Review Article

Assessment of NUDT15 before Thiopurine Treatment in Inflammatory Bowel Disease: An Asian Perspective

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Abstract

Background: Thiopurines, consisting of mercaptopurine and azathioprine, are used as immunosuppressants in treating inflammatory bowel disease. They are used to maintain remission of IBD patients. These drugs sometimes cause severe adverse effects, particularly myelosuppression, hepatoxicity, and pancreatitis. Recent advancements in pharmacogenomics have identified different genetic variants, including TMPT and Nudix hydrolase-15 (NUDT15). NUDT15 polymorphisms have been shown to play an important role in thiopurine-induced adverse reactions in Asians. This review article provides an insight into the NUDT15 testing before initiating thiopurine therapy in Asian patients with IBD.

Conclusion: In this article, the metabolism and pharmacogenetics of thiopurines, the prevalence and impact of NUDT15 variants in Asia, clinical guidelines for the importance of NUDT15 testing, dose adjustment based on NUDT15 genotypes, and monitoring and follow-up of the patients being treated are discussed.

Key words: Inflammatory bowel disease, Thiopurine metabolism, NUDT15 genotypes.

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Introduction:

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is responsible for chronic inflammation of the gastrointestinal tract and requires long-term management strategies.[1,2]

An imbalance between pro-inflammatory and anti-inflammatory responses contributes to persistent inflammation in IBD.[3] Multidisciplinary management is often required, which includes a combination of medications, nutritional support, lifestyle changes, and, in severe cases, surgical interventions.[1] Thiopurines, including azathioprine (AZA) and 6-mercaptopurine (6-MP), are effective immunomodulators for maintaining remission in inflammatory bowel disease (IBD). However, these drugs require careful monitoring to identify toxicity.[4] Adverse effects of these drugs include myelosuppression, hepatotoxicity, and pancreatitis. Myelosuppression is characterized by decreased bone marrow function, which can lead to severe anemia and neutropenia. Regular blood count monitoring is essential to avoid such serious side effects.[5] Therefore, we should weigh the benefits of thiopurines against these potential risks and implement appropriate monitoring strategies to ensure patient safety.[4,5]

The identification of genetic polymorphisms in thiopurine metabolism has significantly enhanced the management of adverse effects associated with thiopurine therapy. While TPMT genotyping is a well-established method for predicting toxicity, its effectiveness is limited in Asian populations due to the lower prevalence of TPMT variants.[6] NUDT15 is under Nudix (nucleoside diphosphate linked to x) hydrolase superfamily. Recent research has highlighted the NUDT15 gene as a crucial factor in thiopurine-induced myelosuppression among Asians, particularly in patients with inflammatory bowel disease (IBD), which contrasts with that of European descent. Testing for NUDT15 variants is crucial for personalized medicine approaches, allowing healthcare providers to tailor treatment strategies and minimize the risk of adverse effects. By integrating NUDT15 testing into clinical practice, clinicians can optimize thiopurine therapy for Asian patients, ensuring safer and more effective treatment outcomes. Thus, NUDT15 testing should be prioritized before initiating thiopurine therapy in this demographic.[7,8]

Thiopurine metabolism and pharmacogenetics

Thiopurines, like azathioprine and 6-mercaptopurine, are prodrugs. These require intracellular activation to produce their immunosuppressive effects. Azathioprine is converted to 6-mercaptopurine (6-MP). Thereafter, it is metabolized through competitive pathways. The primary pathway involves the conversion of 6-MP to active 6-thioguanine nucleotides (6-TGNs). It is crucial for immunosuppression. However, 6-MP can also be inactivated by thiopurine methyltransferase (TPMT) by converting it to 6-methylmercaptopurine (6-MMP). In addition, xanthine oxidase (XO) transforms it into 6-thiouric acid.[9-11]

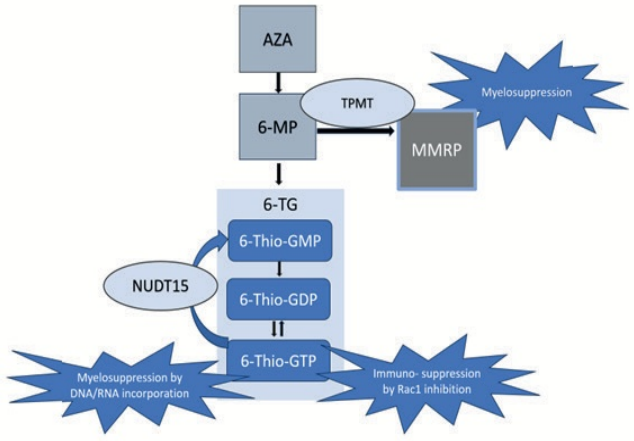

Figure 1. Overview of NUDT15 role in thiopurine metabolism. The azathioprine (AZA) and 6-mercaptopurine (6-MP) undergo a series of reactions that result in the active species, 6-thio-GTP, which are then incorporated into DNA/RNA or can inhibit Rac1 activity (6-thio-GTP). NUDT15 hydrolyzes 6-thio-GTP to the corresponding monophosphates and thereby reduce risk of toxicity by reducing the concentration of active metabolites (6-Thio-GTP) in cells.

