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Observations and Research

Nurse-Provided Medication Guidance for Improving Drug Adherence to Thiopurines in Outpatients With Inflammatory Bowel Disease: A Single-Center Prospective Study

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Background and Aims: Drug adherence is critically important for patients on thiopurines. We examined whether nurse-provided medication guidance improves drug adherence to thiopurines and clinical activity in patients with inflammatory bowel disease (IBD).

Methods: IBD outpatients taking a stable dose of thiopurines for 1 year were enrolled. After a baseline survey including the Morisky Medication Adherence Scale (MMAS)-8, nurses provided medication guidance to each patient using a specialized leaflet. The same survey was conducted 2 and 6 months after the guidance.

Results: Among 110 enrolled patients, 74 met the analysis criteria. In the low adherence group (MMAS-8 <6), the median MMAS-8 score significantly increased from 4 (range 1–5.75) to 5.25 (2–7) at 2 months (P = .0135) to 5.625 (2.5–7.75) at 6 months (P = .0004), but not in overall or the high adherence group (MMAS-8 ≥6). Older age (≥43 years, odds ratio [OR] = 5.63, 95% confidence interval [CI]: 1.59–19.9, P = .0074) and shorter disease duration (<129 months, OR = 6.78, 95% CI: 1.77–26.0, P = .0052) were independently associated with high adherence. Although clinical activity scores did not change during the observation period, the overall mean corpuscular volume (MCV) level significantly increased from 92.3 fL (61.4–105.5) to 92.5 (73.7–107.8) at 2 months (P = .0288) and 93.9 (74.4–107.6) at 6 months (P = .0062). MCV levels significantly increased in the low adherence group at 6 months (92.2 [72.2–105.5] to 94.0 [74.4–107.6], P = .0392) and tended to increase in the high adherence group (92.3 [61.4–101.2] to 93.6 [74.9–99.7], P = .0651).

Conclusions: Nurse-provided medication guidance improved drug adherence to thiopurines in IBD patients with low adherence and can also benefit those with high adherence.

Lay Summary

Nurse-provided medication guidance using a leaflet prepared by a multidisciplinary team significantly improved drug adherence to thiopurines in patients with inflammatory bowel disease with low baseline adherence and can also benefit those with high adherence.

Key Words: nurse-provided medication guidance, thiopurine, drug adherence, multidisciplinary team

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD), collectively called inflammatory bowel disease (IBD), are chronic refractory gastrointestinal inflammatory diseases of unknown cause. The number of IBD patients is steadily increasing, but the pathophysiology of IBD is complex and no radical treatment is available. The goal of treatment is to suppress inflammation and maintain a state of remission for a long period of time after induction therapy.[1] Thiopurine formulations such as azathioprine and 6-mercaptopurine are key drugs for maintaining remission for moderate to severe patients, or steroid-dependent, or steroid-refractory patients.[2, 3] Many patients, however, hesitate to initiate treatment with thiopurines due to their slow efficacy and relatively high frequency of side effects[4]; therefore, it is critical that correct information about the drug is communicated to patients prior to the initiation of treatment.

As IBD is a chronic disease with a young predominant age of 20–30 years and requires long-term treatment,[5] improving self-management abilities of the patients helps them to maintain a high quality of life,[6] and drug adherence is very important for patients undergoing maintenance therapy with thiopurines. Goodhand et al[7] reported that 12% (18/144) of patients were not adherent to thiopurines and nonadherence is more common in young adults. The actual drug adherence to thiopurines, however, is unknown, and no interventional studies have been performed to improve adherence to thiopurines.

The present study investigated whether nurse-provided medication guidance using a leaflet containing information specific to IBD and thiopurines could improve drug adherence to thiopurines.

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Methods

Ethical consideration

This study was conducted in accordance with the latest version of the Declaration of Helsinki. This study was approved by the Kinshukai Ethics Committee, and written informed consent was obtained from each patient prior to the study.

