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Concerns and Side Effects of Azathioprine During Adalimumab Induction and Maintenance Therapy for Japanese Patients With Crohn's Disease: A Subanalysis of a Prospective Randomised Clinical Trial [DIAMOND Study]

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Abstract

Background: Combining a thiopurine with the human anti-tumour necrosis factor-α monoclonal antibody adalimumab for Crohn's disease [CD] treatment is controversial with regard to efficacy and safety. By conducting a subanalysis of a multicentre, randomised, prospective, open-label trial [the DIAMOND study, UMIN registration number 000005146], we studied the risk of discontinuation of thiopurine in combination with adalimumab.

Methods: In the preceding DIAMOND study, we analysed the: [i] timing and reasons for dropout in the monotherapy group and combination group; [ii] risk factors for dropout in the combination group.
Results: There was no significant difference in the dropout rate up to Week 52 between the monotherapy group and combination group [$p = 0.325$]. The main reason for study dropout was active CD in the monotherapy group, whereas it was adverse effects in the combination group [Fisher's exact test, $p < 0.001$]. Kaplan–Meier analyses revealed significantly earlier dropout in the combination group [log-rank test, $p = 0.001$]. Multivariable analysis revealed low body weight to be a risk for dropout due to adverse effects in the combination group.
Conclusions: Combination of azathioprine with adalimumab resulted in dropout in the early stage of the study due to side effects of azathioprine, in comparison with late dropout due to active CD in the adalimumab monotherapy group.

Key Words: Adalimumab; Crohn's disease; anti-TNF-alpha antibody; thiopurine

1. Introduction

In recent years, anti-tumuor necrosis factor [TNF]α monoclonal antibody [mAb] has become the main agent for treatment of Crohn's disease [CD].[1,2] In patients with biologic-naïve CD, a combination of infliximab [a chimeric anti-TNFα mAb] with a thiopurine has shown clinical benefit.[3] Adalimumab is a human anti-TNFα mAb, and the benefits and risks of combination therapy have been controversial.[4–6]

Recently, we reported the results of a prospective randomised controlled trial comparing the efficacy of adalimumab monotherapy and the efficacy of combination therapy with azathioprine for CD patients naïve to biologics and thiopurines [the DIAMOND study].[7] In that study, the rate of clinical remission at Week 26 as the primary endpoint did not differ between the adalimumab monotherapy group and the combination group. As a secondary endpoint, the rate of endoscopic improvement at Week 26 [but not Week 52] was significantly higher in the combination group than in the monotherapy group. With respect to the occurrence of anti-adalimumab antibodies [AAAs], subanalysis of the DIAMOND study demonstrated a beneficial effect of combination therapy. Higher levels of 6-thioguanine nucleotide [6-TGN] affected AAA negativity and the trough level of adalimumab, and AAA occurrence was associated significantly with clinical remission.[8] Another subanalysis of the DIAMOND study revealed that concomitant use of azathioprine with adalimumab had marginal effects on the endoscopic response, and that the trough level of adalimumab was associated with endoscopic response or mucosal healing.[9] Thus, although the DIAMOND study did not show clinical benefit in all patients, subanalyses suggested the reliable clinical benefits of combination therapy in a certain population. Nevertheless, physicians and patients must pay attention to the risk of adverse effects in combination therapy rather than monotherapy. This is especially true for thiopurine-induced acute leukopenia,[10,11] malignancy,[6] and lymphoproliferative disorders, including hepatosplenic T cell lymphoma.[12,13]

The participating centres of the DIAMOND study included several tertiary referral centres with many inflammatory bowel disease [IBD] patients, and registering physicians were very experienced in IBD management and clinical trials. They also had sufficient experience of CD patients treated with anti-TNF agents and thiopurines. Therefore, analysing the reasons for termination of the thiopurine combination group would lead to clarification of the real-world concerns of CD experts.

In anti-TNF antibody therapy for CD, few reports have analysed minutely the reasons for discontinuation of combination therapy with thiopurine. The aim of the present study was to identify the risk factors of stopping combination therapy due to the side effects of thiopurines.

