Pretreatment *HLADQA1-HLADRB1* Testing for the Prevention of Azathioprine-Induced Pancreatitis in Inflammatory Bowel Disease: A Prospective Cohort Study

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INTRODUCTION: **Azathioprine-induced pancreatitis is an idiosyncratic and unpredictable response, occurring in up to 7% of azathioprine-exposed patients with inflammatory bowel disease (IBD). The haplotype *HLADQA1-HLADRB1*07:01A>C* is strongly associated with azathioprine-induced pancreatitis in IBD. We aimed to evaluate whether pretreatment *HLADQA1-HLADRB1*07:01A>C* screening will reduce the risk of azathioprine-induced pancreatitis.**

METHODS: **Participants with IBD were screened for *HLADQA1-HLADRB1*07:01A>C*, and participants with a variant genotype were excluded from azathioprine treatment. Wild-type participants were started on azathioprine and followed for 3 months. The incidence of pancreatitis was compared with unscreened historical controls.**

RESULTS: ***HLADQA1-HLADRB1*07:01A>C* screening resulted in an 11-fold reduction in the incidence of azathioprine-induced pancreatitis (n = 1/328 or 0.30% vs n = 13/373 or 3.4%). In propensity score-matched cohorts (age and sex), *HLA DQA1-HLADRB1*07:01A>C* screening was significantly associated with a reduction in the incidence of AZA-induced pancreatitis independent of weight, glucocorticoid exposure, and smoking status (adjusted odds ratio = 0.075, 95% confidence interval = 0.01–0.58, *P* = 0.01). Up to 45% (n = 271/599) of participants were excluded from azathioprine therapy based on the haplotype in the *HLADQA1-HLADRB1*07:01A>C*-screened cohort.**

DISCUSSION: ***HLADQA1-HLADRB1*07:01A>C* screening reduced the risk of azathioprine-induced pancreatitis; however, using this strategy to guide the use of azathioprine therapy in IBD may eliminate a large proportion of patients from being eligible for treatment with azathioprine. In regions where there is access to other IBD therapies, and given the short-term and long-term toxicities associated with azathioprine, *HLADQA1-HLADRB1*07:01A>C*-screening may be a clinically relevant strategy for enhancing the safe use of azathioprine in IBD. In addition, cost-effectiveness analyses are needed to further solidify the utility of *HLADQA1-HLADRB1*07:01A>C* screening in IBD populations.**

Clinical and Translational Gastroenterology 2021;12:e00332. https://doi.org/10.14309/ctg.0000000000000332

INTRODUCTION

The complexity of the immune-mediated inflammatory bowel diseases (IBDs), Crohn disease (CD), and ulcerative colitis (UC) extends beyond disease mechanisms and includes IBD drug pharmacodynamics. Interindividual responses to IBD medications vary significantly, and rates of adverse drug reactions (ADRs) remain high. Clinicians often rely on a test-and-treat strategy when selecting the best therapy for their patients because of the lack of clinical prediction tools. The inability to identify patients at risk of ADRs suggests a fundamental knowledge gap. Azathioprine (AZA) therapy has a long history of use in IBD (1). The need to promote its safe use in this population is ensured by governmental and private payer health policy requiring patients with IBD to fail low-cost drugs, such as AZA, before approving funding for more potent biologic therapies (2–6).

One approach for encouraging the safe use of AZA in IBD is the increasing advocacy by professional groups and governmental agencies for the use of thiopurine S-methyltransferase

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Received November 17, 2020; accepted February 17, 2021; published online April 5, 2021

(*TPMT*) genetic screening and dose reducing or avoiding its use in the highest risk patients (7–9).