Patients

This single-center prospective observation study was conducted from May 2016 to May 2017 at Kinshukai Infusion Clinic, an IBD-specialized clinic that can provide intravenous and cytapheretic therapies but does not have hospitalization facilities. IBD outpatients at Kinshukai Infusion Clinic who had been continuously prescribed thiopurines and had taken a stable maintenance dose for more than 1 year were enrolled, regardless of whether they were receiving any other IBD treatment. As this study was designed as an exploratory study and there were no similar previous reports, it was impossible to calculate the sample size. We therefore conducted the study on patients who could be recruited at a single IBD-specialized clinic.

Study procedures

Before the nurse-provided medication guidance, patients underwent a questionnaire survey including queries related to their drug adherence to thiopurines. To evaluate drug adherence, the Morisky Medication Adherence Scale (MMAS)-8 score was used with permission.[8] High adherence was defined as an MMAS-8 score of 6 or more, and low adherence was defined as a score of less than 6.[9] In addition, the patients answered a 7-item original questionnaire regarding the general condition of their disease and their understanding of the drug and disease using a visual analog scale (VAS). The detailed questionnaire is shown in Figure S1. The VAS score was quantified, with 0 indicating a low score and 100 indicating a good score.

After the first questionnaire survey was conducted (baseline), nurses provided information on thiopurines and guidance on the necessity of drug administration using a specialized teaching leaflet. The leaflet was originally created by a multidisciplinary team (MDT) consisting of doctors, nurses, and pharmacists at the Kinshukai Infusion Clinic and contained information specific to IBD and thiopurines (Figure S2), and the guidance method and time required to convey the information were standardized among the nurses in advance to avoid individual differences. At 2 and 6 months after providing the guidance, the same questionnaire surveys were conducted without providing additional medication guidance.

Assessment of disease activity

Age at onset, location/extension, and behavior of the diseases were classified based on the Montreal classification.[10] Disease activity was analyzed using the partial Mayo Score (pMayo) for UC[11] and the Crohn's Disease Activity Index (CDAI) for CD.[12] Blood tests were also performed on each survey day to evaluate the white blood cell count (WBC), mean corpuscular volume (MCV), and C-reactive protein (CRP), and albumin (ALB) levels.

Endpoints

The primary outcome of the study was set as a change in the MMAS-8 score between baseline and 6 months after guidance. Secondary outcomes were changes in the disease activity indexes and laboratory data during the observation period, factor analysis affecting drug adherence to thiopurines, and analysis of patients' belief in the benefit of thiopurine therapy.

Statistical analysis

The results of the questionnaire were statistically analyzed using JMP Pro 14.0 (SAS Institute), together with the clinical activity score and blood sampling data of each survey day. Variables are presented as median values with range. The Wilcoxon signed-rank test was performed to compare nonparametric paired values. Categorical values are presented as numbers (%) and differences were analyzed using Pearson's chi-square test. Between-group differences were analyzed using the Kruskal–Wallis test for nonparametric data. In the univariate and multivariate analyses, each category was divided into 2 by the median value and the odds ratio (OR) and corresponding 95% confidence interval (CI) were estimated by logistic regression analysis. A P value of less than .05 was considered statistically significant.

Results

Patient characteristics

There were 1033 IBD patients (530 UC, 503 CD) attending the clinic during the recruitment time, 160 of whom were receiving thiopurines, and informed consent was obtained from 110 of these patients whose dosage remained unchanged for more than 1 year. A questionnaire survey and leaflet-based medication guidance were conducted for all 110 subjects; 36 patients were excluded from the analysis due to discontinuation or an altered dose of thiopurines during the survey period, incomplete data, or other reasons, such as transfer to a different hospital. Finally, 74 patients (34 UC and 40 CD) completed the questionnaire survey at 6 months (Figure S3). The detailed patient characteristics are given in Table 1.

Changes in MMAS-8 scores

We compared the MMAS-8 scores before and after the medication guidance. The median score of all subjects was 7 (range 1–8) at baseline, 7 (2–8) at 2 months, and 7.25 (2.5–8) at 6 months, with no significant difference among them (Figure 1). Patients were then stratified into a high-baseline adherence group (MMAS-8 ≥6) and a low-baseline adherence group (MMAS-8 <6), as previously reported.[9] In the 52 patients in the high adherence group, the MMAS-8 score remained unchanged between each time point (7.875 [6–8], 7.75 [3.5–8], and 8 [3.75–8]). In the 22 patients in the low adherence group, however, the MMAS-8 scores improved significantly from 4 (1–5.75) at baseline to 5.25 (2–7) at 2 months (P = .0135) and 5.625 (2.5–7.75) at 6 months (P = .0004). We then examined the factors associated with high adherence to thiopurines. Univariate analysis followed by multivariate analysis by stratifying each category with continuous variables into 2 based on the median value revealed that patient age of 43 years or more (OR = 5.63, 95% CI 1.59–19.9, P = .0074) and disease duration of fewer than 129 months (OR = 6.78 [95% CI 1.77–26.0], P = .0052) were independent factors associated with high adherence to thiopurines (Table 2).