2. Materials and Methods

2.1. Patients and study design

Data in this analysis are from the preceding DIAMOND trial (University Hospital Medical Information Network [UMIN] registration number 000005146). The methods employed in the DIAMOND study have been described in detail by Matsumoto *et al.*[7]

In brief, DIAMOND was a multicentre, randomised, prospective, open-label study in patients with moderate-to-severe active CD [defined as a Crohn's Disease Activity Index [CDAI] score of 220–450].[14] Enrolled patients were naïve to anti-TNFα agents and immunomodulators, had received a definitive diagnosis of CD ≥3 months previously, and were aged 15–65 years. Enrolled patients were assigned to receive a combination of adalimumab and azathioprine [combination group] or monotherapy with adalimumab [monotherapy group]. All patients received subcutaneous administration of adalimumab at 160 mg at Week 0, 80 mg at Week 2, and 40 mg at every other week thereafter up to 52 weeks. Patients in the combination group were treated initially with azathioprine [25 or 50 mg/day] and the dose could be increased to ≤100 mg during the initial 4 weeks under careful observation. The maximum dose of azathioprine was chosen in consideration of 6-TGN concentrations in Japanese patients with IBD.[15] Clinical efficacy was evaluated at Weeks 26 and 52. 'Clinical remission' was defined as CDAI score <150 points. The decision to discontinue the study due to side effects, increase in disease activity, or other reasons was left to the treating physician.

Criteria for discontinuation of the DIAMOND study were: [i] a request from a patient to drop out after starting the study; [ii] an adverse event; [iii] identification of clearly ineligible patients after study commencement; [iv] achievement of the study aim [e.g., by interim analysis] before reaching the planned number of patients or planned study duration; [v] recommendation/order to cancel by the Examination Review Committee; and [vi] the research physician stating that the study should be cancelled. With regard to [ii], we

judged that patients should drop out of the study if the treating physician stopped azathioprine after considering the adverse effects of azathioprine in the combination group.

2.2. Statistical analyses

Fisher's exact test was used to examine the difference in the completion rate and the difference in the reasons for withdrawal at 52 weeks between the monotherapy group and the combination group. The cumulative continuation rate in each group was assessed using Kaplan–Meier analyses. Factors that contributed to the cumulative continuation rate were estimated by the log-rank test. Since other events can occur unless dropout even after the event occurs, the method for considering competing risks [cumulative incidence, Gray's test, etc.] was not carried out due to the possibility of underestimation.

Multiple logistic regression analysis was used to estimate the odds ratio after adjustment for potential confounders, and to identify the factors independently associated with dropout due to adverse effects in the combination group at Week 26. Covariates included in the model were age, sex, body weight, disease duration, disease location, presence of anal fistulae, smoking status, medication, CDAI score, and C-reactive protein [CRP] level at trial entry. Then, the backward elimination method was applied for the logistic model due to the small number of the events, and covariates were not excluded when p <0.4, to keep at least three covariates for confounding assessment. Analyses of receiver operating characteristic [ROC] curves were done to examine the discriminatory ability of body weight for the risk of study dropout at Week 26 in the combination group. Optimal cut-offs were identified using the Youden Index. Analyses for covariance with evaluation of linearity using polynomial contrasts were undertaken to assess an association between the body mass index [BMI] and 6-TGN level. Statistical analyses were carried out using SPSS v23 [IBM, Armonk, NY, USA]. All statistical tests were two-sided and p <0.05 was considered significant.

2.3. Ethical approval of the study protocol

The study protocol was approved by the ethics review board at each institution and registered publicly [UMIN registration number 000005146]. All patients provided verbal and written informed consent for blood testing and collection of clinical data, before enrolment.

3. Results

3.1. Study population

The demographic and clinical characteristics of patients in the DIAMOND study have been reported previously.[7] Briefly, during the predetermined period of recruitment from June 1, 2011 to June 31, 2014, 176 patients were assigned randomly to the combination group [n = 91] or monotherapy group [n = 85].

One patient was excluded from the study because of a diagnosis of intestinal tuberculosis after study enrolment. In the combination group, 22 patients discontinued the study due to adverse events [including insufficient efficacy] and seven patients due to other reasons [dose escalation of azathioprine after 4 weeks for two patients, consent withdrawal for three patients, and loss to follow-up for two patients]. In the monotherapy group, 19 patients discontinued the study owing to adverse events, and three patients discontinued the study for other reasons [CDAI score not available for two patients and consent withdrawal for one patient] [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online]. Finally, 62 patients in the combination group and 63 patients in the monotherapy group completed the study through Week 52 [Figure 1].

3.2. Outcome of patients experiencing adverse effects in the combination arm versus the monotherapy arm

In the DIAMOND study, 58 patients [32.8%] [33 of 91 in the combination group and 25 of 85 in the monotherapy group] experienced some kind of adverse effect [including an increase in disease activity]. Leukopenia, hair loss, and nausea were observed only in the combination group [Table 1].