Unfortunately, there are no tools in clinical practice to identify individuals at risk of AZA-induced pancreatitis. This is an idiosyncratic and unpredictable response, occurring in up to 7% of AZA-exposed patients that can lead to patient morbidity, hospitalization, delay in effective IBD management, and result in substantial additional health-related costs (10–12). Heap et al. (13) identified a strong association between a class II *HLA* gene region polymorphism (rs2647087) and AZA-induced pancreatitis in an international IBD population. This association was independently validated in our own retrospective IBD cohort (14). To date, the utility of screening individuals with IBD for variation in *HLADQA1-HLADRB1* and excluding patients at high risk of AZA-induced pancreatitis has not been prospectively assessed. We aimed to evaluate whether *HLA DQA1-HLADRB1*07:01A>C* pretreatment genotype testing in an adult IBD population before AZA therapy to guide AZA selection would result in a lower incidence of AZA-induced pancreatitis.

MATERIALS AND METHODS

Subjects

A prospective cohort study was carried out in individuals with IBD seen at the London Health Sciences Centre, a tertiary care center affiliated with Western University, London, Ontario, Canada. Participants were assessed for eligibility and enrolled in the study between March 2017 and February 2020. Eligible participants were greater than 17 years of age, had a histopathological diagnosis of CD or UC with a need for consideration of AZA therapy, and had an unknown *HLADQA1-HLADRB1* status. In addition, participants had never received treatment with thiopurine (AZA or 6-mercaptopurine). Participants were excluded from the study because of the following exclusion criteria: a serum creatinine greater than 2 times the upper limit of normal, a known history of liver disease, or an alanine transferase or alkaline phosphatase greater than 2 times the upper limit of normal, a leukocyte count less than 3.0×10^9/L, a variant *TPMT* genotype, risk factors of pancreatitis (known gallstones, consuming more than 7 alcoholic beverages weekly, and pancreatitis-associated medications with the exception of 5-aminosalicylates or glucocorticoids), and missing data pertaining to their IBD diagnosis.

Ethical considerations

The study protocol was approved by the Western University Health Sciences Research Ethics Board. All subjects provided written and informed consent.

Haplotype analysis

A single blood sample was collected from each participant for DNA extraction and determination of their *HLA DQA1-HLADRB1*07:01A>C* haplotype. DNA was extracted from whole blood using the MagNA Pure Compact instrument (Roche, Laval, Quebec, Canada). A predesigned TaqMan allelic discrimination assay (Applied Biosystems, Carlsbad, CA) was used to determine the presence of wild-type and/or variant alleles in *HLA DQA1-HLADRB1*07:01A>C* (rs2647087). Each genotyping experiment included 3 positive controls and 1 negative control. Five percent of samples were genotyped in duplicate. All duplicated genotypes were in agreement.

Study procedures

High-risk variant carriers (A/C and C/C) were excluded from AZA therapy. Participants were followed for 3-month duration to assess for evidence of pancreatitis. AZA-associated pancreatitis typically occurs within the first month of exposure (13,14). AZA-induced pancreatitis was defined as follows: a minimum elevation in serum lipase 3 times the upper limit of normal with clinical symptoms of nausea, vomiting, and abdominal pain (15). The

