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ORIGINAL ARTICLE

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한국의 염증성 장질환과 자가면역성 간염 환자에서 Azathioprine의 부작용 비교

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Differences in the Adverse Effects of Azathioprine between Inflammatory Bowel Disease and Autoimmune Hepatitis in Korean Patients

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Background/Aims: Azathioprine (AZA) has been widely used in the therapy of inflammatory bowel disease (IBD) and autoimmune hepatitis (AIH). However, studies evaluating the adverse effects of AZA in these two diseases are lacking. The aim of this study was to compare the adverse effects of AZA in Korean IBD and AIH patients.
Methods: Patients with IBD or AIH who were treated with AZA at Keimyung University Dongsan Medical Center (Daegu, Korea) between January 2002 and March 2011 were enrolled. Their medical records were reviewed retrospectively in terms of clinical characteristics and adverse effects of AZA.
Results: A total of 139 IBD patients and 55 AIH patients were finally enrolled. Thirty IBD patients (21.6%) and eight AIH patients (14.5%) experienced adverse effects of AZA. In particular, the prevalence of leukopenia was significantly higher in the IBD group than in the AIH group (p=0.026). T474C mutation was observed in three of 10 patients who were assessed for thiopurine methyltransferase (TPMT) genotype.
Conclusions: IBD patients are at increased risk for the adverse effects of AZA compared with AIH patients, of which leukopenia was the most commonly observed. Therefore, IBD patients receiving AZA therapy should be carefully monitored. **(Korean J Gastroenterol 2014;64:348-355)**

Key Words: Azathioprine; Inflammatory bowel diseases; Hepatitis, autoimmune; Adverse effects

INTRODUCTION

In Korea, the prevalence of inflammatory bowel disease (IBD) has shown a rapid increase owing to westernization of lifestyles and environmental changes during the last two decades.[1] Autoimmune hepatitis (AIH) is a rare chronic liver disease that should be treated immediately after diagnosis.[2] IBD and AIH are representative gastrointestinal diseases for which azathioprine (AZA) is used. AZA belongs to the family of thiopurines and is widely used as a maintenance steroid-sparing agent in both IBD and AIH.[3] In the past, due to safety concerns and delayed effects, clinicians were hesitant to use thiopurines in actual clinical practice even in compliant patients. However, their use has increased gradually

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along with recent studies showing the high efficacy and limited side effects of these agents.[4,5]

AZA-derived side effects can be categorized according to allergic and non-allergic reactions.[4,6,7] Allergic reactions that occur regardless of the administered dose include pancreatitis, fever, arthritis, skin rash, abdominal pain, diarrhea, and hepatitis. Symptoms appear quickly within 1-4 weeks after administration. Re-administration immediately results in manifestation of more severe side effects; therefore, the drugs cannot be used continuously in most cases.[5,6,8] On the other hand, non-allergic reactions include bone marrow suppression, such as leukopenia or thrombocytopenia, infection, and hepatitis. Non-allergic reactions appear relatively late, possibly after several months or years of administration. Although non-allergic reactions are mainly dose dependent, thiopurine methyltransferase (TPMT) genotype has been considered to play an important role in the occurrence of these adverse effects.[4,9]

One study compared the frequencies of the adverse effects occurring within a month after AZA treatment for Crohn's disease (CD) and AIH[3]; the results suggest that the frequencies of these adverse effects may vary according to underlying diseases. However, it remains unclear whether these results can be applied to Asians.[7,10] In Korea, studies on the adverse effects of AZA in IBD patients have been conducted; however, few studies have examined the differences in adverse effects of AZA between IBD and AIH. Therefore, the aim of this study was to compare the adverse effects in patients with IBD and AIH who were treated with AZA in Korea. In addition, we assessed TPMT gene polymorphism analysis in patients whose samples were available.

SUBJECTS AND MEDTHODS

1. Patients and study design

We retrospectively analyzed patients with IBD and AIH in whom AZA treatment was initiated at Keimyung University Dongsan Medical Center in Daegu, Korea, from January 2002 to March 2011. Data concerning the patients' sex, age at the time of diagnosis, and adverse effects after initiation of AZA were obtained. The following information was also collected from medical records: duration of treatment, concurrent use of steroid and mesalazine, and time of starting AZA to adverse effect. Those with a history of adverse effects to thiopurines were excluded. Patients who had initiated AZA therapy at another institution or were lost to follow up were also excluded. The study protocol was approved by the institutional review board of Keimyung University (IRB No. 11-248). Informed consents were waived by the board.

