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ORIGINAL ARTICLE

THE FREQUENCY OF THIOPURINE METHYL-TRANSFERASE POLYMORPHISM IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND ITS ASSOCIATION WITH AZATHIOPRINE INDUCED ADVERSE EFFECTS

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Abstract

Background: *Thiopurine S-methyltransferase (TPMT) is the rate-limiting enzyme in the metabolism of azathioprine (AZA). Genetic polymorphisms in TPMT can increase the risk of adverse effects from AZA. AZA is commonly used as an immunosuppressant to maintain remission in patients with Systemic Lupus Erythematosus (SLE). This study aims to investigate the frequency of TPMT polymorphisms in SLE patients .* ***Methods:*** *This post hoc case–control study was conducted at Bangladesh Medical University and the University of Dhaka from July 2022 to January 2023. Adults (18–65 years) fulfilling American College of Rheumatology criteria for SLE were enrolled. TPMT genotyping was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). Patients were assigned to AZA (n = 120) or non-AZA (n = 217) groups. Exclusion criteria included recent blood transfusion, use of drugs causing myelosuppression or interfering with AZA/6-MP metabolism, concomitant cyclosporine or mycophenolate mofetil therapy, and pregnancy. AZA was initiated for clinical indications at 1 mg/kg/day, escalated to 2 mg/kg/day after two weeks, and continued with four-weekly assessments for 12 week.* ***Results:*** *The mean age of the AZA group was 28.4 ± 9.5 years; 96.65% were female. TPMT polymorphisms were detected in 12 patients (3.56%), all carrying the TPMT*3C allele. Ten patients developed myelosuppression; among AZA-treated patients with TPMT polymorphisms, six of seven (85.7%) developed myelosuppression. Overall, 16 patients (14.4%) develop AZA-related adverse effects.* ***Conclusion:*** *TPMT polymorphisms were uncommon in this study but strongly associated with AZA-induced myelosuppression. Pre-treatment genotyping may improve the safety of AZA therapy in SLE patients.*

Keywords: *Thiopurine Methyltransferase Polymorphism, TPMT polymorphism, Azathioprine, SLE, Myelosuppression*

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Introduction

Systemic lupus erythematosus (SLE) develops due to activation of autoreactive B and T cells, resulting in loss of self-tolerance.[1] This leads to the production of pathogenic autoantibodies directed against nucleic acids and associated proteins.[2] Understanding the pathogenesis of SLE and the role of thiopurine *S*-methyltransferase (TPMT) polymorphisms is essential for optimizing treatment and reducing adverse effects. TPMT testing prior to azathioprine (AZA) therapy can decrease the risk of drug-related toxicity.

Survival in SLE has improved with the development of new therapies; however, mortality remains higher in patients with SLE compared with the general population.[3] Immunosuppressive agents remain the cornerstone of SLE management, and AZA is an important drug for both induction and maintenance therapy.[4] AZA is the only purine analogue used in SLE for renal involvement, mucocutaneous manifestations, thrombocytopenia, and autoimmune haemolytic anaemia. It is also indicated in pregnancy and as maintenance therapy in patients requiring higher steroid doses (prednisolone ≥15 mg).[5]

TPMT is an enzyme responsible for metabolizing and inactivating AZA's active metabolite, thioguanine nucleotide (TGN). Individuals carrying two non-functional TPMT alleles may accumulate excessive TGN, leading to severe toxicity and potentially life-threatening myelosuppression.[6] Common adverse effects of AZA include nausea, vomiting, hepatotoxicity, rash, and myelosuppression.[7] In one SLE study, AZA was discontinued in three patients due to leukocytopenia.[8]

Genetic polymorphisms in TPMT, principally TPMT*3A, TPMT*3C, and TPMT*2, account for 80–95% of variant alleles and are associated with reduced enzymatic activity, helping to predict myelosuppression.[9] However, TPMT genotype alone does not fully explain myelosuppression, which may also result from drug–drug interactions with agents such as metronidazole, allopurinol, non-steroidal anti-inflammatory drugs, mesalamine, and co-trimoxazole.[10] TPMT testing can improve treatment adherence, reduce complications, and enhance disease control in SLE.[11] It is underutilized and often not feasible in low-resource settings, where monitoring with complete blood counts (CBC) remains essential for detecting cytopenias. To our knowledge, no previous study has evaluated TPMT polymorphisms and AZA-related adverse effects in our population. This study aimed to observe adverse effects, TPMT polymorphisms, and disease status in SLE patients.

