Original Article

Induction of mucosal healing by intensive granulocyte/monocyte adsorptive apheresis (GMA) without use of corticosteroids in patients with ulcerative colitis: long-term remission maintenance after induction by GMA and efficacy of GMA re-treatment upon relapse

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This study examined the long-term maintenance rate after inducing remission by intensive granulocyte/monocyte adsorptive apheresis (GMA) without use of corticosteroids (CS) and GMA re-treatment efficacy in the same patients upon relapse with ulcerative colitis. Patients who achieved clinical remission and mucosal healing (MH) by first-time intensive GMA (first GMA) without CS were enrolled. The cumulative non-relapse survival rate up to week 156 was calculated. Patients with relapse during the maintenance period underwent second-time intensive GMA (second GMA) without CS. Clinical remission and MH rates following second GMA were compared to those following first GMA in the same patients. Of the 84 patients enrolled, 78 were followed until week 156 and 34 demonstrated relapse. The cumulative non-relapse survival rate by week 156 was 56.4%. Clinical remission and MH rates after second GMA did not differ from those after first GMA in the same patients (week 6: clinical remission, 100% vs 88.4%, $p = 0.134$; MH, 100% vs 84.8%, $p = 0.074$). In conclusion, MH induction by intensive GMA without use of CS in ulcerative colitis patients contributes to subsequent long-term clinical remission maintenance. GMA re-treatment efficacy was comparable to that of first GMA in the same patients who had relapse.

***Key Words*: ulcerative colitis, intensive GMA, remission maintenance, re-treatment**

Patients affected by ulcerative colitis (UC), a condition characterized by chronic recurrent inflammation of the entire colon, are affected by a variety of symptoms, including diarrhea, fecal urgency, and rectal bleeding.(1) Although there is increasing evidence showing associations with genetic, immune system, and environmental factors, as well as possible microbiota involvement in the pathogenesis of UC, those details remain unclear.(2–4) Nevertheless, several pharmacological agents proven to provide benefits for the condition have been developed, with 5-aminosalicylic acid (5-ASA) the first choice for those with mild to moderate UC.(5) Should that fail, treatment with corticosteroids (CS) is usually then initiated.(5–7) In addition, for refractory UC patients, various biologics are included at the top of the treatment pyramid, with anti-tumor necrosis factor-α (TNF-α) antibodies, vedolizumab (VDZ), ustekinumab (UST), and tofacitinib (TFB) currently available.(8–13)

During treatment for UC patients, gastroenterologists must always keep in mind the risk of opportunistic infections when providing treatments with immune-suppressive drugs, including CS and biologics.(7,14–16) In addition to an increased risk of infection, long-term use of those medications is strongly associated with development of other adverse effects such as osteoporosis and impaired glucose tolerance.(17) In this regard, development of therapeutic strategies for inducing remission in UC patients without use of CS or biologics is a current unmet clinical need.

When considering the pathophysiology of active UC, which is associated with recruitment of large numbers of granulocytes and macrophages into the gastrointestinal tract,(18,19) selective removal of activated granulocytes and monocytes/macrophages may be a reasonable therapeutic option for affected patients. Granulocyte and monocyte adsorptive apheresis (GMA) is an extracorporeal blood circulation method performed with the Adacolumn (JIMRO, Takasaki, Japan), utilized to selectively remove active granulocytes and monocytes from peripheral blood, and numerous studies have reported good therapeutic efficacy and safety of once-a-week GMA (weekly GMA) treatments in CS-dependent as well as -refractory UC patients.(20–26) Previous reports have shown that the clinical efficacy of GMA for active UC patients is superior to that of CS.(19,27) Moreover, a recent meta-analysis revealed GMA to be a safe and effective therapy for UC patients, with higher rates of clinical remission and response as compared to CS shown.(28) However, an important issue is that weekly GMA requires several weeks for induction of clinical remission. To overcome this disadvantage, intensive GMA (twice per week) is now considered favorable, because an open-label prospective randomized multicenter study demonstrated that intensive GMA could induce remission more rapidly

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in active UC patients than weekly GMA.[29]

Currently, a colonoscopy examination is considered to be the most reliable modality for evaluating the efficacy of medical treatments or predicting disease relapse in UC patients.[30,31] We previously reported that intensive GMA without concomitant CS led to more rapid and higher rates clinical remission and mucosal healing (MH) in active UC patients as compared to weekly GMA.[32] Thus, we consider that intensive GMA is a suitable alternative treatment option for active UC patients prior to use of CS. However, there are few reports of long-term prognosis of UC patients who achieved MH by intensive GMA.[33] In addition, nothing is known regarding the efficacy of intensive GMA re-treatment for UC patients who suffer relapse after induction of clinical remission and MH by first-time intensive GMA (first GMA) without use of CS.