The initial AZA dose (50 mg) was kept the same in all patients. The dose of AZA was increased to 2.0-3.5 mg/kg based on the discretion of the clinicians. Patients were recommended to revisit at 1- or 2-week intervals for the first month and then 2- or 3-month intervals thereafter. The observation period for AZA-induced adverse effects was designated to be from the beginning of the administration to the last outpatient clinic visit of the patient. Laboratory tests, including complete blood counts, liver function tests, amylase, and lipase, were performed at each visit to confirm the adverse effects of AZA treatment. Leukopenia was defined as a white blood cell (WBC) count of $< 3{,}000/mm^3$; thrombocytopenia was defined as platelets $< 100{,}000/mm^3$; anemia was defined as a hemoglobin < 10 mg/dL.[6,11] Liver function abnormalities were defined as an alanine aminotransferase or aspartate aminotransferase increase of more than two times compared with the normal upper limit (40 IU/L)[12]; acute pancreatitis was defined as increases in lipase and amylase levels of more than three times compared with the normal level, with compatible symptoms.[9]

Blood samples for TPMT genotyping were obtained at the time of diagnosis. Overall, five samples in the IBD group and five samples in the AIH group were stored in the Human Bio-Resource Bank of our hospital. These were assessed for TPMT genotyping in this study. Genomic DNA was extracted using an Absolute DNA Extraction kit (BioSewoom, Seoul, Korea) according to the manufacturer's manual. The extracted genomic DNA was amplified using polymerase chain reaction (PCR) with the primers for exons 5, 7, and 10 of the TPMT gene. PCR consisted of denaturation at 94°C for 5 min, 35 repeats each at 94°C for 30 sec, 59°C for 60 sec, and 70°C for 30 sec, as well as final elongation at 70°C for 7 min. The enzyme-digested PCR products were subjected to PCR sequencing using the PCR primer used for amplification of each exon as the sequencing primer. They were then analyzed using an ABI3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) after automated DNA sequencing.

2. Statistical analysis

Qualitative data analyses were performed using the chi-square test or Fisher's exact test, whereas quantitative data analyses were performed using an independent-samples t-test. Data analyses were performed using IBM SPSS Statistics software version 19.0 (IBM Co., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

1. Subjects' characteristics

A total of 224 patients (160 with IBD, 64 with AIH) received AZA during the studied period. Among 64 patients with AIH, nine were lost to follow up. Among 160 patients with IBD, eight patients had taken AZA before visiting our hospital, three had a history of AZA-induced side effects, and 10 were lost to follow-up. These patients were excluded from the study. Therefore, 139 patients with IBD (CD, 77; ulcerative colitis, 62) and 55 patients with AIH were eligible for this study (Fig. 1). The characteristics of the studied population treated with AZA are shown in Table 1. The mean age at the time of diagnosis was lower in patients with IBD (32.23±14.74 years) than in those with AIH (49.34±15.39 years) (p=0.001). The proportion of men in the IBD group (64.0%) was higher than that in the AIH group (21.8%) (p=0.001). On the other hand, the proportion of patients who were simultaneously started on steroids and AZA was significantly higher in the AIH group than in the IBD group (100% *vs.* 55.4%, p=0.001).

2. Adverse effects associated with AZA treatment

Table 2 shows the characteristics of patients with adverse effects of AZA. The interval of AZA initiation and the subsequent development of adverse effects did not differ significantly between patients with IBD and AIH. Of the 21 patients with IBD (70.0%) and five patients with AIH (62.5%), AZA treatment was withdrawn due to adverse effects. Serious adverse effects leading to admission to hospital developed in seven (23.3%) patients in the IBD group, two (25%) in the AIH group. Details of the adverse effects in each group are shown in Table 3. A total of 30 of the 139 patients with IBD (21.6%) and eight of the 55 patients with AIH (14.5%) experienced side effects. No difference concerning concomitant steroid therapy at the time of adverse effects occurrence was observed between these groups. In the IBD group, leukopenia, anemia, and thrombocytopenia were observed in 21 (15.1%), six (4.3%), and two (1.4%) subjects, respectively. In addition, nausea and vomiting, pancreatitis, and skin rash were noted in four subjects (2.9%), three subjects (2.2%), and one subject (0.7%), respectively. In the 55 patients with AIH, eight patients (14.5%) showed adverse ef-

