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Incidence of Thiopurine-Induced Severe Myelosuppression in a Nationwide Cohort of Patients With Inflammatory Bowel Disease

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INTRODUCTION: **There is paucity of data on the incidence of severe thiopurine (TP)-induced myelosuppression (TIM) among patients with inflammatory bowel disease (IBD).**

METHODS: **Using the Veterans Affairs Healthcare System, we identified patients with IBD with normal pretreatment TP S-methyltransferase levels who received TPs for 6 months and developed severe TIM.**

RESULTS: **Among 73,392 patients with IBD, 14,760 had received TPs, and 2,823 had a normal TP S-methyltransferase level. The incidence rate of severe TIM was 1.25 per 1,000 patient-years.**

DISCUSSION: **The incidence of severe TIM was very low, calling into question the necessity of frequent long-term complete blood count monitoring among patients with IBD on TPs.**

KEYWORDS: thiopurines; myelosuppression; IBD

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INTRODUCTION

Thiopurines (TPs) (azathioprine and 6-mercaptopurine) are integral in the management of inflammatory bowel disease (IBD) (1). Myelosuppression is a side effect of TPs and a frequent reason for dose reductions and/or treatment discontinuation (1). The reported cumulative incidence of TP-induced myelosuppression (TIM) is 7% usually occurring within a few weeks to months of drug initiation (1,2). Pretreatment testing of enzyme TP S-methyltransferase (TPMT) is recommended to identify patients at risk of TIM. However, even in patients who have normal TPMT activity, European Crohn's and Colitis Organisation guidelines recommend monitoring white blood cell (WBC) counts every 2–3 months after 2 months of drug initiation (2). The British Society of Gastroenterology recommends a full blood count every 3 months (3).

These guidelines are primarily based on expert opinion, and there are limited data on the incidence of severe TIM among patients with IBD on long-term TP treatment. To address this unmet need, we aim to evaluate the incidence of severe myelosuppression among patients with IBD on long-term TP therapy with a normal TPMT level.

METHODS

We conducted a retrospective cohort study using the Veteran Affairs (VA) Healthcare System. Using a previously validated algorithm, we identified all veterans who were diagnosed with IBD from January 1, 2000, to March 4, 2024 (4).

Among this cohort, we specifically identified patients treated with TPs and included only those patients with pretreatment TPMT testing. TPMT enzyme level ≥15 U/mL red blood cell was considered normal. Among TP users with normal TPMT levels, we identified patients who developed severe TIM 6 months after initiation of TPs. Follow-up began 6 months after initiation of therapy because patients undergo frequent dose alternations and discontinuations within this period. Follow-up ended at the first of any of the following, whichever came first—(i) death, (ii) stopped TP, or (iii) end of the study period—May 31, 2024.

Severe TIM was defined as patients having a WBC count $<2,500/mm^3$ or absolute neutrophil count of $<1,000/mm^3$. Individual patients' charts were evaluated to ascertain whether there were any other concomitant factors that could cause myelosuppression. We excluded all patients who were on concomitant allopurinol. Ultimately, we included patients who had severe myelosuppression attributed to TP use only.

RESULTS

A total of 73,392 eligible patients with IBD were included in the VA Healthcare System. Of these, 14,760 patients with IBD had received TPs. Pretreatment TPMT testing was performed in 3,400 patients, and 2,823 patients had a normal TPMT level. Among