Methods

This post hoc case–control study, was conducted in the department of rheumatology at Bangladesh Medical University and the Pharmacokinetics and Pharmacogenetics Laboratory, Department of Pharmacy, University of Dhaka. The study period was from July 2022 to January 2023. A total of 337 individuals were included, comprising patients with systemic lupus erythematosus (SLE) attending both outpatient lupus clinics and inpatient medicine units. A convenient sampling technique was employed to recruit eligible participants.

For the post hoc case–control analysis evaluating the association between TPMT polymorphism and azathioprine (AZA)–induced myelosuppression, a two-proportion power calculation was performed (expected event rates: 80% vs. 2%; power = 80%; á = 0.05), demonstrating that at least six participants per group were required, consistent with established methods for rare genotype comparisons. The study included seven TPMT-mutant cases and 330 wild-type controls, providing adequate statistical power for the secondary analysis.

Patients who give has given informed consent and fulfilled the updated 2019 revised American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for systemic lupus erythematosus (SLE) were eligible for inclusion. Patients were excluded if they declined participation, had recently received a blood transfusion, were taking any medication known to cause myelosuppression, or were using drugs that interfere with the metabolism of azathioprine (AZA) or 6-mercaptopurine (6-MP), such as allopurinol or certain diuretics. Additional exclusion criteria included concomitant therapy with cyclosporine or mycophenolate mofetil, as well as pregnancy. A schematic overview of participant selection and study procedures is presented in Figure 1, and the workflow for thiopurine methyltransferase (TPMT) genotyping is shown in Figure 2.