3.3. Reasons for discontinuation of the study in the combination group versus the monotherapy group

In the combination group up to Week 52, 61 of the 91 patients [67%] continued the study, and 30 [33%] dropped out. In the monotherapy group, the study was continued in 63 of 85 patients [74.1%] and 22 patients [25.9%] dropped out. There was no significant difference [p = 0.325] in the dropout rate between the two groups [Figure 2A]. Interestingly, the reasons for dropout from the study in each group were significantly different. In the combination group, the reason for dropout was the side effects of medications in 14 of 30 patients [46.7%] and disease exacerbation in eight patients [26.7%]. In the monotherapy group, the reason was disease exacerbation in 18 of 22 patients [81.8%] and side effects in one patient [4.6%]. As described above, although there was no significant difference [p = 0.325] between the two groups in the overall rate of study continuation, there was a significant difference between the two groups for the reason for study discontinuation [p <0.001, Fisher's exact test] [Figure 2B]. It was considered that all dropouts due to the adverse events of medication in the combination group were caused by the side effects of the thiopurine used.

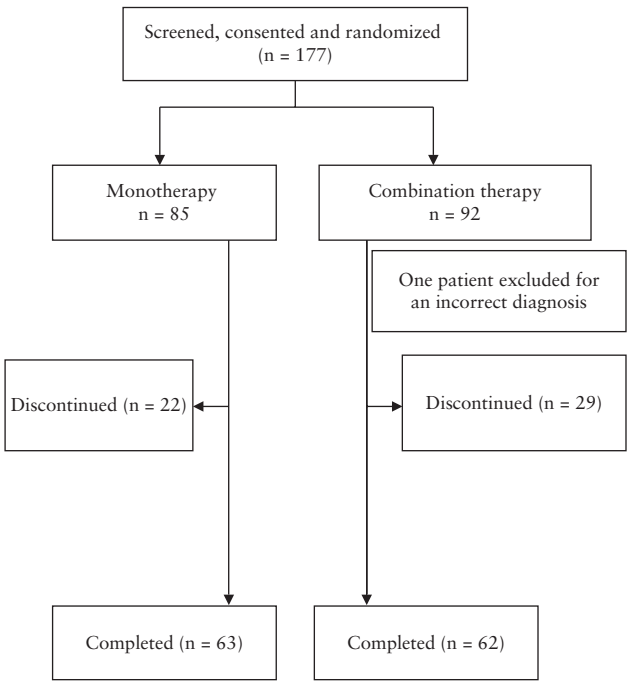

Figure 1. Flowchart of this subanalysis of the DIAMOND study.

Table 1. Adverse events in combination versus the monotherapy group.

	All patients	Combination group	Monotherapy group
All adverse events	58 [32.8%]	33 [36.3%]	25 [29.4%]
Leukopenia	8	8	0
Liver dysfunction	6	5	1
Hair loss	3	3	0
Infection	4	3	1
Skin eruption	2	1	1
Nausea	4	4	0
Obstruction	4	2	2
Increase of disease activity	26	7	19

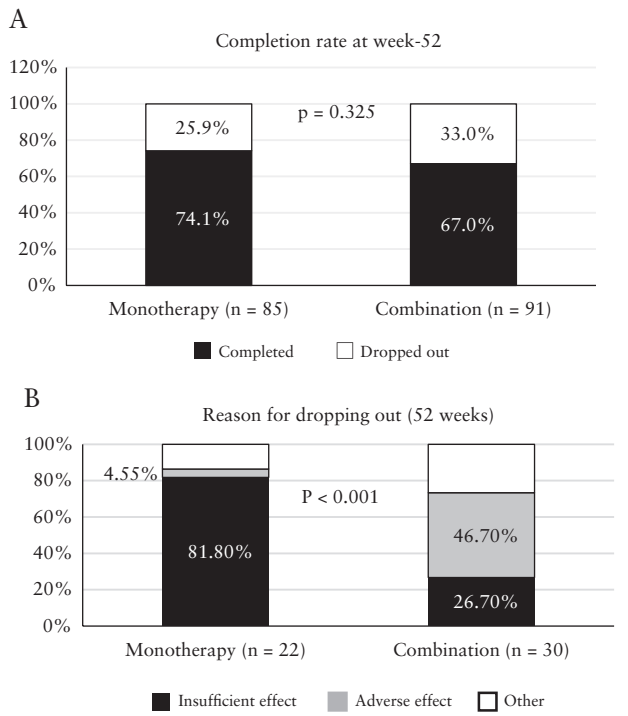

Figure 2. Completion of the study and withdrawal from the study in monotherapy [$n = 85$] and combination therapy [$n = 91$] groups at Week 52. A: Completion rate at Week 52. Completion rate was 74.1% in the monotherapy group and 67.0% in the combination group [$p = 0.325$; Fisher's exact test]. B: Reason for withdrawal in monotherapy [$n = 22$] and combination [$n = 30$] groups at Week 52. The reason for withdrawal was significantly different between the two groups [$p < 0.001$; Fisher's exact test].