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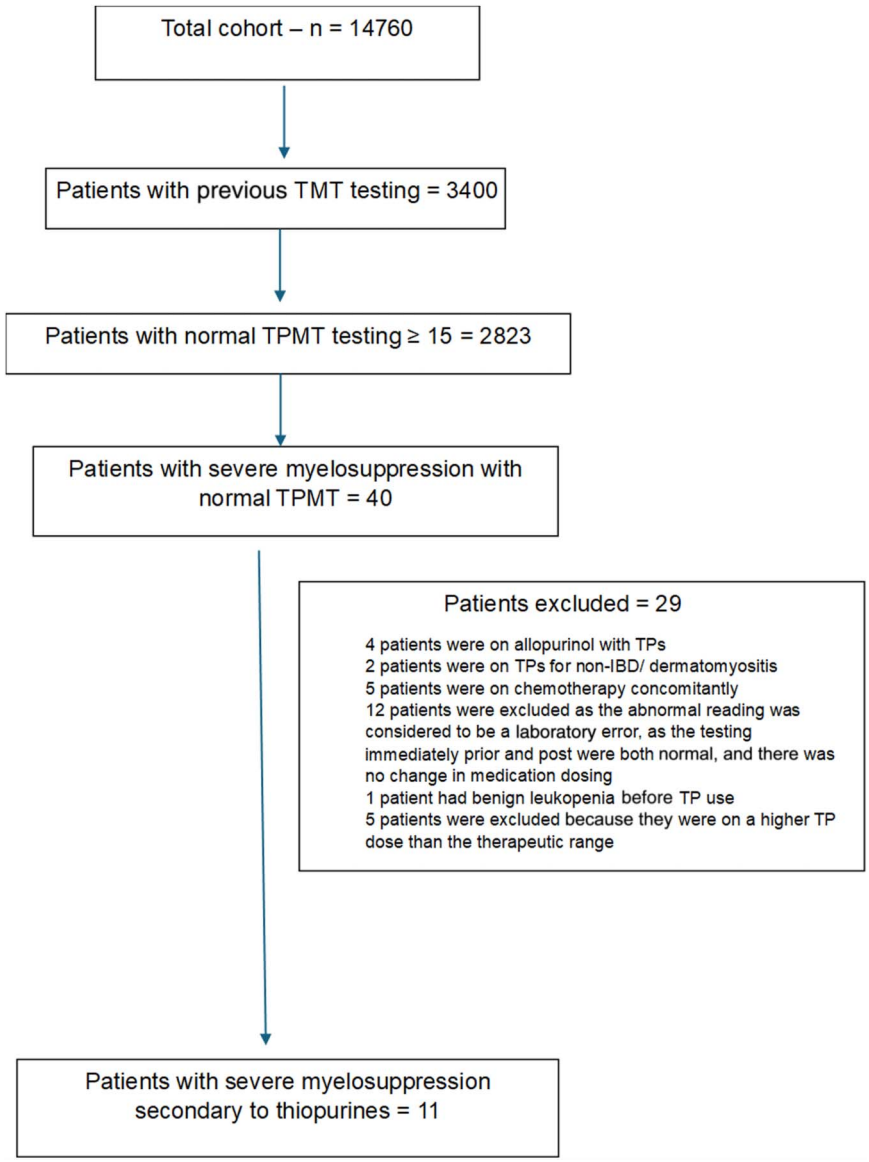

Figure 1. Patient disposition. IBD, inflammatory bowel disease; TIM, TP-induced myelosuppression; TP, thiopurine; TPMT, TP S-methyltransferase.

these patients with a normal TPMT level, 40 patients had severe myelosuppression. After manual adjudication through detailed chart review, only 11 patients were found to have severe myelosuppression secondary to TPs. Figure 1 shows a flow chart highlighting the reasons for exclusion in the remaining 29 patients. Table 1 represents the baseline characteristics of these 11 patients.

The incidence rate (IR) of severe myelosuppression among patients with a normal TPMT test was 1.25 per 1,000 patient-years (PY). The median time to severe myelosuppression was 11 months (range—7 to 41 months [Figure 2]). Seven (63.64%) patients had their TP dose reduced, after which their leukocyte count improved. There was no infection-associated hospitalization or outpatient encounter among these 11 patients.

DISCUSSION

In this study, the overall incidence of severe TIM in patients with normal TPMT levels was quite low at 1.25 per 1,000 PY. All patients who developed severe TIM were diagnosed during routine monitoring.

TPs are associated with adverse outcomes including certain malignancies and myelosuppression (5). The utilization of TPMT has reduced the risk of TIM and the need for dose modification at the start of therapy (6). However, long-term risk of TIM among patients with IBD maintained on TP therapy is unknown. A systemic review examined 66 studies and found that the cumulative incidence of severe TIM was 1.1% and the IR was 9 per 1,000 PY (1). However, none of these studies specifically investigated the IR of severe TIM in patients with a normal TPMT level.