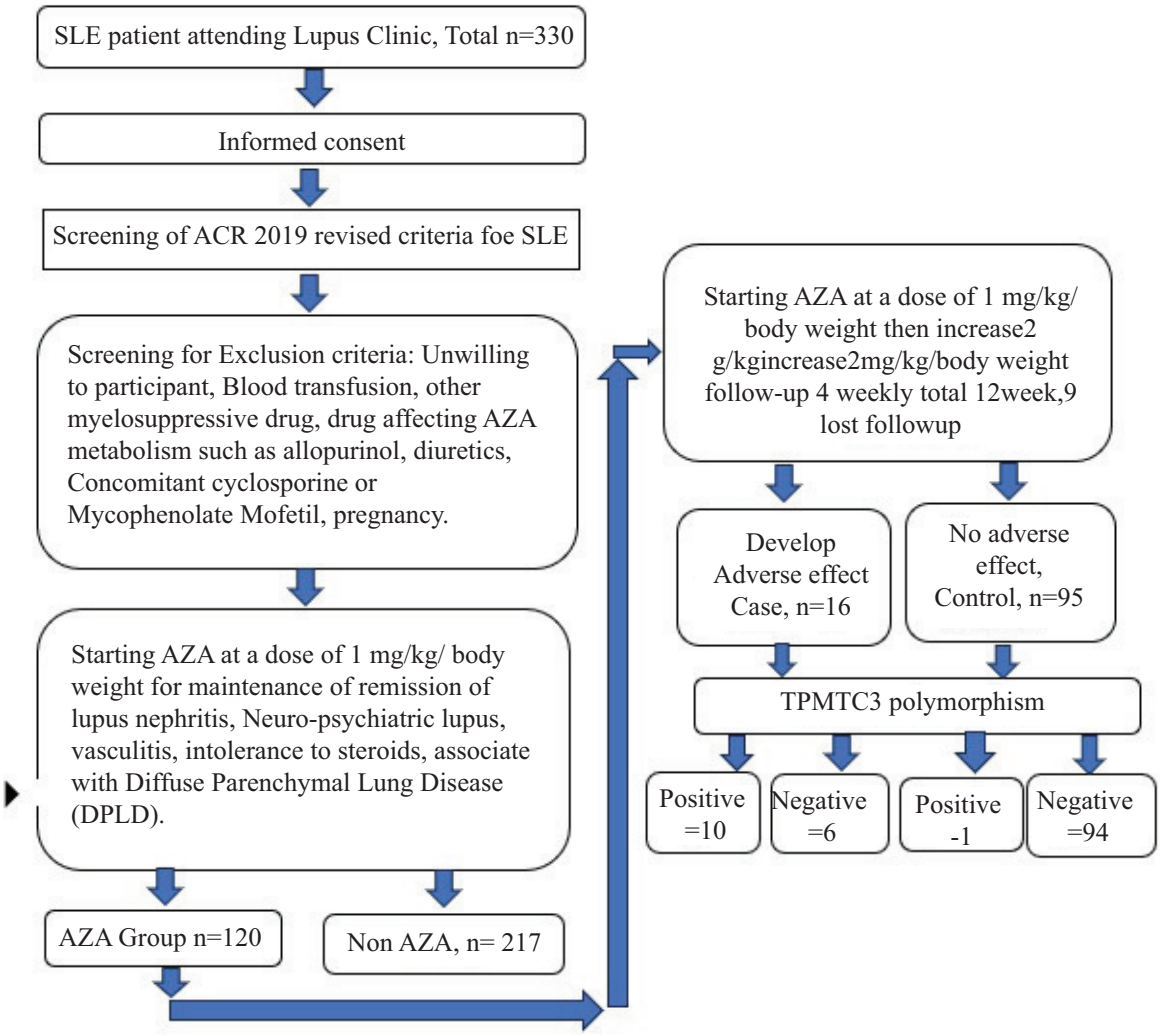

Figure 1: *Patient selection procedure (EULAR)*

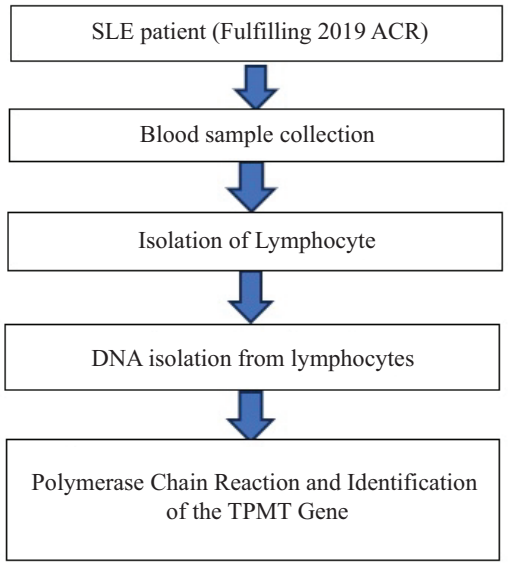

Figure 2: Flow chart of TPMT testing.

Patients were initiated on azathioprine when clinically indicated, including maintenance therapy for lupus nephritis, neuropsychiatric lupus, vasculitis, steroid intolerance, or associated diffuse parenchymal lung disease (DPLD). AZA therapy was started at 1 mg/kg/day, increased to 2 mg/kg/day at the two-week follow-up, and continued thereafter with scheduled assessments every four weeks for a total duration of 12 weeks.

TPMT Genotyping: Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. TPMT genotyping was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), a validated and widely used method for detecting TPMT polymorphisms. PCR primers targeted known TPMT alleles (TPMT2, TPMT3A, TPMT3B, TPMT3C).