Kaplan–Meier analyses revealed a trend towards a higher continuation rate in the monotherapy group than in the combination group, but a significant difference was not observed [$p = 0.214$] [Figure 3A]. However, when the timing and reasons for dropping out were considered, the combination group discontinued the study in the early phase due to adverse effects [$p = 0.001$], whereas almost no dropout was observed in the monotherapy group in the early phase. In patients who dropped out from the study due to exacerbation of disease activity, dropout occurred slowly over time. Although there was no significant difference [$p = 0.069$], dropout due to exacerbation of disease activity was more frequent in the monotherapy group [Figure 3B]. The exact CDAI score was not defined in the criteria of study discontinuation, but the CDAI score at Week 12 was significantly higher in patients who dropped out due to insufficient efficacy than the CDAI score in patients who dropped out due to other reasons, including adverse effects [143.73 vs 82.13, $p < 0.001$]. The difference in the CDAI score at Week 12 from baseline was also significantly different between the two groups [Supplementary Figure 1A, B, available as Supplementary data at *ECCO-JCC* online]. These results indicated that, although no clear criteria for discontinuation of the study due to insufficient efficacy were set, a physician observed the clinical activity objectively and decided to stop the study.

3.4. Clinical course of patients who dropped out from the study due to the side effects of azathioprine

The clinical course of patients who dropped out from the study due to the side effects of azathioprine is shown in Table 2. Among 14 patients who dropped out, five did so due to bone marrow suppression [including leukopenia]. Four of these five patients recovered by stopping azathioprine without the requirement of hospitalisation or granulocyte-colony stimulating factor [G-CSF] administration. The clinical course of the remaining patient is not known.

3.5. Risk factors for dropout until Week 26 in the combination group

Next, we analysed the risk factors for study dropout up to Week 26 in both groups. The adverse effects of azathioprine were the major reason for dropout in the combination group. Hence, we assessed the risk factors for dropout in the patients who dropped out of the study due to the adverse effects of azathioprine [$n = 13$]. When multivariable analysis was undertaken by inputting age, sex, body weight, disease duration, disease behaviour, perianal lesion, smoking, 5-aminosalicylic acid [5-ASA] level, and enteral nutrition as variables, body weight was extracted as an independent factor [Table 3]. Analyses of ROC curves identified a lower body weight [≤48.5 kg for males and females] as a risk factor for study dropout in the combination group. Kaplan–Meier curves showed a significant difference in the cumulative continuation rate in male patients whose body weight was ≥48.5 kg and ≤48.5 kg [$p = 0.001$]. In female patients, the difference between patients whose body weight was >48.5 kg and <48.5 kg was not significantly different [$p = 0.411$] [Figure 4A, B]. The 6-TGN level in patients who dropped out of the study was not measured, so we could not conclude that a higher 6-TGN level was a risk factor for study dropout. We investigated the correlation between the 6-TGN concentration and BMI in the combination group. Quartile analyses revealed an inverse correlation between the 6-TGN concentration and BMI quartile in males [$p = 0.062$], but not in females [$p = 0.951$] [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online].

In the monotherapy group, the major reason for dropout was an increase in disease activity. Multivariate analysis could not identify the risk factors for study dropout due to adverse effects except for an increase in disease activity.

4. Discussion

The present study demonstrated that dropout from the DIAMOND study in the combination group was associated significantly with the side effects of thiopurines in the early phase of the study, whereas it was due to insufficient efficacy in the monotherapy group. Few reports have focused on the people who dropped out from the study. In the DIAMOND study, there was no significant difference between

