OCTN1 variants shape innate immunity and predict individual response to antiTNFα in ulcerative colitis patients: an exploratory study.

ABSTRACT

Background.

Identifying reliable biomarkers of response to biologic therapy remains a major challenge in the management of ulcerative colitis (UC). The organic cation transporter OCTN1, encoded by the SLC22A4 gene, is involved in immune cell activation and has been implicated in IBD susceptibility. We investigated whether the rs1050152 (L503F) polymorphism influences clinical outcomes in UC patients treated with anti-TNFα agents.

Methods.

In this retrospective study, we analyzed UC patients treated with infliximab, adalimumab, or golimumab. Clinical endpoints included one-year steroid-free clinical remission, endoscopic response, and therapy persistence. OCTN1 genotypes at SNP 1050152 (CC, CT, TT) were assessed and correlated with outcomes. Patients with known allergic or anti-drug antibody reactions were excluded to focus on mechanistic responsiveness. A Machine learning- based LASSO regression (C=15, 70% test data and 30% test data) and a neural network-based analysis (10 neurons in hidden layer, regularization α=0.005) were performed through Orange to rank the impact of variables in determining the clinical endpoints. In vitro assays were performed to assess IL-1β secretion in monocytes from genotyped patients under bacterial stimulation.

Results.

Patients with the TT genotype (503F homozygous) demonstrated significantly higher rates of steroid-free remission, endoscopic response, and long-term therapy persistence compared to CC and CT carriers. Logistic regression confirmed the TT genotype as an independent predictor of favorable outcomes. Orange workflow was aimed to rank the importance of the known variables in determining the outcomes. In the machine learning logistic regression, the presence of mutated OCTN1 ranked first among the variables in determining steroid free remission, with an AUC of 0.6; the presence of mutated genotype ranked second in the neural network analysis, with AUC 0.8. In vitro, TT monocytes produced elevated levels of IL-1β, suggesting enhanced innate immune activation in this subgroup.

Conclusions.

Our data suggest that the OCTN1 503F variant may define a pro-inflammatory endotype of UC characterized by enhanced responsiveness to anti-TNFα therapy. These findings support OCTN1 genotyping as a potential predictive biomarker and highlight the need for prospective validation in larger, multi-omic-integrated studies to advance precision medicine in IBD.