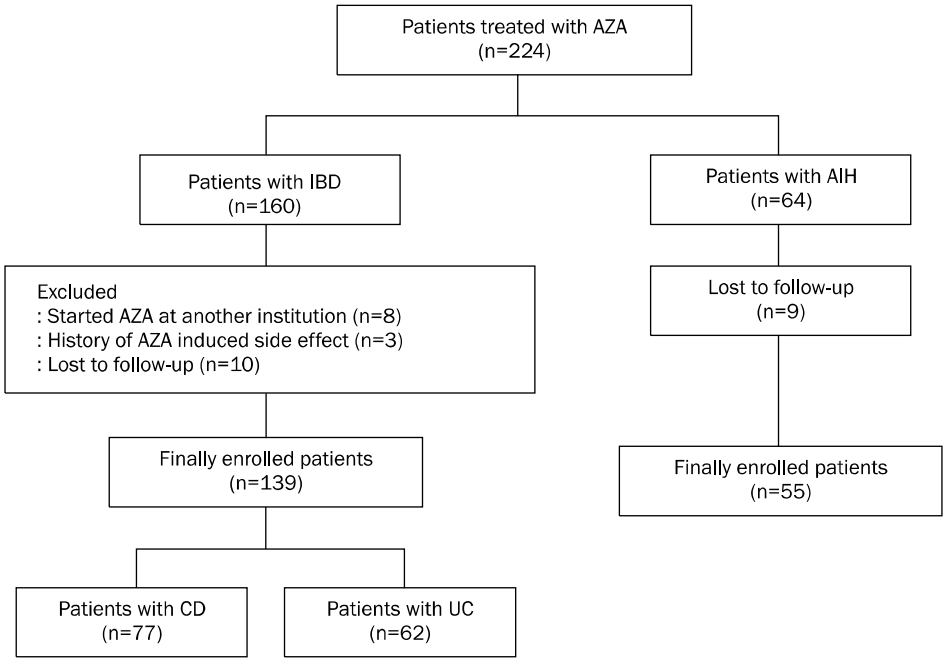

Fig. 1. Flow diagram of enrolled patients. AZA, azathioprine; IBD, inflammatory bowel disease; AIH, autoimmune hepatitis; 6-MP, 6-mercaptopurine; CD, Crohn's disease; UC, ulcerative colitis.

Table 1. Characteristics of the Studied Population Treated with Azathioprine

Characteristic	IBD (n=139[a])	AIH (n=55)	p-value
Age at diagnosed (yr)	32.23±14.74 (19-80)	49.34±15.39 (18-78)	0.001
Sex			0.001
Male	89 (64.0)	12 (21.8)	
Female	50 (36.0)	43 (78.2)	
Duration of AZA treatment (mo)	23.0 (0-93)	24.57 (0-81)	0.186
Initial combination therapy with steroid	77 (55.4)	55 (100)	0.001
TPMT genotype[b]			1.000
TPMT*1	3 (60.0)	4 (80.0)	
TPMT*1S	2 (40.0)	1 (20.0)	

Values are presented as mean±SD (range), n (%), or median (range).
[a]Crohn's disease=77, ulcerative colitis=62.
[b]The results for patients whose samples were available for genotyping. Five patients in IBD and five patients in AIH were included in this analysis. Among patients with adverse effects, TPMT*1S was found in one patient with IBD and one patient with AIH with no significant difference.
IBD, inflammatory bowel disease; AIH, autoimmune hepatitis; AZA, azathioprine.

Table 2. Clinical Details of Patients Who Developed Adverse Effects of Azathioprine

Characteristic	IBD (n=30)	AIH (n=8)	p-value
Concomitant steroid therapy at the time of adverse effects occurrence	22 (73.3)	5 (62.5)	0.667
Interval of adverse effects occurrence after AZA initiation (mo)	7.16 (0-67)	6.11 (0-22)	0.548
Discontinuation of AZA	21 (70.0)	5 (62.5)	0.587
Require hospitalization	7 (23.3)	2 (25.0)	0.214

Values are presented as n (%) or median (range).
IBD, inflammatory bowel disease; AIH, autoimmune hepatitis; AZA, azathioprine.