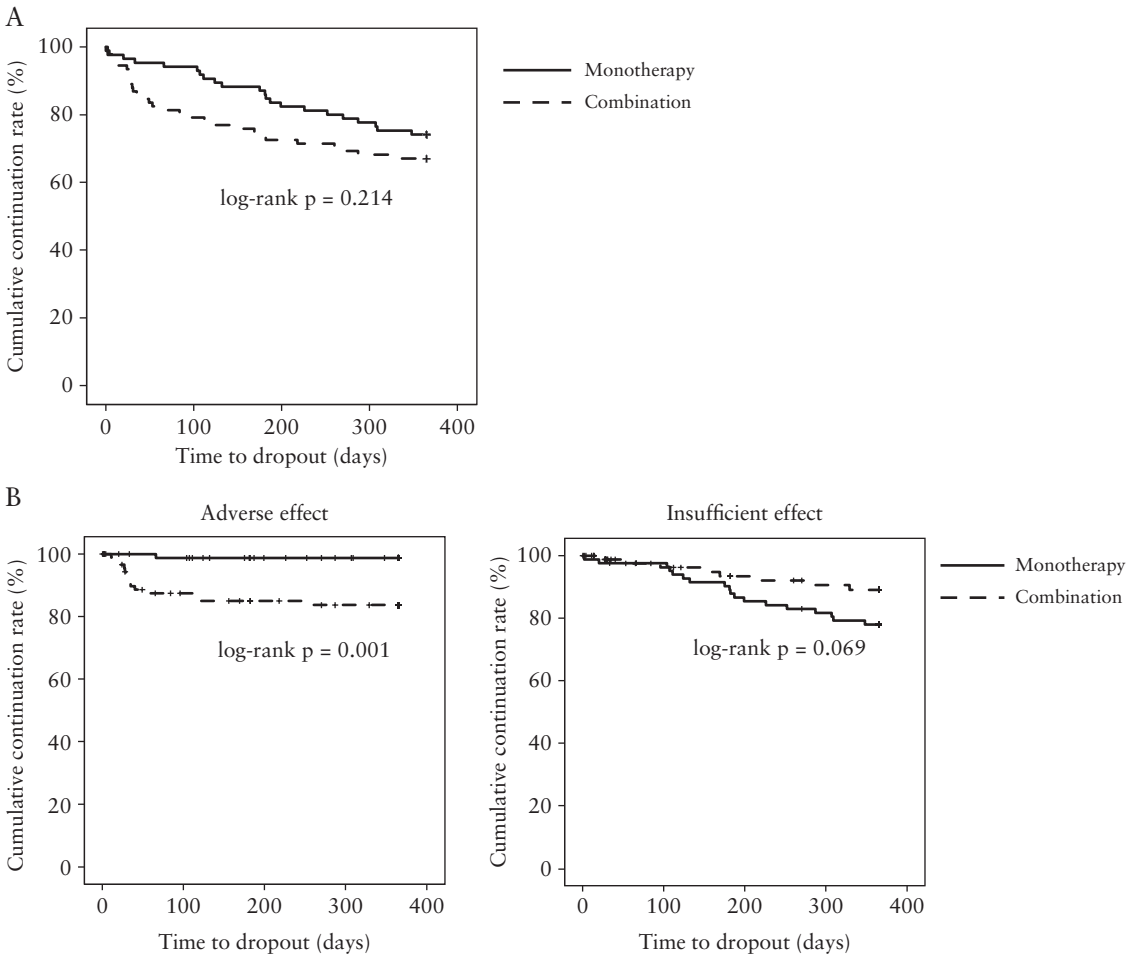

Figure 3. Cumulative continuation rate shown by Kaplan–Meier analyses. A: For all patients. B: Subanalyses according to the reason for dropping out. Cumulative continuation rate in patients who dropped out due to adverse effects [left] and insufficient effect [right]. Statistical analyses were by log-rank tests.

Table 2. Patients who dropped out due to the side effects of thiopurine in the combination group [$n = 14$].

Case no.	Bone-marrow suppression	Nausea	Hair loss	Liver dysfunction	Other	Time of dropout (W)	Outcome
9	○					2	Recovery
22					Lymphadenopathy	2	Recovery
36	○					5	Recovery
44					Fever, ANA, dsDNA	39	Recovery
60			○			16	Recovery
64		○	○	○		4	Recovery
71		○				4	Unknown
86	○		○			4	Recovery
96					Abscess	8	Surgery
116	○					5	Recovery
120	○					17	Unknown
135				○		6	Unknown
152					AMY↑	3	Recovery
157				○		4	Recovery

ANA, anti-nuclear antibody; dsDNA, anti-double stranded DNA IgG antibody; AMY, serum amylase.

the two groups in the rate of clinical remission at Week 26 as the primary endpoint.[7] However, subanalysis revealed that the clinical benefit of combination therapy was due [at least in part] to a lower level of AAAs[8] and endoscopic improvement.[9] Collectively, those results suggested that the benefits of combined use of a thiopurine with adalimumab could be obtained in some populations.