AZA, azathioprine; MP, 6-mercaptopurine; 6-MMPR, 6-methyl-mercaptopurine ribonucleotides; 6-TG, 6-tioguanine;6-Thio-GTP, 6-thio-guanosine triphosphate; 6-Thio-GDP, 6-thio-guanosine diphosphate; 6-Thio-GMP, 6-thio-guanosine monophosphate; Rac1, Ras-related C3 botulinum toxin substrate.[1]

thiopurine medications (Figure 1). The balance among these metabolic pathways is essential, as high levels of 6-TGNs correlate with therapeutic efficacy but also heighten the risk of myelosuppression. Understanding these dynamics is vital for optimizing thiopurine therapy.[12]

Variability in thiopurine metabolism is significantly influenced by genetic polymorphisms in key enzymes, particularly TPMT and NUDT15. TPMT variants can reduce enzyme activity and increase myelosuppression risk. However, their prevalence is significantly low in Asian populations, which reduces their utility for thiopurine toxicity in these populations.[13,14] On the other hand, NUDT15 has emerged as a critical genetic determinant of thiopurine-induced myelosuppression among Asians. It inactivates thiopurine metabolites. Variants like c.415C>T (p.Arg139Cys) are strongly associated with diminished enzyme activity. This results in increased levels of the active metabolites 6-TGTP and 6-TdGTP and can lead to thiopurine intolerance and increased toxicity, particularly myelosuppression.[14-17] Understanding these genetic factors is essential to reducing the risk of adverse effects. Therefore, they can guide treatment decisions and improve patient safety.[14,18]

NUDT15 Variants in Asian populations and their impact on thiopurine toxicity

The prevalence of NUDT15 variants varies significantly among different ethnic groups. In Asian populations, the incidence of NUDT15 allelic mutations is 8.5–16%.[19-21] The mutation variant is rare in Caucasians, with frequencies of less than 1%22. In IBD patients, the frequency is 12% and 10.4%, respectively. The frequency is as high as 32.1% in China with autoimmune hepatitis.[23] The c.415C>T variant is the clinically most significant mutation and is associated with thiopurine-induced leukopenia, particularly in Asian populations. However, other NUDT15 variants, such as rs746071566 (c.55_56insGAGTCG), rs186364861 (c.52G > A), c.137C > G, and c.138T > G, have also been identified and are associated with reduced enzyme activity.[19,24,25] Studies suggested that the predictability of the NUDT15 variant allele for leukopenia is 36%-42.3%.[26,27] Patients carrying one or two copies of the c.415C>T variant are at significantly higher risk of developing severe myelosuppression, often requiring dose reduction or discontinuation of thiopurine therapy. Several studies have been conducted on the clinical utility of NUDT15 genotyping, revealing its significant potential to predict thiopurine toxicity. For example, a study in Japanese patients with IBD found that the c.415C>T variant was associated with a 35.6% risk of leukopenia in heterozygous patients and a 100% risk in homozygous patients, compared to a 7.6% risk in wild-type patients.[28]

Guidelines for NUDT15 testing

Given the high prevalence and significant impact of NUDT15 variants in Asian populations, several clinical guidelines now recommend NUDT15 testing before initiating thiopurine therapy in Asian patients with IBD. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for thiopurine recommends NUDT15 testing, particularly for Asian patients.[29] They recommend adjusting starting doses of thiopurines based on TPMT and NUDT15 genotypes (Table 1). The Korean Association for the Study of Intestinal Diseases (KASID) recommends NUDT15 testing before starting thiopurine to minimize the risk of myelosuppression.[30] The current British Society of Gastroenterology (BSG) guideline recommends NUDT15 genotype testing for IBD patients, if available. The Chinese Society of Gastroenterology (CSG) guidelines for IBD management include NUDT15 genotyping as a recommended pretreatment test. The guidelines suggest that patients with NUDT15 variants should be closely monitored by 6-thioguanine nucleotide levels to guide dosage adjustments.[31] While NUDT15 testing is not yet widely recommended in international guidelines, the American Gastroenterological Association (AGA) and the European Crohn's and Colitis Organization (ECCO) have acknowledged the importance of NUDT15 genotyping in Asian populations. These organizations suggest that NUDT15 testing may be considered in Asian patients, particularly those with a family history of thiopurine-induced toxicity.

