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ORIGINAL ARTICLE

EFFICACY OF AZATHIOPRINE IN MILD OR MODERATE RELAPSE IN CROHN'S DISEASE: CLINICAL AND ENDOSCOPIC EVALUATION

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Aim: The present study was aimed at evaluating the efficacy of azathioprine (AZA) in patients with active and relapsing Crohn's disease (CD) and the usefulness of endoscopy in this evaluation.
Methods: The 53 patients with active CD treated with AZA at our hospital were subjected to the following retrospective analysis: (i) evaluation of the clinical efficacy of AZA through comparison of the Crohn's disease activity index (CDAI); (ii) analysis of the relationship of the clinical efficacy to the difference in the mean corpuscular volume (MCV); (iii) evaluation of mucosal healing through analysis of the scores of the endoscopic findings in 16 patients; and (iv) analysis of the relapse rate.
Results: (i) Among the 53 patients, treatment was rated as having induced complete remission in 22.6%, as being effective in 41.5%, and as being ineffective in 13.3% of patients. The treatment was discontinued in 22.6% of patients. (ii) The post-treatment MCV was significantly increased after treatment. (iii) When the ulcer score estimated after treatment was compared with that before the start of treatment, a significant improvement of the score was noted. (iv) When the non-relapse rate after AZA therapy was calculated in the 41 patients followed up for 12 months, it was 84.8%.
Conclusion: AZA was shown to cause endoscopic mucosal healing as well as clinical efficacy. In the present study, it was inferred that the efficacy of AZA therapy in CD patients is manifested clinically first and that mucosal healing is an effect that occurs later.

Key words: azathioprine, Crohn's disease, endoscopy, mucosal healing.

INTRODUCTION

Azathioprine (AZA), an immunosuppressant drug, has been evaluated as being highly useful in the management of patients with Crohn's disease (CD), both in Japan and overseas.[1–6] In the treatment of CD, alleviation of the symptoms and signs of inflammation is often used as the goal of treatment. Evaluation of the responses of CD patients to treatment is thus also based on the treatment effect on the symptoms and signs of inflammation. However, the existing clinical activity indices for this disease, such as the CDAI, do not seem to faithfully reflect the state of the intestinal mucosa in CD patients. Although healing of the bowel lesions in CD patients in response to AZA therapy has been reported overseas, no full-scale study of this topic has yet been conducted in Japan. Under these circumstances, the present study was undertaken to evaluate the efficacy of AZA as a means of treating mild to moderately severe CD relapse and the usefulness of colorectal examination in assessing the efficacy of AZA therapy. We defined 'mild to moderate' as conditions in which the CDAI is >200 but <450. In other words, the present study was designed to compare the scores of the endoscopic findings (barium study findings in some patients) evaluated retrospectively before and after treatment and to explore the relationship between the treatment efficacy and the clinical findings. In addition, the relapse rate after treatment was also analyzed.

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METHODS

Subjects

Between March 2001 to April 2007, 106 patients with CD received AZA therapy at our hospital because of mild to moderate relapse. Of these patients, the 53 patients in whom the efficacy of treatment with AZA alone could be evaluated were enrolled as the subjects of this study, whereas the remaining 53 patients were excluded for the following reasons: (i) calculation of the CDAI was not possible because of the presence of a stoma; (ii) the treatment period was less than 6 months and evaluation of the efficacy was therefore not possible; (iii) concomitantly given infliximab therapy seemed to markedly affect the results of the assessment of the clinical efficacy (Table 1). Among the 53 subjects of this study, analysis of the colorectal endoscopy findings was possible in 16 patients (including three patients for whom the results of a barium study carried out before the treatment were additionally available). Of these 16 patients, 13 were male and three were female. The disease type was the

Table 1. Background characteristics of Crohn's disease patients treated with azathioprine

Male : female	38 : 15
Initial disease type (ileitis : ileo-colitis : colitis)	8 : 36 : 9
Age (years)	34.3 ± 9.2†
Duration of disease (years)	11.8 ± 7.6†
Prior operation	46.2%
Average treatment period (months)	24.2 ± 22.0†
CDAI before the treatment	245.0 ± 60.4†

†Mean ± SD.
CDAI, Crohn's disease activity index.

