Exploratory Study of the Effectiveness of Granulocyte and Monocyte Adsorptive Apheresis Before Initiation of Steroids in Patients With Active Ulcerative Colitis (EXPECT Study): A Multicenter Prospective Clinical Trial

Kazuki Kakimoto, MD, PhD,[*] Minoru Matsuura, MD, PhD,[†] Takumi Fukuchi, MD,[‡] Hitoshi Hongo, MD, PhD,[§] Tsuguhiro Kimura, MD, PhD,[§] Nobuo Aoyama, MD, PhD,[¶] Yorihide Okuda, MD, PhD,[‖] Kazuki Aomatsu, MD, PhD,[**] Noriko Kamata, MD, PhD,[††] Yoko Yokoyama, MD, PhD,[‡‡] Chiemi Mizuno, MD,[§§] Takuya Inoue, MD, PhD,[*] Takako Miyazaki, MD, PhD,[*] Shiro Nakamura, MD, PhD,[*] Kazuhide Higuchi, MD, PhD,[*] and Hiroshi Nakase, MD, PhD[¶¶]

Background: Granulocyte and monocyte adsorptive apheresis (GMA) has been used for therapy of steroid-dependent/refractory ulcerative colitis (UC). The aim of this study was to investigate the effectiveness of GMA in UC patients not receiving steroids.

Methods: We conducted a single-arm, open-label, and multicenter prospective clinical trial. UC patients who had insufficient responses to 5-aminosalicylic acid received GMA twice a week for 5 weeks.

Results: The response rate of all patients was 58.2% (39/67). Of the 39 patients who achieved a response, 74.4% achieved endoscopically confirmed mucosal healing.

Conclusions: GMA shows effectiveness in inducing remission in UC patients not receiving steroid.

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*2nd Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka, Japan; †Department of Gastroenterology and Hepatology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan; ‡Department of Gastroenterology and Hepatology, Iseikai Hospital, Osaka, Osaka, Japan; §Department of Gastroenterology, Fujita Gastroenterological Hospital, Takatsuki, Osaka, Japan; ¶Department of Gastroenterology, Gastrointestinal Endoscopy and IBD Center, Aoyama Medical Clinic, Kobe, Hyogo, Japan; ‖Department of Gastroenterology, Otemae Hospital, Osaka, Osaka, Japan; **Department of Gastroenterology, Izumiotsu Municipal Hospital, Izumiotsu, Osaka, Japan; ††Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Osaka, Japan; ‡‡Department of Intestinal Inflammation Research, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; §§Department of Gastroenterology and Hepatology, Saiseikai Suita Hospital, Suita, Osaka, Japan; ¶¶Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan

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Address correspondence to: Hiroshi Nakase, MD, PhD, AGAF, Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan (hiro_nakase@sapmed.ac.jp).

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Lay Summary

EXPECT study demonstrates that granulocyte and monocyte adsorptive apheresis has promising effectiveness with regard to inducing remission in patients with active ulcerative colitis (UC) who are not receiving steroid treatment. The first episode of UC was an independent predictor of a response in multiple logistic regression.

Key Words: inflammatory bowel disease, granulocyte and monocyte adsorptive apheresis, COVID-19, steroid naive

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disorder causing persistent mucosal inflammation in the large intestine with a relapsing and remitting pattern. Dysregulation of the mucosal immune response against intestinal microorganisms plays a crucial role in the pathogenesis of UC, although the exact etiology and pathology remain unclear.[1] In the colonic mucosa of patients with active UC, the infiltration of large numbers of granulocytes with enhanced migratory capacity and viscous power, activated macrophages and lymphocytes can be observed, and these immune cells, which produce inflammatory cytokines such as TNFα and IL-1β, contribute to the pathology of UC.[2] Therefore, blocking the migration of granulocytes and monocytes into the colonic mucosa is reasonable as a therapeutic strategy for UC.

