The clinical efficacy and safety of granulocyte and monocyte adsorptive apheresis in patients with Crohn's disease: A multicenter retrospective cohort study

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Research Article

Abstract

Background: A remission induction therapy of granulocyte and monocyte adsorptive apheresis (GMA) with Adacolumn was given to patients with active Crohn's disease (CD). However, establishing an appropriate treatment strategy for GMA in patients with active CD remains unclear.

Methods: This multicenter retrospective cohort study encompassed patients with CD who underwent GMA in seven independent institutions in Japan from January 2010 to March 2023. All clinical data were obtained from medical records. This study aimed to evaluate the clinical efficacy, safety, and subsequent clinical progression after GMA in patients with CD.

Result: This study enrolled 173 patients with active inflammatory bowel disease who underwent GMA with Adacolumn, and among them, 16 patients with CD with mild to moderate disease activity were analyzed. Concomitant medication, including steroids, immunomodulators, and biologics, was used in 93.7% of all cases. The overall remission and response rates were 25.0% and 68.8%, respectively. The response rate between groups concerning the frequency and total GMA sessions revealed no significant difference. Six (37.5%) patients experienced adverse events (AEs). All AEs were related to the trouble in blood access and recovered soon without any sequelae. Regarding the factors associated with response to GMA, the responder group had a significantly longer disease duration (336 vs 44 months, $p = 0.036$) and exhibited a relatively lower rate of intestinal strictures and a median score of a simple endoscopic score for CD (SES-CD) (9.1 vs 60 %, $p = 0.063$ and 10 vs 21.5, $p = 0.091$, respectively). Further, all patients responding to GMA received biologics that were continuously used before and after GMA. Furthermore, 36.4% of patients remained on the same biologics 52 weeks after GMA. Notably, all patients who continued the same biologics had previously experienced a loss of response to anti-tumor necrosis factor-α agent.

Conclusion: Therefore, GMA may exhibit heightened effectiveness in patients with moderately active CD without severe endoscopic activity. Moreover, it represents a potential novel therapeutic option for refractory CD, particularly with insufficient response to biologics.

Introduction

Crohn's disease (CD) is a gastrointestinal tract idiopathic and chronic inflammatory disease. The introduction of early immunosuppression to prevent irreversible bowel damage and disability is central to the therapeutic strategy.[1] Anti-tumor necrosis factor α (anti-TNF-α) agent administration is a crucial component of the therapeutic regimen for patients with CD. However, approximately one-third of patients with CD experience a loss of response (LOR) and require dose escalation after anti-TNF-α therapy initiation.[2]

Granulocyte and monocyte adsorptive apheresis (GMA) with Adacolumn (JIMRO Co., Takasaki, Japan) has been used as a nonpharmacological treatment modality for patients with active inflammatory bowel disease (IBD) in Japan. The mechanism of GMA involves Adacolumn, which is filled with cellulose

acetate beads, interacting with fragment crystallizable gamma receptors expressed at the surface of activated leukocytes and selectively adsorbing granulocytes and monocytes from the systemic circulation.[3] GMA is mainly used for patients with ulcerative colitis (UC) in remission induction therapy, and numerous studies have reported its clinical efficacy and safety.

Recent studies have described the combined efficacy of GMA with biologics in patients with UC with refractory cases[4−6] and/or LOR to anti-TNF-α agent cases.[7−8] However, clinical data on GMA for patients with CD are significantly less, and its clinical position in therapeutic strategy remains unclear. Therefore, this study aimed to examine the efficacy, safety, and subsequent clinical course after GMA and to clarify the appropriate treatment strategy in patients with CD.

Material and methods

Study design and ethics

This multicenter retrospective cohort study included all patients with active IBD who underwent GMA with Adacolumn in seven independent institutions in Hokkaido, Japan, from January 2010 to March 2023. These institutions included Furano Hospital, Nakashibestsu Town General Hospital, Nayoro City General Hospital, Engaru Kosei General Hospital, Asahikawa Kosei General Hospital, Asahikawa City Hospital, and Asahikawa Medical University Hospital. The ethics committees of Asahikawa Medical University (approval no. 21004) and of each institution reviewed and approved the research methodology following the Helsinki Declaration (1964, and later versions).