In the present study, the cumulative non-relapse survival rate by week 156 was evaluated in UC patients who had achieved clinical remission and MH with first GMA without the use of CS. Additionally, the efficacy of GMA re-treatment (second-time intensive GMA, second GMA) without use of CS was investigated in patients who demonstrated relapse during the maintenance period after achieving remission under first GMA.

Materials and Methods

Ethical considerations. In this retrospective observational study, clinical records provided by Iseikai Hospital and Osaka Saiseikai Nakatsu Hospital of patients examined from April 2010 to April 2019 were used. The protocol was approved by the ethics committee of both hospitals before commencing the investigation. This study was conducted in accordance with the Declaration of Helsinki, consolidated Good Clinical Practice guidelines, and applicable regulatory requirements

Patients. Diagnosis of UC was based on clinical, endoscopic, radiologic, and histological parameters. Fecal bacterial culture results yielded no evidence of specific pathogens in any of the patients. Disease activity was evaluated by clinical activity index (CAI; Rachmilewitz index).[34] Intensive GMA was performed for active patients (CAI ≥5). Consecutive UC patients over 20 years old who had achieved clinical remission and MH induced by first GMA without use of CS were consecutively enrolled. Clinical remission was defined as a CAI score ≤4 points, while MH was defined as a Mayo endoscopic score (MES) of 0 or 1.[8]

GMA procedure. Intensive GMA was performed without use of CS for UC patients as previously described.[29,32,35,36] Blood access was gained through the antecubital vein in one arm, while the return to the patient was through the antecubital vein in the contralateral or same arm, both through a 19-gauge needle. GMA was performed at a flow rate of 30 ml/min for 60 min, with the aim to expose 1,800 ml of blood per session (one session). As intensive GMA, two GMA sessions per week were performed five times (total of 10 sessions per five weeks).

Evaluation of cumulative non-relapse survival rate after first GMA. Patients who had achieved clinical remission and MH under first GMA without the use of CS, and received oral maintenance treatment with 5-ASA and/or thiopurine were observed until week 156. The dose of thiopurine was adjusted to achieve a white blood cell count <5,000/ml and then converted to 6-mercaptprine. Disease relapse was diagnosed when a CAI score of >7 points was confirmed despite receiving the maximum dose of 5-ASA or adjusted dose of thiopurine.[35–37] The cumulative non-relapse rate was calculated at weeks 26, 52, 104, and 156 after achieving clinical remission and MH by first GMA. Various clinical parameters were then compared between relapsed and non-relapsed patients in order to determine relapse-associated factors.

Efficacy and safety of intensive GMA re-treatment without CS treatment. For the relapsed UC patients, intensive second GMA without CS treatment was given using the same procedure protocol as with first GMA, with primary efficacy evaluated based on clinical remission rates at weeks 2, 4, and 6 after starting second GMA (twice per week) in the same patients (week 6; one week after the end of 10 sessions over five weeks). Clinical remission was defined as CAI ≤4. Secondary efficacy was assessed by a comparison of MES and MH rates at week 6. Adverse events were examined and recorded at each visit, and patients who achieved clinical remission with intensive GMA continued to be followed.

Statistical analysis. Data are presented as the mean ± SD. The cumulative non-relapsing survival rate was calculated using the Kaplan–Meier method. Categorical and continuous data were compared with those in other cases using a two-tailed Fisher's exact test, a chi-square test, or Student's *t* test. Categorical and continuous data in the same cases were compared using a McNemar test or paired *t* test. A p value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed with StatMate V (ATMS Co., Ltd., Tokyo, Japan).