Apheresis therapy is a treatment for inflammatory bowel disease (IBD) patients that was developed in Japan.[3] The mechanism underlying apheresis therapy is based on local immunomodulation achieved by removing leukocytes (granulocytes, monocytes, and activated lymphocytes) from the peripheral blood with special columns.[4] With no additive drugs, apheresis therapy appears to be a natural biologic therapy and may be a groundbreaking treatment method. Granulocyte and monocyte adsorptive apheresis (GMA), which involves the use of cellulose acetate beads as an adsorption column, mainly adsorbs activated granulocytes and monocytes in the peripheral blood during extracorporeal circulation. Through the removal of activated granulocytes and monocytes from peripheral blood, GMA exerts several anti-inflammatory effects, such as decreasing the expression of adhesion molecules, such as L-selectin, on immune cells and increasing the number of regulatory T cells.[5–7]

Generally, when patients with active UC fail to achieve clinical remission with 5-aminosalicylate (5-ASA) treatment, we consider the use of steroids. However, among patients receiving steroid therapy for the induction of remission, 11% have steroid-refractory disease, and 38% of those with an initial response develop steroid dependency within 2 years.[8] Long-term use of steroids increases the risk of serious drug-related adverse events (AEs) such as osteoporosis, psychiatric symptoms, infections, impaired glucose tolerance, and femoral head necrosis. Therefore, the withdrawal or reduction of steroid therapy without the exacerbation of the patient's symptoms is an important goal of UC treatment. Additionally, recent SECURE-IBD data suggest that steroid administration is associated with the severity of COVID-19.[9–11] Therefore, nonsteroidal treatment is required for the induction of remission in active UC patients during the COVID-19 pandemic. It was acknowledged that GMA was effective for steroid-dependent/refractory UC with the reduction of steroids.[12,13] A meta-analysis demonstrated that GMA is effective at inducing clinical remission in patients with active UC in comparison with steroids (odds ratio [OR]: 2.23; 95% confidence interval [CI]: 1.38–3.60).[14] Notably, the rate of the occurrence of AEs associated with apheresis was significantly lower than that associated with steroids (OR: 0.24; 95% CI: 0.15–0.37).[14] Of note, several reports have indicated that GMA is highly effective at inducing remission in steroid-naive patients with UC.[15–17] However, the role of GMA in the spectrum of IBD treatments is still debated, and the efficacy of apheresis with regard to the induction of remission in patients with steroid-naive active UC has not yet been established. Therefore, we conducted an exploratory study of the effectiveness of GMA before initiation of steroids in patients with active UC (EXPECT study).

METHODS

Study Population

This study (UMIN registration no. 000013702) was a multicenter, single-arm, prospective, open-label study in patients with moderate to severe active UC that was conducted in Japan during the period from October 2013 to December 2017. The diagnosis of UC was based on the criteria determined by the Japanese Ministry of Health, Labor and Welfare. The patients were males and females with UC between the ages of 16 and 75 years old. Mild to moderate UC was defined by a Mayo score more than 3 points but fewer than 10 points.[18] Patients with mild to moderate UC despite treatment with a high dose of 5-ASA for more than 2 weeks (4000 mg/d of time-dependent release formulation of mesalazine [Pentasa] or 3600 mg/d of pH-dependent release formulation of mesalazine [Asacol]) who were naive or free to steroids were enrolled in the trial. We defined patients with no previous steroid treatment as "steroid naive" and those without steroid treatment within 6 months before trial registration as "steroid free." In this study, steroids included all dosages but there were no UC patients who had been treated with either budesonide or beclomethasone.

The exclusion criteria were as follows: (1) patients with a contraindication to GMA (granulocyte count 2000/mm^3 or fewer, complication with severe infection, complication with severe cardiac disorder/renal disorder, and extreme dehydration);

(2) patients starting treatment or receiving an increased dose of 5-ASA within 2 weeks before the trial registration date; (3) patients treated with cytapheresis (GMA or leukocytapheresis) within 4 weeks before the trial registration date; (4) patients treated with new or higher doses of thiopurine drugs within 8 weeks before the trial registration date; (5) patients with a history of treatment with biologics; (6) patients from whom informed consent could not be obtained; and (7) patients deemed unsuitable for GMA by the attending physician. All the authors had access to the study data and reviewed and approved the final manuscript.