Data collection

CD diagnosis for all patients was based on the criteria established by the Japanese Ministry of Health, Labor and Welfare. Patients with CD with stoma were excluded from this study because these patients cannot calculate the CD activity index (CDAI). All clinical data were obtained from medical records. Baseline characteristics, including age, gender, extent of CD according to the Montreal classification, disease course, disease duration, body weight, intestinal complication, including stricture, fistula, perianal lesion, and short bowel syndrome, clinical history, CDAI, simple endoscopic score for CD (SES-CD), white blood cell (WBC) count, hemoglobin level (g/dL), platelet count, serum total protein (TP) level (g/dL), serum albumin (ALB) level (g/dL), C-reactive protein (CRP) level (mg/dL), enteral nutrition, concomitant medications, including 5-aminosalicylic acid (5-ASA), corticosteroid/budesonide, immunomodulators, biologics, and duration of biologic administration during the entry into GMA were collected. Follow-up clinical data after GMA, including CDAI, WBC count, hemoglobin level (g/dL), platelet count, TP level (g/dL), ALB level (g/dL), and CRP level (mg/dL), were also collected to assess the clinical efficacy of GMA. These follow-up clinical data were determined within 7 days from the last GMA, or the day on which GMA was canceled. In addition, enteral nutrition, maintenance medications after GMA, including 5-ASA, corticosteroids, immunomodulators, and biologics and the duration of continued maintenance medication until 52 weeks were collected to evaluate the sustained efficacy after GMA.

GMA treatment strategy with Adacolumn

The Japan Ministry of Health approved GMA with Adacolumn (JIMRO Co., Takasaki, Japan) as a remission induction therapy for all patients with active IBD. The participating institutes contraindicated GMA in patients with a neutrophil count of < 1500/mm^3; hemoglobin of < 8 g/dL; a history of allergic reaction to anticoagulant; or a serious cardiac, pulmonary, hepatic, or renal disorder. The standard GMA treatment plan involved 10 sessions with Adacolumn twice a week for five consecutive weeks. The blood via venipuncture of an antecubital vein entered Adacolumn and then returned to the patient via the column outflow line. The GMA protocol consisted of filtering 1800 mL per session at a rate of 30 mL/min. All GMA data, including the total number of sessions, frequency, and AEs, were obtained from the medical records.

Endpoints and definitions

Clinical outcomes were evaluated within 7 days after GMA initiation and at 52 weeks thereafter. Evaluation items included the response rate (RR) following GMA, AEs, the change in laboratory test values before and after GMA, and the duration of sustained efficacy until 52 weeks. The clinical factors associated with the response to GMA and the change maintenance therapy up to 52 weeks were statistically investigated to elucidate these evaluation items. Patients missing certain clinical information at a certain point were still included in this study.

Clinical response was defined as a decrease of > 30% in CDAI score from the baseline after GMA, while clinical remission was defined as a decreased CDAI score of < 150 after GMA. Relapse was defined as a CDAI of ≥ 150 or a change in the maintenance medication following GMA. Primary non-response to biologics was defined as an inadequate response to biologics during the remission induction therapy, while LOR to biologics was defined as relapse despite the continuous biologic administration in the maintenance therapy.

Statistical analyses

Numerical data are presented as either median with minimum–maximum or interquartile ranges (IQR). The Mann–Whitney U-test or Fisher's test was used to compare the demographic characteristics of patients with and without responses. The Wilcoxon test was used to compare laboratory test values before and after GMA. Kaplan–Meier methods were used to estimate sustained clinical efficacy after GMA. The Mann–Whitney U-test or Fisher's test was used to analyze demographic parameters that affect the duration of continued maintenance medication after GMA. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of all patients