The patient met indications for azathioprine (AZA) for maintenance of remission in lupus nephritis,

neuropsychiatric lupus, vasculitis, steroid intolerance, and associated diffuse parenchymal lung disease (DPLD). AZA was started at 1 mg/kg/day, increased to 2 mg/kg/day at the two-week follow-up, and continued with four-weekly follow-ups for a total of 12 weeks. Figure 1 and 2 shown patient selection and TPMT testing.

Patients were carefully selected from the SLE clinic and inpatient services at BSMMU under the supervision of the study investigators. Only patients capable of providing a complete and reliable medical history were interviewed; individuals who were mentally unstable, too ill to communicate, or lacking essential medical records were excluded. Information obtained from interviews was cross-checked against medical records to ensure accuracy.

The study procedures and objectives were explained to all participants before enrollment. Written informed consent was obtained from each patient, and all individuals received appropriate clinical evaluation and treatment during the study. Each participant was assigned a unique identification number to maintain anonymity. Participation was voluntary, and patients were free to refuse or withdraw at any time without affecting their standard of care.

To verify medication adherence, patients were asked to present empty azathioprine blister strips at each follow-up visit. Data collected through the structured questionnaire were routinely reviewed for completeness and consistency, ensuring adherence to standardized interviewing procedures. Any modifications to the questionnaire or data collection process were undertaken following guidance from the supervising investigator. A midterm assessment of the study was conducted to evaluate the uniformity and reliability of data collection. In cases where information was incomplete or unclear, patients were re-interviewed to obtain the required details. All data were thoroughly cleaned and validated prior to computer entry and statistical analysis.

Simple descriptive measures like percentage, mean, and standard deviation of different variables were calculated. Variables were described as mean and standard deviation for quantitative data. The chi-square test was used to compare the prevalence of polymorphism alleles in SLE patients who received and did not receive AZA. The Mann-Whitney test was used for nonparametric data. A Z test was used to compare the proportion. The difference between means was compared using the Mann-Whitney U test. A p-value less than or equal to 0.05 was considered significant. All data analysis was done using the SPSS/PC statistical software package.

Results

Azathioprine (AZA) is an important immunosuppressive agent widely used in the management of systemic lupus erythematosus (SLE). Patients carrying thiopurine S-methyltransferase (TPMT) gene polymorphisms are known to be at increased risk of developing significant AZA-induced myelosuppression. This study aimed to determine the prevalence of TPMT gene polymorphisms among SLE patients. A total of 348 patients were initially enrolled, but 11 were excluded due to sample preservation issues, resulting in a final cohort of 337 patients.

Among these, 120 patients received AZA therapy. Nine were lost to follow-up, leaving 111 patients for further evaluation. These patients were categorized into two groups based on treatment outcomes: those who developed adverse effects (cases=16) and those who did not (controls=95).

At baseline, the mean SLE Disease Activity Index (SLEDAI) scores were 5.1 ± 2.40 in the case group and 5.35 ± 2.56 in the control group, with no statistically significant difference between them (P = 0.43). The demographic characteristics of the study population are presented in Table 1 and Baseline SLE score in the Table II.

Table I

Demographic characteristics of study subjects (n=337).

Characteristics	Variable	Total, n=337(%)	AZA, n=120(%)	Non-AZA n=217(%)	P value
Age	Mean± SD	27.5± 8.8	28.4±9.5	27.27± 8.6	0.201 *
Weight	Mean SD	53.0± 6.7	53.2± 6.50	53.0± 6.8	0.689 *
	Female	335 (99.3)	115 (95.8)	209 (96.3)	-
Marital status	Married	249 (71.6)	88 (75.2)	150 (69.1)	-
	Unmarried	99 (28.4)	29 (24.8)	67 (30.9)	-
Occupation	Housewife	222 (63.8)	74 (63.8)	148 (68.2)	-
	Student	94 (27.1)	30 (25.9)	62 (28.57)	-
	Service	20 (5.07)	9 (7.8)	11 (5.06)	-
	Others	12 (4.03)	7 (2.5)	3 (1.38)	-
SLEDAI	-	-	4.32±2.57	6.39±4.62	0.018

*Unpaired student t-test, AZA, azathioprine; SD, standard deviation; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index,there were 120 patients in the AZA group and 217 in the non-AZA group. There was a significant difference in baseline disease activity between the AZA and non-AZA group (p value 0.018).

