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Azathioprine Intolerance in Japanese Patients with Antineutrophil Cytoplasmic Antibody-associated Vasculitis

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Abstract

Objective To assess the safety of azathioprine (AZA) in Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Methods We retrospectively enrolled 67 consecutive AAV patients who had initiated AZA treatment from January 2006 to August 2014 at Okayama University Hospital. We evaluated the development of severe adverse events (AEs), AZA discontinuation due to total AEs (severe AEs included) within 1 year, and AZA-associated risk factors.

Results The patients' median age was 70 years old. Forty-nine women and 18 men participated at the initiation of the study. Fifty-eight (87%) patients experienced AEs, and 36 experienced severe AEs (21 hepatic and 11 cytopenic severe AEs). Thirty-one (46%) patients discontinued treatment because of AEs. Abnormal hepatic laboratory test results at the treatment initiation were more frequent in patients with hepatic severe AEs and were associated with treatment discontinuation. The leukocyte and neutrophil counts at the treatment initiation were lower in the patients who discontinued treatment because of cytopenic AEs than in those who continued treatment. Only two patients experienced flare-ups during treatment.

Conclusion The AE-associated AZA discontinuation rate in Japanese AAV patients was relatively high. AZA use warrants caution in patients with abnormal hepatic laboratory test results or low leukocyte or neutrophil counts.

Key words: adverse events, anti-neutrophil cytoplasmic antibody-associated vasculitis, azathioprine

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic disorder associated with ANCA that predominantly affects small vessels and is classified into microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (1). A nationwide prospective inception cohort study in Japan revealed that AAV classification, the type of organs involved, the age of onset, and the treatment patterns were different from those in Western countries (2, 3).

Azathioprine (AZA) is a widely used drug for the treatment of autoimmune diseases. AZA has been used as a standard AAV treatment following successful remission with cyclophosphamide (CYC) (4-6). However, toxic adverse events (AEs), including nausea, vomiting, myelosuppression, and hepatotoxicity, develop frequently and limit the clinical benefits of AZA. According to clinical trials of AAV, the incidence of myelotoxicity was 16-34% and 1.7-11% in patients who discontinued AZA because of AEs, such as hepa-

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totoxicity and digestive intolerance (5-8). Previous studies on inflammatory bowel disease (IBD) have shown that female gender and high 6-thioguanine nucleotides concentrations in red blood cells were associated with the development of AEs (9, 10). Further, female gender and a lower body mass index were risk factors for the development of AEs resulting in thiopurine discontinuation (10, 11). It is well known that genetic polymorphisms of metabolizing enzymes such as thiopurine S-methyltransferase (TPMT) are related to the dose-dependent toxicity of AZA (12). Indeed, a guideline advises measuring the pre-treatment TPMT enzyme level, although this is still controversial (9, 13).

A previous nationwide prospective 24-month cohort study of AAV revealed that, at the 12-month assessment interval, AZA was used in only 26% of the patients in Japan (14). Why AZA is used less frequently for Japanese AAV patients than Western ones remains unclear. There is no evidence of AZA tolerability among Japanese AAV patients, although some studies have shown that AZA withdrawal was 4.4% among Japanese systemic lupus erythematosus (SLE) patients (15) and 19% among Japanese IBD patients (9). Furthermore, the risk factors for AZA toxicity in AAV patients have never been evaluated.

The objectives of the present study were (i) to clarify the safety of AZA in Japanese patients with AAV and (ii) to identify the risk factors for the development of severe AEs and the discontinuation of AZA because of total AEs.

Materials and Methods

Patient selection

We retrospectively reviewed the medical records of consecutive AAV patients who had initiated AZA treatment from January 2006 to August 2014 at Okayama University Hospital. All patients fulfilled the criteria for primary systemic vasculitis as proposed by the European Medicines Agency algorithm (16). The dose of AZA was determined under the direction of the attending physician but was adjusted as follows: initial dose of AZA was 50-100 mg/day; this dose was reduced by 25 mg if the patient was aged >60 years and/or had an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. AZA was stopped if the white blood cell (WBC) count was <4,000/μL and was restarted at a dose reduced by at least 25 mg once the WBC recovered to ≥4,000/μL.