Study Design

We performed GMA twice a week for 5 consecutive weeks. The circulation conditions for each treatment were a flow rate of 30 mL/minute and a circulation time of 60 minutes. For anticoagulants, we used either heparin or nafamostat mesylate. A patient who underwent 10 GMA treatments and a patient who discontinued treatment after fewer than 10 GMA treatments due to lack of effectiveness were defined as the target cases for the evaluation of effectiveness or the per protocol population. The dose change of oral 5-ASA was not allowed during the GMA treatment course, while the dose reduction of topical 5-ASA was acceptable.

Outcomes and Definitions

The Mayo score was determined before the start of GMA and 1 week after the end of last GMA. Additionally, mucosal inflammation was assessed at each colonoscopy according to the Mayo endoscopic subscore (MES) and ulcerative colitis endoscopic index of severity (UCEIS) score before GMA and 1 week after the end of GMA.[18,19] Clinical remission was defined as a Mayo score of 2 points or fewer and each subscore of 0 or 1. The definition of a response is a partial Mayo score of 2 points or higher and a decline in the score of over 30% after the treatment. Mucosal healing (MH) was defined as a MES of 0 or 1. Furthermore, we also recorded any AEs that occurred during the study period.

The primary endpoint was the rate of clinical response at the end of GMA. In addition, the secondary endpoints were the rates of clinical remission and MH in the patients who achieved a clinical response and remission. We also evaluated the changes in the serum levels of inflammatory markers (eg, C-reactive protein [CRP]) after GMA.

Defining an event with concomitant symptoms even in the absence of a clear causal relationship during the period of GMA as AEs, we evaluated the incidence of AEs in the population.

Statistical Analysis

We used Fisher exact test for categorical variables and the Mann–Whitney *U* test for continuous variables in terms of a comparison of demographic variables between the steroid-naive group and the steroid-free group or between the remission group and the nonremission group. We also used the Wilcoxon signed rank test for a comparison of continuous variables before/after GMA. The response rate according to the disease extent of UC (E1 vs E2 vs E3) was compared using a Cochran–Armitage test. The predictive factor for GMA effectiveness was examined by multiple logistic regression. Odds ratios with 95% CIs were calculated for selected variables. The statistical significance level was set as $P < 0.05$ (2-sided test). All statistical analyses were performed using JMP 13.2.1 software (SAS Institute, Cary, NC, USA).

Ethical Considerations

The protocol of the clinical trial was approved by the IRB at each institution. Informed consent to participate in the study was obtained from each participant before inclusion.

RESULTS

Baseline Characteristics

Between October 2013 and December 2017, 74 patients were enrolled in this study (Supplementary Figure). Seven patients were excluded: 4 patients could not continue GMA treatment for all 10 sessions and 3 patients withdrew their consent. A total of 67/74 patients (90.5%) composed the per protocol population for the evaluation of effectiveness. In the per protocol population, 3 patients who had increased disease activity during GMA and needed alternative treatments were included in the nonresponder group. The remaining 64 patients completed 10 GMA treatments. Table 1 shows the clinical background of the 67 patients in the per protocol population (35 male patients and 32 female patients). The median duration of UC was 37.5 (interquartile range [IQR] 4–78) months. A total of 43.3% of the UC patients had extensive disease. At baseline, 19.4% of the patients had received concomitant thiopurine. The median Mayo score, MES, and UCEIS score were 8 (IQR 7–9), 2 (IQR 2–2), and 4 (IQR 4–5), respectively. Approximately 70.1% and 29.9% of the patients were in the steroid-naive group and the steroid-free group, respectively. The disease duration in the steroid-naive group was significantly shorter than that in the steroid-free group. The proportion of patients with first episodes of UC in the steroid-naive group was significantly higher than that in the steroid-free group. There were no significant differences in the levels blood markers, such as CRP, at baseline between the steroid-naive and steroid-free groups.

