RESEARCH LETTER

CYP2C19 Genotype Is Not Associated With the Risk of Microscopic Colitis

Microscopic colitis (MC) is a cause of chronic diarrhea, defined by grossly normal appearing mucosa with lymphocytic invasion or collagen deposition on histology.[1] The pathophysiology of MC remains unclear. Medications from diverse classes, including proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), histamine 2 receptor antagonists (H2RAs), 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs), have been described as potential causes of MC.[2–4]

These medications have varied mechanisms of action. As such, we hypothesized that altered drug metabolism may be the unifying feature to explain a potential association between medications and MC risk. A number of these drugs (PPIs, H2RAs, and SSRIs) are metabolized by the cytochrome P450 isoform CYP2C19. CYP2C19 genetic variants have been shown to alter enzyme activity and have been linked to differential therapeutic responses. For *Helicobactor pylori* treatment, individuals with CYP2C19 variants which result in "slow metabolism" of PPIs had 4 times the odds of eradication of *Helicobactor pylori* compared with individuals with "normal metabolism" (95% confidence interval [CI] 1.35–13.05).[5] Among patients with reflux esophagitis, CYP2C19 "rapid metabolism" phenotype was associated with 1.66 times the odds of lack of response to PPI (95% CI 1.02–2.66) compared with "poor metabolism."[6] In this study, we assessed whether the CYP2C19 genotype was associated with the odds of MC.

To investigate the relationship between CYP2C19 and MC, we performed a case-control study, as previously described.[7] Participants were identified among patients referred to the University of North Carolina Hospitals for elective outpatient colonoscopy for indication of diarrhea. Patients had to report loose to watery stool consistency during the week before colonoscopy to be included. We excluded patients with history of inflammatory bowel disease, evidence of gross inflammation on endoscopy, or clinical biopsies with neutrophilic or eosinophilic colitis. Participants completed detailed surveys with information on demographics, medical, surgical and reproductive history, prescription, and over-the-counter medication use in the prior year. Patients were classified as microscopic colitis cases or controls based on the reading of the study pathologist. The genotype of CYP2C19 was measured on consecutive cases and controls who had blood collected and completed the interview. Participants were categorized as extensive metabolizers (EM), intermediate metabolizers (IM), or ultrarapid metabolizers (UM) based on CYP2C19 genotype, as previously described (Supplemental Text).[8] "EM" were considered the reference group. Data analysis was conducted using Stata 17.0 (StataCorp).[9] Exposure variables were examined in univariate analysis using chi-squared (categorical) or *t* tests (continuous). We used logistic regression to calculate crude and adjusted odds ratios for microscopic colitis risk by CYP2C19 phenotype.

CYP2C19 genotype information was obtained on 45 cases of MC and 162 controls. The cases were older (mean age 64.3 years [standard deviation 12.0] vs 54.8 years [standard deviation 11.9]) and had a higher level of education (72.1% college or postgrad vs 63%) than controls. Cases were more likely to be female (82.2% vs 69.1%), to identify as White race (97.7% vs 87.7%), and to have lower body mass index (BMI; mean BMI 25.3 kg/m^2 [standard error 7.2] vs 29.4 kg/m^2 [standard error 7.2]) compared with controls. Non-MC controls were more likely to be current smokers (25.9% vs 14.0%). Marital status was not different between groups. Controls were more likely to use PPIs (50% vs 32.6%), NSAIDs (52.9% vs 44.2%), and H2RAs (20.3% vs 11.6%) compared with MC cases; however, these differences were not statistically significant after adjusting for age, sex, and education as previously reported.[7] SSRI and HMG-CoA reductase inhibitor use was not different between groups (Table A1).

We next examined the relationship between CYP2C19 phenotype and case-control status. There was no association between CYP2C19 phenotype by case-control status ($P = 0.126$). In an unadjusted model of CYP2C19 phenotype, ultrarapid metabolizers (UM) had twice the odds of microscopic colitis as compared to extensive metabolizers (EM; OR 2.21, 95% CI 1.01–4.84). The association was not significant when controlling for age, education, and BMI (adjusted OR 1.91, 95% CI 0.76–4.78; Table 1). Combining UM and IM to compare to EM further diminished the relationship (adjusted OR 1.65, 95% C1 0.71–3.81; Table A2).

Finally, we examined the relationship between CYP2C19 phenotype and medication use. There were no significant differences in odds of MC for those who reported using medications metabolized by CYP2C19 (PPI, H2RA, or SSRI) compared with those who did not use those medications (Table A3). This was true for all CYP2C19 subgroups: UM, IM, and EM, and across all medication groups.

Previous studies defining the degree of effect of medications on MC risk are inconsistent. For PPI, ORs range anywhere from 0.64[10] to 7.04,[3] with some variation attributable to the selection of controls. Overall, the results in this study are consistent with our primary analysis, which showed no association between medication use and MC risk.[7] Stratification by CYP2C19 genotype to examine for more specific differences in odds of MC did not modify this relationship.

Table 1. Odds of Microscopic Colitis by CYP2C19 Phenotype

Phenotype	Number of cases	Number of controls	Odds ratio	95% confidence interval	Adjusted odds ratio[a]	95% confidence interval
Extensive metabolizer	13	70	Reference	-	Reference	-
Intermediate metabolizer	11	41	1.44	0.59–3.52	1.29	0.45–3.71
Ultrarapid metabolizer	21	51	2.21	1.01–4.84	1.91	0.76–4.78

[a]Adjusted for age, education, and body mass index.

This study was limited by modest sample size and self-report of medication use. A larger sample size would allow for comparisons of interactions among drugs, such as in NSAIDs and PPIs. The modest sample size also limits the ability to detect small differences, which may be clinically meaningful. A future study could examine more genotypes, including those termed "poor metabolizers," which are not currently represented.[8] Finally, we examined only one of the cytochrome P450 isoforms; CYP3A4, CYP2C9, and CYP2D6 may be of interest because of their role in metabolism of HMG-CoA reductase inhibitors, NSAIDs, and beta blockers, respectively.

In conclusion, we conducted a case-control study of patients with microscopic colitis compared with controls with diarrhea to identify factors that may increase the risk of MC. We hypothesized that CYP2C19 genotype might explain a potential relationship between medication use and odds of MC. After adjusting for potentially confounding variables, we did not identify a relationship between CYP2C19 genotype and MC overall or stratified by medications. In the continued absence of a biological mechanism to explain why so many different classes of medicine are linked with MC, one might question whether these associations are true.

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Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.09.013.

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Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; EM, extensive metabolizers; H2RA, histamine 2 receptor antagonist; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; IM, intermediate metabolizers; MC, microscopic colitis; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; UM, ultrarapid metabolizers**

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2022.09.013

Received January 28, 2022. Accepted September 27, 2022.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
This research was supported, in part, by grants from the National Institutes of Health (P30 DK034987, R01 DK105114, T32DK007737).

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data will be available to other researchers.

Reporting Guidelines:
STROBE, SAGER.