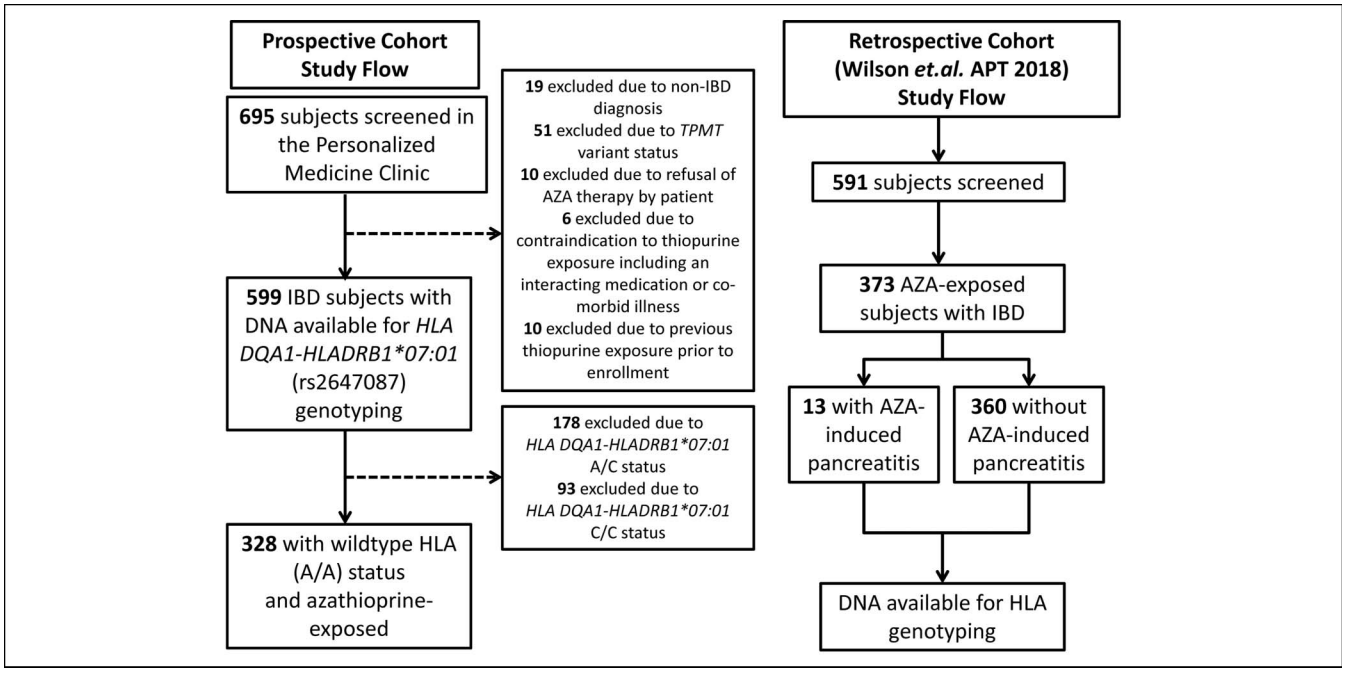

Figure 1. Study enrollment and follow-up. AZA, azathioprine; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; TPMT, thiopurine-S-methyltransferase.

Table 1. Demographic characteristics of patients being evaluated for azathioprine-induced pancreatitis

Variables	Preemptive genotyping cohort (n = 328)	Retrospective cohort (14) (n = 373)	*P*
Age, yr, mean (range)	42.4 (18–86)	41.3 (18–79)	ns
Female sex, n (%)	178 (54.0)	203 (54.4)	ns
Weight, kg, mean ± SD	79.3 ± 20.6	76.6 ± 18.8	ns
Crohn disease, n (%)	213 (65.0)	245 (65.7)	ns
Ileal	134 (40.9)	79 (32.2)	ns
Colonic	38 (11.4)	48 (19.6)	ns
Ileocolonic	156 (47.7)	118 (48.2)	ns
Ulcerative colitis, n (%)	115 (35.0)	128 (34.3)	ns
Pan-colitis	69 (60.0)	81 (63.3)	ns
Left-sided colitis	40 (35.0)	41 (32.0)	ns
Proctitis	6 (5.0)	6 (4.7)	ns
Median disease duration, yr (interquartile range)	3.67 (11.83)	3.96 (8.42)	ns
Smoking history, n (%)	114 (34.8)	153 (41.0)	ns
5-Aminosalicylate exposure, n (%)	145 (44.2)	160 (42.9)	ns
Biologic exposure, n (%)	189 (58.0)	224 (60.1)	ns
Anti-TNF	139 (74.0)	197 (88.0)	0.01
Anti-integrin	33 (17.0)	20 (9.0)	ns
Anti-IL12/23	17 (9.0)	7 (3.0)	ns
Combination therapy[a], n (%)	92 (28)	71 (18.9)	ns
Glucocorticoid exposure, n (%)	286 (87.2)	301 (80.8)	ns
Immunomodulator exposure, n (%)			
Methotrexate	37 (11.3)	55 (14.7)	ns
Thiopurine	328 (100.0)	373 (100.0)	ns
Surgery, n (%)	55 (16.8)	96 (25.7)	ns
HLA DQA1-DRB1 AA, n (%)	328 (100.0)	190 (50.9)	—
HLA DQA1-DRB1 AC, n (%)	0 (0.0)	142 (38.0)	—
HLA DQA1-DRB1 CC, n (%)	0 (0.0)	41 (11.0)	—