Table 1. Patient characteristics at baseline.

	All	UC	CD
Patients, *n* (%)	74 (100)	34 (46)	40 (54)
Age, years, median (range)	43 (19–79)	45 (13)	42 (19–59)
Sex, *n*, M : F	54 : 20	23 : 11	31 : 9
Disease duration, months, median (range)	129 (32–414)	114 (32–251)	193 (43–414)
Disease onset, A1/A2/A3, *n*	11/55/8	2/25/7	9/30/1
Disease location in CD, L1/L2/L3/L4	—	—	7/11/22/4
Disease behavior in CD, B1/B2/B3/p	—	—	11/23/6/23
Disease extension in UC, E1/E2/E3	—	0/15/19	—
Thiopurine treatment duration, months, median (range)	50 (15–222)	52 (17–222)	48 (15–150)
Concomitant use of biologics, infliximab/adalimumab, *n*(%)	44 (59)/6(8)	14 (41)/2(6)	30 (75)/4(10)
Clinical activity, pMayo (UC), CDAI (CD), median (range)	—	1 (0–5)	82 (0–241)
WBC, $\times 10^3$ mm^{-3}, median (range)	5.8 (2.8–14.0)	5.5 (3.7–9.2)	6.4 (2.8–14.0)
MCV, fL, median (range)	92.3 (61.4–105.5)	95.9 (72.6–105.5)	90.0 (61.4–105.4)
CRP, mg/dL, median (range)	0 (0–6)	0 (0–0.3)	0.1 (0–6)
ALB, g/dL, median (range)	4.3 (2.9–5.1)	4.5 (3.8–5.1)	4.0 (2.9–5.1)

Abbreviations: ALB, albumin; CRP, C-reactive protein; CD, Crohn's disease; CDAI, Crohn's disease activity index; MCV, mean corpuscular volume; pMayo; partial Mayo score; UC, ulcerative colitis; WBC, white blood cell count.

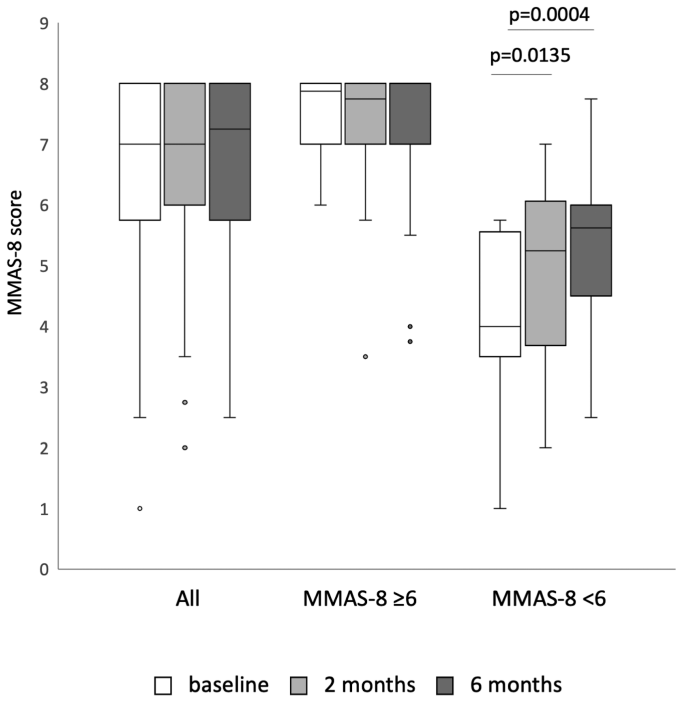

Figure 1. Changes in the baseline MMAS-8 scores at 2 months and 6 months after the nurse-provided medication guidance. Boxplots show median and lower/upper quartiles; whiskers show inner fences. MMAS-8, Morisky Medication Adherence Scale.

