiopurines.

Methods: IBD patients treated with thiopurines were identified from the prospectively maintained ENEIDA registry of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU). We included as cases those patients who met the Atlanta diagnostic criteria for pancreatitis and had an imaging test that ruled out biliary origin. We included as controls those patients without pancreatitis after at least two years of treatment with thiopurines. Blood samples were collected, and DNA was extracted from leukocytes for all participants and, subsequently, pooled samples were sequenced. Sequencing of a panel of genes (CASR, CEL, CDLN2, CFTR, CPA1, CTRC, PRSS1, and SPINK1) was carried out in the NextSeq500 platform. Variants detected were classified as pathogenic, variants of unknown significance, and benign according to the American College of Medical Genetics and Genomics (ACMGG) guidelines.

Results: Ninety-five cases and 105 controls were enrolled, 57% were women. Pancreatitis was diagnosed at a median age of 39±13 years old. No patient had previous history of chronic or acute pancreatitis. There were no differences between thiopurine-treated patients with and without pancreatitis in age, sex, and age at IBD onset. We identified 81 benign variants (50 in cases and 67 in controls) and a total of 35 distinct rare pathogenic and unknown significance variants (10 in CEL, 21 in CFTR, 1 in CDLN2, and 3 in CPA1). Of these 35 variants (12 in cases and 18 in controls), 6 were classified as pathogenic (1 in cases and 5 in controls), belonging to the CEL and CFTR genes, and 30 as variants of uncertain significance (21 in cases and 22 in controls). There were no significant differences between the groups of cases and controls, both in totals and by genes. None of the cases or controls carried pancreatitis-predisposing variants within the CASR, CPA1, PRSS1, and SPINK1 genes. None of the analysed samples with pancreatitis carried a pathogenic CFTR mutation. Four different variants of unknown significance were detected in the CDLN and CPA1 genes. One of them was in the CDLN gene in a single patient with pancreatitis, and 3 variants in the CPA1 gene in 5 control individuals.

Conclusion: In patients with IBD, there is no predisposition to thiopurine-induced pancreatitis associated with genes known to cause pancreatitis.