Table II

Shows base line SLE DAI between Case (n=16) and control(n=95)

Test	Case (n=16)	Control(n=95)	Total (n=111)	95% CI	P value
SLEDAI	5.1 ± 2.40	5.35 ± 2.56	5.3 ± 2.5	“1.53 to 1.03)	0.43

Table III

The observed frequency of positivity of TPMT polymorphism among the case and control group, (AZA group, n = 111)

Variable	Result	Case n=16, (%)	Control n=95(%)	Total n=111	OR (95% CI)	P value
TPMT 3C	Positive	6 (37.5)	1 (1.0)	7 (6.3)	56.4 (6.1–518)	<0.001*
	Negative	10 (62.5)	94 (99.0)	104 (93.7)	-	–
-	Total	16(100)	95(100)	111(100)	-	-
Myelosuppression in TPMT	Positive	6(85.7)	4(3.8)	10	OR=150, (14.4–1546)	0.001*
-	Negative	1(14.3)	100(96.2)	101	-	-
-	Total	7	104	111	-	-
WBC(×10y /L)-TPMT positivity	Positive	7.73±1.03	6	-	1.72 (0.14–3.30)	0.037**
	Negative	6.01±1.6	4	-	-	-
RBC in TPMT positivity	Positive	4.01±0.25	6		“0.22 (“0.61–0.17)	0.179**
	Negative	4.23±0.21	4	-	-	-
Platelet count in TPMT Positivity	Positive	280±34.6	6	-	26.3 (“1.0–53.6)	0.058**
	Negative	253.7±15.8	4	-	-	-
SLEDAI Score	5.10 ± 2.40	5.35 ± 2.56	-	-	“0.25 (“1.53–1.03)	0.43**

WBC/Cu mm of Blood, RBC In million/Cu mm of Blood, Platelet in Thousand /cu mm of Blood, Fisher’s Exact*, Mann–Whitney U / t-test**, t test ***, OR = Odds Ratio; Continuous variables are presented as mean ± SD; categorical variables as n (%). Fisher’s exact test was used for categorical comparisons with small expected counts. Mann–Whitney U or t-test was applied for continuous variables depending on normality assumptions.95% CI provides a range of plausible values for the mean difference (continuous) or OR (categorical).

AZA group: Ten patients developed myelosuppression. Six (85.7%) had TPMT polymorphism. One patient did not develop myelosuppression despite TPMT polymorphism. Four patients had myelosuppression but no polymorphism. There was a significant difference in the frequency of AZA-induced myelosuppression between TPMT gene polymorphism-positive and negative patients (p= 0.0001).

The total TPMT polymorphism-positive patients in the AZA group were 7, and myelosuppression developed in 6 (85.7%). Among the six myelosuppressed patients, leucopenia developed in all patients (100%). According to severity, mild was 3 (50%), moderate was 2 (33%), and severe was 1(16.7%). However, four patients in the AZA group with no TPMT polymorphism developed leucopenia; 2 (50%) were mild and 2 (50%) were moderate, but no one had a severe form of leucopenia.

In the AZA group, 10 patients developed myelosuppression. Most cases occurred within the first 4 weeks of treatment, with no new instances observed beyond 8 weeks. Notably, 80% of myelosuppression events occurred at a dose of 2 mg/kg/day.

A total of 111 patients received AZA in this study. Of these, 104 did not carry TPMT polymorphisms (variants 3C, 3A, or 2), yet several still experienced AZA-related adverse effects. Myelosuppression occurred in 4 (3.8%) of these patients, all of whom had normal liver function.