Results

Patient enrollment. The flowchart of patient enrollment used in the present study is shown in Fig. 1. A total of 119 active UC patients (44.8 ± 16.9 years old, male/female 58/61, mean CAI 10.0 ± 3.1, MES 2.3 ± 0.5) underwent first GMA without CS treatment. Among those, 90 achieved clinical remission after first GMA, while six did not achieve MH. A total of 84 patients with clinical remission and MH were initially enrolled, after which six dropped out because of lack of follow-up data, resulting in analysis of 78, whose baseline characteristics are shown in Table 1. Of the 78 patients enrolled, those who achieved MES 0 and MES 1 with first GMA were 28 and 50, respectively. All patients received 5-ASA and/or thiopurines for maintaining clinical remission.

Cumulative non-relapse survival rate by week 156 after first GMA. Thirty-four patients suffered relapse during the maintenance period. The cumulative non-relapse curve is shown in Fig. 2. The overall cumulative non-relapse survival rates in patients who achieved both clinical and endoscopic remission from first GMA at weeks 26, 52, 104, and 156 were calculated to be 87.2, 71.1, 57.6, and 56.4%, respectively.

Characteristics of relapsed and non-relapsed UC patients. Forty-four patients maintained clinical remission during the study period, while 34 experienced relapse within 156 weeks. Their baseline characteristics separated by relapse and non-relapse status are shown in Table 2. The rate of relapse during the maintenance period was significantly lower in the MES 0 (28.6%; 8/28) as compared to the MES 1 (52.0%; 26/50, $p = 0.045$) group. Furthermore, the mean MES before and after first GMA was significantly higher in patients with as compared to without relapse (before: 2.4 ± 3.6 vs 2.2 ± 0.4, $p = 0.049$; after: 0.8 ± 0.4 vs 0.5 ± 0.5, $p = 0.046$). There were no significant differences between the two groups in regard to age, gender, duration of disease, involved area of disease, degree of CAI score, or maintenance medication.

Clinical efficacy of intensive GMA re-treatment in relapsed UC patients. Table 3 shows clinical data obtained before starting second GMA in the 34 patients who experienced relapse as compared to those data in the same patients before starting first GMA. As expected, age and duration of disease after relapse were significantly greater as compared to the previous examination showing active UC (p<0.001), while gender rates were the same, because these were time-dependent comparisons conducted with the same cases. In the relapsed patients, the involved area was most often the left-side colon ($n = 31$) (p =

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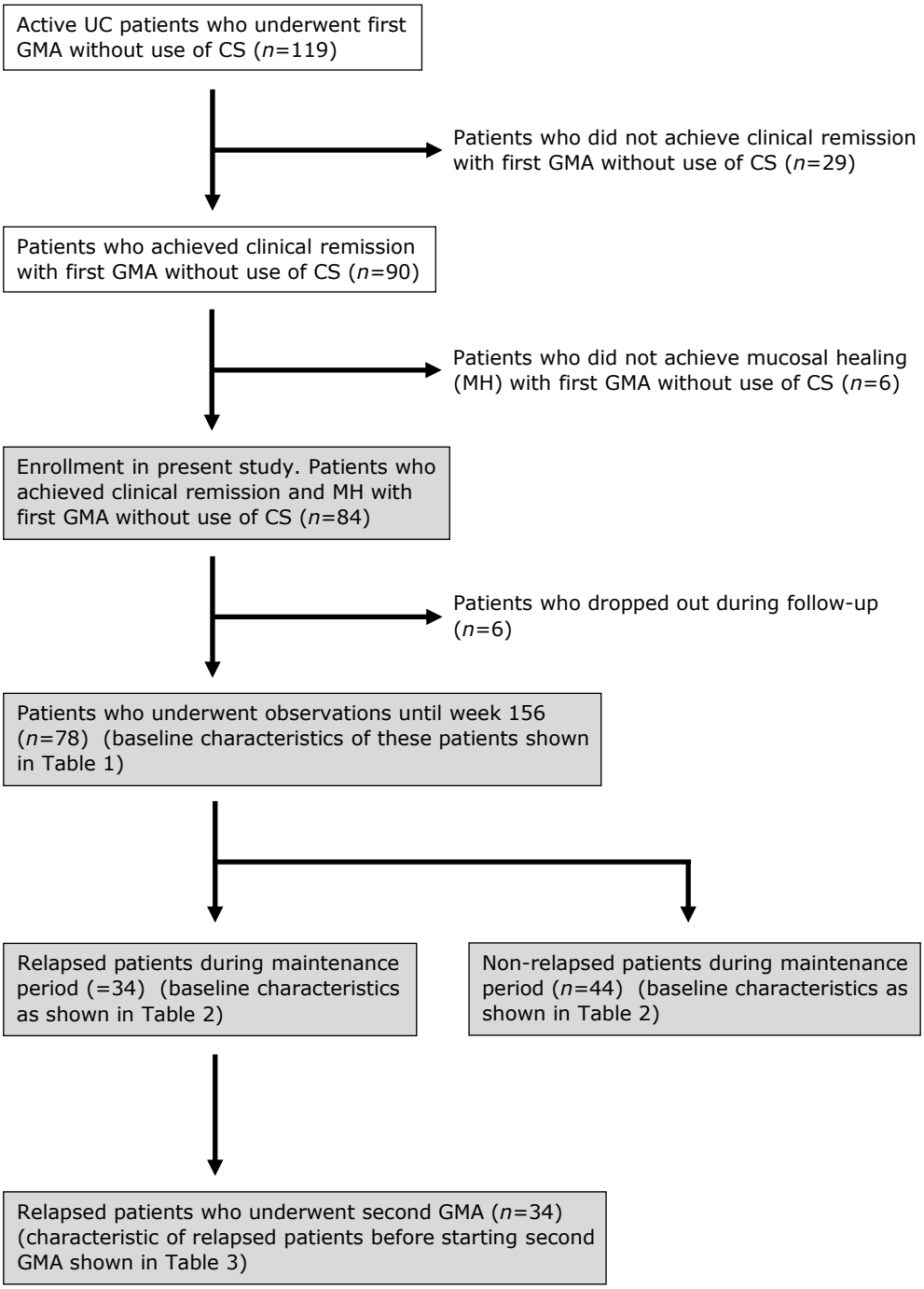

