

Monitoring and Safety of Azathioprine Therapy in Inflammatory Bowel Disease

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Azathioprine is the most common drug used to maintain clinical remission in inflammatory bowel disease. This drug is also important as a steroid-sparing agent in steroid-dependent and chronically active inflammatory bowel disease. Nevertheless, many questions remain concerning the optimal treatment regimens of azathioprine. The dose of azathioprine has to be reduced or the therapy has to be discontinued frequently because of drug-induced toxicity. In this review, we discuss monitoring of thiopurines, adverse events, malignant complications and how to use azathioprine safely and usefully. (**Pediatr Gastroenterol Hepatol Nutr 2013; 16: 65 ~ 70**)

Key Words: Azathioprine, Inflammatory bowel diseases

INTRODUCTION

Thiopurines used for inflammatory bowel disease (IBD) treatment are azathioprine (AZA) and 6-mercaptopurine (6-MP). AZA is the most common drug used to maintain clinical remission in Crohn's disease and ulcerative colitis [1,2]. This drug is also important as a steroid-sparing agent in steroid-dependent and chronically active IBD. However, the dose of AZA has to be reduced or the therapy has to be discontinued in 9-28% of patients because of drug-induced toxicity [3]. Bone marrow suppression, gastrointestinal disturbances, hepatotoxicity, pancreatitis, fever and rash are among the most frequent

reasons for AZA reduction/cessation in some patients [4]. Although there are some adverse reactions that clinicians should be aware of, monitoring 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) levels enables safe and long-term remission in IBD patients [5,6].

METABOLISM AND MONITORING OF THIOPURINES

Thiopurines undergo complex metabolism. Three important enzymes of xanthine oxidase (XO), thiopurine S-methyl transferase (TPMT), and hypoxanthine phosphoribosyl transferase (HPRT) act

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competitively in the process of converting AZA/6-MP to inactive and active metabolites [7,8]. AZA is converted via a non-enzymatic reaction to 6-MP, which is subsequently metabolized either through TPMT to 6-MMP or, alternatively, by XO to thiouric acid. Furthermore, 6-MP may be converted by HPRT to thioinosine monophosphate. Subsequently, the enzyme inosine triphosphate pyrophosphatase (ITPA) catalyses the trivial cycle to thioinosine triphosphate and conversely, to avoid the accumulation of thioinosine monophosphate, and from guanosine monophosphate synthetase to 6-TGN [9-12].

6-TGN appears to be one of the active metabolites responsible for therapeutic efficacy. Several studies have found significant correlations between 6-TGN concentration and clinical response in IBD and use a therapeutic range for 6-TGN concentration of 235-450 pmol/ 8×10^8 red blood cells (RBC) [6,13-15]. A 6-TGN concentration of >235 pmol/ 8×10^8 RBC is associated with clinical response [6,13]. The cutoff concentration above 450 pmol/ 8×10^8 RBC is based on an increased risk of side effects (myelotoxicity and nodular regenerative hyperplasia of the liver) without an increase in efficacy [15,16]. Patients with erythrocyte 6-MMP concentrations above 5,700 pmol/ 8×10^8 RBC are at increased risk of hepatotoxicity and are unlikely to respond to treatment by increasing the drug dose [13,17,18]. These patients are probably preferentially metabolizing AZA via TPMT to form 6-MMP and may benefit from reduction of thiopurine dose by 50-75%, and careful monitoring of hematological indices and metabolites [19].

Dose recommendations for AZA vary slightly between Western guidelines, with a daily dose of 2-3 mg/kg AZA recommended by the American Gastroenterological Association (AGA) [20], and a daily dose of 1.5-2.5 mg/kg AZA recommended by the European Crohn's and Colitis Organisation (ECCO) [21]. However, these recommendations do not necessarily hold true for other ethnicities. Several Japanese studies showed that Japanese IBD patients might reach sufficient 6-TGN values with substantially lower AZA dosages in adults, children and adolescents [22-24].

A number of coadministered drugs may potentially influence thiopurine metabolism [7,10,25]. In vitro studies have confirmed that 5-aminosalicylic acid compounds are inhibitors of TPMT [26,27]. The higher frequency of leucopenia is observed in patients using this combination [26]. Other frequently prescribed TPMT inhibitors include acetylsalicylic acid and furosemide [7]. Allopurinol inhibits XO, resulting in increase in 6-TGN concentrations [28]. Roblin et al. [29] reported interactions between AZA and infliximab. They observed that the mean 6-TGN level was significantly increased within 1-3 weeks after the first infliximab infusion, and a decrement in leucocyte count. These modifications were normalized 3 months after infusion.

TPMT MONITORING

TPMT is the most frequently studied enzyme of AZA metabolism and the only one usually tested for in routine clinic. TPMT status can be checked for based on phenotype or genotype tests. TPMT genotyping consists of detecting single nucleotide polymorphism responsible for TPMT inactivation. A good correlation exists between TPMT activity and genotyping [30]. Based on TPMT and genetic polymorphism, the general population can be divided in three groups: wild type homozygous TPMT with high methylation activity (88%), heterozygous for a deficient TPMT allele with intermediate activity (11%) and homozygous for deficient TPMT alleles with a low activity (0.3%) [31]. The human TPMT gene is located on chromosome 6p22.3 and consists of 10 exons and nine introns. To date, 27 alleles responsible for possible TPMT activity deficiency have been described: *2, *3A, *3B, *3C, *3D, and *4 to *25 [32].