Table 3. Adverse Effects of Azathioprine by Disease

Variable	IBD (n=139)	AIH (n=55)	p-value
Total adverse effects[a]	30 (21.6)	8 (14.5)	0.266
Bone marrow suppression			
Leukopenia	21 (15.1)	2 (3.6)	0.026
Anemia	6 (4.3)	2 (3.6)	1.000
Thrombocytopenia	2 (1.4)	3 (5.5)	0.141
Acute pancreatitis	3 (2.2)	0	0.564
Nausea/vomiting	4 (2.9)	1 (1.8)	1.000
Skin rash	1 (0.7)	1 (1.8)	0.488

Values are presented as n (%).
[a]The number of patients who developed more than one adverse effect. Thirty seven adverse events occurred in 30 IBD patients. Nine adverse events developed in eight AIH patients.
IBD, inflammatory bowel disease; AIH, autoimmune hepatitis.

fects during AZA treatment. Leukopenia, anemia, and thrombocytopenia were identified in two (3.6%), two (3.6%), and three (5.5%) subjects, respectively. Acute pancreatitis induced by AZA occurred in three patients (2.2%) in the IBD group only, although it did not show statistical significance. The occurrence of leukopenia after AZA administration was significantly higher in the IBD group than in the AIH group (15.1 *vs.* 3.6, p=0.026).

3. Development of leukopenia

Table 4 shows the comparisons of patients who developed leukopenia. In subgroup analyses of patients who developed leukopenia, patients in the AIH group were significantly older than those in the IBD group (74.00±1.41 *vs.* 38.05±10.31, p=0.001). Between IBD and AIH groups who developed leukopenia, there were no significant differences according to sex, concomitant steroid and mesalazine treatment, median interval of the occurrence of leukopenina occurrence after AZA initiation, initial WBC count, leukopenic WBC count, and requirement of hospitalization for leukopenia.

Four patients with IBD and one patient with AIH were admitted to hospital due to leukopenia. Details of these patients are shown in Table 5. Two patients with IBD and one patient with AIH had fever and chills. Pneumonia developed in two patients with IBD. All of these five patients were taking steroid at the time of leukopenia occurrence. Coadministration of mesalazine was observed in 3 of the 4 patients with IBD. After stopping AZA, leukopenia returned to normal in these five patients.

4. TPMT gene polymorphism results

TPMT genotyping was performed in five patients with IBD and five patients with AIH. Among them, two patients with IBD and one patient with AIH showed TPMT*1S. Meanwhile, TPMT*1 was observed in three patients with IBD and four patients with AIH (Table 1). In TPMT*1S, the thymine (T) of the 474th nucleic acid of the 7th exon is replaced with a cytosine (C), which indicates the T474C mutation (Fig. 2). Among patients with adverse effects, TPMT*1S was found in one patient with IBD and one patient with AIH without statistical difference.

Table 4. Comparisons of Patients with IBD and AIH Who Developed Leukopenia While Taking AZA

Characteristic	IBD (n=21)	AIH (n=2)	p-value
Age (yr)	38.05±10.31	74.00±1.41	0.001
Sex			0.178
Male	13 (61.9)	0	
Female	8 (38.1)	2 (100)	
Initial combination therapy with steroid and AZA	11 (52.4)	2 (100)	0.486
Concomitant steroid therapy at the time of leukopenia occurrence	9 (42.9)	1 (50.0)	1.000
Concomitant mesalazine therapy at the time of leukopenia occurrence	16 (76.2)	0	0.083
Interval of leukopenia occurrence after AZA initiation[a] (mo)	5.1 (0.12-24)	0.93 (0.23-1.63)	0.376
Initial WBC count (/mm^3)	6,541.90±2,498.02	5,785.00±2,340.52	0.685
Leukopenic WBC count (/mm^3)	2,360.50±655.51	2,160.00±367.70	0.679
Required hospitalization	4 (19.0)	1 (50.0)	0.395

Values are presented as mean±SD, n (%), or median (range).
IBD, inflammatory bowel disease; AIH, autoimmune hepatitis; AZA, azathioprine; WBC, white blood cell.