HLA, human leukocyte antigen; IL, interleukin; ns, not significant; TNF-α, tumor necrosis factor α.
[a]Combination therapy refers to the simultaneous administration of a biologic and an immunomodulator (one of methotrexate or azathioprine).

diagnosis of pancreatitis had to be made within 3 months of AZA exposure in the absence of other causative factors (alcohol, gallstones, and other drugs causing pancreatitis), as detailed in their medical record at the time of assessment.

The prospective cohort was compared with a group of participants enrolled in a retrospective cohort study published in 2018 by our group (14). Participants in the retrospective study were AZA-exposed patients with IBD genotyped for the *HLA DQA1-HLADRB1*07:01A>C* haplotype after AZA exposure. Subjects included in this cohort were recruited between 2012 and 2017.

Clinical data including age, sex, weight, smoking, duration of IBD, drug exposures, hospitalization, and surgeries were collected. In addition, data pertaining to any diagnosis of AZA-induced pancreatitis or other AZA-ADR were collected over the 3-month follow-up period. The primary outcome was the percentage of clinically diagnosed AZA-induced pancreatitis occurring within the 3-month observation period between the *HLA DQA1-HLADRB1*07:01A>C*-screened cohort and the unscreened, historical control population.

Statistical analyses

Statistical analyses were carried out using SPSS version 17.1 and R version 3.5.3. Given the reported frequency of AZA-induced pancreatitis in the literature (5%), a minimum of 230 participants and 293 participants were needed in the *HLA DQA1-HLADRB1*07:01A>C*-screened and control cohorts, respectively, to detect a 90% difference in the incidence of pancreatitis assuming a power of 80% with a 2-sided *P* value threshold of 0.05. Descriptive statistics were used to summarize data obtained for all cohorts. Propensity score matching was used to balance the distribution of the covariates age and sex between the *HLA DQA1-HLADRB1*07:01A>C*-screened and historical control cohorts based on the nearest available matching on the estimated propensity score method (16). The risk of AZA-induced pancreatitis associated with *HLA DQA1-HLADRB1*07:01A>C* screening vs not screening was evaluated in the matched cohort by logistic regression analysis with adjustment for weight, glucocorticoid exposure, and smoking status. A *P* value <0.05 was considered significant, and the results are expressed as the odds ratio (OR) with 95% confidence intervals (CIs).

RESULTS

Figure 1 highlights participant flow through the study. Overall, 599 individuals with IBD (UC, n = 210; CD, n = 389) were followed as part of the prospective cohort study and screened for the *HLA DQA1-HLADRB1*07:01A>C* haplotype. Of the 599 participants, 328 had the wild-type A/A haplotype and 271 had a variant haplotype (one of A/C or C/C). Only the wild-type participants from the *HLA DQA1-HLADRB1*07:01A>C*-screened cohort received AZA *and* were compared with the historical control population (n = 373). A total of 701 participants were included in the final analyses of the unmatched cohorts (*HLA DQA1-HLADRB1*07:01A>C*-screened cohort with an A/A genotype, n = 328; historical controls, n = 373), whereas 656 participants were included in the final analyses of the propensity-matched cohorts (*HLA DQA1-HLADRB1*07:01A>C*-screened cohort with an A/A genotype, n = 328; historical controls, n = 328). Demographic data are summarized in Table 1 for the unmatched cohorts. The minor allele frequency was 0.304 and 0.300 in the *HLA DQA1-HLADRB1*07:01A>C*-screened (before exclusion of the variant genotype carriers) and historical control cohorts, respectively. Other baseline characteristics were similar between the 2 groups except for tumor necrosis factor-α inhibitor (anti-TNF) exposure, where a greater number of individuals in the historical control cohort had been exposed to an anti-TNF agent vs the *HLA DQA1-HLADRB1*07:01A>C*-screened group (Table 1).