This retrospective cohort study enrolled 173 patients with active IBD who underwent GMA with Adacolumn. Among them, 156 patients with active UC and one with CD who underwent ileostomy were excluded, leaving a total of 16 patients for analysis (Fig. 1). Table 1 shows the baseline characteristics of these patients. The median age (min–max) was 45 (16–63) years, and 13 (81.3%) patients were male. Moreover, 2 (12.5%) patients had ileal type and 14 (87.5%) had ileocolonic type according to the Montreal classification. All 16 (100%) patients had CD relapse. The median disease duration (IQR) was 157 (58.3–370.1) months. The median body weight was 51.1 (48.8–55.6). Four (25.0%) patients had intestinal strictures, 1 (6.3%) had enterocutaneous fistula, 10 (62.5%) had perianal lesions, and 5 (31.3%) had short bowel syndrome. The median CDAI and SES-CD were 255 (235.5–327.9) and 10 (9–19), respectively. The median WBC count, hemoglobin value, platelet count, TP value, ALB value, and CRP value were 6615 (5132.5–7715), 10.1 (9.8–10.4) g/dL, 26.3 (19.4–34.3), 6.9 (6.3–7.1) g/dL, 2.8 (2.5–3.2) g/dL, and 0.38 (0.11–1.31) mg/dL, respectively. Enteral nutrition was performed in 11 (68.8%) patients. GMA was concomitantly conducted with 5-ASA in 8 (50.0%), corticosteroid/budesonide in 6 (37.5%), immunomodulators in 5 (31.3%), anti-TNF-α agent in 13 (81.3%), ustekinumab in 1 (6.3%), and vedolizumab in 1 (6.3%) patient. Among the 15 patients who received biologics, two with vedolizumab or ustekinumab had primary non-response to biologics, and 13 with anti-TNF-α agents were LOR to biologics. The median biologic administration duration was 58 (4.5–79).

Table 1
Baseline characteristics of all patients.

Variables		
Age, years	median (IQR)	45 (16–63)
Gender, male	N (%)	13 (81.3)
Extent of CD (Montreal classification)		
L1 ileal	N (%)	2 (12.5)
L3 ileocolonic	N (%)	14 (87.5)
Disease course		
Relapse/Remitting	N (%)	16 (100)
Duration of disease, month	median (IQR)	157 (58.3-370.1)
Body weight, kg	median (IQR)	51.1 (48.8–55.6)
Stricture	N (%)	4 (25.0)
Fistula	N (%)	1 (6.3)
Perianal lesion	N (%)	10 (62.5)
Short bowel syndrome	N (%)	5 (31.3)
Disease activity at entry		
CDAI	median (IQR)	255 (235.5-327.9)
SES-CD	median (IQR)	10 (9–19)
Laboratory data at entry		
WBC count	median (IQR)	6615 (5132.5–7715)
Hemoglobin, g/dL	median (IQR)	10.1 (9.8–10.4)
Platelet count	median (IQR)	26.3 (19.4–34.3)
TP, g/dL	median (IQR)	6.9 (6.3–7.1)
ALB, g/dL	median (IQR)	2.8 (2.5–3.2)
CRP, mg/dL	median (IQR)	0.38 (0.11–1.31)
Enteral nutrition	N (%)	11 (68.8)
Concomitant medication with GMA		
5-aminosalicylic acid	N (%)	8 (50.0)

Variables		
Corticosteroid/Budesonide	N (%)	6 (37.5)
Immunomodulators	N (%)	5 (31.3)
Anti-TNF-alpha agent	N (%)	13 (81.3)
Ustekinumab	N (%)	1 (6.3)
Vedolizumab	N (%)	1 (6.3)
Primary non-response to biologics	N (%)	2 (12.5)
Loss of response to biologics	N (%)	13 (81.3)
Duration of administration of biologics, month (N = 15)	median (IQR)	58 (4.5−79)

Overall clinical efficacy and safety of GMA

Figure 2 summarized all data about GMA, including the clinical efficacy, frequency, and total number of sessions. Clinical assessments were conducted on all 16 patients, of whom four achieved clinical remission while 11 responded to GMA. The overall remission rate (ReR) and RR were 25.0% and 68.8%, respectively (Fig. 2A). Concerning the GMA regimen, 6 (37.5%) patients received GMA once a week, while 10 (62.5%) received GMA twice a week. RR for once a week and twice a week were 83.3% and 60.0%, respectively (Fig. 2B). Seven (43.8%) patients underwent 5 sessions of GMA, and 9 (56.2%) patients underwent 10 sessions of GMA. The total number of GMA sessions depended on the disease activity of CD, patient tolerance, and GMA therapy response. RR for 5 and 10 GMA sessions were 66.7% and 77.8%, respectively (Fig. 2C). All 16 patients received filtering of 1,800 mL per session at a rate of 30 mL/min in each GMA session. RR was not significantly different between groups concerning the frequency and total session of GMA. However, ReR for twice a week and 10 sessions of GMA was higher than that for once a week and five sessions of GMA.