Changes in clinical activity scores

The median value of pMayo for UC was 1 (0–5) at baseline, 1 (0–6) at 2 months, and 0.5 (0–5) at 6 months, and that of CDAI was 82 (0–241) at baseline, 69 (0–291) at 2 months, and 74 (0–292) at 6 months. These scores did not differ significantly during the time course (Figure S4). The number of patients in clinical remission (pMayo ≤2 or CDAI ≤150[13]) was 59 (80%) at baseline, 61 (82%) at 2 months, and 60 (81%) at 6 months.

Table 2. Factors associated with high adherence to thiopurine formulations at baseline.

	Univariate OR (95% CI), *P*	Multivariate OR (95% CI), *P*
Disease (UC)	3.11 (1.09–9.84), .0332	1.56 (0.39–6.21), .527
Age (≥43)	3.94 (1.32–11.7), .0137	**5.63 (1.59–19.9), .0074**
Disease duration (<129 months)	5.44 (1.73–17.1), .0037	**6.78 (1.77–26.0), .0052**
ALB (≥4.3)	2.24 (0.80–6.20), .1211	1.26 (0.34–4.68), .729

Abbreviations: ALB, albumin; UC, ulcerative colitis; OR, odds ratio; CI, confidence interval.
Bold indicates statistically significant results.

Changes in laboratory data

At baseline, patients in the high adherence group had significantly higher ALB values and tended to have low CRP levels compared with those in the low adherence group (Table 3). Trend analysis in all subjects showed that MCV levels significantly increased from 92.3 (61.4–105.5) at baseline and 92.5 (73.7–107.8) at 2 months to 93.9 (74.4–107.6) at 6 months (P = .0288 and P = .0062, respectively). MCV levels significantly increased over 6 months in the low adherence group (92.2 [72.2–105.5] to 94.0 [74.4–107.6], P = .0392) and tended to increase in the high adherence group (92.3 [61.4–101.2] to 93.6 [74.9–99.7], P = .0651; Figure 2).

VAS score for knowledge about disease and medicine, and side effects of thiopurines

As another secondary outcome, we collected answers to 7 questions in VAS format (Figure S1). At the baseline analysis, patients in the high adherence group had higher VAS scores for knowledge of their general condition than patients in the low adherence group (72 [10–100] vs 56 [16–96], P = .0456; Figure 3). Trend analysis showed that patients in the high adherence group had significantly higher VAS scores

Table 3. Patient characteristics in the high-baseline adherence group (MMAS-8 ≥6) and the low-baseline adherence group (MMAS-8 <6).

	MMAS-8 ≥6, *n* = 52	MMAS-8 <6, *n* = 22	*P*
Disease, UC, *n* (%)	28 (54)	6 (27)	**.0360**
Age, years, median (range)	45 (19–79)	36 (20–53)	**.0020**
Sex, *n*, M:F	39:13	15:7	.5461
Disease duration, months, median (range)	116 (32–414)	167 (57–330)	**.0295**
Thiopurine treatment duration, months, median (range)	50 (15–222)	48 (18–120)	.4769
Concomitant use of biologics, *n* (%)	33 (64)	17 (77)	.2460
Clinical remission, yes, *n* (%)	41 (79)	16 (73)	.5674
WBC, $\times 10^3$ mm^{-3}, median (range)	5.7 (2.8–14.0)	6.0 (3.5–11.7)	.7449
MCV, fL, median (range)	92.2 (72.2–105.5)	92.3 (61.4–101.2)	.1342
CRP, mg/dL, median (range)	0 (0–2.5)	0.1 (0–6)	.0527
ALB, g/dL, median (range)	4.3 (2.9–5.1)	4.1 (3.3–4.8)	**.0411**

Abbreviations: ALB, albumin; CRP, C-reactive protein; MCV, mean corpuscular volume; UC, ulcerative colitis; WBC, white blood cell count; MMAS-8, Morisky Medication Adherence Scale.
Bold indicates statistically significant results.

for knowledge of the effect (62.5 [8–100] to 75 [19–100], P = .0028) and side effects (52.5 [0–100] to 71 [0–100], P = .0048) of thiopurines after 6 months (Figure 3).

