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Original Article

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Adverse Events Associated with Azathioprine Treatment in Korean Pediatric Inflammatory Bowel Disease Patients

Ji Young Chun, Ben Kang, Yoo Min Lee, Soo Youn Lee*, Mi Jin Kim† and Yon Ho Choe

*Departments of Pediatrics, *Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, †Department of Pediatrics, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea*

Purpose: This study was aimed to evaluate the frequency and course of adverse events associated with azathioprine treatment in Korean pediatric patients with inflammatory bowel disease.
Methods: Total of 174 pediatric patients (age range, 1 to 19 years) with inflammatory bowel disease who received azathioprine in order to maintain remission at Samsung Medical Center (Seoul, Korea) from January 2002 through December 2012 were included in this study. Medical records of these subjects were retrospectively reviewed regarding the development of adverse events associated with azathioprine treatment.
Results: Ninety-eight patients (56.3%) of 174 patients experienced 136 episodes of adverse events, requiring dose reduction in 31 patients (17.8%), and discontinuation in 18 patients (10.3%). The mean dose of azathioprine that had been initially administered was 1.32±0.42 mg/kg/day. Among the adverse reactions, bone marrow suppression developed in 47 patients (27.0%), requiring dose reduction in 22 patients (12.6%) and discontinuation in 8 patients (4.6%). Other adverse events that occurred were gastrointestinal disturbance (15.5%), hair loss (12.1%), pancreatitis (7.5%), arthralgia (6.9%), hepatotoxicity (2.9%), skin rash/allergic reactions (2.9%), headache/dizziness (2.3%), sepsis (0.6%), and oral mucositis (0.6%).
Conclusion: Bone marrow suppression, especially leukopenia was most commonly associated with azathioprine treatment in Korean pediatric inflammatory bowel disease patients. Close observation for possible adverse events is required in this population with inflammatory bowel diseases who are under treatment with azathioprine. **(Pediatr Gastroenterol Hepatol Nutr 2013; 16: 171～177)**

Key Words: Inflammatory bowel diseases, Crohn disease, Ulcerative colitis, Azathioprine, Adverse reactions, Bone marrow suppression, Leukopenia

INTRODUCTION

Azathioprine (AZA) is widely used in the treatment of inflammatory bowel disease (IBD). AZA is proven to be effective for the maintenance of remission in both Crohn's disease (CD) and ulcerative

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Corresponding author: Yon Ho Choe, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Irwon-dong, Gangnam-gu, Seoul 135-710, Korea. Tel: +82-2-3410-3539, Fax: +82-2-3410-0043, E-mail: i101016@skku.edu

colitis (UC), induction of remission in CD, and in reducing steroid use in steroid dependent or chronically active IBD [1]. However, due to some adverse drug reactions associated with this immunosupressant drug, approximately up to 20% are required to withdraw from its use [2]. Adverse drug reactions of AZA can be divided into dose-dependent pharmacologically explainable events and dose-independent hypersensitivity reactions [3]. The former can occur at any time of treatment, and are well-known to be associated with the formation of potentially toxic metabolites. They include myelosuppression, infectious complications, and malignancies. The latter often occur within 2-4 weeks after the initiation of treatment and results in fever, rash, arthralgia, pancreatitis, hepatitis, and gastrointestinal disturbances.

Recently, we have experienced some severe adverse events associated with AZA in pediatric IBD patients. One is Sweet syndrome, in which severe hypersensitivity to AZA is thought to play a role. A case of severe prolonged pancytopenia was also observed, in which the patient required admission and use of granulocyte-colony stimulating factor (G-CSF) for recovery from myelosuppression. Adverse drug reactions associated with AZA in IBD treatment have been reported in some large population studies in adults [4-7]. Due to the recent increase in the incidence of pediatric IBD, studies regarding adverse drug reactions associated with AZA is required in the pediatric population. However, studies among pediatric population are scarce, and there have been no reported studies among Korean pediatric patients. Therefore, the aim of this study was to evaluate adverse events associated with AZA in Korean children and adolescents with IBD.