Table 2. Background characteristics of Crohn's disease patients evaluated by endoscopy

Male : female	13 : 3
Disease type (ileo-colitis : colitis)	12 : 4
Age (years)	33.1 ± 8.4†
Duration of disease (years)	10.1 ± 5.7†
Average treatment period (months)	31.4 ± 22.7†
Interval before the initial and the last endoscopy (months)	33.6 ± 23.2†

†Mean ± SD.

Table 3. Concomitant treatment during azathioprine treatment in patients with Crohn's disease ($n = 53$)

	No. patients	Average concomitant use period (months)
5-ASA	7 (13.2%)	26.0 ± 14.8† (6–43)
5-ASA + HEN	16 (30.2%)	23.6 ± 14.8† (0.7–85)
HEN	4 (7.5%)	25.2 ± 13.6† (6–45)
PSL	27 (50.9%)	2.0 ± 0.6† (0.8–3.0)
TPN	5 (9.4%)	2.0 ± 1.2† (0.4–2.1)

†Mean ± SD.
5-ASA, aminosalicylic acid; HEN, home enteral nutrition (average dose 825.0 ± 287.5 Kcal); PSL, prednisolone; TPN, total parental nutrition.

large-bowel type in four patients, small and large bowel type in nine patients and small-bowel type in three patients. The mean age of the 16 patients was 33.1 ± 8.4 years, the mean duration of the illness was 10.1 ± 5.7 years, and the mean interval between the first and second endoscopy was 33.6 ± 23.2 months (Table 2).

Concomitant therapies used in the 53 patients are listed in Table 3. At the start of the AZA therapy, five patients (9.4%) were receiving total parental nutrition (TPN). In these patients, TPN was completed in 8 weeks, on average, after the start of AZA therapy, indicating that it was unlikely to affect the results of the evaluation of the efficacy of AZA at 6 months after the start of treatment. Oral steroid therapy (prednisolone; PSL) was concomitantly used in 27 patients (50.9%) at the start of AZA therapy, but the PSL dose was gradually tapered subsequently, being altogether discontinued by 13 weeks; therefore, concomitant PSL therapy was also considered unlikely to affect the efficacy of AZA evaluated after 6 months of treatment. Home enteral nutrition (HEN) and 5-aminosalicyclic acid (5-ASA) therapy had been started before the beginning of AZA therapy and did not seem to significantly affect the results of the evaluation of the efficacy of AZA. For this reason, HEN and 5-ASA therapy were continued without changing the respective dose levels.

Evaluation and analysis

Clinical efficacy

The CDAI at 6 months after the start of AZA therapy was compared with that determined at the time of starting AZA therapy to evaluate the clinical efficacy of AZA. The treatment was rated as producing complete remission (decrease of CDAI to less than 150 points after treatment), as being effective (decrease of CDAI by 70 points or more, but failing to reach under 150), as being ineffective (cases not satisfying the criteria for either complete remission or the treatment being effective) or as being discontinued (because of the development of adverse reactions). In practice, the mean CDAI estimated at 6 and 7 months after the start of treatment was compared with that estimated at the start and 1 month before the start of AZA treatment).

ΔMCV and clinical efficacy

Changes in the mean corpuscular volume (MCV [femtoliter, fl]) after AZA treatment as compared with the values measured before treatment were analyzed to examine whether or not the change in the MCV after AZA treatment relative to the value before the start of treatment could serve as an indicator of the clinical efficacy of AZA. This analysis was conducted on 41 patients, after excluding 12 of 53 patients in whom treatment had to be discontinued because of adverse reactions. In other words, ΔMCV (defined as the difference in MCV measured at 6 months after the start of AZA therapy and that measured before the start of AZA therapy) was compared between two groups (a group consisting of patients in whom the clinical treatment response was labeled as complete remission or effective [Rem/Eff group] and a group in which the clinical treatment response was labeled as ineffective [Ineff group]).