This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for epidemiologic research in Japan. The study protocol was approved by the ethics committees of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (authorization number: 1606-502). Informed consent to participate in the study was obtained from the patients, as well as permission to have their data published.

Data collection

The data at the time of the diagnosis of each patient included their demographic information, disease activity using Birmingham Vasculitis Activity Score (BVAS) (17), and ANCA positivity. At the initiation of the AZA treatment, the following data were collected: purpose of the administration, dosage of AZA, the concomitant use of drugs, laboratory data, previous treatments, and concomitant dosage of glucocorticoids. The dosage of AZA was adjusted at the discretion of the attending physicians. Abnormal hepatic laboratory test results at the initiation of the treatment were defined as an aspartate aminotransferase (AST), alanine aminotransferase (ALT), or γ-glutamyltranspeptidase (γ-GTP) level exceeding the normal range of our hospital. An abnormal renal laboratory test result at the initiation of the treatment was defined as an eGFR less than 60 mL/min/1.73 m^2.

Outcomes

The primary safety outcomes of this study were the development of severe AEs and the discontinuation of AZA due to AEs within one year of treatment. Severe AEs were important as a highly reproducible outcome based on distinct definitions, while the discontinuation of AZA was important as a clinically relevant outcome. We extracted information on the AEs from the medical charts and laboratory data. Hepatic AEs were evaluated by determining the AST, ALT, and γ-GTP levels, and cytopenic AEs were evaluated by determining the WBC and platelet (PLT) counts and hemoglobin (Hb) level. Renal AEs were evaluated by determining the serum creatinine level, while other AEs were evaluated according to the medical chart records. AEs were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0; http://evs.nci.nih.gov/ftp1/CTCAE/About.html) (Supplemental Data). Severe AEs were originally defined as new or worsened AEs compared to those at baseline that were classified higher than grade-2 severity.

The secondary outcome was relapse, which was defined as the recurrence or worsening of disease activity (BVAS >0 and/or interstitial pneumonia) and/or elevated C-reactive protein (CRP) level without other causes.

Statistical analyses

Continuous variables were compared using Student's *t*-test or the Mann-Whitney *U* test as appropriate, and categorical variables were compared using a chi-squared test. The tests were two-tailed, and differences at $p<0.05$ were considered significant. All statistical analyses were performed using the Statistical Package of JMP for Windows software program, version 11.0.2 (SAS Institute, Cary, NC, USA).

Table 1. All Adverse Events.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Unclassifiable
Abnormal hepatic laboratory test results	9	9	9	3		
Cytopenia	20	10	1			
Abnormal renal laboratory test results	17	9	1			
Infection		2	3			3
Gastrointestinal symptoms		2				2
Hair loss						2
Skin cancer			1			
Unspecific symptoms						2[a]

The severities were scored using the Common Terminology Criteria for Adverse Events version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html) (Supplemental data).

[a]Dizziness occurred in one patient, and dry mouth, insomnia, and light-headedness in the other patient.

Results

Patient characteristics and treatment effectiveness

Of the 67 AAV patients included in the study, 34 were classified as MPA, 13 as GPA, 3 as EGPA, and 17 as unclassifiable AAV. At the diagnosis of AAV, the median age of all patients was 69 years [interquartile range (IQR), 63-76], and 49 (73%) patients were women. Myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA were positive in 53 (82%) and 5 (8%) patients, respectively. The BVAS was 14 (IQR, 10-19), and the organs involved were ear, nose, and throat (13%), chest (21%), kidneys (76%), and nervous system (42%). A median dose of 40 mg of prednisolone was initiated as remission induction therapy, and concomitant CYC was used in 51 of the 67 (76%) patients.