Effectiveness

The clinical remission and response rates of all patients after 10 GMA treatments were 25.4% (17/67) and 58.2% (39/67), respectively (Figs. 1A, B). In the 39 patients who achieved a clinical response, 74.4% (29/39) achieved MH. Of note, all 17

TABLE 1. Baseline Demographic Variables of the 67 Patients in This Study Stratified by History of Steroid Use

	Total (n = 67)	Steroid Naive (n = 47)	Steroid Free (n = 20)	*P*
Demographic variables				
Sex: male/female	35/32	27/20	8/12	0.285
Age (years), median (IQR)	41 (29–54)	39 (29–54)	46 (25–53.3)	0.869
Duration of disease (months), median (IQR)	37.5 (4–78)	17 (1–62)	63 (36–180)	0.001
Disease extent: E1 (proctitis)/E2 (left sided)/E3 (extensive)	8/29/29	7/21/18	1/8/11	0.350
Clinical course: first episode/relapsing–remitting	20/47	20/27	0/20	<0.001
Concomitant medication				
5-Aminosalicylic acid; mesalazine/asacol	24/43	17/30	7/13	0.816
Thiopurine, number of patients (%),	13 (19.4%)	8 (17.0%)	5 (25.0%)	0.507
Mayo score, median (IQR)	8 (7–9)	8 (8–9)	8 (7–9)	0.352
Mayo endoscopic score, median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)	0.060
Modified UCEIS score, median (IQR)	4 (4–5)	4 (4–5)	5 (4–5)	0.285
WBC (10^9/L), median (IQR)	6.8 (5.5–8.1)	6.9 (6.1–8.0)	6.1 (5.2–9.5)	0.416
Granulocyte (10^9/L), median (IQR)	4.5 (3.3–5.9)	4.7 (4.0–5.8)	4.0 (3.3–7.3)	0.459
Lymphocyte (10^9/L), median (IQR)	1.4 (1.1–1.9)	1.4 (1.2–1.9)	1.3 (1.0–1.9)	0.412
Monocyte (10^9/L), median (IQR)	0.5 (0.4–0.7)	0.6 (0.4–0.7)	0.5 (0.2–0.7)	0.412
Platelet (10^9/L), median (IQR)	298 (251–363)	303 (243–366)	293 (255–339)	0.881
CRP (mg/L), median (IQR)	5.2 (1.4–13.9)	4.4 (1.4–20.0)	6.0 (2.0–11.9)	0.952

WBC, white blood cell.

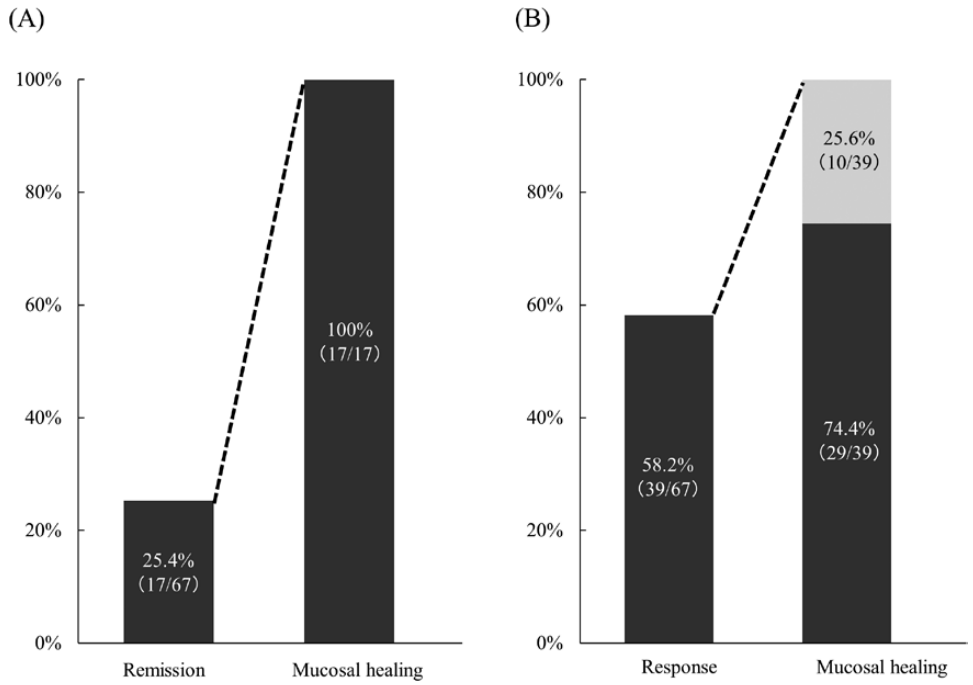

FIGURE 1. The remission rate of all patients after GMA, and the MH rate in the 17 patients who achieved clinical remission (A), the response rate of all patients after GMA, and the MH rate in the 39 patients who responded to GMA (B).