Other adverse effects in the TPMT wild-type group included vomiting in 2 patients (1.92%), both of whom temporarily discontinued AZA but were able to resume treatment. No specific cause for the vomiting was identified. Two additional patients (1.92%) developed an erythematous, macular, and itchy rash with urticarial features. The rash appeared within hours of

Table IV

Observed adverse effects of AZA in both TPMT polymorphism positive and negative patients (n=111).

Adverse effect		AZA (n=111)	TPMT positive n=7	TPMT negative n=104	P value
Myelosuppression	Yes	10 (9.0%)	6(85.7%)	4 (3.8)	<0.001
	No	101 (91.0%)	1(14.3%)	100 (96.2)	
ALT raised	Yes	2 (1.8%)	2(28.6%)	0	<0.001
	No	109 (98.2%)	5(71.4%)	104 (100.0%)	
Vomiting	Yes	2 (1.8%)	0 (00)	2 (1.92%)	1.0
	No	109 (98.2%)	7 (100%)	104 (98.08)	
Rash	Yes	2 (1.8%)	0 (00)	2 (1.92%)	1.0
	No	109 (98.2%)	7 (100%)	103 (98.08)	
Pancreatitis	Yes	01 (0 9%)	0 (00)	1 (0.96%)	1.0
	No	110 (99.1%)	7 (100%)	104 (99.03)	
Diarrhea	Yes	01 (0 9%)	0 (00)	1 (0.96%)	1.0
	No	110 (99.1%)	7 (100%)	104 (99.03)	
Abdominal pain	Yes	01 (0 9%)	0 (00)	1 (0.96%)	1.0
	No	110 (99.1%)	7 (100%)	104 (99.03)	

ingestion and resolved in short time. On rechallenge, the rash reappeared but was milder; symptoms were managed with antihistamines, and AZA was successfully reintroduced at a lower dose and gradually titrated to the target dose. No patients reported fever, sore throat, or other concurrent symptoms.

One patient developed drug-induced pancreatitis. Additionally, one patient (0.96%) developed diarrhea, and another (0.96%) experienced abdominal pain. In both cases, no alternative cause was identified. Among the seven patients with TPMT 3C polymorphism, 6 (85.7%) developed myelosuppression. Hepatotoxicity was also observed in this group: two patients (28.6%) had elevated serum alanine aminotransferase (ALT) levels (140 U/L and 165 U/L, respectively). Viral hepatitis was excluded via negative HBsAg, anti-HCV, and anti-HAV serologies, and there was no history of other hepatotoxic drug intake. A summary of these adverse effects is presented in Table 4

Discussion

This study investigated the prevalence of thiopurine S-methyltransferase (TPMT) gene polymorphisms in patients with systemic lupus erythematosus (SLE) and examined the association between TPMT genotype and azathioprine (AZA)-related adverse effects. AZA is widely used as an immunosuppressant in SLE to control disease activity and maintain remission. However, its clinical use is often limited by adverse effects such as leukopenia, hepatotoxicity, and gastrointestinal intolerance.

TPMT plays a key role in AZA metabolism, and genetic variations in this enzyme influence individual susceptibility to drug toxicity.[12] The importance of AZA in managing autoimmune conditions like SLE and rheumatoid arthritis has been highlighted by previous studies, underscoring its central role in rheumatologic therapy.[13,14] In the present study, DNA was extracted from peripheral leukocytes, and TPMT polymorphisms were identified using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), a method previously validated in similar investigations.[15] TPMT enzyme activity varies considerably among individuals, largely due to these genetic polymorphisms.[16]

A total of 337 SLE patients were initially enrolled, with 120 receiving AZA. After excluding 11 patients due to unsuccessful DNA extraction, 337 patients (13 males and 324 females) were included in the final analysis. Among the AZA-treated cohort, 9 patients were further excluded due to irregular follow-up, resulting in 111 patients evaluated according to the study's follow-up schedule. This sample size is consistent with comparable studies in the field, including those by J.B. June et al. (342 patients).[17] Newman WG et al. (333 patients).[19] and Dongying Chen et al. (126 patients).[20]