AZA was initiated for remission maintenance in 48 of 67 (72%) patients and for remission induction in 19 (28%). Of the 48 patients in whom AZA was initiated for remission maintenance, 42 had been treated with CYC, and 6 had never been treated with a concomitant immunosuppressant. Of the 19 patients subjected to remission induction, 4 received this therapy because of difficulty in CYC continuation, and 10 received it at relapse. In 5 newly diagnosed patients subjected to remission induction, general, cutaneous, nervous system, renal, and chest (including interstitial pneumonia) manifestations were observed in 3, 2, 2, 1, and 1 patients, respectively. At treatment initiation, the median age was 70 years (IQR, 63-76), and the median initial AZA dose was 0.63 mg/kg/day (IQR, 0.53-0.99; 25 mg/day in 36 patients, 50 mg/day in 28 patients, and 100 mg/day in 3 patients). The concomitant prednisolone dose was 10 mg/day (IQR, 7.5-12.5). Antihyperuricemics was not used concomitantly, and sulfamethoxazole/trimethoprim was used in 43 (64%) patients. Abnormal hepatic and renal laboratory test results were found in 18 (27%) and 45 (67%) patients, respectively, at the initiation of AZA. The median AST, ALT, γ-GTP, and eGFR values were 18 U/L (IQR, 14-25), 17 U/L (IQR, 11-24), 23 U/L (IQR, 14-41), and 48.2 mL/min/1.73 m^2 (IQR, 36.8-63.9), respectively. The median WBC count, Hb level, and PLT count were 7,890/μL (IQR, 6,910-9,400), 11.5 g/dL (IQR, 10.9-12.5), and 25.4×10^4/μL (IQR, 21.9-33.4×10^4), respectively. The median CRP level was 0.12 mg/dL (IQR, 0.03-0.42). The maximum dose of AZA for 1 year was 0.98 mg/kg/day (IQR, 0.58-1.20; 25 mg/day in 22 patients, 50 mg/day in 30 patients, 75 mg/day in 4 patients, and 100 mg/day in 11 patients).

Adverse events with AZA treatment

During the observational period, 58 (87%) patients (remission maintenance initiated in 42 patients and remission induction in 16) experienced AEs (105 events). The details and severity scores according to CTCAE v4.0 are shown in Table 1. Of those 58 patients, 36 (62%) experienced severe AEs according to our definitions. The characteristics of the patients who experienced frequent severe AEs were compared to those of a control group of 25 patients who did not experience severe AEs (non-severe AE group). Six patients were excluded from this analysis because their severities were unclassifiable.

In the 21 patients with severe hepatic AEs (hepatic severe AE group), abnormal hepatic laboratory test results at the initiation of the treatment were more frequent than in the non-severe AE group (p=0.047, Table 2). The median AST, ALT, and γ-GTP levels were also significantly higher in the hepatic severe AE group than those in the non-severe AE group (p=0.0018, p=0.02, and p=0.0089, respectively; Table 2).

No significant differences were found between the 11 patients with cytopenic severe AEs and the non-severe AE group (Table 2).

Discontinuation of AZA

AZA was discontinued in 31 patients (46%) because of AEs within a median of 48 days (IQR 22-91) from starting treatment, and because of abnormal hepatic laboratory test results (12 patients), cytopenia (12 patients), infection (3 patients), gastrointestinal symptoms (3 patients), and other abnormalities (alopecia: 1 patient, skin cancer: 1 patient, and unspecific symptoms: 2 patients). AZA was discontinued in 22 (61%) of the 36 patients with severe AEs. To compare the characteristics between patients who discontinued and continued treatment, we set the group of 35 patients who

Table 2. Demographic and Laboratory Data at the Initiation of the AZA Treatment in the Hepatic severe AE, Cytopenic severe AE, and Non-severe AE Group.