Our study findings indicate a low incidence of severe TIM among patients with normal TPMT levels. The majority of those who had severe TIM recovered their counts with dosage adjustments. Current guidelines suggest WBC monitoring every 2–3 months after the passage of a few months after the initiation of TP (2,3). Based on our findings, we suggest that TP use is safe

Table 1. Baseline characteristics

Characteristics	N = 11
Male, n (%)	9 (81.82)
Race, n (%)	
White	11 (100.00%)
Age, yr, median (range)	50.60 (27.54–75.55)
Type of inflammatory bowel disease	
Ulcerative colitis	4 (36.36)
Crohn's Disease	7 (63.64)
Concomitant medications at baseline	
No drugs	2 (18.18)
Mesalamine	4(36.36)
Infliximab	2 (18.18)
Adalimumab	1 (9.1)
Vedolizumab	1 (9.1)
Ustekinumab	1 (9.1)
Drug details	
6-Mercaptopurine	3 (27.27)
Median dose, mg/kg	1.34 (0.77–1.47)
Azathioprine	8 (72.73)
Median dose, mg/kg	2.15 (1.50–2.46)

Data are presented as median (range) for continuous measures and n (%) for categorical measures.

among patients with normal TPMT levels and frequent WBC monitoring may not be required, especially in young patients, ultimately reducing the healthcare burden. There may be utility in testing for TIM among older male patients who have a higher risk of myelodysplasia (MDS) and in whom leukopenia precedes the development of MDS, but in younger patients, the risk of MDS is almost nonexistent (7). Another interesting aspect of our study was that only 23% of patients had a TPMT test performed before starting TPs. It highlights the importance of educating physicians and/or implementing an alert system for pretreatment TPMT testing.

The strengths of our study include the utilization of this large nationwide cohort, which included a geographically diverse patient pool from 170 VA healthcare centers across the United States, a comprehensive chart review to identify severe myelosuppression, and an extensive follow-up starting from January 1, 2000, to March 4, 2024, with a median follow-up of 35 months (range—0 months to 300 months) while being on TP therapy (8). The limitations of our study include the presence of a predominantly male cohort in the VA, thus limiting the external validity of the study. We were unable to evaluate for the *NUDT15* gene as this was not checked commonly, and it is also more prevalent in Asian and Hispanic populations (9). Similarly, TP metabolites were also rarely checked.

In conclusion, using a large nationwide cohort of patients with IBD, the incidence of severe TIM was very low in patients with normal TPMT levels. This calls into question the necessity for frequent CBC monitoring among younger patients with IBD on long-term TPs, who may be spared the inconvenience of getting blood draws every 3 months. The frequency of WBC monitoring could possibly be decreased to every 6 months after 1 year of initiation of therapy as was also suggested by 2 other studies (10,11).

CONFLICTS OF INTEREST

Guarantor of the article: Nabeel Khan, MD.
Specific author contributions: N.K. has participated in study supervision, study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. D.P. has participated in study concept and design, interpretation of data, drafting of the manuscript, and critical revision of the manuscript. R.S. has participated in study concept and design, acquisition of data, interpretation of data, and drafting of the manuscript. All the authors have reviewed and approved the final version of this article.
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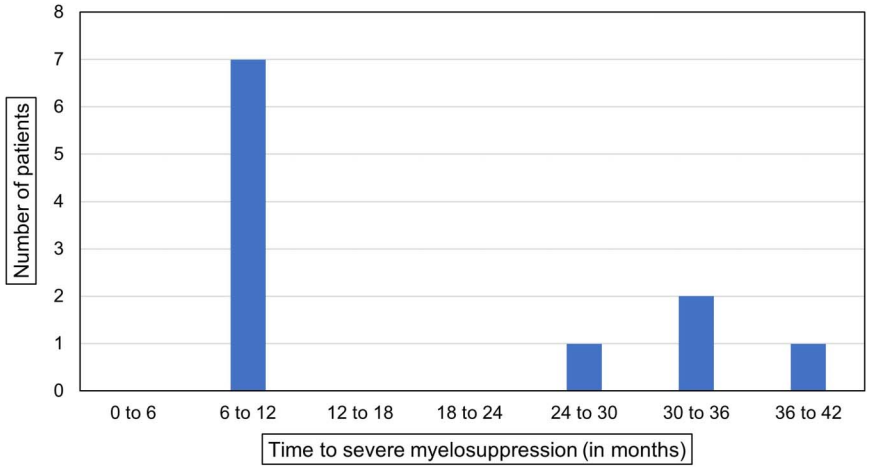

Figure 2. Time to severe myelosuppression.

Pharmacosmos. D.P. and R.S. have nothing to disclose regarding conflicts of interest.

Data availability statement: The data for this manuscript cannot be made available in accordance with the Health Insurance Portability and Accountability Act (HIPAA) rules. However, deidentified data (without patient name and SSN) can be made available on reasonable request.

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