Previous studies have reported variable concordance between TPMT genotype and enzyme activity. Dongying

Chen et al. observed that heterozygous patients exhibited significantly lower TPMT activity, but genotype and phenotype correlations were minimal.[20] Most cases of severe leukopenia occurred within the first 14 days of treatment, particularly when AZA was initiated at lower doses (1–2 mg/kg/day).[20] Similarly, Lynae et al. reported comparable dosing regimens and follow-up periods, with dose escalation from 1 mg/kg/day to 2 mg/kg/day after two weeks.[21] These studies informed the dosing and follow-up strategies used in the present research.

In our study, the frequency of TPMT polymorphism was 3.56%, with only the TPMT*3C allele detected. TPMT*3A, TPMT*3B, and TPMT*2 alleles were not observed. This aligns with findings from Dongying Chen et al. (3.17% in Chinese SLE patients) [20] and Sandeep K. et al. (4.7% in Indian SLE patients).[22] Similarly, Jun et al. (2005) reported a 5% frequency in Korean SLE patients, predominantly TPMT*3C, with no other variants detected [17].Comparable results have also been observed in Thai populations.[23] These findings support the observation that TPMT*3C is the predominant variant in Asian populations, whereas TPMT*3A is more common in Caucasians.[25]

Regarding AZA-related adverse effects, 16 patients (14.4%) experienced complications, mainly hematologic. Leukopenia was the most common effect, occurring in 9% of patients, comparable to the 11.1% rate reported by Dongying Chen et al.[20] Importantly, all patients with the TPMT*3C polymorphism developed leukopenia, indicating a strong association between this variant and hematologic toxicity. Non-hematologic adverse effects included hepatotoxicity (1.8%), vomiting (1.8%), rash (1.8%), diarrhea (0.9%), abdominal pain (0.9%), and pancreatitis (0.9%). No association was found between TPMT polymorphism and these non-hematologic effects, consistent with prior studies showing such reactions are generally transient.[20]

Conclusion

In this study of Bangladeshi patients with systemic lupus erythematosus (SLE), the frequency of TPMT polymorphism was found to be 3.56%. A significant proportion of patients with this genetic variation experienced azathioprine (AZA)-induced myelosuppression. However, hematological adverse effects were also observed in patients without the TPMT polymorphism, suggesting that factors beyond TPMT genotype may contribute to AZA toxicity. These findings underscore the importance of close monitoring for AZA-related side effects, regardless of TPMT genetic status.

Limitations

Limitations of the study include the relatively small sample size and short follow-up period. The study did not account for potential interactions with concurrent medications, and AZA doses were relatively low. It was not possible to exclude all other causes of adverse effects, and sample transport to an external laboratory may have introduced variability. Irregular patient follow-up and the inability to measure thioguanine—an important metabolite responsible for toxicity—limited dose escalation. The cost of TPMT testing is also high.

This study is the first to report the frequency of TPMT polymorphism and its clinical implications in the Bangladeshi SLE population, providing valuable pharmacogenetic insights. Understanding the relationship between TPMT genotype and AZA toxicity can aid in predicting adverse effects and personalizing therapy for SLE patients in this population.

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Author Contributions

Md. Masud Karim: Conceptualization, methodology, data collection, data curation, writing-original draft preparation. M. Masudul Hassan: Methodology, supervision, validation, writing-review and editing. Mohammad Abul Kalam Azad: Project administration, supervision, critical revision of the manuscript, correspondence. Aminur Rahman: writing, review, editing and critical revision of the manuscript . Md. Nazrul Islam: Supervision, scientific oversight, and final approval of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflict of Interest

None

Availability of Data and Materials

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU/2014/12348). All participants provided written informed consent before enrollment. All procedures adhered to the ethical standards of the institutional research committee and the Declaration of Helsinki.

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