	Hepatic severe AE (n=21)[a]	Cytopenic severe AE (n=11)[a]	Non-severe AE (n=25)
Age, median (IQR), year	70 (65-75)	68 (63-71)	70 (64-80)
Male/Female, n (%)	7 (33)/14 (67)	5 (45)/6 (55)	6 (24)/19 (76)
Maximum daily dose of AZA			
25 mg/day, n	5	4	9
50 mg/day, n	10	6	8
75 mg/day, n	1	1	3
100 mg/day, n	5	0	5
Abnormal hepatic laboratory test results, n (%)	10 (48)*	4 (36)	5 (20)
Abnormal renal laboratory test results, n (%)	14 (67)	9 (82)	15 (60)
WBC, median (IQR), /μL	9,170 (7,490-11,060)	7,090 (5,820-10,490)	7,610 (6,650-8,750)
Hb, median (IQR), g/dL	11.8 (10.9-12.6)	10.9 (10.7-11.4)	11.5 (10.9-13.2)
PLT, median (IQR), $\times 10^4$/μL	25.1 (22.2-34.3)	25.1 (19.1-28.7)	24.7 (20.7-31.8)
AST, median (IQR), U/L	25 (18-31)*	20 (13-30)	15 (14-20)
ALT, median (IQR), U/L	24 (15-31)*	21 (8-26)	17 (11-21)
γ-GTP, median (IQR), U/L	35 (24-75)*	31 (16-58)	19 (14-33)
eGFR, median (IQR), mL/min/1.73 m^2	48 (40.5-70.9)	40.7 (32.4-59.8)	53.3 (38.7-62.3)

Severe AEs were originally defined as new or worsened AEs compared to those at baseline, and which were classified higher than grade-2 severity.

[a]Includes 3 patients with both hepatic and cytopenic severe AEs.

*$p<0.05$ in the comparison between the severe hepatic AE and non-severe AE group.

AZA: azathioprine, AE: adverse event, IQR: interquartile range, WBC: white blood cells, Hb: hemoglobin, PLT: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyltranspeptidase, eGFR: estimated glomerular filtration rate

continued treatment as the control group. One patient who discontinued treatment due to flare-up was excluded from this analysis.

Of the 12 patients who discontinued treatment because of hepatic AEs, 11 experienced hepatic severe AEs. Abnormal hepatic laboratory test results at the initiation of the treatment were identified as the predictive factor for AZA discontinuation for both hepatic and cytopenic AEs [6 (50%) of 12 patients: p=0.024 and 6 (50%) of 12 patients: p=0.024, respectively]. Among the 31 patients with abnormal hepatic laboratory test results at the initiation of the treatment, 18 discontinued treatment because of AEs.

Cytopenic severe AEs were experienced in only 6 of the 12 patients who discontinued treatment because of cytopenic AEs. The other 6 patients discontinued treatment because of mild cytopenia. Leukocyte and neutrophil counts at the initiation of treatment were significantly lower in the patients who discontinued treatment because of cytopenic AEs (p=0.016 and p=0.013, respectively) than in those who continued treatment (Table 3). Of the 12 patients who discontinued AZA because of cytopenic AEs, 9 were treated with CYC prior to the initiation of AZA. The median time from the last CYC administration to AZA discontinuation because of cytopenic AEs was 105 days (IQR 64.5-351.5).

After AZA discontinuation, 27 patients were treated with glucocorticoids alone, 3 with mizoribine, and 1 with mycophenolate mofetil. Two (6%) of 36 patients experienced flare-ups during AZA treatment compared to 9 (29%) of 31 patients after AZA discontinuation (p=0.010).