Discussion

In the present prospective observation study, we demonstrated that nurse-provided medication guidance significantly improved treatment adherence to thiopurines, especially in the low adherence group. The proportion of patients with low adherence was 30% (22/74), higher than that in a previous report (12%),[7] both of which were analyzed with the same criteria for low adherence as an MMAS-8 score of <6. We limited our study to patients who had been continuously prescribed thiopurines at a stable dose for more than 1 year, which may have limited the number of patients with low adherence included in the study. In another study with different assessment methods and not limited to thiopurines, nonadherence was reported in at least a third of IBD patients,[14] similar to our finding.

Although improved medication adherence was observed, there was no significant change in the clinical activity scores, such as pMayo and CDAI, or in indicators of active inflammation such as CRP.[15, 16] The potential reason for this is that most of the patients were in remission because all patients were seen on an outpatient basis and more than 1 year has passed since the start of oral administration of thiopurines. We identified older age and shorter disease duration as independent factors associated with high-baseline adherence to thiopurines. This finding is consistent with previous reports,[7, 17] supporting the notion that this study was performed in a general patient population.

Thiopurines inhibit DNA synthesis in bone marrow precursor cells, which leads to megaloblastic erythropoiesis.[18, 19] In this theoretical background, WBC and MCV values are generally used as easily measured surrogate markers for 6-thioguanine nucleotide concentrations to monitor the therapeutic effects of thiopurine administration.[20] In the present study, the significant increase in MCV provides strong evidence that medication adherence to the thiopurine formulation improved in the 6 months after the nurse-provided medication guidance, even though other inflammatory activity indexes and disease activity were unchanged. Because this study targeted patients who had been taking thiopurines continuously for more than 1 year after the dose was maintained, we predicted that a change in MCV and in clinical activity would not be observed in the high adherence group. Interestingly, however, MCV tended to increase in the high adherence group, suggesting that nurse-provided medication guidance can improve drug adherence, regardless of baseline MMAS-8 scores.

Patients in the high-baseline adherence group had significantly increased VAS scores for knowledge of both the effects and side effects of thiopurines at 6 months after the medication guidance. These data may account for the increase in MCV values even in the high adherence group. Although this was not reflected by a change in the MMAS-8 score at 6 months, it is possible that patients in the high adherence group also changed their medicine-taking habits after receiving the medication guidance. Patients in the low adherence group had significantly lower VAS scores for knowledge of their general condition than those in the high adherence group, suggesting that medication guidance could contribute to improve drug adherence by enhancing patients' understanding of the importance of adherence to the drug therapy to improve their general condition.

This cohort included outpatients who have not changed their thiopurine dose for more than 1 year, and many of whom have concomitant use of biologics and are clinically stable. We have shown in Table 3 that there was no difference in concomitant use of biologics or clinical remission between the high and low adherence groups, indicating that these categories do not affect medication adherence. However, validation study is necessary in another cohort to verify whether these categories can affect the medication adherence.

In the present study, all the medication guidance was provided by nurses, but the leaflet preparation and guidance methods were being considered by our MDT, and this study is the achievement of collaborative work by the MDT. Previous reports have shown that proximity to MDT is important for active involvement in treatment, including improved medication adherence, increased knowledge of the disease, and patient participation in shared decision-making,[21, 22] and the results of the present study also indicate the importance of MDT.

The present study has some limitations. First, objective evaluations of adherence such as pill counts and medication event monitoring systems were not performed due to cost