Evaluation of the endoscopic findings in the terminal portions of the large bowel and ileum and the area of anastomosis

We attempted to identify the time-point at which healing of the colorectal mucosa would take place both before and after the start of AZA treatment and to explore the correlation between the endoscopic/barium study findings and the clinical response. These analyses were conducted on the 13 patients who underwent colorectal endoscopy both before and after AZA therapy and on the three patients who underwent a barium study before AZA therapy and endoscopy after AZA therapy ($n = 16$). The type of disease was the 'small and large bowel type' and 'small bowel type' in 12 of the 16 patients. Primarily, the lesions in the ileocecal area in these 12 patients were evaluated. Of the 12 subjects, five had undergone resection of the ileocecum and two had undergone partial colectomy. In these seven patients, examination was focused on the area of anastomosis. Colorectal

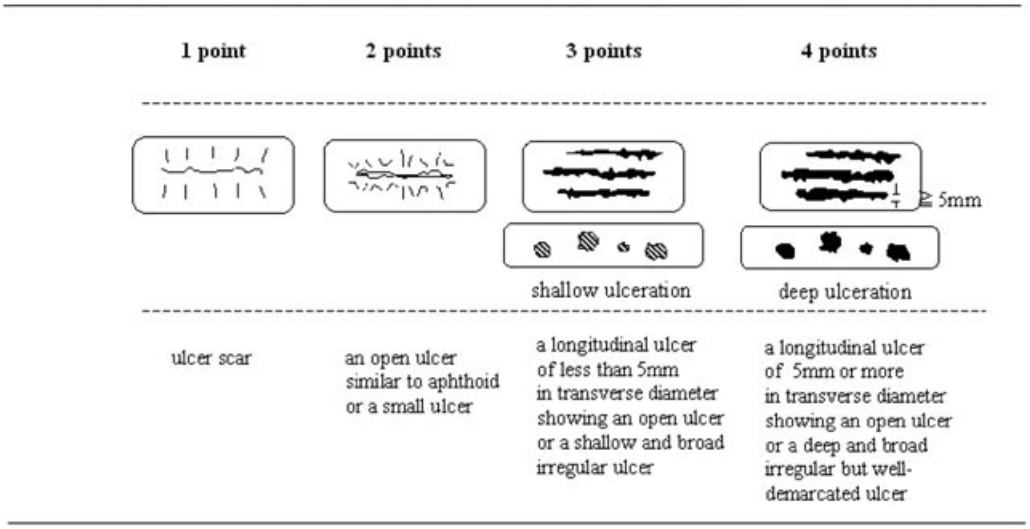

Fig. 1. Schematic illustration of ulcer score of the colonic lesion of Crohn's disease (CD).

endoscopy/barium study findings before and after treatment were scored in these patients. According to the original recording system for the colorectal endoscopic findings in CD patients proposed by Sou *et al.*[7], the scores for polyposis, ulcers and stenosis are evaluated separately. However, in their study, there was no case in which stenosis posed any significant problem. For this reason, we used only the ulcer scoring in this system for the present study (Fig. 1).

The large bowel was divided into five parts: (i) ileum end; (ii) cecum to ascending colon; (iii) transverse colon; (iv) descending colon to sigmoid colon; and (v) rectum. The scores for each of these parts were calculated and totaled to yield the ulcer score. Scarred ulcers were assigned a score of 1 point (Fig. 2a), aphthous or small ulcers were assigned as score of 2 points (Fig. 2b), small ulcers measuring 5 mm or less in width, or extensively scattered shallow ulcers were assigned a score of 3 points (Fig. 2c), and longitudinal ulcers measuring over 6 mm in width, or extensively distributed deep and evident ulcers were assigned a score of 4 points (Fig. 2d).

Relapse of disease after AZA therapy

For long-term evaluation of the effect of AZA in maintaining remission in patients with CD,[8–11] the clinical course after AZA therapy was followed in 41 patients (excluding treatment-discontinued patients) to check for relapse of the disease. A judgment of relapse was made when the CDAI exceeded 200 at 6 months or more after the start of AZA therapy. The cumulative relapse rate was calculated using the Kaplan–Meier method.

Statistical analysis

Statistical analysis of the data was conducted using the *t*-test, Kaplan–Meier method and Fisher's exact test. All data were expressed as mean ± SD. A significant difference was assumed to exist at *P*-values <0.05.

RESULTS

Clinical efficacy

Among the 53 patients, at 6 months after the start of treatment, the treatment was rated as producing complete remission in 12 patients (22.6%, CDAI 265.2 ± 66.5 to 90.2 ± 23.2), being effective in 22 patients (41.5%, CDAI 276.6 ± 42.4 to 180.0 ± 24.0), and being ineffective in seven patients (13.3%, CDAI 177.7 ± 13.5 to 185 ± 23.3); treatment was discontinued in 12 patients (22.6%), as shown in Table 4. Discontinuation of AZA treatment was attributable to the development of adverse reactions in all patients (granulocytopenia in three patients, thrombocytopenia in one patient, nausea in three patients, headache in one patient, abdominal pain in one patient, hepatic dysfunction in one patient, skin eruption in one patient, and malaise in one patient).

