

## LETTER TO THE EDITOR

**Bhat M, Lu Y, Marcil V, et al. Tumour necrosis factor-alpha polymorphism increases the risk for nonvariceal upper gastrointestinal bleeding in patients taking proton pump inhibitors. *Can J Gastroenterol Hepatol* 2014;28(9):488.**

To the Editor:

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is associated with significant morbidity, affecting 50 to 150 per 100,000 adults annually (1). Patients with NVUGIB may present with melena, hematochezia or coffee-ground emesis, often accompanied by a decrease in hemoglobin levels and even hemodynamic instability. Nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection are the principal risk factors for NVUGIB, accounting for >95% of cases. Taking proton pump inhibitors (PPIs) is a known protective factor against NVUGIB.

There has recently been growing interest in a possible genetic predisposition to NVUGIB, with investigation of single nucleotide polymorphisms (SNPs) associated with bleeding events. Of particular interest have been mutations in proinflammatory genes or genes that regulate NSAID/PPI metabolism, which may contribute to excessive inflammation and ulceration in the context of *H pylori* infection and NSAID use. A recent pharmacogenomic study (2) found that a CYP2C9 polymorphism was associated with peptic ulcer disease independently of NSAID and PPI use. *H pylori* infection of the gastric mucosa leads to chronic inflammation and ulcerogenesis, particularly when it is the highly virulent triple-positive strain positive for *cag*, *vacA*s1 and *babA*23. Inflammatory cytokines, such as tumour necrosis factor-alpha (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-6 and IL-8, are released as a form of immune defense, leading to recruitment of neutrophils and mononuclear cells to the lamina propria. Accordingly, elevated TNF- $\alpha$  levels correlate with the extent of gastric inflammation. A large Taiwanese study investigating TNF- $\alpha$  polymorphisms among patients with dyspepsia (3) discovered that individuals with -1031C and -863A mutations exhibited increased gastric neutrophil infiltration. Additionally, these mutations independently predicted risk of gastric and duodenal ulcers in *H pylori*-infected individuals. Hence, these TNF- $\alpha$  polymorphisms were found to at least partially account for susceptibility to *H pylori*-induced inflammation and ulcerogenesis. In contrast, a recent meta-analysis of 16 studies found no significant association between various TNF- $\alpha$  SNPs and duodenal ulcers (4). Nonetheless, the calculations in this study revealed that the statistical power of this meta-analysis was poor, with inhomogeneous patient populations. The authors of this meta-analysis concluded that the findings were not definitive, and deserved to be further evaluated in a larger and more homogeneous patient population.

The above literature describing a genetic predisposition for bleeding events applies principally to East Asian patient populations. Therefore, we decided to study whether such genetic associations could be elicited in the Canadian context. We performed a pilot study to assess the association of SNPs involved in NSAID metabolism (CYP2C9) and inflammatory response (TNF- $\alpha$ ) with NVUGIB events. Patients who were part of the REASON-II NVUGIB study population at the McGill University Health Centre (Montreal, Quebec) were recruited (5). Study controls were asymptomatic patients undergoing screening colonoscopy, and excluded if there was any history of NVUGIB. DNA extracted from serum was genotyped for SNPs in the proinflammatory TNF- $\alpha$  (rs1799724, rs1800630, rs1799964) and NSAID-metabolizing CYP2C9 genes (rs1799853, rs1057910). Using STATA version 10, we assessed for any association between SNPs and NVUGIB events using logistic regression analysis and stratifying according to *H pylori* status, NSAID and PPI use. Our study included 23 patients and 46 controls of comparable age and sex, with NSAID (26.1% versus 6.7%) and

PPI use (21.7% versus 13.0%) being more prevalent among patients. The TNF- $\alpha$ 1031C SNP, a proinflammatory cytokine polymorphism, was more common among patients with NVUGIB (OR 2.2 [95% CI 0.9 to 5.1]; P=0.084), particularly among those using PPIs (OR 20.0 [95% CI 0.9 to 429.9]; P=0.056) or not taking NSAIDs (OR 3.2 [95% CI 1.1 to 9.0]; P=0.027) at the time of the bleeding event. There was a trend in association of the TNF- $\alpha$ 863A SNP with NVUGIB in patients not taking NSAIDs (OR 2.7 [95% CI 0.9 to 8.6]; P=0.071). We did not detect an association between CYP2C9 polymorphisms and NVUGIB, a result similar to that obtained in the study by Musumba et al (2).

In conclusion, our pilot study demonstrates that TNF- $\alpha$ 1031C SNP confers a risk for NVUGIB events among patients taking PPIs, a finding compatible with previous studies showing increased risk for peptic ulceration with this particular SNP (3,6). An additional novel finding in our study was that the TNF- $\alpha$ 1031C SNP was more common among NVUGIB patients not taking NSAIDs. This indicates that predisposition to inflammation plays an important role in the pathogenesis of NVUGIB, and can lead to events despite PPI use and abstention from NSAIDs. It is possible that CYP2C9 SNPs impairing NSAID metabolism interact with TNF- $\alpha$ , stimulating inflammation to precipitate NVUGIB events. Large, population-wide studies are required to confirm this finding, which could impact future pharmacogenomic approaches to therapy of inflammatory conditions such as peptic ulcer disease.

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