Case 1

A 9-year-old girl was hospitalized with fever, and numerous erythematous, pustular lesions with tenderness on her face and both arms. Due to her prednisolone-dependent ulcerative colitis, AZA treatment with a dose of 1 mg/kg/day had been initiated 10 days before admission. Laboratory tests showed leukocytosis and markedly raised erythrocyte sedimentation rate and C-reactive protein level on admission. Despite antibiotic treatment after admission, fever continued and skin lesions worsened. Skin biopsy was performed, and pathologic examination revealed massive neutrophilic infiltrates in the entire dermis. Tissue culture results were negative for bacterial and fungal infection. Considering the clinical course, laboratory findings, and histopathologic examinations, Sweet syndrome was suspected. Two days after discontinuing treatment with AZA, the fever subsided and skin lesions showed improvement.

Case 2

A 15-year-old boy who had been diagnosed with CD was admitted with complaints of high fever and oral lesions for 2 days. Treatment with AZA had been initiated 1 month before with a dose of 2.5 mg/kg/day, which had been prescribed at an other hospital. Neutropenia occurred 7 days after treatment with AZA and drug doses were reduced to 1 mg/kg/day. The initial laboratory test at admission showed pancytopenia, with a white blood cell count of 1,700/mm^3, an absolute neutrophil count of 70/mm^3, hemoglobin of 11.7 g/dL, and a platelet count of 45,000/mm^3. Despite discontinuation of treatment with AZA, pancytopenia worsened and high fever continued. Blood culture results were negative for bacteral and fungal infection. After 10 days of treatment with antibiotics, G-CSF and blood transfusion, his pancytopenia showed improvement and the fever subsided. Not until 5 months after discontinuation of AZA did his pancytopenia fully recover.

MATERIALS AND METHODS

Patients aging from 1 to 19 years who had been diagnosesd as CD or UC at Samsung Medical Center (Seoul, Korea) from January 2002 to December 2012, and had been followed up for at least 6 months were initially included in this study. Among these patients, those who had received treatment with

AZA were the ultimate study subjects in this study. CD and UC were diagnosed according to the Porto criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. Patients were required to visit the outpatient clinic at least once per month before remission of the disease, and once every 2 to 3 months after remission was obtained. Laboratory tests were conducted in order to monitor disease activity and adverse drug reactions at each visit.

Medical records of the subjects were retrospectively reviewed to obtain clinical and laboratory data regarding adverse events associated with AZA treatment. Myelosuppression was defined as a decrease of any one of the following cells of the hematologic system; leukocytes, neutrophils, and platelets. Leukopenia was defined as a white blood cell count $<3.0\times10^9$/L, neutropenia as an absolute neutrophil count $<1,000\times10^9$/L, and thrombocytopenia as a platelet count $<100,000\times10^6$/L. As hematochezia is common in inflammatory bowel disease, investigation of hemoglobin levels were excluded from the criteria for determining myelosuppression. However, pancytopenia was defined when leukopenia, neutropenia, thrombocytopenia, and anemia were all present. Hepatotoxicity was defined as elevation of both aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) levels, more than 2-folds of the upper normal limit.

This study was approved by the institutional review board of Samsung Medical Center.

RESULTS

From January 2002 to December 2012, 174 patients received treatment with AZA. All patients except two patients were free of underlying medical conditions. One patient had been diagnosed as end stage renal disease and had been receiving hemodialysis. Another patient had been diagnosed as renal cell cardinoma and had received chemotherapy previously. The mean dose of AZA that was administered was 1.25±0.41 mg/kg/day. Demographic and clinical characteristics of the patients are shown in Table 1.

Adverse drug reactions of AZA were observed in 98 patients (56.3%). Seventy-four patients experienced only one adverse event, while 24 patients experienced two or more events. Treatment with AZA was discontinued in 18 patients (10.3%), and the dose was reduced in 31 patients (17.8%) (Table 2).