Table 5. Characteristics of Patients Who Were Admitted to Hospital due to Leukopenia

Case	Age (yr)/sex	Disease	Time to leukopenia (mo)	Clinical manifestation	Concomitant steroid therapy	Concomitant mesalazine therapy	Recover after discontinuation
1	20/male	IBD	1.13	Pneumonia	Yes	Yes	Yes
2	25/male	IBD	3.8	Fever and chills	Yes	Yes	Yes
3	36/male	IBD	3.51	Pneumonia	Yes	No	Yes
4	31/female	IBD	4.27	Fever and chills	Yes	Yes	Yes
5	51/female	AIH	0.83	Fever and chills	Yes	No	Yes

IBD, inflammatory bowel disease; AIH, autoimmune hepatitis.

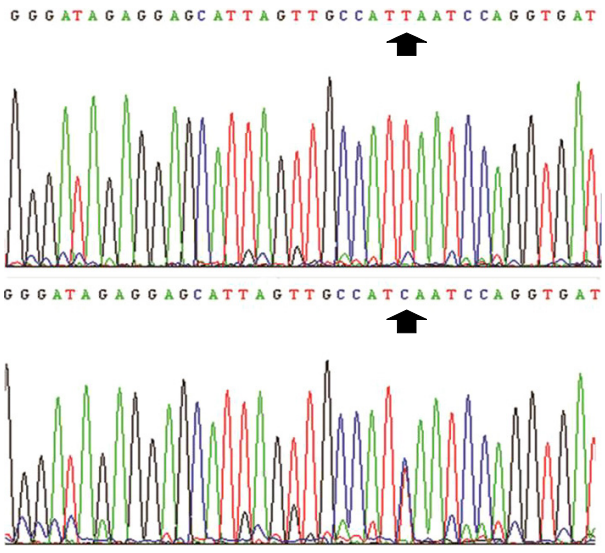

Fig. 2. Electropherogram showing the alteration of a single nucleotide in the 7th exon. Genotyping of the 7th exon shows that three patients have two different alleles of thymine (T) and cytosine (C). This heterozygous T474C silent mutation was confirmed for TPMT*1S.
G, guanine; A, adenine.

DISCUSSION

According to Bajaj et al.,[3] the incidence of allergic reactions was higher in the CD group (29%) than in the AIH group (5%). Concerning allergic reactions, except for nausea and vomiting, significant differences were found between the CD (19%) and AIH (12.5%) groups (p=0.001). However, neither the mechanisms of the differences in the allergic reactions between the two groups nor the non-allergic reactions, including leukopenia, were investigated. Therefore, this study analyzed the adverse effects, including bone marrow suppression, in patients with IBD and AIH. In addition, we analyzed the TPMT gene polymorphism, which is known to be the mechanism of conventional AZA adverse effects, albeit in a very small number of subjects.

Despite the reported frequency of adverse effects of AZA of 18-25% in patients with IBD and < 10% in patients with AIH, serious adverse effects are uncommon.[8,13,14] In a report by Connell et al.,[6] bone marrow suppression was observed in

only 5% among 739 IBD patients treated with AZA. In most patients, leukocyte and platelet counts normalized after AZA was discontinued. Consistent with previous studies, in this study, there were no serious adverse effects or deaths, and all adverse effects resolved after the discontinuation or dose reduction of AZA.

In the current study, the common adverse effect associated with AZA treatment in Korean patients is bone marrow suppression, particularly leukopenia. AZA treatment had to be interrupted because of adverse effects in 30 among the 139 patients with IBD (21.6%) and eight among the 55 patients with AIH (14.5%). In addition, we found that the frequency of leukopenia was significantly higher in the IBD group (15.1%) than in the AIH group (3.6%). The reported frequency of leukopenia was as high, at 11-20%.[15,16] However, the frequency was around 2-5% when leukopenia is defined as a WBC count of $< 3{,}000/mm^3$.[6,17] In Korea, a remarkably high frequency of leukopenia was reported, up to 41.3%, compared with those in foreign studies.[18,19] The reasons for the discrepancies among the studied populations remain unknown. However, some studies have suggested that the different genetic backgrounds of TPMT genotype according to ethnic groups are responsible for these discrepancies.[20,21] In addition, concomitant medications might also influence TPMT enzyme activity and can affect the safety and efficacy of thiopurines. Mesalazine, which is widely used in patients with IBD, has been reported to inhibit TPMT activity *in vitro*.[22,23] This drug interaction might affect patients who inherit the characteristic of producing lower levels of the TPMT enzyme, and has important clinical significance in bone marrow suppression. However, we could not demonstrate any relationship between mesalazine medication and leukopenia occurrence, probably due to small sample size.