Discussion

To our knowledge, this study is the first to focus on the safety of AZA in AAV patients. AZA was initiated for maintenance therapy in 72% of the patients enrolled in the study, and concomitant CYC was used for remission induction in 76% of the enrolled patients. AEs developed in 58 of the 67 patients, 36 of whom experienced severe AEs. AZA treatment was discontinued in 46% of the patients because of AE development within 1 year of treatment. Treatment discontinuation due to hepatic AEs and cytopenic AEs was more frequent in the patients with abnormal hepatic laboratory test results at the initiation of the treatment. Approximately half of the patients who discontinued treatment because of cytopenic AEs experienced cytopenic severe AEs. The other patients discontinued the treatment because of mild cytopenic AEs. Leukocyte and neutrophil counts at the initiation of the treatment were predictive for treatment discontinuation due to cytopenic AEs.

We observed a considerably high discontinuation rate of AZA treatment due to AEs. In previous clinical trials of AAV, the proportion of patients ceasing AZA because of AEs, including hepatotoxicity and digestive intolerance, was lower than that in the present study (1.7-11%), despite the longer median observational period of 28-39 months (5-7). Clinical trials of AZA treatment for SLE have shown that the withdrawal rate was 0-5% during the study period of 42-72 months (18, 19). Furthermore, observational studies in SLE patients have shown that only 4.5-6.4% of patients discontinued AZA treatment, which is representative of what is observed in daily clinical practice (15, 20, 21). Considering

Table 3. Demographic and Laboratory Data at the Initiation of the AZA Treatment in Patients who Discontinued the Treatment Due to Hepatic or Cytopenic AEs and Those who Continued the Treatment.

	Discontinuation due to hepatic AEs (n=12)[a]	Discontinuation due to cytopenic AEs (n=12)[a]	Continued (n=35)
Age, median (IQR), year	69.0 (59.5-75.8)	69.5 (58.8-75.0)	70.0 (65.0-77.0)
Male/Female, n (%)	5 (42)/7 (58)	4 (33)/8 (67)	8 (23)/27 (77)
Concomitant sulfamethoxazole/trimethoprim, n (%)	8 (67)	9 (75)	21 (60)
Abnormal hepatic laboratory test results, n (%)	6 (50)*	6 (50)**	6 (17)
Abnormal renal laboratory test results, n (%)	9 (75)	7 (58)	25 (71)
WBC, median (IQR), /μL	8,420 (7,530-10,070)	6,430**(5,320-8,077.5)	8,020 (7,090-9,490)
Hb, median (IQR), g/dL	11.8 (11.1-12.9)	11.7 (10.7-13.0)	11.4 (10.9-12.3)
PLT, median (IQR), $\times 10^4$/μL	25.9 (21.8-33.9)	28.7 (19.2-33.6)	24.3 (21.9-34.2)
Lym, median (IQR), /μL[b]	1,307 (960-1,750)	924 (800-1,358)	903 (626-1,694)
Neu, median (IQR), /μL[b]	6,600 (5,800-8,150)	5,650 (3,925-6,550)**	6,600 (5,900-8,500)
AST, median (IQR), U/L	24 (15-32)	20 (14-27)	18 (14-22)
ALT, median (IQR), U/L	22 (15-30)	24 (9-26)	17 (11-22)
γ-GTP, median (IQR), U/L	39 (16-84)	37 (12-63)	22 (15-34)
eGFR, median (IQR), mL/min/1.73 m^2	46.6 (41.4-62.4)	51.0 (33.5-84.4)	48.2 (33.1-62.2)

[a]Includes 2 patients with both hepatic and cytopenic AEs.

[b]Data were missing for 2 patients.

*$p<0.05$ in the comparison between patients who discontinued treatment because of hepatic AEs and continued patients.

**$p<0.05$ in the comparison between patients who discontinued treatment because of cytopenic AEs and continued patients.

AZA: azathioprine, AEs: adverse events, IQR: interquartile range, WBC: white blood cells, Hb: hemoglobin, PLT: platelets, Lym: lymphocytes, Neu: neutrophils, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyltranspeptidase, eGFR: estimated glomerular filtration rate

these low AZA treatment discontinuation rates in previous AAV and SLE studies, we conclude that the high discontinuation rate of AZA in the present study was not caused by disease specificity but by other factors.