Fig. 1. Flowchart of patient enrollment. Gray squares indicate related procedures. UC, ulcerative colitis; GMA, granulocyte and monocyte adsorptive apheresis; first GMA, first-time intensive GMA; second GMA, second-time intensive GMA.

0.016) and the main therapy location was usually the outpatient clinic ($n = 31$) ($p = 0.041$). The mean CAI score before starting first GMA (10.2 ± 3.6) was significantly greater as compared to that before starting second GMA (8.9 ± 2.2) ($p = 0.042$), while the mean MES score before starting first GMA (2.4 ± 0.5) was not significantly different than that before starting second GMA (2.2 ± 0.4) ($p = 0.160$).

GMA re-treatment (second GMA) was performed for the 34 UC patients who suffered relapse without use of CS. Clinical remission (CAI $\leq$4) rates in association with second GMA as compared to first GMA in the same patients are shown in Fig. 3A (gray and while columns, respectively). Clinical remission rates after starting re-treatment (second GMA) were 32.4% at week 2 and 50.0% at week 4, lower as compared to those during first GMA (50% at week 2, $p = 0.070$; 85.3% at week 4, $p<0.001$). On the other hand, the rate of remission at week 6 (88.2%), one week after the end of second GMA, was not different from that at that same time period during the first GMA course (100%) ($p = 0.134$). The remission rate at week 6 after starting first GMA was 100% (Fig. 3A, white column), as patients who achieved clinical remission with GMA were enrolled in the present study. Furthermore, the mean time to clinical remission in the second GMA

Table 1. Baseline characteristics* of UC patients who achieved clinical remission and mucosal healing by first GMA without use of corticosteroids (n = 78)

Age (years)		43.2 ± 15.0
Gender (male/female)		38/40
Duration of disease (months)		58.6 ± 93.0
Involved area of disease		
	Entire colon	24
	Left-side colon	54
Clinical activity index (CAI; mean)		1.9 ± 1.1
[CAI (mean) before 1st GMA]		[9.8 ± 3.1]
Mayo endoscopic score (MES)		
	Number of patients (MES 0/1)	28/50
	Mean of MES	0.6 ± 0.5
[MES (mean) before 1st GMA]		[2.2 ± 0.4]
Maintenance medication		
5-ASA	No. of patients (received/not)	75/3
	Dose (mg/day)	3,407.7 ± 754.9
Thiopurine	Number of patients (received/not)	45/33
	Dose# (mg/day)	13.7 ± 13.2

*Evaluated at time of remission induction by first-time intensive granulocyte and monocyte adsorptive apheresis (first GMA). UC, ulcerative colitis; 5-ASA, 5-aminosalicylate. #Thiopurine dose was converted to 6-mercaptprine. Data are presented as the mean ± SD.

cases (27.9 ± 16.8 days) was significantly longer than that during the first GMA course (21.2 ± 12.7 days).