The mean CDAI for the entire population ($n = 53$) decreased significantly from 245.0 ± 60.4 before the treatment to 167.7 ± 53.4 at 6 months after the treatment ($P < 0.0001$). The mean AZA dosing period and the mean AZA dose in each of the response groups were as follows: 29.5 ± 25.8 months and 54.2 ± 18.0 mg, respectively, in the group showing complete remission, 31.6 ± 18.6 months and 48.9 ± 5.3 mg, respectively, in the group in which the treatment was rated as effective, 29.3 ± 23.4 months and 46.4 ± 9.4 mg, respectively, in the group in which the treatment was rated as ineffective, and 2.6 ± 1.9 months and 50.0 ± 0 mg, respectively, in the group in which the treatment was discontinued.

ΔMCV

The ΔMCV was measured in 41 patients as described above (Table 5). The 12 patients in whom the treatment was rated as producing complete remission and the 22 patients in whom the treatment was rated as effective showed marked improvement of the CDAI after the treatment, accompanied by a marked increase of the ΔMCV (7.2 ± 4.0 fl). In the seven

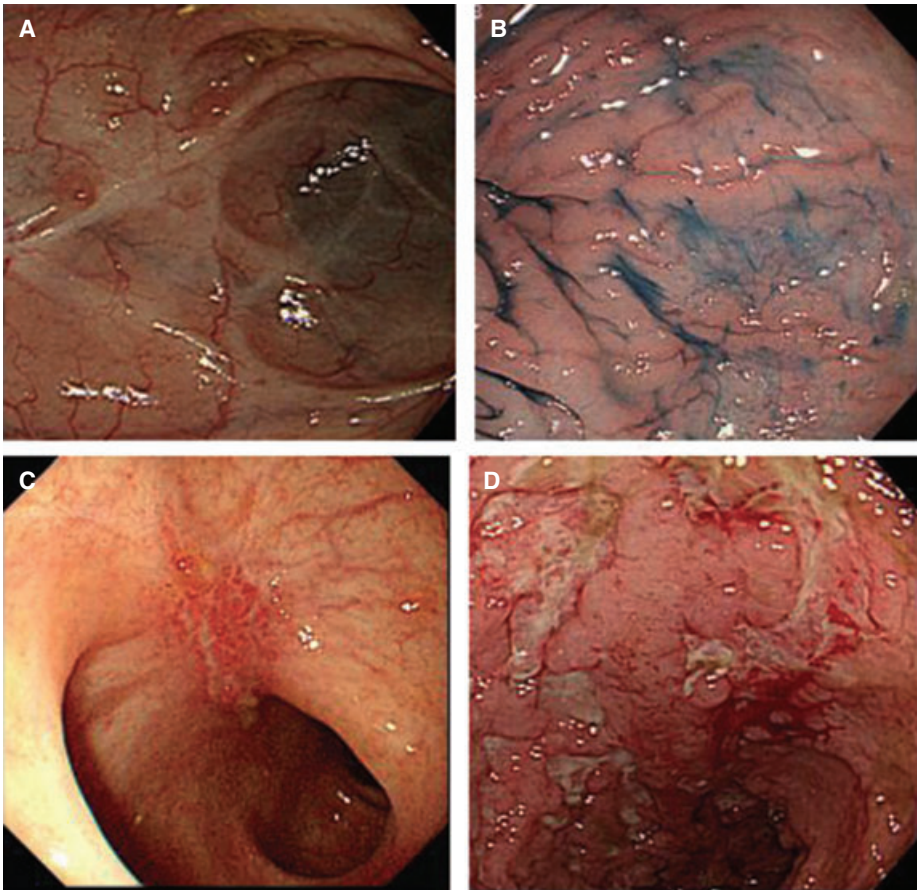

Fig. 2. (a) Ulcer scars (1 point); (b) aphthous or small ulcers (2 points); (c) small ulcers measuring 5 mm or less in width or extensively scattered shallow ulcers (3 points); (d) longitudinal ulcers measuring over 6 mm in width, or extensively distributed deep and evident ulcers (4 points).