patients with clinical remission achieved MH. The Mayo score of all patients was significantly decreased from 8 (7–9) to 4 (2–7.5) after GMA (Fig. 2A). The UCEIS score was also significantly decreased from 4 (4–5) to 3 (1–4) (Fig. 2B). There was no significant difference in the response rate among E1, E2, and E3 patients (62.5% vs 62.1% vs 51.7%, $P = 0.442$).

Factors Associated With a Response to GMA

With regard to patients with or without a history of steroid treatment, there was no significant difference in the response rate between the steroid-naive and steroid-free groups (61.7% vs 50.0%) (Fig. 3A). However, we found that the response rate in patients with first episodes of UC type was significantly higher than that in the patients with relapsing–remitting UC (80.0% [16/20] vs 48.9% [23/47], $P = 0.029$) (Fig. 3B).

As shown in Table 2, there were no significant differences in sex, age, disease duration, UC location, history of steroid administration, IM combination use rate, Mayo score, UCEIS score, and CRP level at the start of GMA between the responder group and the nonresponder group. Also, in steroid-naive patients, there were no significant differences in those variables between the responder group and the nonresponder group (Supplementary Table 1). Supplementary Table 2 shows that the white blood cell, granulocyte and monocyte counts and serum level of CRP were significantly decreased after GMA compared to before GMA. Additionally, we found that the first episode of UC (OR: 4.952, 95% CI: 1.292–18.981, $P = 0.012$) was an independent predictor of a response in multiple logistic regression analysis (Table 3).

Safety Evaluation

We recorded all AEs in the 74 patients in the safety evaluation population during the clinical trial. Table 4 shows the AEs. Only 6 patients (8.1%) had AEs. Most AEs were fever and nausea (2.7%). All AEs were reversible, and there were no severe AEs. Therefore, there was no case involving the discontinuation of GMA due to AEs.

DISCUSSION

The results of our first prospective study indicated the effectiveness of GMA in patients with mild to moderate UC who failed to respond to 5-ASA treatment alone. We found that 58.2% of all patients responded to GMA treatment with relatively fewer AEs, and 74.4% (29/39) of the patients who responded to GMA treatment achieved MH. These data strongly suggest the promising effectiveness of GMA in patients with mild to moderate active UC based on the achievement of MH.

Steroids have been widely used for the induction of remission in IBD patients since the 1950s. Evidence of the benefits of oral steroid therapy comes from 2 early studies of active UC.[20,21] Steroids are optimal drugs for controlling severe intestinal inflammation in IBD. Generally, when an adequate response is not achieved with an adequate dose of 5-ASA for induction treatment in patients with UC, second-line treatment with steroids is considered in clinical practice.[22] However, several previous studies based on basic research indicated that the pharmacological inhibition of NF-kappa B, which is the main mechanism of action of steroids, interrupted both epithelial regeneration and the barrier function of the colonic mucosa in colitis models.[23,24] Thus, steroid treatment is not sufficient to achieve MH. Alternative treatments with thiopurine and biologics have been used to avoid the long-term use of steroids. However, the safety of the long-term administration of these drugs has not yet been confirmed because these drugs carry risks such as infection, lymphoproliferative disease, and skin cancers. In addition to treatment with these drugs, GMA is an alternative option for the induction treatment of patients with active UC in Japan. Since Shimoyama et al[3] first reported the effectiveness of GMA with regard to the induction of remission in patients with refractory UC, many reports regarding the effect of GMA treatment on IBD have been published in Japan[15] and Western countries.[12,13] Furthermore, a meta-analysis by Yoshino et al[14] demonstrated that intensive GMA was significantly better at inducing remission than steroids.