Endoscopic efficacy of intensive GMA re-treatment in relapsed UC patients. Endoscopic efficacy was also assessed for second as compared to first GMA in the same patients. The mean MES scores at week 6 were not different (0.9 ± 0.9 vs 0.8 ± 0.4, p = 0.423) (Fig. 3B-a), while there was also no significant difference for endoscopic remission rate at week 6 (100% vs 84.8%; p = 0.074) (Fig. 3B-b). The rate of endoscopic remission (MES = 0 or 1) at week 6 for first GMA was 100% (Fig. 3B-b, white column), since patients who achieved MH with GMA were enrolled in the present study.

Treatment safety. During the present GMA procedures, one patient in the first GMA group complained of headaches and one in the second GMA group experienced nausea. However, those adverse effects did not prevent them from continuing the GMA treatments. No other serious side effects were observed throughout this study.

Discussion

The present study showed that 56.4% of UC patients who achieved MH by first GMA without concomitant CS and with 5-ASA and/or IM during therapy maintained clinical remission for a period of 156 weeks. In relapsed patients who received second GMA, clinical and MH rates without use of CS were 88.2% and 84.8%, respectively (at week 6). Thus, achievement of MH by GMA without concomitant CS contributed to long-term remission maintenance. Moreover, GMA retreatment following relapse was shown to induce clinical remission and MH.

A number of previous reports have noted that achievement of MH in UC patients leads to reductions in the rates of disease relapse and hospitalization.[38–40] A Norwegian population-based cohort study demonstrated that MH was significantly associated with a low risk of future colectomy in UC patients.[30] Furthermore, accumulating associated evidence indicates that MH may be an important indicator of the efficacy of treatment as well as a prognostic marker for long-term maintenance in such UC patients.[30,31] Our group previously reported that intensive GMA without use of CS induced clinical remission in 70–80% of active UC patients as well as endoscopic remission (MH) in 60–70% of those.[32,35,36] Of the present patients who underwent first GMA, 70.6% (84/119) achieved clinical remission and MH (Fig. 1). Thus, GMA is currently recognized as a useful therapeutic option for inducing clinical remission as well as MH in UC patients.

Among reports showing maintenance of clinical remission in UC patients after GMA, Yamamoto *et al.*[31] noted a higher maintenance rate of clinical remission in UC patients who achieved MH by GMA as compared to those who did not. In addition,

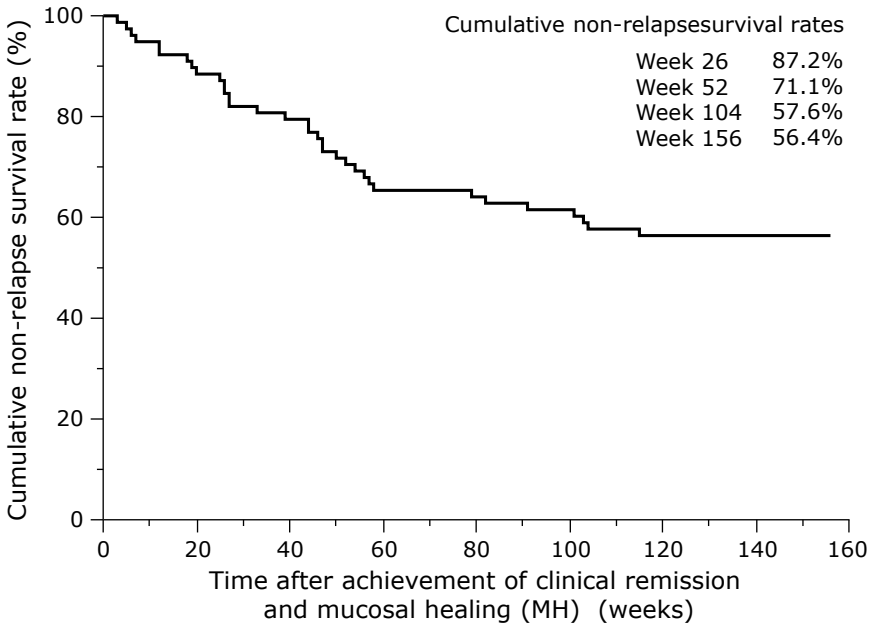

Fig. 2. Cumulative non-relapse curve for ulcerative colitis (UC) patients who achieved clinical remission and mucosal healing (MH) with first-time intensive granulocyte and monocyte adsorptive apheresis (first GMA) without use of corticosteroids. The cumulative non-relapse survival rates after first GMA at weeks 26, 52, 104, and 156 was estimated to be 87.2, 71.1, 57.6, and 56.4%, respectively.