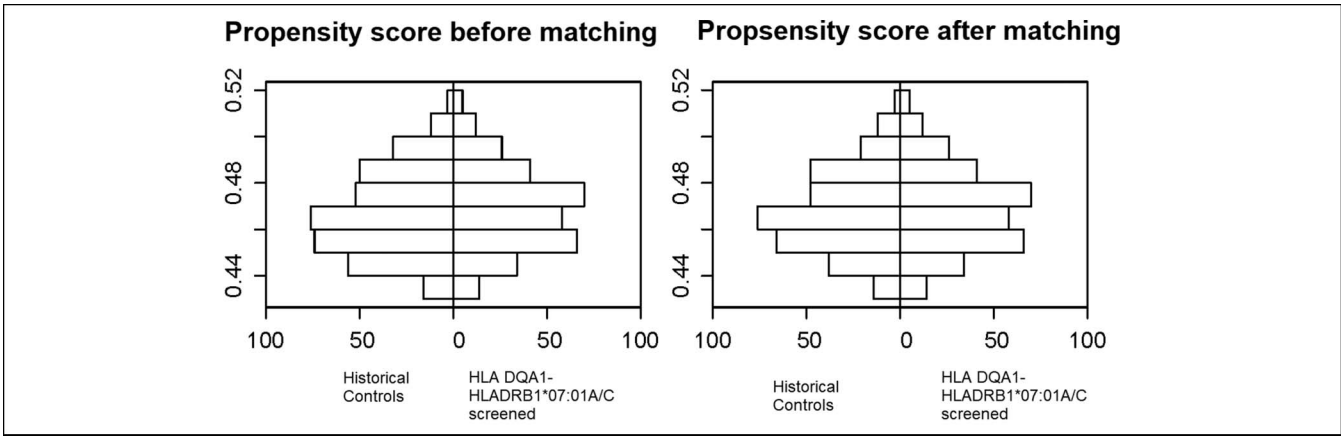

Figure 2. Histograms showing the propensity score distribution in the *HLA DQA1-HLADRB1*07:01A>C*-screened and unscreened cohorts before and after matching.

Twenty-three individuals in the *HLA DQA1-HLADRB1*07:01A>C*-screened group (with an A/A genotype, n = 328) reported nonpancreatitis ADRs that necessitated treatment cessation or dose reduction including hepatotoxicity (4/328), infection (6/328), nausea with or without vomiting (9/328), and myelosuppression (4/328).

Figure 2 highlights the propensity score distribution in the *HLA DQA1-HLADRB1*07:01A>C*-screened and historical control cohorts before and after matching based on the covariates age and sex. The incidence of AZA-induced pancreatitis in the unmatched cohorts was 0.30% (n = 1) in the *HLA DQA1-HLADRB1*07:01A>C*-screened cohort and 3.4% (total n = 13/373; A/A, n = 1/190; A/C, n = 6/142, n = 6/41) in the historical control group. After matching the *HLA DQA1-HLADRB1*07:01A>C*-screened (n = 328) and historical control (n = 328) using the nearest available matching on the estimated propensity score method, *HLA DQA1-HLADRB1*07:01A>C* screening was significantly associated with a reduction in the incidence of AZA-induced pancreatitis independent of weight, glucocorticoid exposure, and smoking status (adjusted OR = 0.075, 95% CI = 0.01–0.58, $P = 0.01$). Estimates of the regression coefficients in the logistic regression are shown in Table 2. As expected, there was no difference in the incidence of AZA-induced pancreatitis in the wild-type individuals (A/A) in the *HLA DQA1-HLADRB1*07:01A>C*-screened cohort and the wild-type individuals (A/A) in the historical control cohort (n = 1 or 0.03% vs n = 1 or 0.05%; adjusted OR = 0.574, 95% CI = 0.036–9.25, $P = 1.00$). In the *HLADQA1-HLADRB1*07:01A>C*-screened cohort, the time-to-pancreatitis was 21 days in the sole-affected participant. In the historical control population, the median time to AZA-induced pancreatitis was 25 days (interquartile range, 11 days). All participants who developed pancreatitis required hospitalization, although the disease course was mild with a median length of stay of 2 days (interquartile range, 1). Drugs associated with pancreatitis were an exclusionary criterion, except for 5-aminosalicylates and glucocorticoids. Of the participants who developed pancreatitis, 42.9% (n = 6/14) were concurrently on prednisone vs 83.4% (n = 573/687) of the participants who did not develop pancreatitis. None of the participants who developed pancreatitis were receiving concurrent therapy with a 5-aminosalicylate at the time of pancreatitis diagnosis.