However, most of the patients enrolled in those studies were steroid dependent and refractory to steroids or biologic therapies. Until now, there has been no prospective study investigating the effectiveness of GMA in the induction of remission in patients with active UC who did not respond to 5-ASA treatment before starting steroid therapy. Therefore, we conducted this study to evaluate the effectiveness of GMA as a second-line therapy for active UC.

To date, there have been several retrospective studies showing the effectiveness of GMA treatment in patients with steroid-naive UC. Suzuki et al[16] reported that the rate of the induction of remission in patients with steroid-naive UC by GMA was 85% (17/20). Tanaka et al[17] reported a significantly higher induction of remission rate of 84.6% (22/26) in steroid-naive patients in comparison with 57.9% (11/19) in steroid-dependent UC patients. The rates of the induction of remission in these case series were higher than the rate in the present study (25.4%). In the present study, we investigated the contribution of the previous use of steroids to GMA treatment outcomes and found a higher rate of the induction of remission in the steroid-naive group than in the steroid-free group, although there was not statistically significant difference between the 2 groups (61.7% vs 50.0%, $P = 0.425$). Additionally, we found that the response rate of patients with first episodes of UC was significantly higher than those with relapsing–remitting UC, and the former type of UC was a significant independent predictor of remission in multiple logistic regression analysis. Yokoyama et al[25] reported that patients suffering from their first episode responded well to GMA and achieved a favorable long-term disease response. Taken together, the patient population, with regard to the clinical phenotype and the

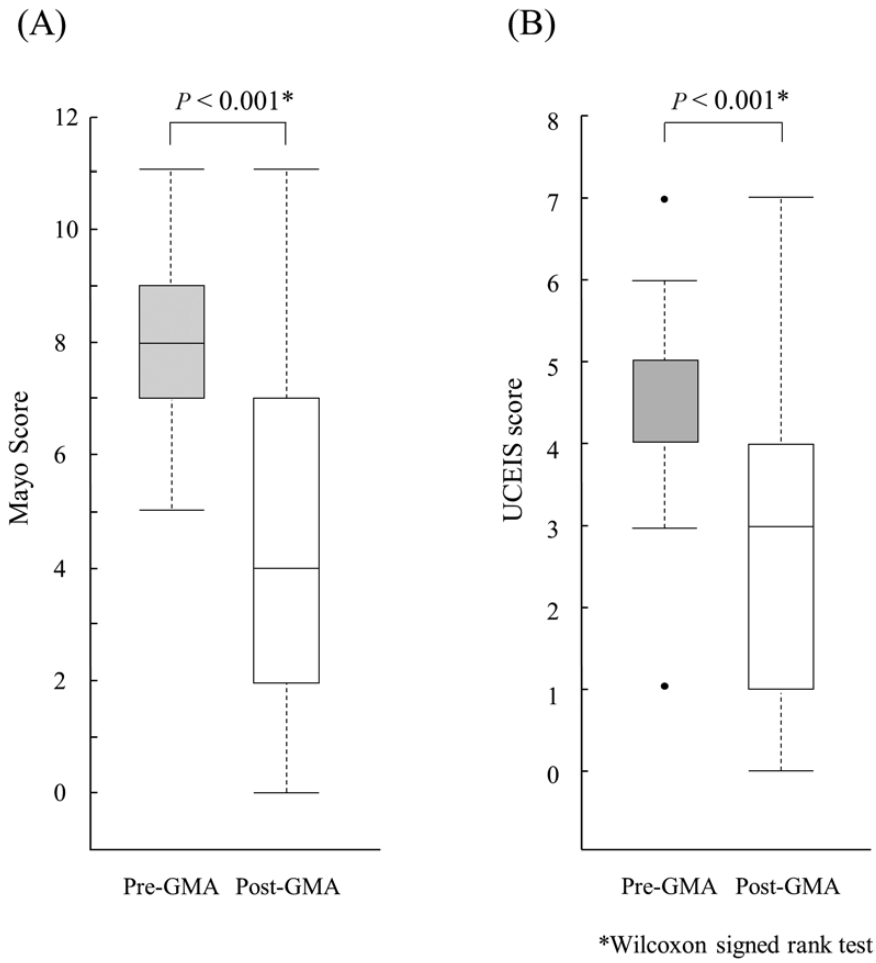

FIGURE 2. Comparison of scores before and after GMA; Mayo score (A) and UCEIS score (B).

history of steroid use, might contribute to the different rates of the induction of remission between the current study and previous studies.