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Table 2. Baseline characteristics* of relapsed and non-relapsed UC patients during maintenance period after achieving clinical remission and mucosal healing by first GMA without use of corticosteroids

		Relapsed UC (n = 34)	Non-relapsed UC (n = 44)	p value
Age (years)		42.1 ± 14.2	44.0 ± 15.6	0.573
Gender (male/female)		15/19	23/21	0.475
Duration of disease (months)		59.6 ± 83.2	57.9 ± 100.9	0.938
Involved area of disease				
	Entire colon	12	12	0.447
	Left side colon	22	32	
Clinical activity Index (CAI; mean)		1.9 ± 1.1	2.0 ± 1.1	0.959
[CAI (mean) before 1st GMA]		[10.2 ± 3.6]	[9.5 ± 2.7]	0.330
Mayo endoscopic score (MES)				
	Number of patients (MES 0/1)	8/26	20/24	0.045
	Mean of MES	0.8 ± 0.4	0.5 ± 0.5	0.046
[MES (mean) before 1st GMA]		[2.4 ± 3.6]	[2.2 ± 0.4]	0.049
Maintenance medication				
5-ASA	Number of patients (received/not)	32/2	43/1	0.411
	Dose (mg/day)	3,423.5 ± 903.5	3,395.5.0 ± 627.3	0.872
Thiopurine	Number of patients (received/not)	20/14	25/19	0.859
	Dose# (mg/day)	13.4 ± 13.6	13.9 ± 13.1	0.877

*Evaluated at time of remission induction by first-time intensive granulocyte and monocyte adsorptive apheresis (first GMA). UC, ulcerative colitis; 5-ASA, 5-aminosalicylate. #Thiopurine dose converted to 6-mercaptprine. Data are presented as the mean ± SD.

Table 3. Characteristics before starting second GMA after relapse as compared to before starting first GMA in the same patients

		Before 1st GMA (n = 34)	Before 2nd GMA (n = 34)	p value
Age (years)		42.1 ± 14.2	43.3 ± 14.3	<0.001
Gender (male/female)		15/19	15/19	—
Duration of disease (months)		59.6 ± 83.2	74.5 ± 92.3	<0.001
Involved area of disease				
	Entire colon	12	3	0.016
	Left-sided colon	22	31	
Therapy location				
	Inpatients	9	3	0.041
	Outpatients	25	31	
Clinical activity Index (CAI; mean)		10.2 ± 3.6	8.9 ± 2.2	0.042
Mayo endoscopic score (MES; mean)		2.4 ± 0.5	2.2 ± 0.4	0.160
Concomitant medication				
5-ASA	Number of patients (received/not)	32/2	31/3	0.997
	Dose (mg/day)	3,423.5 ± 903.5	3,388.2 ± 1,084.3	0.862
Thiopurines	Number of patients (received/not)	20/14	25/9	0.074
	Dose¶ (mg/day)	13.4 ± 13.6	20.3 ± 16.2	<0.001

5-ASA, 5-aminosalicylate. ¶Thiopurine dose converted to 6-mercaptprine. Data are presented as the mean ± SD.

Iida *et al.*[33] reported a three-year maintenance remission rate after GMA in CS naïve UC patients of 83.3%, which was significantly higher as compared to CS-dependent (68.8%) and -refractory (23.1%) patients. As for the present patients, 56.4% of those who achieved MH with first GMA and without use of CS maintained clinical remission for up to 156 weeks. In our study, the mean CAI score before first GMA (9.8 ± 3.1, Table 1) was higher as compared to that (8.0) in patients enrolled in the study of Iida *et al.*,[33] which might be a reason for the lower clinical remission rate seen in our cohort. On the other hand, the mean MES values before and after first GMA in the UC as compared to non-relapsed UC patients were significantly higher, while there were no significant differences between the groups in regard to other clinical characteristics examined in this study (Table 2). Interestingly, recent studies have revealed a difference in subsequent relapse rate during the follow-up period between patients with MES 0 and those with MES 1.[41,42] Similarly, in the present cohort, the rate of relapse during the maintenance period was significantly lower in the MES 0 as compared to the MES 1 group (Table 2). Those findings suggest that endoscopic activities before and after first GMA are possible predictors of relapse in UC patients who achieve clinical remission and MH with inten-