A significantly higher frequency of myelosuppression was observed among the adverse events. Myelosuppression occurred in 47 patients (27.0%) at a mean dose of 1.36±0.44 mg/kg/day after a mean administration period of 8.87 months (range, 1-37 month). Among the 47 patients, leukopenia alone was observed in 43 patients

Table 1. Characteristics of Korean Pediatric IBD Patients under AZA Treatment

Characteristic	Crohn's disease	Ulcerative colitis	Total
Patient	128 (73.5)	46 (26.5)	174
Male to female ratio	4.5 : 1	1.4 : 1	2.6 : 1
Age (yr)	13.5 (1-19)	13.0 (4-18)	13.4 (1-19)
Body weight (kg)	55.29±13.48	53.47±14.09	54.81±13.63
Azathioprine dose (mg/kg/day)	1.24±0.42	1.30±0.37	1.25±0.41
Comedication			
Steroid	6	3	9 (5.2)
Mesalazine	110	43	153 (87.9)
Infliximab	57	9	66 (37.9)
Adalimumab	2	0	2 (1.1)

Values are presented as number (%), median (range), mean±standard deviation, or number only. IBD: inflammatory bowel disease, AZA: azathioprine.

Table 2. Frequency and Course of Adverse Events Associated with AZA Treatment in Korean Pediatric IBD Patients (n=174)

Adverse drug reactions	Patient	Dose of AZA (mg/kg/day)	Dosage of AZA (month)	Medical decision		
				Withdrawal	Reduction	Observation
Total	98 (56.3)	1.32±0.46	10.71±14.49	18 (10.3)	31 (17.8)	49 (28.2)
Bone marrow suppression	47 (27.0)	1.36±0.44	8.87±8.97	8 (4.6)	22 (12.6)	17 (9.8)
Sepsis	1 (0.6)	1.96	2	1 (0.6)	0	0
Nausea/vomiting	27 (15.5)	1.38±0.46	10.41±16.31	10 (5.7)	8 (4.6)	9 (5.2)
Hepatitis	5 (2.9)	1.68±0.30	10.41±14.20	0	0	5 (2.9)
Pancreatitis	13 (7.5)	1.18±0.50	19.46±20.82	3 (1.7)	1 (0.6)	9 (5.2)
Headache/dizziness	4 (2.3)	1.73±0.47	24.5±30.57	1 (0.6)	1 (0.6)	2 (1.1)
Oral mucositis	1 (0.6)	1.64	65	1 (0.6)	0	0
Skin rash	5 (2.9)	1.12±0.46	4.20+6.10	2 (1.1)	1 (0.6)	2 (1.1)
Arthralgia	12 (6.9)	1.26±0.41	14.33±13.30	0	1 (0.6)	11 (6.3)
Hair loss	21 (12.1)	1.11±0.43	3.67±4.41	1 (0.6)	5 (2.9)	15 (8.6)

Values are presented as number (%), mean±standard deviation, or number only. AZA: azathioprine, IBD: inflammatory bowel disease.

(91.5%), neutropenia alone in 4 patients (8.5%), and pancytopenia in 5 patients (10.6%). Pancytopenia was observed in five patients after a mean administration period of 2.8 months (range, 1-7 months). Treatment with AZA was discontinued in all patients with pancytopenia and was spontaneously recovered in four patients. However, persistent pancytopenia and neutropenic fever occurred in one patient, requiring infusion of G-CSF for recovery. Among the 43 patients with leukopenia, leukocyte counts between 2.0 and 3.0×10^9/L, between 1.0 and 2.0×10^9/L, and less than 1.0×10^9/L were each observed in 38 patients, 3 patients, and 2 patients, respectively. Treatment with AZA was discontinued in three patients with leukopenia. However, after recovery, AZA was readministered at a lower dose. The final mean dose of AZA that was administered was 0.97±0.52 mg/kg/day.