Table 4. Therapeutic effect evaluated by CDAI or clinical features in patients with Crohn's disease ($n = 53$)

Clinical efficacy	No. patients	
Remission[†]	12 (22.6%)	64.1%
Effective[‡]	22 (41.5%)	
Ineffective[§]	7 (13.3%)	35.9%
Discontinuation by adverse reaction	12 (22.6%)	

[†]Remission (CDAI < 150 points).
[‡]Effective (CDAI decreased by at least 70 points, but >150 points).
[§]Ineffective (neither remission nor efficacy).
CDAI, Crohn's disease activity index.

Table 5. Changes in CDAI and MCV during azathioprine treatment in patients with Crohn's disease ($n = 41$)

	Patients with remission and effective results	Patients with ineffective results	*P*-value*
No. patients	34	7	
CDAI before AZA	263.3 ± 52.1	177.7 ± 13.5	$P = 0.001$
CDAI after 6 months	146.9 ± 48.0	185.0 ± 23.3	$P = 0.0175$
ΔMCV	7.2 ± 4.0	3.2 ± 7.2	$P = 0.049$

**t*-test.
AZA, azathioprine; Crohn's disease activity index; MCV, mean corpuscular volume.

patients in whom the treatment was rated as ineffective, however, the improvement in CDAI was unsatisfactory and the ΔMCV was small (3.2 ± 7.2 fl). The ΔMCV in the group in whom the treatment was rated as producing complete remission or being effective (Rem/Eff group) was significantly greater than that in the group in which the treatment was rated as being ineffective (Ineff group) ($P = 0.049$).

Evaluation of the colorectal endoscopy/barium study findings

In the 16 patients who underwent colorectal endoscopy/barium study, the mean ulcer scores before and after treatment were calculated. The mean ulcer score improved significantly from 6.2 ± 4.6 before treatment to 2.9 ± 3.0 after treatment ($P = 0.0024$, Fig. 3). The changes in the ulcer score in individual patients were analyzed and rated on a three-category scale: (i) complete mucosal healing (scarring of all ulcers); (ii) partial mucosal healing (improvement of the score by 5 or more); and (iii) no change (not satisfying the criteria for either (i) or (ii)). Nine patients (56.2%) were rated as showing complete mucosal healing, three patients (18.8%) as showing partial mucosal healing, and four patients (25.0%) as showing no change. The mean interval between the first and second endoscopic examinations was

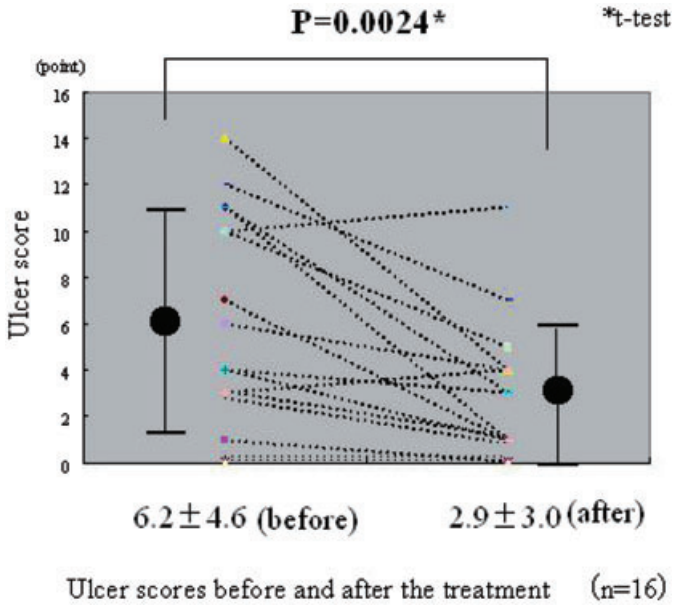

Fig. 3. Mucosal healing evaluated by ulcer score using serial observation at the initial and the last endoscopy. Significant improvement of the score was noted after the treatment (2.9 ± 3.0) as compared with that before the treatment (6.2 ± 4.6) ($P = 0.0024$). The average interval was 33.6 ± 23.2 months.

Table 6. Correlation between endoscopic and clinical activity evaluation in Crohn's disease patients with azathioprine treatment

		Endoscopic evaluation	
		Complete or partial mucosal healing	No change
Clinical activity evaluation	Remission or effective	12	1
	Ineffective	0	3

Fisher's exact test $P = 0.0071$.

22.6 ± 10.2 months in the Rem group, 20.8 ± 9.5 months in the Eff group, and 17.9 ± 26.6 months in the Ineff group.