In real-world clinical practice, however, adalimumab has been used as monotherapy. Peyrin-Biroulet *et al*. investigated 350 adult

Table 3. Multivariate logistic regression of the association between withdrawal due to adverse effects and associated potential factors.

Parameter	*p*	HR	95% CI	
			Lower	Upper
Sex	0.391	0.533	0.126	2.245
Body weight	0.041	0.923	0.855	0.997
Disease duration	0.371	0.94	0.821	1.076

The backward elimination method applied for model 1 after including factors.

CI, confidence interval; HR, hazard ratio.

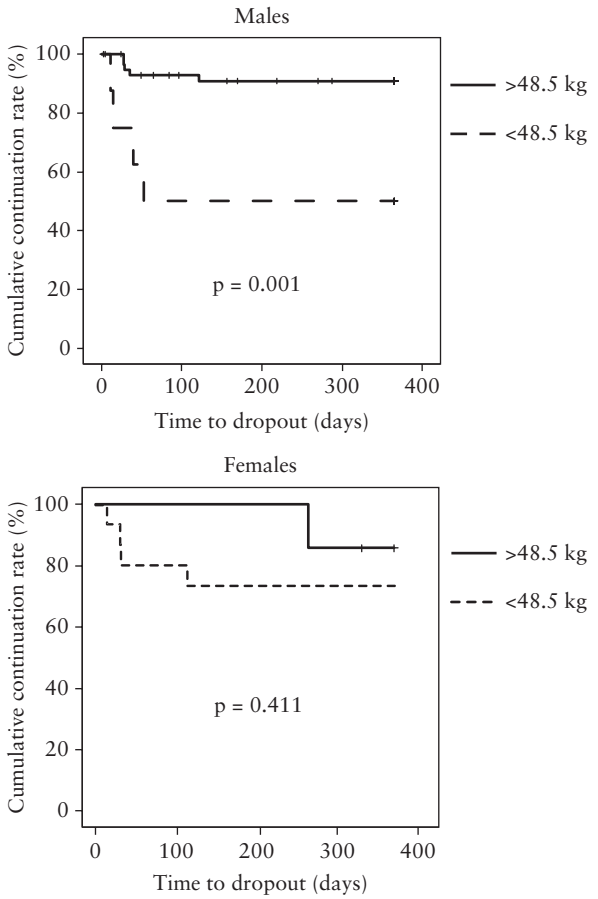

Figure 4. Lower body weight was a risk factor for study dropout due to adverse effects in the combination group. Kaplan–Meier curves showed the cumulative continuation rate in male patients whose body weight was >48.5 kg and <48.5 kg [upper panel] and female patients whose body weight was >48.5 kg and <48.5 kg [lower panel]. Statistical analyses were by log-rank tests.

CD patients who received infliximab or adalimumab monotherapy retrospectively. In their study, an immunomodulator was initiated simultaneously in 15% of CD patients treated by anti-TNF monotherapy. The type of an anti-TNF agent [infliximab more often than adalimumab] was a factor associated with a greater need for starting immunomodulation.[16] The reasons for the use of adalimumab as monotherapy were: a lower risk of induction of anti-drug antibodies when compared with infliximab; the benefit of concomitant use of thiopurines with adalimumab in prospective studies have not been established; concern regarding the adverse effects of thiopurines.

In this subanalysis of the DIAMOND study, the completion rate through Week 52 did not show a significant difference between monotherapy and combination groups. However, the reasons of study dropout were significantly different between these two groups. Dropout due to insufficient efficacy [active disease] increased slowly over time, and tended to be more frequent in the monotherapy group. In the combination group, dropout due to the side effects of [presumably] thiopurines occurred in the early phase of the study. The physicians involved in the DIAMOND study had sufficient clinical experience of IBD management and thiopurine use. These results suggest that even highly experienced physicians are concerned about the risk of the acute side effects of thiopurines [e.g., acute leukopenia] but not the risk of long-term use [e.g., malignant lymphoma].