The second frequently observed adverse event of AZA was gastrointestinal disturbances. Nausea and vomiting occurred in 27 patients (15.5%) at a mean dose of 1.38±0.46 mg/kg/day after a mean administration period of 10.4 months (range, 1-69 months). Withdrawal was required in 10 patients and dose adjustment was performed in 8 patients. Hepatotoxicity was observed in 5 patients (2.9%) at a mean dose of 1.68±0.30 mg/kg/day after a mean administration period of 10.4 months (range, 1-30 months). The mean level of AST and ALT was 140.4 and 155.4 IU/L, respectively. All patients with elevated AST and ALT continued treatment with AZA without dose adjustment. AST and ALT levels conducted later showed spontaneous normalization. Pancreatitis occurred in 13 patients (7.5%) at a mean dose of 1.18±0.50 mg/kg/day after a mean administration period of 19.5 months (range, 1-57 months). Three patients discontinued treatment with AZA, and one patient continued medication with dose adjustment. In the patients who had discontinued AZA, re-administration was attempted with dose adjustment after clinical symptoms disappeared and amylase levels normalized. However, pancreatitis recurred in 2 patients, and eventually treatment with AZA was terminated.

Headache and/or dizziness occurred in 4 patients (2%) at a mean dose of 1.73±0.47 mg/kg/day after a mean administration period of 24.5 months (range, 1-69 months). Withdrawal of AZA was required in one patient due to headache, and dose adjustment was performed in one patient. Arthralgia occurred in 12 patients (6.9%) at a mean dose of 1.26±0.41 mg/kg/day after a mean administration period of 14.3 months (range, 1-50 months). Only in one patient was the dose of AZA reduced. Hair loss occurred in 21 patients (12%) at a mean dose of 1.11±0.43 mg/kg/day after a mean ad-

ministration period of 3.7 months (range, 1-19 months). One patient stopped taking AZA by himself, and five patients continued taking the medication with dose adjustment. Skin rash occurred in 5 patients (2.9%) at a mean dose of 1.12±0.46 mg/kg/day after a mean administration period of 4.2 months (range, 1-15 months). Administration of AZA was discontinued in two patients with rash. One was diagnosed as having Sweet syndrome due to AZA-induced hypersensitivity. The rash disappeared after discontinuation of AZA. Sepsis due to salmonella infection occurred 2 months after treatment with AZA in one patient who had been concomitantly treated with steroids and mesalamine. Sepsis was controlled by antibiotic treatment and withdrawal of both steroids and AZA. Oral mucositis occurred in one patient at a dose of 1.64 mg/kg/day after an administration period of 65 months. The oral mucositis spontaneously improved after discontinuation of AZA.

DISCUSSION

This study is the first to describe adverse drug reactions associated with AZA in Korean pediatric patients with IBD. The present results show higher incidence and different distribution of adverse drug reactions compared with previous reports conducted in Caucasian patients. Winter et al. [4] reported that adverse drug events to AZA occured in 44 patients (33.8%) of 130 adult IBD patients in the United Kingdom. The mean dose for treatment with AZA was 1.6 mg/kg/day. The most common adverse event in this study was gastrointestinal disturbance (11%), followed by myelosuppression (7.7%), and hepatitis (6.9%). Ansari et al. [5] reported that 83 patients (38%) of 207 adult IBD patients experienced adverse drug events to AZA in another study conducted in the United Kingdom. The mean dose of AZA administration was 2 mg/kg/day. Gastrointestinal disturbance (15.7%) was most frequently observed, while myelotoxicity was observed in 3.2%. Gearry et al. [6] reported that adverse drug events to AZA occured in 56 patients (26%) of 216 adult IBD patients in New Zealand. Hepatitis (34%) was the most frequently observed adverse event, while bone marrow suppression was observed in 7%. Gisbert et al. [7] reported that 74 patients (18.8%) of 394 adult IBD patients experienced adverse drug events to AZA in a study conducted in Spain. The mean dose for treatment with AZA was 2-2.5 mg/kg/day. The most common adverse event in this study was gastrointestinal disturbance (48.5%), followed by bone marrow suppression (23.0%). Meanwhile, Kim et al. [8] reported that leukopenia was observed in 75 patients (56.4%) in a study conducted in 133 Korean IBD adults under AZA medication. Other adverse events observed were gastrointestinal disturbance (24.1%), arthralgia (4.5%), hepatitis (4.5%), and skin rash (3.0%). The mean dose of AZA administration was 1.5-2.5 mg/kg/day. According to the results of these adult studies, bone marrow suppression was more frequently observed in the Korean study compared to other Western studies. Leukopenia was more common in Korean IBD patients under AZA treatment despite the similar mean dose administration of AZA, implying the role of ethnic difference in the occurence of leukopenia.

