EVIDENCE-BASED GI
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Thiopurine use in IBD patients associated with one additional case of acute myeloid leukemia/ myelodysplastic syndrome per about 7500 patient-years of use

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STRUCTURED ABSTRACT

Question: Do thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) increase the risk of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in inflammatory bowel disease (IBD) patients?

Design: Retrospective cohort study using nationwide electronic medical record data

Setting: US Veterans Affairs Healthcare System

Patients: 56,314 Veterans with Crohn's disease or ulcerative colitis diagnosed between 2000-18 based on ICD-9/ICD-10 codes

Exposure/Intervention: (a) never exposed to thiopurines; (b) past use of thiopurines; (c) current use of thiopurines < 2 years; or (d) current use of thiopurines $\geq$ 2 years

Outcome: AML or MDS initially identified by ICD codes and/or CPT codes followed by review of individual patient records.

Data Analysis: Multivariable Cox proportional hazards regression model in order to reduce confounding of the results by age, sex, race, IBD subtype, other IBD medications, medical comorbidities, and environmental/military toxic exposures

Funding: Pfizer pharmaceutical company provided an unrestricted research grant. Pfizer had no role in any portion of study.

Results: Among 56,314 veterans with IBD, 107 subsequently developed AML/MDS. Compared to no exposure to thiopurines, current thiopurine use was associated with 2-3X higher adjusted rates of AML/MDS. Adjusted HR = 3.05 (95% CI: 1.54-6.06) for < 2 years of use and adjusted HR = 2.32 (95% CI: 1.22-4.41) for > 2 years of exposure. Overall, risk is still quite low with AML/MDS rate of 17.0 per 100,000 person-years of follow-up in IBD patients at baseline and 1 additional case of AML/MDS for approximately 7500 person-years of thiopurine exposure (Table 1).

Table 1. AML/MDS Diagnoses

Thiopurine exposure	Rate per 100,000 person-years (95% CI)*	Adjusted hazard ratio	Person-years of thiopurine use to cause one additional AML/MDS diagnosis*
Never	17.0 (16.9 - 17.1)	REF	REF
Current, <2 years cumulative use	30.4 (29.8 - 31.0)	3.1 (1.5 - 6.1)	7463
Current, ≥2 years cumulative use	30.3 (29.8 - 30.9)	2.3 (1.2 - 4.4)	7519
Past	17.7 (17.4 - 18.0)	1.5 (0.8 - 2.7)	N/A

Notes: Adapted from Tables 2 and 3 from N. Khan et al. Am J Gastroenterol 2021
* Unadjusted

Why is this important? Thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) have been a mainstay of inflammatory bowel disease (IBD) treatment for decades. However, because they are only moderately effective as monotherapy and because of the growing availability of biologic and biosimilar agents, the future role of thiopurines for IBD treatment is uncertain. Furthermore, thiopurines are associated with multiple adverse effects of pancreatitis, non-melanoma skin cancer, lymphoma, and myelosuppression. Although myelosuppression is a known adverse event, no prior well-designed studies are available to estimate the risk of AML/MDS with thiopurines.

This rigourous study has several strengths which increase the likelihood of producing accurate and unbiased results:

- Cohort: The older age of the veteran cohort enhances the study's statistical power to detect a potential association between thiopurine use and AML/MDS because AML/MDS is more common in elderly individuals. Additionally, the algorithm used to identify veterans with IBD has previously been validated and demonstrated to have 95% positive predictive value[1].

- Exposure (thiopurine use): Because many veterans who receive healthcare through the Veterans Affairs Healthcare System also have pharmacy benefits, the investigators likely correctly identified thiopurine use.

- Outcome (AML/MDS): The investigators validated all AML/MDS outcomes through chart review. Notably, only 107/344 patients identified with AML/MDS by administrative codes actually had AML/MDS subsequent to IBD. Other studies relying solely on administrative codes, such as studies using insurance claims data, could come to substantially different conclusions based on misclassification of the AML/MDS outcome.

***Key Study Finding*:** Current thiopurine use is associated with a 2-3X increase in the risk of AML/MDS in IBD patients. However, since the baseline risk of AML/MDS is very low in IBD patients, there is only about one additional AML/MDS case per 7500 person-years of thiopurine use.

Caution: Observational research studies always come with the caveat that association does not equal causation. A major area of weakness for many observational studies is inadequate control of confounding. This occurs when the association between the exposure and the outcome is actually due to the association of each of these with a third condition, called a confounder. In this study, the authors controlled for confounding by several relevant demographic and medical variables such as age and biologic IBD medication exposure. Although the etiology of AML/MDS is largely idiopathic, the strongest identified risk factors are chemical exposures, prior chemo- and radiation therapy, and certain genetic abnormalities. The investigators accounted for these using the data on environmental and military toxin exposure available in the electronic health record, but these are likely under-recorded as these

confounders potentially occurred decades prior to thiopurine use. However, the impact of confounding by these factors are likely to be small as they probably do not influence whether a veteran with IBD receives a thiopurine or not. A second limitation is the lack of data on thiopurine metabolism. Because many of the adverse effects of thiopurines are mediated by metabolites[2], stratification of the cohort by TPMT activity, TPMT genotype, or NUDT15 genotype[3] may help determine if there are subpopulations of patients with IBD who are at higher risk for thiopurine-induced AML/MDS.

***My practice*:** This rigorous study demonstrated a strong association between current thiopurine use and AML/MDS, which gives us pause when considering thiopurines for our patients—particularly the elderly and individuals with prior radiation exposure. However, since there is only one additional case per nearly 7500 person-years of thiopurine exposure, we individualize our decision-making and use combination therapy (e.g. thiopurine plus infliximab) if needed to control IBD disease activity while including this as a potential risk when educating IBD patients about risks of thiopurine therapy.

***For future research*:** Based on the association of thiopurines with non-melanoma skin cancer, lymphoma[4], and now AML/MDS plus the growing armamentarium of IBD medications, thiopurines may not be a major part of IBD therapy, especially for the elderly, in the near future.

References

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