This study revealed AEs in 6 (37.5%) patients during and after GMA. Table 2 lists all AEs. Five patients had difficulty in securing blood vessels during GMA and one developed vascular pain (not vasculitis) after GMA. All AEs were related to the trouble in blood access, and physical AEs were not observed. These cases were all mild and recovered soon without any sequelae, but GMA was discontinued in two patients after the fifth GMA session due to the patient's refusal. Four patients completed all planned GMA sessions.

Table 2
All adverse events during and after GMA.

Variables		All cases	continued GMA	canceled GMA
All AEs	N (%)	6 (37.5)	4 (25)	2 (12.5)
Difficulty in securing blood vessels	N (%)	5 (31.3)	4 (25)	1 (6.3)
Vascular pain	N (%)	1 (6.3)	0 (0)	1 (6.3)

Identification of clinical factors associated with response to GMA

Patients were divided into the responder and non-responder groups based on their clinical activity assessed by the CDAI after GMA. Table 3 shows the clinical factors associated with response to GMA. The disease duration was significantly longer in the responder group (336 vs 44 months, $p = 0.036$). Moreover, the rate of intestinal strictures and the median of SES-CD were relatively lower in the responder group (9.1 vs 60%, $p = 0.063$ and 10 vs 21.5, $p = 0.091$, respectively). The remaining clinical factors did not exhibit any significant differences between the two groups.

Table 3
The clinical factors associated with response to GMA.

Variables		Responder (N = 11)	Non-responder (N = 5)	p value
Age, years	median (IQR)	52 (31.5–58.5)	22 (22–51)	0.126
Gender, male	N (%)	10 (90.9)	3 (60)	0.214
Extent of CD (Montreal classification)				
L1 ileal	N (%)	2 (18.2)	0 (0)	1.000
L3 ileocolonic	N (%)	9 (81.8)	5 (100)	-
Duration of disease, month	median (IQR)	336 (109–378)	44 (18–97)	**0.036**
Body weight, kg	median (IQR)	50.1 (48.7–53.3)	50.5 (47.9–51.7)	0.533
Stricture	N (%)	1 (9.1)	3 (60)	0.063
Fistula	N (%)	0 (0)	1 (20)	0.313
Perianal lesion	N (%)	7 (63.6)	3 (60)	1.000
Short bowel syndrome	N (%)	5 (45.5)	0 (0)	0.119
Disease activity at entry				
CDAI	median (IQR)	260 (241.1-345.1)	237 (213-288.7)	0.282
SES-CD	median (IQR)	10 (8.5–14.5)	21.5 (20.3–22.8)	0.091
Laboratory data at entry				
WBC count	median (IQR)	6830 (5125–7655)	6400 (5690–8910)	0.692
Hemoglobin, g/dL	median (IQR)	10.1 (9.6–10.3)	10.2 (10.1–11.4)	0.332
Platelet	median (IQR)	21.6 (19.1–31.7)	34.1 (24.5–39.1)	0.234
TP, g/dL	median (IQR)	6.8 (6.2–7.1)	7.2 (6.9–7.3)	0.257
ALB, g/dL	median (IQR)	2.9 (2.5–3.3)	2.7 (2.5–3.2)	0.775
CRP, mg/dL	median (IQR)	0.22 (0.1–1.2)	0.42 (0.33–1.28)	0.648

Variables		Responder (N = 11)	Non-responder (N = 5)	p value
Enteral nutrition	N (%)	9 (81.8)	2 (40)	0.245
Concomitant medication with GMA				
5-aminosalicylic acid	N (%)	4 (36.4)	4 (80)	0.282
Corticosteroid	N (%)	5 (45.5)	1 (20)	0.588
Immunomodulators	N (%)	2 (18.2)	3 (60)	0.245
Anti-TNF-alpha agent (loss of response)	N (%)	10 (90.9)	3 (60)	0.214
Ustekinumab (primary non-response)	N (%)	0 (0)	1 (20)	0.313
Vedolizumab (primary non-response)	N (%)	1 (9.1)	0 (0)	1.000
Duration of administration of biologics, month	median (IQR)	69 (6.5−79)	9 (2.5−56.8)	0.472