Several studies have suggested that patients on steroids have a decreased incidence of adverse effects.[8,24] In this study, the development of total adverse effect was not significantly different between IBD and AIH, despite all patients with AIH on initial concomitant steroid therapy compared to 55.4% of IBD patients. Meanwhile, we observed that all patients admitted to hospital due to leukopenia were on concomitant steroid medication. Thus, we conclude that steroid may play a role as a predisposition to infection in patients with AZA-derived leukopenia.

Concerning the efficacy and toxicity of AZA, individual differences appear primarily because of the differences in TPMT activity, which is known to be associated with TPMT allele polymorphism.[25] The decrease of TPMT activity is known to be affected by the mutation allele type. Bone marrow suppression, the most common adverse effect of non-allergic reactions, showed a reverse correlation with TPMT activity.[13] Thus, it might be estimated by measuring the TPMT genotype and activity. On the basis of this theory, some studies have suggested that leukopenia can be prevented by measurement of the TPMT genotype or activity before AZA treatment.[9,26,27] Meanwhile, in other studies, bone marrow suppression and mutation of the TPMT genotype were not correlated in IBD or AIH.[10,22,27]

Similarly, TPMT genotype was not associated with adverse effects in our study. However, because only small samples were investigated in our study, it is premature to conclude the relationship between the TPMT polymorphism and adverse effects. Conduct of more large scaled studies is warranted in the future.

In an analysis of the data of 621 patients with IBD who were treated with AZA by Fraser et al.,[4] leukopenia was found in 29 patients (4.3%) and the duration of leukopenia onset after AZA administration varied. In the current study, the median interval of leukopenia onset after AZA use was 5.1 months in the IBD group and 0.93 month in the AIH group (Table 2). Thus, regular monitoring of complete blood count is required because serious bone marrow suppression can occur anytime during long-term use of the drug. In real clinical practice, the efficacy of AZA is evaluated on the basis of clinical indicators of symptoms or steroid termination, whereas adverse effects are identified through laboratory tests. The diverse frequencies of AZA-derived adverse effects can be presented in both IBD and AIH. Therefore, patients receiving AZA should be carefully monitored and well informed about the potential adverse effects.

This study has some limitations. First, the number of subjects differed between the two groups because of the retrospective design of this study. Second, the concomitant use of steroid or mesalazine differed between groups, thereby resulting in confounding variables. Third, the number of subjects who had results of TPMT genotype was too small, thus selection bias would exist. Fourth, 6-thioguanine nucleotide, the active factor of thiopurines, was not measured; thus, its relation with leukopenia in TPMT metabolism was not clearly

elucidated. Nevertheless, this study is significant because it is the first study comparing the adverse effects of AZA in two representative gastrointestinal diseases in Koreans.

In conclusion, the risk for the adverse effects of AZA was higher in patients with IBD compared to AIH, of which leukopenia was the most commonly observed. Therefore, patients with IBD receiving AZA should be closely monitored for possible adverse effects. Further large-scale studies are warranted in order to validate the effective use of AZA and the relation between AZA adverse effects and mutation of TPMT genotype according to disease.