In the patients who showed response to the AZA treatment, the clinical efficacy was significantly correlated with improvement in the colorectal endoscopy/barium study findings (Table 6, Fisher's test, $P = 0.0071$).

Disease relapse after AZA therapy

Of the 53 patients, 41 patients were followed up clinically, after excluding the 12 patients in whom the treatment with AZA was discontinued because of the development of adverse reactions. The non-relapse rate among these 41 patients was calculated using the Kaplan–Meier method. In all of the 41 patients, the CDAI decreased to 200 or less at 6 months after the start of treatment. Therefore, a judgment of relapse was made when the CDAI exceeded 200 (Fig. 4). The mean follow-up period of the patients was 27.3 ± 20.8 months (range: 6–85 months). The non-relapse

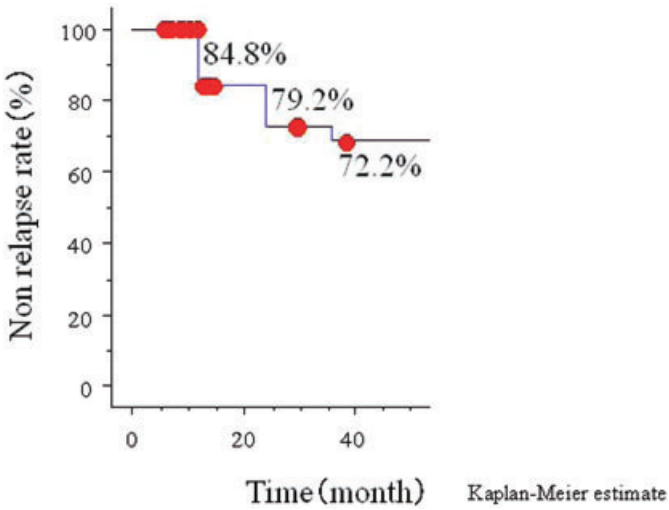

Fig. 4. Cumulative non-relapse rate in patients with Crohn's disease (CD) on long-term treatment with azathioprine (AZA). The non-relapse rate was 84.8% at 12 months, 79.2% at 24 months and 72.2% at 36 months after the start of AZA therapy.

rate was 84.8% at 12 months, 79.2% at 24 months and 72.2% at 36 months after the start of AZA therapy.

The 16 patients who also underwent endoscopy after AZA therapy were divided into two groups according to the post-treatment endoscopic score: the mucosal healing group (score of 1 or 0; $n = 8$) and the mucosal non-healing group (any score other than 1 or 0; $n = 8$). The relapse rate did not differ significantly between the two groups ($P = 0.582$).

DISCUSSION

In the present study, changes in the CDAI from the start of AZA treatment to 6 months after the start of the therapy were analyzed to evaluate the efficacy of AZA in introducing remission in patients with CD. In approximately 60% of all the patients, the treatment was rated as producing complete remission or as being effective at 6 months after the start of treatment. Present *et al.*[12] previously conducted a cross-over study in which 83 patients with CD who had failed to respond to salazosulfapyridine (SASP) or prednisolone (PSL) therapy were treated with 6-merucaptopurine (6-MP) at a mean dose of 1.5 mg/kg. In that study, 6-MP was rated as being effective in inducing disease remission as compared to the placebo. Ewe *et al.*[13] evaluated the effect of AZA (2.5 mg/kg) in inducing remission in 42 patients with active CD, and the percentage of patients showing remission was significantly higher in the AZA treatment group (76%) than in the placebo group (38%). D'Haens *et al.*[14] demonstrated that treatment with AZA in combination with infliximab resulted in early induction of remission, and that this combined therapy could be switched to maintenance therapy with AZA alone after the induction of remission. Thus, in Western countries, AZA seems to be used as a major treatment agent in CD patients after remission induction. It seems, therefore, essential to evaluate the incidence of relapse of CD after the

start of AZA therapy. In Japan, however, there are scarcely any published studies on this treatment issue in patients with CD.