Studies have been mostly conducted in adults, with only few studies in the pediatric population. Despite the scarcity of studies in the pediatric population, this difference among different races was also observed in children and adolescents. Kirschner [9] reported that 44 patients (46.3%) of 95 pediatric patients experienced side effects associated with AZA treatment for IBD in USA. Hepatitis (13.7%) was most commonly observed, followed by recurrent fever (4.2%), pancreatitis (4.2%), gastrointesinal intolerance (4.2%), and recurrent infections (3.1%). Kader et al. [10] reported that among 20 pediatric IBD patients with normal thiopurine S-methyltransferase (TPMT) levels, 3 patients (15.0%) exhibited side effects in an other study conducted in the USA. Hepatitis was reported in 2 patients (10%) and leukopenia was reported in 1

patient (5%). Tajiri et al. [11] reported that 14 patients (40%) of 35 UC patients experienced adverse drug effects to AZA or 6-MP treament in a study conducted in Japan. Leukopenia was reported reported in 11 patients (27.5%), aplastic anemia in 1 patient (2.5%), pancreatitis in 1 patient (2.5%) and liver dysfunction in 1 patient (2.5%). Considering the results of our study and these studies, bone marrow suppresion was more frequently observed in East Asians compared to Caucasians, similar to the studies in adults.

The occurrence of bone marrow suppression in AZA treatment is known to be strongly associated with the active metabolite 6-thioguanine nucleotides (6-TGN) [12]. 6-TGN levels are mainly determined by the activity of TPMT, which is known as the major enzyme related in the metabolism of thiopurines. Patients with low TPMT activity have elevated 6-TGN levels when treated with standard doses of thiopurines and are at greatly increased risk of bone marrow suppression [13,14]. Approximately 89% of Caucasians carry 2 wild-type alleles resulting in normal or high TPMT activity, 11% are heterozygous and have intermediate activity, and 0.3% are homozygous for low activity alleles and display no detectable TPMT activity [15]. According to a study regarding the frequency and distribution among different races, the overall frequency of mutant TPMT alleles in East Asians was 4.7%, which was comparatively lower than that for Caucasians [16]. However, not only is bone marrow suppresssion capable of occuring in the presence of normal TPMT activity, but also the overall occurence of bone marrow suppression is higher in the normal TPMT population [17]. This implies that there are other mechanisms other than TPMT activity contributing to the occurence of leukopenia in IBD patients with AZA treatment and is insufficient in explaining the high incidence of leukopenia among the East Asian polpulation compared to Caucasians.

Some pharmacogenetic factors have been recently identified to attribute to the variability in responses to AZA treatment, such as inosine triphosphatase, glutathione S-transferase, xanthine oxidase, aldehyde oxidase, methylene tetrahydrofolate reductase, and the adenosine triphosphate-binding cassette sub-family C member 4 (ABCC4) [12]. According to some studies performed in the Japanese population, a single-nucleotide polymorphism in ABCC4 G2269A was reported in 15-19%, proprosing the unexplained high occurrence of bone marrow suppression associated in the Japanese population despite lower administration doses of AZA compared to Caucasians [18,19]. Further studies on the clinical significance of genetic polymorphisms of enzymes involved in the metabolism of thiopurines is required in Korean pediatric patients with IBD under AZA treatment.

The main limitation of this study is that this study was retrospectively conduted under a small study scale at a single center. Another limitation is that possible drug interactions between AZA and other co-administrated drugs were not analyzed in this study. Moreover, the efficacy of AZA when administrated at a low dose was also not mentioned. Further large scaled, multi-center, prospective studies regarding these issues are required in the future.

In conclusion, bone marrow suppression, especially leukopenia was the most commonly associated adverse drug reaction associated with AZA treatment in Korean pediatric IBD patients, and therefore close observation for possible adverse events is required in this population. Further studies in order to determine the underlying mechanisms related to the higher occurrence of bone marrow suppression in this population are required in the future.

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