In the present study, five patients in the combination group dropped out of the study due to bone marrow suppression, but four patients recovered by discontinuation of thiopurine use without serious clinical effects. This finding suggests that bone marrow suppression in these patients was mild and different from thiopurine-induced severe acute leukopenia. The prevalence of thiopurine-induced acute severe leukopenia in an East Asian population has been reported to be 1%.[10,17] In Asian populations, a variant of the nucleotide triphosphate diphosphatase *[NUDT]15* gene has been identified as an independent risk for thiopurine-induced acute severe leukopenia and total hair loss, and neither are correlated with thiopurine methyltransferase [TPMT] activity or the 6-TGN level.[10] Thiopurine-induced acute severe leukopenia in an Asian population is a very serious side effect. Patients with total hair loss should be administered G-CSF during long-term hospitalisation. The DIAMOND study was started before identification of the *NUDT15* variant, and thiopurine-induced acute severe leukopenia could not be predicted at that time. Hence, it was presumed that the attending physicians were extraordinarily sensitive to identifying the side effects of thiopurine. This seems to have led to an increase in the dropout rate due to side effects in the combination group in the early phase of the study. In Japan, development of a diagnostic kit for the *NUDT15* variant is under way and, if this becomes available, the fear of thiopurine-induced acute severe leukopenia could be reduced considerably. In this subanalysis of the DIAMOND study, more patients in the monotherapy group dropped out of the study due to active disease. In addition, combination therapy seems to have some benefits for CD patients with regard to the trough level of adalimumab and endoscopic improvement.[8,9] Hence, even with adalimumab, concomitant use of thiopurines could be beneficial in some patients if serious side effects in the acute phase can be avoided and it can be used safely for a long time. That is, in Asian populations including Japanese people, there is a specific concern of acute leukopenia associated with the *NUDT15* variant, which was also shown in the DIAMOND study, but examination of the *NUDT15* variant before starting thiopurine therapy alleviates this anxiety. By carrying out *NUDT15* screening, it is possible that many patients will be able to benefit from combination therapy.

We attempted to extract the risk factors for study dropout due to side effects in the combination group. Interestingly, lower body weight was extracted as a risk factor in males and females among the many variables tested. This tendency was not recognised in the monotherapy group. Indeed, the 6-TGN concentration and BMI were inversely correlated in male patients. The relationship between the 6-TGN level and body weight is controversial. A comparison between an individualizsd regimen with monitoring of the 6-TGN level and a weight-based standard regimen failed to show the superiority of the individualised regimen in CD patients.[18] That finding supports the notion that a weight-based standard regimen can be used

in daily clinical practice. Poon *et al.* reported that the BMI as well as smoking and the TPMT level were associated with the 6-TGN level in multivariable analysis. An increase in the BMI of 5 kg/m^2 was associated with a decrease in the 6-TGN level of 8%.[19] Recently, a multicentre, double-blind, randomised controlled trial compared the efficacy and safety of weight-based vs individualised dosing of azathioprine in adults and paediatric patients with CD. Results showed that the clinical remission rate at 16 weeks as the primary outcome did not show a significant difference between the weight-based arm and TPMT-based individualised-dosing arm, although the clinical remission rate at 16 weeks and 6-TGN level tended to be superior in the latter.[20] Conversely, Derijks *et al.* reported no correlation between the steady-state 6-TGN concentration and dose per kilogram body weight of 6-mercaptopurine or 6-thiguanine.[21,22]

Azathioprine at 50 mg/day was set as the target in the DIAMOND study, and the 6-TGN concentration might increase in patients with lower body weight, so concentration-dependent side effects may have appeared in the combination group. The utility of monitoring of the 6-TGN level at the start of thiopurine administration has not been established. However, in patients with lower body weight, starting initially with a low dose of a thiopurine to avoid side effects would seem rational. Conversely, in patients of high body weight, higher doses may be required to obtain an effective 6-TGN concentration.

Our study had several limitations. First, the actual number of registered cases in the DIAMOND study was lower than that in the schedule, so the study was underpowered statistically. Second, the concentrations of adalimumab and 6-TGN were not measured at the time of study dropout, so we could not investigate the relationship between the dropout event and 6-TGN level in the combination group. Third, study discontinuation was decided at the physician's discretion. It seems that the judgment of insufficient efficacy was reasonable [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online]. With regard to leukopenia, the number of white blood cells was not set as a specific criterion for study discontinuation, so it may have been influenced by the judgement of the treating physician. Finally, the DIAMOND study was an open-label study. Physicians knew which patients took azathioprine in the combination group, so physicians might have concerns regarding the adverse effects of azathioprine. This knowledge may have been reflected in their judgement of dropouts.

In several countries [including Japan], examination of expression of the *NUDT15* variant and measurement of TPMT activity, 6-TGN concentration, and trough level of adalimumab are not possible in daily clinical practice. In this regard, the trend of dropout observed in the DIAMOND study may reflect real-world clinical practice. Despite the limitations mentioned above, our study revealed physicians' concern about thiopurine use in adalimumab maintenance therapy in real-world practice. Furthermore, the results of our subanalysis may support monitoring of the 6-TGN concentration, and low-dose administration initially should be considered for patients with lower body weight.