Next, we focused on the effect of GMA on the achievement of MH in active UC patients without the administration of steroids. Currently, disease activity is evaluated objectively based on endoscopic findings, calprotectin levels, and ultrasound imaging. The relevance of the endoscopic activity of UC has been translated into the new concept of "MH" as a therapeutic goal because accumulating evidence indicates the favorable prognostic value of a healed mucosa with regard to the clinical outcome of UC. Ardizzone et al[26] reported that 63% of 157 UC patients achieved clinical remission after the first course of steroid treatment, and only 60.6% of the patients with clinical remission achieved MH. In the present study, 74.4% (29/39) of the patients who responded to GMA treatment achieved MH. It should be noted that all (100%) of the 17 patients with clinical remission achieved MH. Taken together, our current data are promising for the following reasons: (1) GMA can be made available to the patients with UC who need to avoid the use of steroids as much as possible. (2) GMA contributes to a superior achievement of MH at the point of mucosal regeneration by avoiding steroid use.

In clinical practice, the safety profile is critically important when choosing among several treatments. Therefore, we examined the safety of GMA in this study. There were some AEs in our study, such as fever, nausea, and headache, but no serious AEs. The rate of GMA-associated AEs in this study seems to be lower than those reported in previous studies. We believe that the lower rate of AEs might be associated with the fact that the enrolled patients did not receive any steroids. There have been many reports regarding the safety of GMA treatment in elderly patients,[27] pregnant women,[28] pediatric patients,[29] and patients with concomitant infection with cytomegalovirus.[30] Based on our current results and previous data, we reconfirmed that GMA is a natural biologic therapy with few AEs due to the lack of the administration of drugs.

Meanwhile, we should always concern about the cost of IBD treatments. Of course, the cost of GMA is higher than that of conventional PSL treatment when we perform GMA as

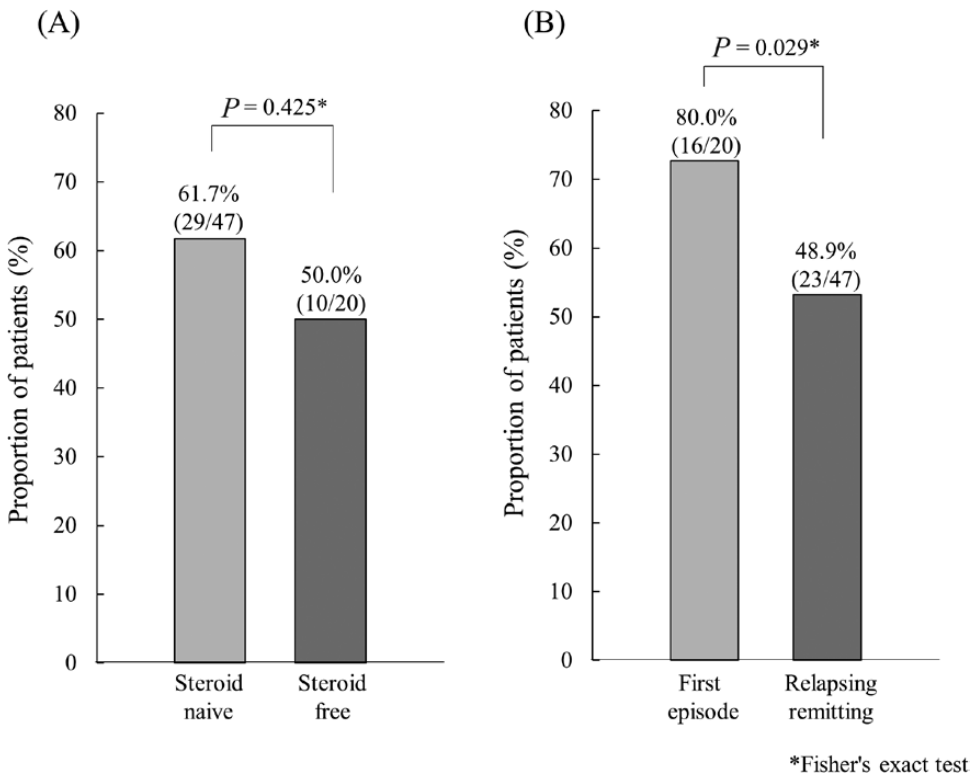

FIGURE 3. The response rate after GMA in patients with or without a history of corticosteroid exposure (A); with a first episode or the relapsing–remitting type (B).