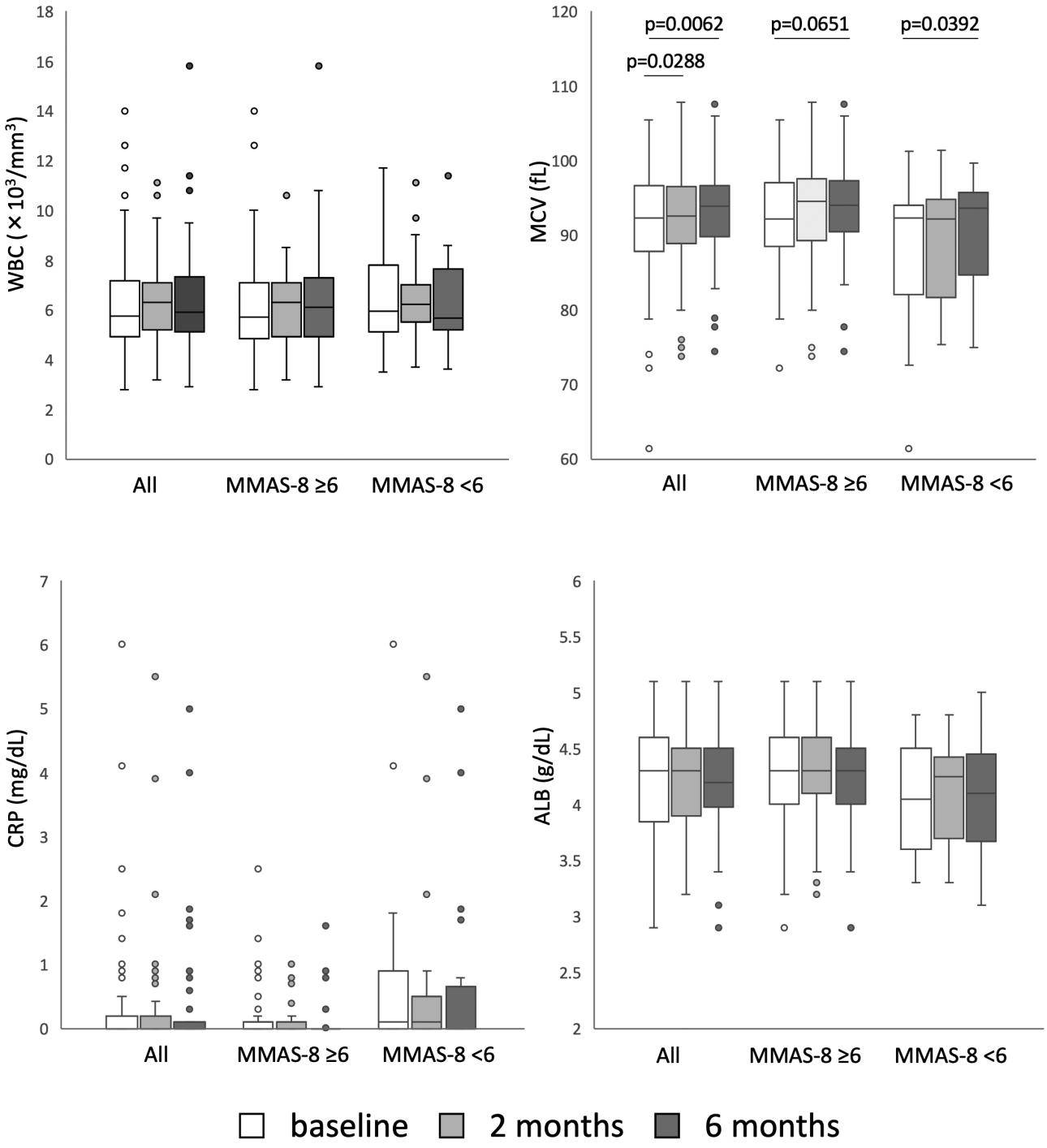

Figure 2. Changes in baseline laboratory data at 2 months and 6 months after the nurse-provided medication guidance. Boxplots show median and lower/upper quartiles; whiskers show inner fences. ALB, albumin; CRP, C-reactive protein; MCV, mean corpuscular volume; WBC, white blood cell count; MMAS-8, Morisky Medication Adherence Scale.

and patient inconvenience. Second, as this study was not a randomized controlled study, it was not possible to compare guidance and nonguidance groups separately. Third, the number of patients with low adherence was relatively small, which made it difficult to detect differences between the low and high adherence groups. A randomized controlled study with a larger number of participants will be necessary to confirm the significance of nurse-provided medication guidance regarding treatment with thiopurines.