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Conflict of Interest

THis: honoraria: Pharma, AbbVie, Celgene, Janssen Pharmaceutical, Pfizer, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical, JIMRO, Mochida Pharmaceutical, and Nichi-Iko Pharmaceutical; commercial research funding: Pharma, AbbVie, Daiichi-Sankyo, Takeda Pharmaceutical, Pfizer, and Mochida Pharmaceutical. TM: fees for promotional materials: Tanabe Mitsubishi Pharmaceutical, Abbvie,Pharma, and Jansen Pharmaceutical. KW: honoraria: Pharma, AbbVie, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical, JIMRO, Mochida Pharmaceutical, Janssen Pharmaceutical, and Takeda Pharmaceutical; commercial research funding: Pharma, AbbVie, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical, JIMRO, and Astellas Pharma. HN: honoraria: Mitsubishi Tanabe Pharma, Machida Pharmaceutical, Janssen Pharmaceutical, and Abbvie; commercial research funding: Hoya Group, Pentax Medical, Boehringer Ingelheim GmbH, and Daticho Sankyo. SM: honoraria: Eisai, AbbVie, Mitsubishi Tanabe Pharma, and Janssen Pharmaceutical. NY: honoraria: AbbVie, Mitsubishi Tanabe Pharma, and Mochida Pharmaceutical. SK: honoraria: AbbVie, Mitsubishi Tanabe Pharma, and Janssen Pharmaceutical. ME: honoraria: AbbVie, and Mitsubishi Tanabe Pharma; commercial research funding: EA Pharma, AbbVie, and Mitsubishi Tanabe Pharma. TM: honoraria: Eisai, AbbVie, and Mitsubishi Tanabe Pharma. YN: honoraria: Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, and Janssen Pharmaceutical; commercial research funding: EA Pharma. TK: honoraria: Pharma, AbbVie, Janssen Pharmaceutical, Pfizer, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical, Yakult Honsha, ZERIA Pharmaceutical, Miyarisan Pharmaceutical, Eli Lilly Japan, Astellas Pharma, and Sumitomo Dainippon Pharma; commercial research funding: Eisai, JIMRO, Nippon Kayaku, Daiichisankyo, Tsumura, Taiho Pharmaceutical, Otsuka Pharmaceutical, Otsuka Pharmaceutical, Ezaki Glico, RPM, and Yakult Bio-Science Foundation. YS: honoraria: AbbVie, Mitsubishi Tanabe Pharma, ZERIA Pharmaceutical, Mochida Pharmaceutical, Kyorin Pharmaceutical, Pharma, and Janssen Pharmaceutical; commercial research funding: AbbVie, Mitsubishi Tanabe Pharma, JIMRO, Mochida Pharmaceutical, Nippon Kayaku, and KISSEI. MW: honoraria: Mitsubishi Tanabe Pharma, Eisai, Kyorin Pharmaceutical, JIMRO, Ajinomoto, AbbVie, Takeda Pharmaceutical, Kyowa Hakko Kirin, Zeria Pharmaceutical, Asahi Kasei Medical, Pharma, Astellas Pharma, Mochida Pharmaceutical, Janssen Pharmaceutical, Gilead Sciences, and Celgene; commercial research funding: Asahi Kasei Medical, Ajinomoto, AbbVie, Pharma, Eisai, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Kyowa Hakko Kirin, Zeria Pharmaceutical, JIMRO, Takeda Pharmaceutical, Nippon Kayaku, Mochida Pharmaceutical, Daiichi Sankyo, Ono Pharmaceutical, Astellas Pharma, MSD, Dainippon Sumitomo Dainippon Pharma, Bristol-Myers, and Chugai Pharmaceutical. THib: honoraria: Mitsubishi Tanabe Pharma, AbbVie, and Pharma.

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Study concept and design [THis, HN, TM, KW, TK, YS, MW, THib], acquisition of data [SM, NY, TI, SK, TN, ME, MN, ToM, YN], analysis and interpretation of data [THis, TM, HN, KW, MNo], drafting of the manuscript [THis, TM, HN, KW, MNo], critical revision of the manuscript for important intellectual content [YS, MW, THib], statistical analysis [MNo]. and study supervision [YS, MW, THib].

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Supplementary Data

Supplementary data are available at ECCO-JCC online.

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