TABLE 2. Variables Associated With Response to GMA in the 67 UC Patients

	Responder (n = 39)	Nonresponder (n = 28)	*P*
Demographic variables			
Sex: male/female	19/20	16/12	0.621
Age (years), median (IQR)	44 (32–53)	40 (25.3–57)	0.814
Duration of disease (months), median (IQR)	39 (2–130)	36 (14–63)	0.891
UC location: E1 (proctitis)/E2 (left sided)/E3 (extensive)	5/18/15	4/24/28	0.696
Clinical course: first episode/relapsing–remitting	16/23	4/24	0.029
History of steroid administration (steroid free/steroid naive)	74.4% (10/29)	64.2% (10/18)	0.425
Concomitant with thiopurine, number of patients (%)	6 (15.4%)	7 (25%)	0.363
Mayo score, median (IQR)	8 (8–9)	8 (7–9)	0.566
Modified UCEIS score, median (IQR)	4 (4–5)	5 (4–5)	0.535
WBC (10^9/L), median (IQR)	6.8 (5.4–8.4)	6.8 (5.5–7.8)	0.830
Granulocyte (10^9/L), median (IQR)	4.5 (3.3–6.0)	4.5 (3.7–5.8)	0.726
Lymphocyte (10^9/L), median (IQR)	1.4 (1.2–1.9)	1.3 (1.1–1.9)	0.304
Monocyte (10^9/L), median (IQR)	0.6 (0.4–0.8)	0.5 (0.4–0.7)	0.189
Platelet (10^9/L), median (IQR)	307 (249–373)	282 (252–335)	0.381
CRP (mg/L), median (IQR)	5.8 (1.5–18.8)	4.2 (1.0–10)	0.400

WBC, white blood cell.

TABLE 3. Multivariate Analysis of Factors Predictive of a Response to GMA Therapy

		95% CI		
	OR	Lower	Upper	*P*
Variables				
Age (years)	1.003	0.968	1.041	0.874
Female sex	2.657	0.818	8.639	0.095
First episode	4.952	1.292	18.981	0.012
Baseline monocyte count	0.999	0.997	1.001	0.456

TABLE 4. Adverse Events

	No. Patients (%)
Event	
Total	6 (8.2)
Fever	2 (2.7)
Nausea	2 (2.7)
Abdominal pain	1 (1.4)
Dysphoria	1 (1.4)
Headache	1 (1.4)

a first-line treatment for steroid-naive patients with active UC. However, we think that GMA could be cost-effective from the perspective of the safety profile on this nonpharmacological treatment intervention,[31,32] particularly during COVID-19 pandemic. Therefore, as we showed in this study, it is important to find subpopulation of UC patients who well respond to GMA.

There are several limitations of our trial. First, we could not precisely estimate the efficacy of GMA with regard to the induction of remission in steroid-naive UC patients because it was a single-arm study that did not use a placebo control, and not all enrolled patients were steroid naive. Second, the maintenance of remission is of paramount important for UC patients during long-term follow-up. Therefore, we should investigate the long-term effectiveness of GMA in UC patients without steroid treatment after the induction of remission. Third, the dose of 5-ASA varied in the enrolled patients in this study.

In conclusion, the current study demonstrates that GMA has promising effectiveness with regard to inducing remission in patients with active UC who are not receiving steroid treatment. In particular, we found high therapeutic effectiveness in UC patients with no history of steroid treatment and first episodes of UC. Additionally, we reconfirmed the safety of GMA, and it is possible that this treatment could be used during the COVID-19 pandemic because it enables patients to avoid using steroids. From the perspective of mucosal regeneration, further study will be needed to confirm the long-term clinical outcomes in UC patients who respond to GMA treatment and are not taking steroids.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

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