Role of Thiopurine S-Methyltransferase Genotyping Prior to Thiopurine Initiation in Inflammatory Bowel Disease Patients at University of Chicago Medicine

Ashlee Vaclavik, PharmD, Caleb Navarro, PharmD, Alaina Tarantino, PharmD, BCPS
The University of Chicago Medicine

Background

- Inflammatory bowel disease (IBD) is an autoimmune disorder often treated with thiopurines (azathioprine or mercaptopurine)
- The enzyme thiopurine S-methyltransferase (TPMT) is responsible for metabolizing thiopurines
- TPMT enzyme deficiency is associated with an increased risk of adverse effects (ADE), particularly cytopenias and infections
- The American Gastroenterological Association recommends routine TPMT testing prior to thiopurine initiation to guide dosing, however this is a conditional recommendation based on low quality evidence

Objective

- To identify how prescribers at University of Chicago Medicine (UCM) are using TPMT testing results to guide thiopurine dosing and potential areas for improvement in managing thiopurine therapy

Methods

Primary Outcome
- Maximized thiopurine dosing based upon measured TPMT enzyme activity

Secondary Outcomes:
- Adverse effects (ADE)
- Discontinuation rates due to ADE

Study Design
- Single center, retrospective chart review of IBD patients seen at UCM and prescribed a thiopurine between June 1, 2022 and June 1, 2023
- IBD included either Crohn's Disease, ulcerative colitis, or microscopic colitis

Data and Statistical Analysis
- A chi-squared test was used to compare proportions of patients who underwent TMPT activity testing and reached the maximum weight-based dose of a thiopurine to those who did not
- Fisher's exact tests were used to analyze secondary outcomes
- A Freeman-Halton extension was used to factor immunosuppressive therapy into the outcome

Results

Figure 1: **Comparing Rates of Adverse Effects Among Those With Known TPMT Status and Those Without**

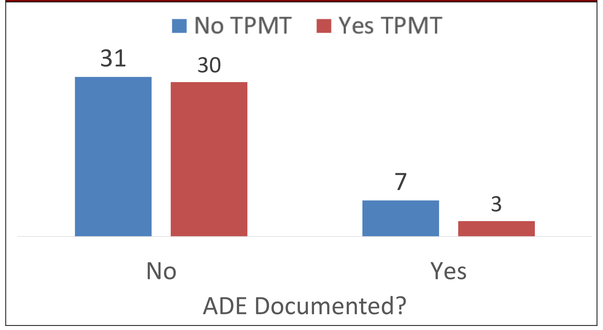

Figure 2: **Comparing Rates of Adverse Effects Among Those With Known TPMT Status and Those Without in the Setting of Concurrent Immunosuppressive Therapy with a Biologic Agent**

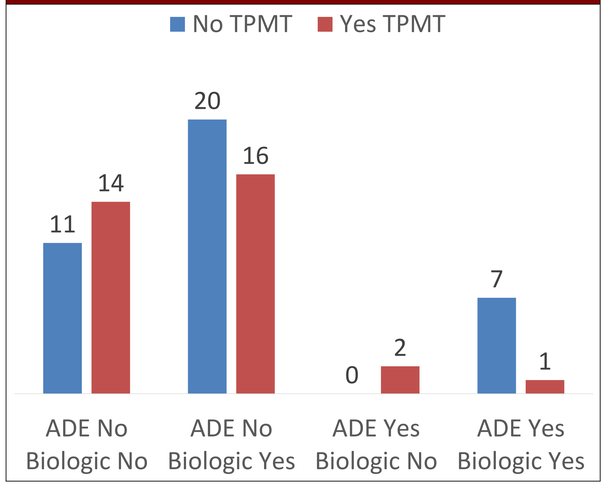

Table 1: Adverse Effects

	Known TPMT Status N=33 (46%)	Unknown TPMT Status N=38 (54%)
Hematologic Toxicity	1 (3%)	4 (11%)
Liver Dysfunction	2 (6%)	1 (3%)
Other	0 (0%)	2 (5%)

Table 2: Baseline Characteristics

	Known TPMT Status N=33 (46%)	Unknown TPMT Status N=38 (54%)
Age, y	46.5 [23-74]	44 [22-82]
Female Male	17 (52%) 16(48%)	23 (61%) 15 (39%)
Weight, kg	75.4 [54.4-205.7]	75.4 [49-145.2]
Crohn's Disease Ulcerative Colitis Microscopic Colitis	20 (61%) 11 (33%) 2 (6%)	22 (58%) 14 (37%) 2 (5%)
TNF-α	17 (52%)	27 (71%)
AZA 6-MP	24 (73%) 9 (27%)	27 (71%) 11 (29%)
Normal metabolizer Intermediate metabolizer	25 (76%) 8 (24%)	-
AZA mg/day, mg/kg/day 6-MP mg/day, mg/kg/day	112.5, 1.41 75, 1.01	100, 1.34 75, 0.97

Table 3: Endpoints

	Known TPMT Status N=33 (46%)	Unknown TPMT Status N=38 (54%)	
Maximized thiopurine dose	10 (30%)	10 (26%)	X2 (1, 71) =0.14, p=0.71
Experienced ADE	3 (9%)	7 (18%)	Fisher's exact p=0.32
Experienced ADE and concomitant biologic therapy	1 (3%)	7 (18%)	Fisher's exact p=0.06

Conclusions

- There was no relationship between TPMT testing and weight-based dose maximization by prescribers
- There were no reports of discontinuation due to ADE in either group
- Twice as many patients without known TPMT status experienced ADE compared to those with known TPMT status
- TPMT activity should be used from a safety standpoint to identify patients at risk of ADE from thiopurines prior to initiating therapy
- TPMT activity should be assessed from a safety standpoint when thiopurines are utilized to prevent antibody formation to biologic agents
- Future studies should continue to evaluate thiopurine use and the utility of TPMT testing to prevent adverse effects when used concurrently with biologic agents

Limitations

- Does not capture patients in whom thiopurine therapy was avoided due to result of deficient TPMT enzyme activity
- Small sample size resulted in outcomes that were not statistically significant
- Reported self-discontinuation may be related to an undocumented/unreported ADE
- There was possible confusion differentiating between TPMT activity tests and TPMT metabolite tests among prescribers when ordering the blood draw

References

1. Lewis JD, Abramson O, Pascua M, et al. Timing of myelosuppression during thiopurine therapy for inflammatory bowel disease: implications for monitoring recommendations. Clin Gastroenterol Hepatol. 2009 Nov;7(11):1195-201.
2. Feuerstein JD, Nguyen GC, Kupfer SS, et. al. American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017 Sep;153(3):827-834.

Disclosures

The authors of this presentation have no financial interests with commercial entities that may have a direct or indirect interest in the subject matter of this presentation