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REFERENCES

1. Kim ES, Kim WH. Inflammatory bowel disease in Korea: epidemiological, genomic, clinical, and therapeutic characteristics. Gut Liver 2010;4:1-14.
2. Liberal R, Grant CR, Longhi MS, Mieli-Vergani G, Vergani D. Diagnostic criteria of autoimmune hepatitis. Autoimmun Rev 2014;13:435-440.
3. Bajaj JS, Saeian K, Varma RR, et al. Increased rates of early adverse reaction to azathioprine in patients with Crohn's disease compared to autoimmune hepatitis: a tertiary referral center experience. Am J Gastroenterol 2005;100:1121-1125.
4. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. Gut 2002;50:485-489.
5. Manns MP, Czaja AJ, Gorham JD, et al; American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193-2213.
6. Connell WR, Kamm MA, Ritchie JK, Lennard-Jones JE. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut 1993;34:1081-1085.
7. Chun JY, Kang B, Lee YM, Lee SY, Kim MJ, Choe YH. Adverse events associated with azathioprine treatment in korean pediatric inflammatory bowel disease patients. Pediatr Gastroenterol Hepatol Nutr 2013;16:171-177.
8. de Jong DJ, Goullet M, Naber TH. Side effects of azathioprine in patients with Crohn's disease. Eur J Gastroenterol Hepatol 2004;16:207-212.
9. Gisbert JP, Niño P, Rodrigo L, Cara C, Guijarro LG. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. Am J Gastroenterol 2006;101:2769-2776.
10. Kim JH, Cheon JH, Kim WH. The frequency and the course of the adverse effects of azathioprine/6-mercaptopurine treatment in patients with inflammatory bowel disease. Korean J Gastroenterol 2008;51:291-297.
11. Saibeni S, Virgilio T, D'Incà R, et al. The use of thiopurines for the treatment of inflammatory bowel diseases in clinical practice. Dig Liver Dis 2008;40:814-820.
12. Bastida G, Nos P, Aguas M, et al. Incidence, risk factors and clinical course of thiopurine-induced liver injury in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2005;22:775-782.
13. Ben Ari Z, Mehta A, Lennard L, Burroughs AK. Azathioprine-induced myelosuppression due to thiopurine methyltransferase deficiency in a patient with autoimmune hepatitis. J Hepatol 1995;23:351-354.
14. Czaja AJ. Drug therapy in the management of type 1 autoimmune hepatitis. Drugs 1999;57:49-68.
15. George J, Present DH, Pou R, Bodian C, Rubin PH. The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. Am J Gastroenterol 1996;91:1711-1714.
16. Sandborn WJ, Tremaine WJ, Wolf DC, et al. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. Gastroenterology 1999;117:527-535.
17. Present DH, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. Ann Intern Med 1989;111:641-649.
18. Kim JH, Cheon JH, Hong SS, et al. Influences of thiopurine methyltransferase genotype and activity on thiopurine-induced leukopenia in Korean patients with inflammatory bowel disease: a retrospective cohort study. J Clin Gastroenterol 2010;44:e242-e248.
19. Kim DU, Kim YH, Kim BJ, et al. The efficacy of low dose azathioprine/6-mercaptopurine in patients with inflammatory bowel disease. Hepatogastroenterology 2009;56:1395-1402.
20. Jun JB, Cho DY, Kang C, Bae SC. Thiopurine S-methyltransferase polymorphisms and the relationship between the mutant alleles and the adverse effects in systemic lupus erythematosus patients taking azathioprine. Clin Exp Rheumatol 2005;23:873-876.
21. Jung YS, Cheon JH, Park JJ, et al. Correlation of genotypes for thiopurine methyltransferase and inosine triphosphate pyrophosphatase with long-term clinical outcomes in Korean patients with inflammatory bowel diseases during treatment with thiopurine drugs. J Hum Genet 2010;55:121-123.
22. Venkat Raman G, Sharman VL, Lee HA. Azathioprine and allopurinol: a potentially dangerous combination. J Intern Med 1990;228:69-71.
23. Szumlanski CL, Weinshilboum RM. Sulphasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. Br J Clin Pharmacol 1995;39:456-459.
24. Korelitz BI. Steroids may prevent leukopenia, interfering with response to IV azathioprine in treatment of Crohn's disease.

Gastroenterology 2000;118:1281-1282.
25. Dubinsky MC. Azathioprine, 6-mercaptopurine in inflammatory bowel disease: pharmacology, efficacy, and safety. Clin Gastroenterol Hepatol 2004;2:731-743.
26. Black AJ, McLeod HL, Capell HA, et al. Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. Ann Intern Med 1998;129:716-718.
27. Heneghan MA, Allan ML, Bornstein JD, Muir AJ, Tendler DA. Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. J Hepatol 2006;45:584-591.