Among the published reports concerning relapse in patients with CD, Willoughby *et al.*[8] reported a double-blind study designed to determine the effects of AZA used in combination with prednisolone (60 mg/day) in 22 patients with active CD. In their study, 10 of the 11 AZA-treated patients followed a favorable course during the 24-week follow-up period, whereas eight of the 11 placebo-treated patients showed early relapse of the disease. These results indicate that AZA induces disease remission relatively early in the course of treatment. In regard to the criteria for the judgment of relapse, some investigators judge the occurrence of disease relapse when the CDAI exceeds approximately 200.[10,15] We also adopted this criterion for the judgment of relapse (CDAI exceeding 200) in the present study. When we analyzed the relapse rate as judged on the basis of evaluation of the endoscopic findings in relation to the use of this criterion, the relapse rate did not differ significantly between the mucosal healing group and the mucosal non-healing group, but the patients often showed a tendency for improvement in the endoscopic findings, suggesting that improvement of the endoscopic findings bear a correlation with the clinical efficacy of treatment. In other words, the results suggest that patients showing endoscopic improvement in response to AZA therapy can also be rated clinically as responders to the therapy, even in the absence of complete mucosal healing. Bouhnik *et al.*[9] reported the relapse rate of CD among 157 patients treated with AZA. According to their report, the relapse rate was 11% at 1 year and 32% at 5 years after the start of treatment. These values are close to those recorded in the present study.

Ardizzone *et al.*[15] and Hanauer *et al.*[16] reported that AZA was useful for maintaining remission after intestinal resection in CD patients. Cosnes *et al.*,[17] however, reported that treatment with immunosuppressants after this type of surgery did not reduce the re-operation rate. Vilien *et al.*[1] reported that remission was maintained in 11 (85%) of 13 CD patients by AZA therapy, the percentage differing significantly from that in the non-AZA-treated group, which was only seven (47%) in 15 ($P = 0.043$). In the present study, the percentage of patients in whom the treatment was rated as having induced remission or as being effective at 6 months after the start of AZA therapy was 64.1%, close to the percentage reported by Vilien *et al.* The subjects of our study had relatively high CDAI values before treatment as compared with the patients in the study by Vilien *et al.* Candy *et al.*[10] randomly allocated patients into a steroid therapy group and an AZA + steroid therapy group and evaluated the effects of each of these therapies in maintaining remission in patients with CD. In their study, remission was maintained in 42% of the patients at 15 months after the start of therapy in the AZA + steroid group therapy, whereas the corresponding percentage was 7% in the steroid therapy group.

Su and Lichtenstein[4] analyzed the remission maintenance rate among patients with CD in remission by means of meta-analysis of data from five randomized controlled trials. In their analysis, the percentage of patients showing maintenance of disease remission was 67% in the AZA-treated group and 52% in the placebo group. On the basis of this result, Su *et al.* concluded that AZA is useful for maintenance of remission in patients with CD. Thus, the usefulness of AZA for maintaining disease remission appears to be beyond question.

In regard to the dose level of AZA, the mean dose level of this drug used in the present study was 50.0 ± 9.8 mg/bodyweight per day. The mean dose level per kg bodyweight was 1.0 mg/kg per day, and the mean bodyweight of the study subjects was 50.8 ± 7.9 kg. Hibi *et al.*[18] reported that treatment with 6-merucaptopurine (6-MP) at a dose level of 20–30 mg/day was effective in patients with CD. This dose level is lower than the average dose levels of the drug reportedly used in studies conducted overseas. This difference seems to reflect an ethnic difference in thiopurine methyltransferase (TPMT) activity. Kubota and Chiba[19] reported that the mean TPMT activity in Japanese people is 26.8 ± 5.8 pmol/h per mg Hb, a value lower than that reported for Western populations. It seems therefore rational to consider that the optimum dose of AZA for Japanese patients is 1 mg/kg per day.

The size of patients' red blood cells has generally been found to increase as a result of AZA therapy, and a sufficient concentration of AZA would have to be maintained in the blood as a condition for that to occur. However, it is difficult to measure AZA concentrations in blood, and some sort of index is needed to monitor the dose. As a solution to this problem, it has been reported that variations in MCV can be used as an indirect means of evaluating of 6-thio-guanine nucleotides (6-TGN), a metabolite of AZA, and measurements of variations in MCV values are expected to serve as a guide to adjusting the dose.[20]

Indirect proof was needed that the AZA concentration in the blood was being maintained in our study. As shown in Table 5, there were significantly larger variations in MCV between before and after administration in the 'remission' and 'effective' groups than in the 'ineffective' group. Thus, it appeared that variations in MCV can serve as a guide to the expression of efficacy of AZA, and these hypotheses were found to be supported.