DISCUSSION

Acute pancreatitis remains a prevalent source of hospitalization and morbidity worldwide (17). Drug-induced pancreatitis, although a less common etiology, is being increasingly recognized for its importance because of the expanding number of traditional and homeopathic medications available and the increasing prevalence of chronic illnesses requiring long-term pharmacologic therapy (18). AZA is a well-established cause of drug-induced pancreatitis (18).

There is increasing recognition of the potential value of *HLA DQA1-HLADRB1*07:01A>C* screening for identifying individuals at high risk of AZA-induced pancreatitis; however, its role as a predictive tool for guiding application of AZA therapy in IBD has not been established (19). In this first prospective study, we show that the incidence of AZA-induced pancreatitis can be significantly reduced in a population screened for variation in *HLADQA1-HLADRB1*07:01A>C*, where the haplotype is used to guide AZA treatment. An 11-fold reduction in the incidence of AZA-induced pancreatitis is seen in the total population of *HLA DQA1-HLADRB1*07:01A>C*-screened participants.

For the purposes of this study, all variant carriers (A/C and C/C) were treated as though of equal risk of pancreatitis and excluded from AZA therapy. This is despite the fact that in past retrospective studies, pancreatitis risk is several-fold higher in homozygous variant carriers (C/C) (13,14). In this study, the prevalence of the combined variant genotypes (A/C and C/C) was

Table 2. Estimates of the regression coefficients in a logistic regression model for the age and sex propensity score-matched cohort (n = 656)

Variables	Estimate	SE	*P*
Intercept	−3.94	1.22	0.001
*HLA DQA1-HLADRB1*07:01A>C*-screened	−2.59	1.04	0.01
Glucocorticoid exposure	−0.56	0.62	0.36
Smoking status	0.16	0.56	0.78
Weight, kg	0.01	0.01	0.29

HLA, human leukocyte antigen.

45.2% and 49.1% in the *HLADQA1-HLADRB1*07:01A>C*-screened and historical control populations, respectively. In clinical practice, this would translate to 40%–50% of patients being ineligible for treatment with AZA and requiring alternate treatments such as methotrexate in CD, tofacitinib in UC, or a biologic agent for either condition. Some may take issue with the idea of eliminating AZA from the IBD armamentarium for a large number of patients. One possible solution, whether *HLADQA1-HLADRB1*07:01A>C* screening is adopted, may be to avoid AZA therapy in *only the highest risk population* (those with a C/C genotype) and accept the slightly higher risk of AZA-induced pancreatitis (~4%) in those with an A/C genotype. However, emerging recommendations from professional IBD groups and regulatory agencies continue to emphasize that AZA be avoided as monotherapy in patients with IBD because of its associated drug-related toxicities and increasingly recognized lack of efficacy (7,20,21). In addition, its use in combination with anti-TNF agents has been demonstrated to be associated with a substantial increased risk of infection and malignancy over time (22,23). This has led to the exploration of the possibility and timing of treatment deescalation whereby AZA or methotrexate is stopped and the anti-TNF is continued as monotherapy for disease control (24). These points, as well as the increasing number of novel agents being approved for use in IBD, highlight the diminishing role of AZA in IBD and the need to select for its use under the safest of conditions.