Dose adjustment based on NUDT15 genotype

One of the important applications of NUDT15 testing is dose adjustment based on genotypes. Several non-functional alleles of the NUDT15 gene determine the tolerated thiopurine dosage of the patient.[21,22] Patients with NUDT15 variants may require lower starting doses of thiopurines to reduce the risk of myelosuppression. The 2018 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline update suggests that patients with intermediate

metabolizers should start with 30% to 80% of the standard dose.[18,29] However, this type of patient has some variability in the tolerated thiopurine dosages. A small proportion of these patients do not require significant thiopurine dose reduction.[22,32] Therefore, this allele-based dose adjustment applies mainly to starting doses; decisions about subsequent doses can be taken on regular monitoring of clinical myelosuppression. Patients with homozygous NUDT15 variants are at high risk of severe myelosuppression and may consider alternative therapies.[29] As alternative therapies to thiopurines, biologic agents like anti-tumor necrosis factor (TNF) therapies and small-molecule drugs like Janus kinase (JAK) inhibitors can be considered. However, the choice of alternative treatment should be based on disease severity, patient pReferencess, and other clinical factors.[33,34]

Studies suggest that East Asian descent has a significant proportion of NUDT15 poor metabolizers, which is about one in every 50 patients. This frequency is more common than the TPMT poor metabolizer phenotype in Europeans. This can explain the importance of testing NUDT15 genotyping in the Asian populations.[22]

Dosing of thiopurine by NUDT15 phenotype[18,29]

Table 1: Dosing of thiopurine by NUDT15 phenotype

Types	Risk	Dosing recommendation
Normal Metabolizer -Two normal function alleles(NUDT15*1/*1)	↔	Normal starting dose‡
Intermediate metabolizer -One normal function allele and one non-functional allele (NUDT15*1/*2, NUDT15*1/*3) OR Possible Intermediate Metabolizer -One uncertain function allele and one non-function allele (e.g., NUDT15*2/*5, NUDT15*3/*6)	↑	30% to 80% of normal starting dose‡
Poor Metabolizer -two non-functional alleles (NUDT15*2/*2, NUDT15*2/*3, NUDT15*3/*3)	↑↑	Consider Alternative therapy
* Allele. ‡Allow 2-4 weeks to reach steady-state after each dose adjustment in accordance with the risk level. ‡Adjust doses of thiopurine based on the degree of myelosuppression		

Monitoring and follow-up

British Society of Gastroenterology (BSG) suggests complete blood count (FBC), urea and electrolytes, and liver function tests (LFT) at baseline and at 2, 4, 8, 12 weeks, and thereafter every three months.[35] Even with dose adjustment, this is crucial to detecting signs of toxicity early with NUDT15 variants, especially the c.415C>T mutation cases.[18] It is recommended to reduce or temporarily stoppage of the thiopurine dose with regular follow-up when toxicities develop. For myelosuppression, reduction of thiopurine dose (when white cell count (WCC) < 3.5x109/L) or stoppage (when WCC <1.5x 109/L) with close white cell monitoring is vital. Thioguanine (TGN) and methyl mercaptopurine nucleotide (MeMP) levels should be assessed before considering thiopurine again.

For hepatotoxicity, the drug should be withheld until normalization of the LFT. Once toxicity resolves, re-challenge with a low dose of thiopurine with allopurinol can be an option. For pancreatitis, alternative treatment should be considered.[35,36] Physicians should make the patients aware of the symptoms of myelosuppression, hepatotoxicity, and other potentially serious side effects, such as fever, fatigue, abdominal pain, and bruising, and advise seeking medical attention as early as possible.[37,38]

Challenges and future directions

There are multiple challenges to practicing NUDT15 testing, especially in the Asian population. The cost of genetic testing can be an issue in the widespread adoption of NUDT15 testing, particularly in resource-limited settings. Though the cost of genotyping has decreased in recent years, preventing severe adverse effects may justify the investment. Efforts to increase the accessibility of NUDT15 testing, such as through insurance coverage and public health initiatives, are needed to ensure that all patients who could benefit from testing have access to it.[39]

Thiopurine dose adjustment should be based on the NUDT15 genotype. However, there is no standard guideline for IBD patients on the optimal dosing strategy for patients with NUDT15 variants. Further research is needed to establish a standardized dosing consensus in IBD patients. It will reduce the risk of toxicity and ensure the need for effective immunosuppression.[29,40] In addition to the NUDT15, other factors like TPMT and ITPA, environmental factors, concomitant medications, and infections can influence thiopurine metabolism and toxicity. Future research should explore the interaction between NUDT15 and other genetic and environmental factors to develop more comprehensive predictive models for thiopurine toxicity.[40]

Conclusion:

The prevalence of NUDT15 variants is high in Asian populations, which is the reason behind their strong association with thiopurine-induced myelosuppression in this group of people. It is therefore important to assess NUDT15 genotyping to minimize the adverse effects and optimize treatment outcomes. By identifying the genetic mutation of NUDT15, the risk of thiopurine-induced toxicity can be prevented by tailoring the treatment strategies. The integration of NUDT15 testing into clinical practice can make a significant advancement in personalized medical care for IBD. Clinical guidelines and consensus now recommend NUDT15 testing, especially for the Asian population. Dose adjustment based on genotype should be a standard practice. However, Cost, availability of the test, and standardized dosing guidelines are the current challenges for this genetic testing. Future research should focus on addressing these challenges. In addition, interaction between NUDT15 and other genetic and environmental factors should be explored. By integrating NUDT15 testing into clinical practice, we can improve the safety and efficacy of thiopurine therapy for Asian patients with IBD.

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