It is known that the variation of TPMT mutations in Caucasians is different from that in other ethnic groups [33,34]. TPMT *3A is the most prevalent-mutant allele in Caucasians [35]. On the other hand, TPMT *3C is the most prevalent mutant allele in Japanese and Chinese patients [36-38]. Also in studies about TPMT polymorphisms in the Korean adult population, TPMT *3C is observed as hetero-

zygotic allele and no TPMT *2, *3A, or *3B are observed [39-41].

Patients with low TPMT activity have elevated 6-TGN when treated with standard doses of AZA and are at greatly increased risk of myelosuppression [42,43]. Whereas patients with very high TPMT activity are either resistant to thiopurine drugs due to shunting of AZA down the 6-MMP pathway [35,44,45] or require a high dose to achieve efficacy, but at the risk of hepatotoxicity due to high 6-MMP concentrations [13,17].

A total of 109 patients were evaluated TPMT in Samsung Medical Center (Seoul, Korea). The distribution of the TPMT genotype was as follows: 102 patients had *1/*1 (wild type), one had *3C/*3C (homozygote), four had *1/*3C, one had *1/*6, and one had *1/*16 (heterozygote). The patient with *3C/*3C mutation required low dose of AZA, 0.18 mg/kg/day for maintain an optimal therapeutic range.

ADVERSE EVENTS

Most adverse events occur within the first 3 months [46]. Adverse events of AZA can be divided into dose-dependent, pharmacologically explainable events on one hand and dose-independent, hypersensitivity reactions on the other [7,47]. The first type of adverse events can occur in any time of the treatment, are well-known to be associated with the formation of potentially toxic metabolites. They include myelosuppression, infectious complications, and malignancies [7]. The others often occur within 2-4 weeks after start of treatment and result in symptoms like fever, rash, arthralgia, pancreatitis, hepatitis, and gastrointestinal disturbances [4]. The most common adverse event to reduce the dose of AZA or to discontinue the treatment is myelosuppression [48].

In AZA therapy, one of the potentially serious side effects is bone marrow suppression. AZA-induced myelotoxicity has been attributed to the low activity of TPMT caused by TPMT genetic polymorphism [49,50]. TPMT polymorphism results in greater con-

version of AZA to 6-TGN likely due to bone marrow suppression [3,9]. Therefore, the monitoring of 6-TGN concentrations has been reported to be helpful for managing IBD patients undergoing AZA therapy, since it may identify the optimal AZA dose to maximize efficacy while minimizing the risk of toxicity [5,51].

A total of 174 patients with IBD were treated with AZA in Samsung Medical Center from 2002 to 2012. Among them, 98 patients (56.3%) were experienced adverse events of AZA with 136 episodes. Most common adverse event of AZA was bone marrow suppression (27%). Gastrointestinal disturbances (15.5%) such as anorexia, nausea and vomiting, and hair loss (12.1%) were also frequently observed. Therefore, the dose of AZA was reduced in 31 patients (17.8%) and administration of AZA was stopped in 18 patients (10.3%). These present results show higher adverse event rates than previously reported western studies. The cause of these differences is not clear. One explanation for this might be the ethnic difference. Despite the low-dose (1.25 ± 0.41 mg/kg/day) use than standard dose (2.0-2.5 mg/kg/day), 17.8% of patients were needed to reduce dose of AZA and 10.3% were discontinued AZA treatment.

MALIGNANT COMPLICATIONS

Treatment with AZA is associated with a potential risk of developing lymphoma [52], including hepatosplenic T-cell lymphoma (HSTCL) [53]. AZA might play a role in the development of HSTCL in patients with IBD, and when such treatment is combined with tumor necrosis factor- α inhibitors, the risk might be amplified [54]. The possible role that immunosuppression plays in promoting certain malignancy has been well described. Immunosuppression is associated with HSTCL in approximately 25-30% of reported cases in the general population. Many of these cases have occurred in patients undergoing renal or heart transplantation treated with AZA and prednisone with or without cyclosporine [55-57]. Also, a recent meta-analysis including observational data from 3,891 patients with IBD re-

ported a 4-fold increased risk of lymphoproliferative disease in patients with IBD treated with AZA [52]. Although the relative risk of lymphoma is increased, the absolute risk still remains rather small, and currently available data show that the benefits of AZA used in IBD greatly outweigh its risks [58].

CONCLUSION

AZA has been generally used for treating chronic active lesions or for the maintenance of remission in IBD. The use of AZA in patients with IBD and ways to monitor therapy have been well documented. However, in clinical practice, the possibility of 6-TGN measurement to monitor therapy seems underused. Monitoring 6-TGN concentrations is helpful in developing a therapeutic strategy for IBD patients. Although TPMT genotype and thiopurine metabolite monitoring could not completely explain the thiopurine-induced adverse events, it could be helpful to examine TPMT genotypes before administering AZA and to measure 6-TGN concentrations during prescribing AZA in IBD patients.

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