In conclusion, nurse-provided medication guidance is effective toward improving adherence to thiopurines in IBD outpatients, especially those with low adherence. Nurse-provided medication guidance can also benefit patients with high adherence. In recent years, IBD treatment options have drastically increased, and it is important for patients to participate in their own disease management.[21] The outcomes of continuous, long-term education should be clarified to decrease disease flares and hospital visits.

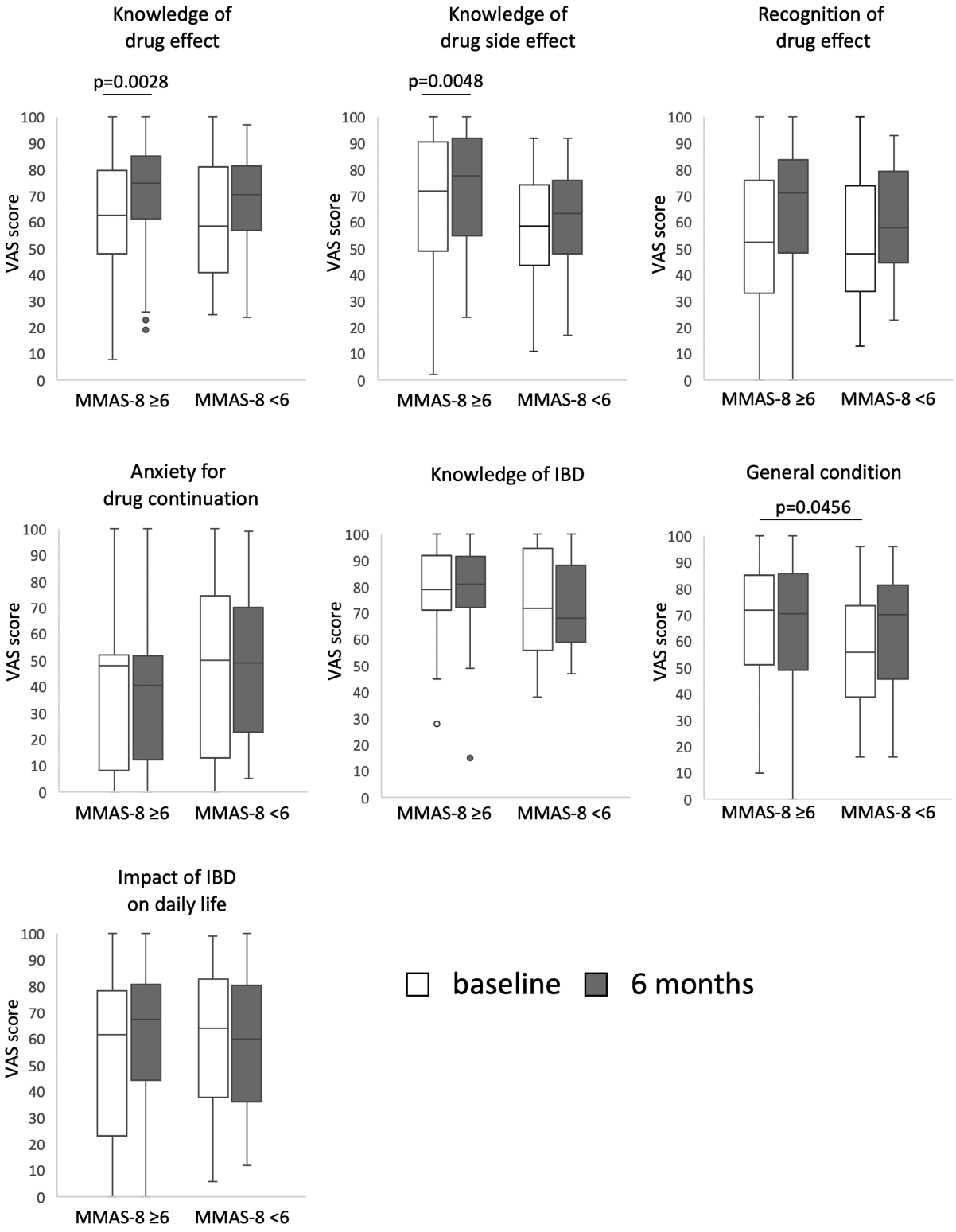

Figure 3. Changes in the baseline VAS scores for the questionnaire regarding patients' knowledge of their general disease condition and their understanding of the drug and disease at 6 months after the nurse-provided medication guidance. VAS, visual analog scale; MMAS-8, Morisky Medication Adherence Scale; IBD, inflammatory bowel disease.