D'Haens *et al.*[21] defined mucosal healing as the disappearance of ulcers in the terminal parts of the ileum or large bowel. Recently, close attention has been paid to the natural history of CD among patients showing mucosal healing. They reported improvement of large bowel lesions in 70% of 20 AZA-treated patients during a 2-year follow-up period. This percentage is close to the percentage (75.0%) recorded in the present study (this represents the percentage of patients who showed complete or partial mucosal healing on endoscopic evaluation during the follow-up period of 25.7 months, on average). Vermeire *et al.*[22] reported that among various drug therapies and other treatments for the mucosal lesions, AZA can induce mucosal healing to some extent; however, its efficacy becomes apparent rather slowly. Froslie *et al.*[23] also reported that mucosal healing is an important indicator in the evaluation of treatment responses in patients with inflammatory bowel diseases, and that it is also closely related to the prognosis after treatment. A comparison of two groups (50 CD patients who showed mucosal healing and 80 patients who failed to show mucosal healing at 1 year after the start of treatment) revealed a lower incidence of endoscopic relapse during 5 years after the start of treatment ($P = 0.02$) and a lower requirement of steroids ($P = 0.02$) in the mucosal healing group as compared with that in the non-healing group.

Few published reports pertain to attempts at including colorectal endoscopy/barium study findings (mucosal healing etc.) in the evaluation of the efficacy of AZA. Well-known reports involving scoring of the colorectal endoscopy/barium study findings in patients with CD include the modified Crohn's Disease Endoscopic Index of Severity (CDEIS) reported by Daperno *et al.*[24] and the CDEIS reported by Modigliani *et al.*[25] In Japan, discussions of the effect of AZA therapy on intestinal mucosal lesions in CD appear to be inadequate. In the present study, the colorectal mucosal findings before and after AZA treatment were evaluated. Complete mucosal healing or partial mucosal healing was seen in 75.0% of all the patients evaluated. There was a significant correlation between the clinical findings and the colorectal endoscopy/barium study findings. That is, a tendency towards improvement in the colorectal endoscopy/barium study findings was noted in 12 of the 16 patients in whom the AZA therapy was rated as having induced remission or as being effective. This result suggests that AZA stimulates mucosal healing of the large bowel in CD, thereby increasing the percentage of patients showing clinical response to treatment. In the past, the responses of CD patients to AZA therapy were often evaluated on the basis of clinical parameters, such as the CDAI. The results of the present study suggest that evaluation by diagnostic imaging can also play a significant role in the evaluation of the responses to treatment in CD patients.

In regard to the timing of the post-treatment colorectal evaluation, the mean interval from the first to the second evaluation by diagnostic imaging in the 16 patients in the present study was about 34 months. Mucosal healing was noted in eight of these 16 patients.

D'Haens[21] *et al.* assessed the mucosal healing of CD patients treated with AZA and that the mean interval of the colorectal endoscopy examination in their study was 34.3 ± 17.6 months. Moreover, they also conducted a multicenter collaborative study of the efficacy of combination therapy with AZA and infliximab in CD patients and evaluated the endoscopic study after administration for 26 months.[14] The evaluation by re-examination after 2 years is not late necessarily, and our average examination interval appears to be valid.

Considering the above-cited report that the clinical efficacy of AZA appeared within 1 year,[1] it is general knowledge that clinical efficacy occurs faster than 1 year and mucosal healing occurs later than the clinical remission in response to AZA. In our study, although the assessment of the clinical efficacy and colonoscopic evaluation were not carried out at the same time, it seems likely that the clinical efficacy appears first and endoscopic responses appear slightly later in patients treated with AZA.

The present study may be of value in that the clinical efficacy and endoscopic healing were evaluated separately, although the study was retrospective in nature. It seems particularly noteworthy that the effectiveness of AZA therapy was also successfully confirmed by endoscopic evaluation. As far as reports on the treatment of CD primarily using AZA are concerned, the number of reports dealing with evaluation of colorectal lesions before and after treatment is quite scant not only in Japan, but also overseas. Such studies are often confined to evaluation of the area of anastomosis in patients after ileocecal resection. Reports dealing with systematic evaluation of the entire large bowel are rare, except for the report by D'Haens *et al.*[21] Therefore, it would be desirable that data from a larger number of cases are collected to determine the clinical responses and improvement in the colorectal endoscopy/barium study findings induced by treatment in patients with CD to allow a more detailed analysis on this subject.

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