In addition, *HLA DQA1-HLADRB1*07:01A>C* screening is relatively inexpensive. The cost of genotyping at our local facility is $43.75 (CAD) per genotyping test per patient, whereas the costs associated with hospitalization for acute pancreatitis alone can extend above $10,000 US ($13,134 CAD) per patient (11,25). In our population, this would have led to important upfront cost savings (genotyping costs for 701 patients, $30,668.75 CAD and estimated hospital costs for 1 acute pancreatitis admission, $13,134 CAD vs $170,742 CAD for 13 acute pancreatitis hospital admissions). The costs related to delays in IBD management or alternate drug selection are unknown. For completeness, we recognize that a cost-effectiveness analysis is needed to further solidify the utility of *HLA DQA1-HLADRB1*07:01A>C* screening in IBD populations for guiding AZA therapy. This would ensure that genetic screening and the downstream effects on treatment selection would not lead to higher costs as a trade-off for avoiding a significant, but less common ADR.

Key strengths of this study are its prospective design and cohorts reflective of real-world IBD populations. This enhances the translatability of this strategy to clinical practice if the appropriate infrastructure and access are in place. In addition, the rate of pancreatitis in the historical controls mirrors the rates of AZA-induced pancreatitis seen in other IBD studies and validates that the findings in the prospective cohort are not over-inflated (12,26).

Conversely, the use of a historical control for comparison is a limitation. However, there was little difference between the patient populations or the standard of IBD care between the 2 cohorts, thus minimizing the risk of chronology bias. In addition, propensity score matching was used to balance the covariates age and sex in the matched cohorts to reduce bias.

Accordingly, *HLA DQA1-HLADRB1*07:01A>C* screening substantially reduced the risk of pancreatitis during AZA treatment in patients with IBD. However, using this strategy may eliminate a large proportion of patients with IBD from being eligible for treatment with AZA. In regions where there is access to other IBD therapies, and given the significant short- and long-term toxicities associated with AZA, *HLA DQA1-HLADRB1*07:01A>C* screening may be a clinically relevant strategy for enhancing the safe use of AZA in IBD. In addition, cost-effectiveness analyses are needed to further solidify the utility of *HLA DQA1-HLADRB1*07:01A>C* screening in IBD populations.

CONFLICTS OF INTEREST

Guarantor of the article: Aze Wilson, MD, PhD.

Specific author contributions: R.B.K.: supervised the study. A.W., J.C.G., T.P., N.C., B.Y., M.S., and M.B.: involved in data acquisition. A.W.: responsible for the study concept and design. Q.W. and A.W.: carried out all data analyses. R.B.K. and A.W.: involved in data interpretation. A.W.: drafted the article. R.B.K., J.C.G., T.P., N.C., B.Y., M.S., and M.B.: carried out critical revisions. All authors had full access to all the data. All authors reviewed and approved the final version of this article.

Financial support: This work was supported by the Wolfe Medical Research Chair in Pharmacogenomics (R.B.K.), Ontario Research Fund-Research Excellence (Round 8 to R.B.K.), and the Academic Medical Organization of Southwestern Ontario (INN18-005 to R.B.K. and A.W.; S17-004 to A.W.).

Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Azathioprine is associated with a drug-induced pancreatitis in up to 7% of patients with inflammatory bowel disease (IBD).
- ✓ The haplotype, *HLADQA1-HLADRB1*07:01A>C*, is associated with azathioprine-induced pancreatitis in patients with IBD.
- ✓ The impact of screening for the *HLADQA1-HLADRB1*07:01A>C* haplotype to guide azathioprine prescribing in IBD is unknown.

WHAT IS NEW HERE

- ✓ Using the *HLADQA1-HLADRB1*07:01A>C* haplotype as a screening tool in patients with IBD to guide the use of azathioprine significantly reduces the incidence of azathioprine-induced pancreatitis.

TRANSLATIONAL IMPACT

- ✓ *HLADQA1-HLADRB1*07:01A>C* screening may be a useful tool for avoiding an important azathioprine-associated adverse event.

ACKNOWLEDGMENT

We kindly acknowledge the generous contributions of the members of the Western University Gastroenterology Division.

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