Author Contributions

S.S., K.S., and H.I. planned and conducted the study. K.S. collected the data; S.S., K.S., M.M., T.T., and H.I. interpreted the data; and S.S. and K.S. drafted the manuscript. Each author has approved the final draft submitted.

Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

Funding

None declared.

Conflict of Interest

S.S. and H.I. report personal fees from Mitsubishi-Tanabe Parma Corporation. T.T. reports personal fees and grant from Mitsubishi-Tanabe Pharma Corporation. K.S. and M.M. have no conflicts of interest to declare.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Turner D, Ricciuto A, Lewis A, et al.; International Organization for the Study of IBD. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology.* 2021;160(5):1570–1583.
2. Colombel JF, Sandborn WJ, Reinisch W, et al.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010;362(15):1383–1395.
3. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology.* 2014;146(2):392–400.e3.
4. Bradford K, Shih DQ. Optimizing 6-mercaptopurine and azathioprine therapy in the management of inflammatory bowel disease. *World J Gastroenterol.* 2011;17(37):4166–4173.
5. Nakase H, Uchino M, Shinzaki S, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. *J Gastroenterol.* 2021;56(6):489–526.
6. Kennedy AP, Nelson E, Reeves D, et al. A randomised controlled trial to assess the effectiveness and cost of a patient orientated self management approach to chronic inflammatory bowel disease. *Gut.* 2004;53(11):1639–1645.
7. Goodhand JR, Kamperidis N, Sirwan B, et al. Factors associated with thiopurine non-adherence in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2013;38(9):1097–1108.
8. Moon SJ, Lee WY, Hwang JS, et al. Accuracy of a screening tool for medication adherence: a systematic review and meta-analysis of the Morisky medication adherence scale-8. *PLoS One.* 2017;12(11):e0187139.
9. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich).* 2008;10(5):348–354.
10. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut.* 2006;55(6):749–753.
11. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987;317(26):1625–1629.
12. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National cooperative Crohn's disease study. *Gastroenterology.* 1976;70(3):439–444.
13. Shinzaki S, Matsuoka K, Tanaka H, et al. Leucine-rich alpha-2 glycoprotein is a potential biomarker to monitor disease activity in inflammatory bowel disease receiving adalimumab: PLANET study. *J Gastroenterol.* 2021;56(6):560–569.
14. Jackson CA, Clatworthy J, Robinson A, Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: a systematic review. *Am J Gastroenterol.* 2010;105(3):525–539.
15. Shinzaki S, Kuroki E, Iijima H, et al. Lectin-based immunoassay for aberrant IgG glycosylation as the biomarker for Crohn's disease. *Inflamm Bowel Dis.* 2013;19(2):321–331.
16. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest.* 2003;111(12):1805–1812.
17. Campos S, Portela F, Sousa P, Sofia C. Inflammatory bowel disease: adherence to immunomodulators in a biological therapy era. *Eur J Gastroenterol Hepatol.* 2016;28(11):1313–1319.
18. Nakajima S, Akiyama K, Kawai K, et al. Spin-correlated radical pairs in synthetic hairpin DNA. *Chemphyschem.* 2007;8(4):507–509.
19. Thomas CW Jr, Lowry PW, Franklin CL, et al. Erythrocyte mean corpuscular volume as a surrogate marker for 6-thioguanine nucleotide concentration monitoring in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Inflamm Bowel Dis.* 2003;9(4):237–245.
20. Spencer E, Norris E, Williams C, Dubinsky MC. The impact of thiopurine metabolite monitoring on the durability of thiopurine monotherapy in pediatric IBD. *Inflamm Bowel Dis.* 2019;25(1):142–149.
21. Lamb CA, Kennedy NA, Raine T, et al.; IBD Guidelines eDelphi Consensus Group. British Society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019;68(suppl 3):s1–s106.
22. Hibi T, Panaccione R, Katafuchi M, et al. The 5C concept and 5S principles in inflammatory bowel disease management. *J Crohns Colitis.* 2017;11(11):1302–1308.