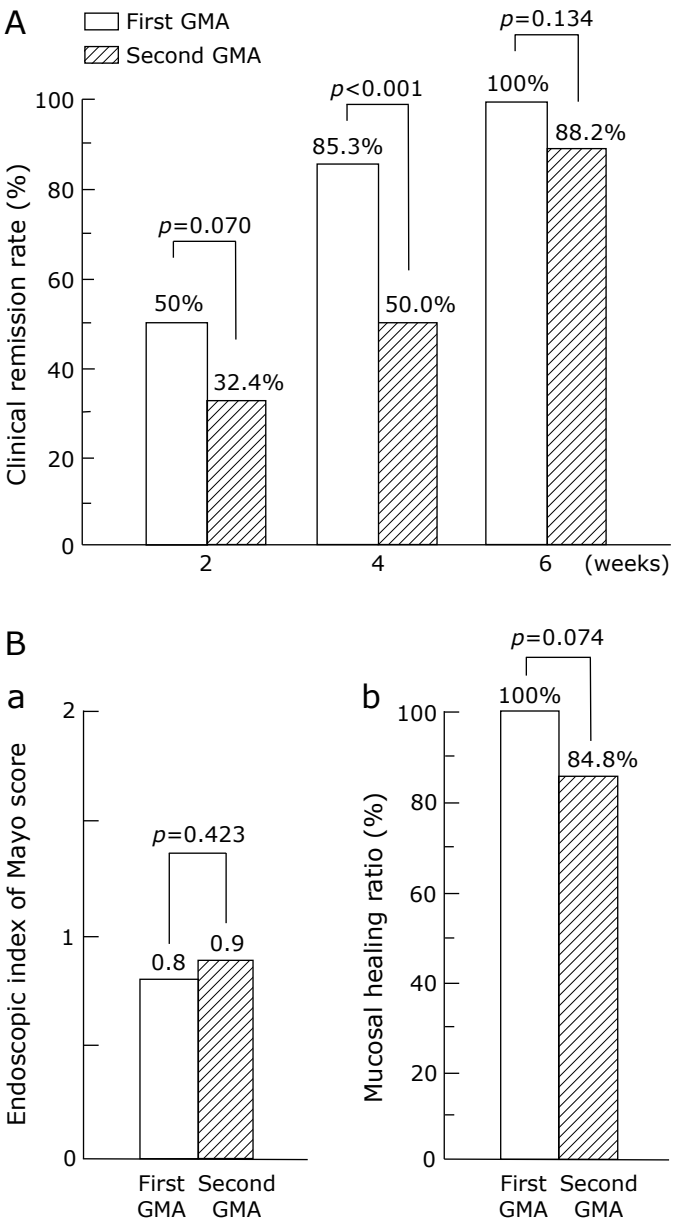

Fig. 3. (A) Comparison of clinical remission rates every two weeks following first- and second-time intensive granulocyte and monocyte adsorptive apheresis (first, second GMA) in the same ulcerative colitis (UC) patients. The clinical remission rates after starting second GMA (32.4% at week 2, 50% at week 4) were lower as compared to those with first GMA (50% at week 2, $p = 0.070$; 85.3% at week 4, $p<0.001$). The remission rate at week 6 (88.2%) after starting second GMA was not significantly different from that (100%) with first GMA ($p = 0.134$). (B) Endoscopic scores obtained with Mayo scoring system (MES) and mucosal healing (MH) rate at week 6 [one week after completion of the first- and second-time intensive granulocyte and monocyte adsorptive apheresis (first, second GMA)]. There was no significantly difference between first and second GMA for MES (a) or MH rate (b).

sive GMA. Thus, gastroenterologists should keep in mind the possibility of relapse even up to three years after GMA, especially in cases with severe endoscopic findings before induction treatment and remaining inflammation after beginning that treatment.