The majority of patients enrolled in the present study experienced AZA-related AEs: hepatic AEs were observed in 45% of the patients, while this rate ranged from 3.8-6.3%, 3.8-21.4%, and 16% in previous studies of AAV (5, 6), SLE (18, 22), and IBD (23), respectively. The abnormal hepatic laboratory test results found at the initiation of the present AZA treatment may have been an effective predictor of hepatic severe AEs and AE-related discontinuation of AZA treatment. In previous clinical trials, patients presenting with abnormal hepatic laboratory test results were excluded from the study; therefore, the rates of hepatic AEs and hepatic AE-related discontinuation of AZA treatment might have been considerably lower in these previous studies. However, observational studies also found a lower frequencies of hepatic AEs and a hepatic AE-related AZA treatment discontinuation than in the present study (hepatic AEs occurred in 1.1% of SLE patients and 0.8-4% of IBD patients). Abnormal hepatic laboratory test results were less frequent in these observational studies than in our present study; therefore, the relatively frequent occurrence of abnormal hepatic laboratory test results might be one of the main causes underlying the high discontinuation rate of AZA treatment in the present study. In contrast, the renal function was not related to AEs in the present study. This may be because the initial dose of AZA was adjusted according to the eGFR.

The rates of cytopenic AEs in the present study were comparable to those observed in previous studies: 16-34% in AAV (5, 7, 8), 18-32% in SLE (18, 19, 21), and 7.4-21% in IBD (9-11). However, discontinuation of AZA due to cytopenic AEs was more frequent in the present study than in previous studies: 0-1.3% in AAV (5, 6), 1.9-4.5% in SLE (18, 20), and 8.3% in IBD (9). The initial dose of AZA was lower in the present study (0.63 mg/kg/day) than in a previous study (2 mg/kg/day for maintenance therapy during the first year). The frequent discontinuation of AZA treatment in the present study might be reflective of the fact that the initial AZA dose used was too low to re-administer AZA at an even lower dose to prevent or reduce the occurrence of cytopenic AEs.

Previous studies have shown that immunosuppressants are used only limitedly in Japanese patients with AAV (3, 24). In particular, CYC is not frequently used in Japan for patients with MPA/renal-limited vasculitis (RLV) (24, 25). The relatively low use of AZA in Japan might be associated with this relatively infrequent use of CYC. However, the frequent occurrence of AEs in the present study led to the discontinuation of AZA treatment despite the considerably higher CYC usage in the study cohort. These results suggest that low use of AZA in Japan is associated not only with infrequent use of CYC but also with the frequent occurrence of AEs. A recent clinical trial suggested that rituximab might be used for not only remission induction but also remission maintenance (7). Rituximab may be an alternative to AZA in these patients.

The current study has three limitations. First, a treatment protocol of AZA was not provided, and each attending physician decided whether or not to discontinue the treatment;

thus, AE occurrence might have been overestimated. However, we assessed AEs on the basis of the laboratory data for hepatic and cytopenic AEs. Therefore, the overestimation bias was relatively low, at least for these AEs. Second, we failed to elucidate why 27% of the patients enrolled in the present study exhibited abnormal hepatic laboratory test results at the initiation of the treatment. This issue may be resolved in a larger-scale cohort study of Japanese patients with AAV. Third, each comparison included only a small number of patients, and a multivariate analysis could not be performed, resulting in the possible persistence of confounding factors.

In conclusion, AZA treatment was difficult to continue in approximately 50% of Japanese AAV patients because of AEs. Although the treatment was appropriate for remission maintenance of AAV in tolerable patients, it may not be suitable for patients with abnormal hepatic laboratory test results, low leukocyte counts, or low neutrophil counts.

Author's disclosure of potential Conflicts of Interest (COI).

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