Few reports regarding the efficacy of GMA retreatment in relapsed UC patients have been presented. In a study by Lindberg *et al.*,[43] 14 inflammatory bowel disease (IBD) patients who experienced relapse after showing initial remission with first GMA were re-treated with GMA, of whom 13 (93%) went into a second remission. However, the sample size of that study was small and the relapse cases included a higher number of Crohn's disease as compared to UC patients, while IBD patients refractory to CS and/or infliximab (IFX) were included as subjects. In the present study, all UC patients who relapsed during the maintenance period underwent re-treatment (second GMA) without concomitant CS and 88.2% again achieved clinical remission. In addition, there was no significant difference between the MES values obtained just prior to starting first and second GMA (Table 3). Thus, GMA re-treatment seems to be effective in patients who have suffered relapse.

On the other hand, the clinical efficacy of second GMA in our relapsed UC patients developed more slowly as compared to first GMA (Fig. 3A), even though clinical status was milder before starting second GMA including a lower CAI value, narrower area of UC involvement, and greater prevalence of outpatient status for treatment among the patients with relapse (Table 3). Nevertheless, despite the slower response to second GMA, the majority of relapsed patients again achieved clinical remission without use of CS. In this regard, GMA might be considered as a low tolerance immunosuppressive induction therapy for UC patients. Additional reports and analysis will be necessary to fully elucidate the anti-inflammatory efficacy of GMA re-treatment for UC patients suffering from relapse.

To avoid unnecessary use of CS, several biologics, such as anti- TNF-α antibodies, UST, VDZ, and TFB, are available as alternative options for induction of remission in UC patients and maintenance treatment.[8–13] However, the efficacy of biologics for inducing and maintaining remission has been shown to be not always sufficient in clinical practice.[44] An anti-drug antibody can sometimes develop in patients undergoing biologic therapy, which leads to loss of response caused by neutralization of drug efficacy as well as increased clearance of the drug.[45] In addition to the efficacy of biologics, adverse events are important issues for clinical use of these drugs. A recent systematic review and meta-analysis revealed that as compared to monotherapy with a TNF-α antagonist, combination therapies for IBD that include TNF-α antagonists are associated with a higher risk of serious infection, whereas monotherapy with an immunosuppressive agent is associated with a lower risk.[46] Lemaitre *et al.*[47] also demonstrated that use of anti-TNF monotherapy was associated with a small but significantly increased risk of lymphoma as compared with exposure to thiopurine, while the risk was higher when given in combination with thiopurine than when each of those treatments used alone. To evaluate the comparative safety of non-TNF-α targeted biologics and small molecules for treatment of UC, further studies will be required. In contrast, intensive GMA is a temporary therapy that has sufficient effects for inducing clinical and endoscopic remission, and its greatest advantage is that treatment can be safely performed without serious adverse events.[29,32,35,36]

This study has several limitations, including its retrospective nature. Furthermore, cases from only two hospitals were used for analysis. Additional investigations that use patients prospectively enrolled from a larger number of institutions and hospitals will be necessary to elucidate the prognosis of patients following induction of remission by GMA as well as the efficacy of retreatment in the same patients who experience relapse. Moreover, whether histological assessment is related to relapse rate after achieving remission by first GMA was not examined. Recent studies have demonstrated that histological healing is closely associated with reduced risk of relapse in patients with UC, [48,49] thus further investigations that consider histological assessment results will be necessary.

In conclusion, for the goal of MH in UC patients, intensive

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GMA prior to use of CS and biologics can be a suitable choice. Such cases generally have a favorable clinical prognosis, including a sufficient rate of clinical remission maintenance, as well as superior re-induction rate of clinical and endoscopic remission by GMA re-treatment even when disease relapse occurs.

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Abbreviations

CAI	clinical activity index
CS	corticosteroids
GMA	granulocyte/monocyte adsorptive apheresis
MES	Mayo endoscopic score
MH	mucosal healing
TFB	tofacitinib
TNF-α	tumor necrosis factor-α
UC	ulcerative colitis
UST	ustekinumab
VDZ	vedolizumab

Conflict of Interest

SI received scholarship donations from Takeda Pharmaceutical Co., Ltd. and Nippon Kayaku Co., Ltd., and lecture fees from Takeda Pharmaceutical Co., Ltd., and Abbvie GK. KS received a lecture fee from AstraZeneca plc.

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