The Change in laboratory test values before and after GMA

The change in laboratory test values before and after GMA were compared in all patients, responders, and non-responders (Fig. 3). No significant difference was found in WBC count, hemoglobin level, platelet count, and TP level before and after GMA in all patients, responders, and non-responders. However, the ALB level after GMA was significantly higher than that before GMA in all patients (2.8 to 3.1, p = 0.039), but not in responders and non-responders. In addition, the CRP level was significantly higher after GMA than that before GMA only in non-responders (0.42 to 1.14, p = 0.043), but not in all patients and responders. Blood transfusions were performed in two patients, and no one received albumin products.

Sustained clinical efficacy after GMA

Eleven patients who exhibited a response to GMA were followed up for 52 weeks. Table 4 shows the post-GMA characteristics of these patients. Of the cohort, one patient (9.1%) had intestinal strictures, none had enterocutaneous fistula (0%), 7 (63.6%) had perianal lesions, and 5 (45.5%) had short bowel syndrome. The median CDAI was 165.7 (139.9−196.2). The median WBC count, hemoglobin value, platelet count, TP value, ALB value, and CRP value were 6530 (5850−8505), 10.4 (9.6−11.7) g/dL, 20.5 (17−33.6), 7 (6.9−7.3) g/dL, 3.1 (2.7−3.7) g/dL, and 0.41 (0.10−0.61) mg/dL, respectively. Enteral nutrition was employed in 9 (81.8%) patients. Following GMA, 5-ASA was prescribed for maintenance medication in 4 (36.3%) patients, corticosteroid/budesonide in 1 (9.1%), immunomodulators in 4 (36.3%), anti-TNF-α agent was administered in 10 (90.9%), and vedolizumab in 1 (9.1%). All patients who responded to GMA were administered biologics, and these patients continued the same biologics as before GMA. Of the

cohort, one patient discontinued immunomodulators during GMA, one patient initiated budesonide, and three patients received immunomodulators on biologics following GMA.

Table 4
The post-GMA characteristics of all patients.

Variables		
Stricture	N (%)	1 (9.1)
Fistula	N (%)	0 (0)
Perianal fistula	N (%)	7 (63.6)
Short bowel syndrome	N (%)	5 (45.5)
Disease activity at entry		
CDAI	median (IQR)	165.7 (139.9-196.2)
Laboratory data at entry		
WBC count	median (IQR)	6530 (5850−8505)
Hemoglobin g/dL	median (IQR)	10.4 (9.6−11.7)
Platelet count	median (IQR)	20.5 (17-33.6)
TP, g/dL	median (IQR)	7 (6.9−7.3)
ALB, g/dL	median (IQR)	3.1 (2.7−3.7)
CRP, mg/dL	median (IQR)	0.41 (0.10−0.61)
Enteral nutrition	N (%)	9 (81.8)
Maintenance medication after GMA		
5-aminosalicylic acid	N (%)	4 (36.3)
Corticosteroid/Budesonide	N (%)	1 (9.1)
Immunomodulators	N (%)	4 (36.3)
Anti-TNF-alpha agent (loss of response)	N (%)	10 (90.9)
Vedolizumab (primary non-response)	N (%)	1 (100)

The same biologics were continued in four of the 11 (36.4%) patients up to 52 weeks. The median time of continuous same biologics following GMA was 30 weeks (Fig. 4). Patients monitored for up to 52 weeks after GMA were divided into two groups based on their biologic treatment regimen, including those who continued with the same biologics and those who switched biologics. Table 5 outlines the clinical factors potentially associated with switching biologics after GMA. No significant differences were observed

between the groups based on these clinical factors. However, all four patients who continued the same biologics were LOR to anti-TNF-α agents.

Table 5
The clinical factors potentially associated with switching biologics after GMA.

Variables		Continued same biologics (N = 4)	Switched biologics (N = 7)	p-value
Stricture	N (%)	1 (25)	0 (0)	0.364
Perianal fistula	N (%)	3 (75)	4 (57.1)	1.000
Short bowel syndrome	N (%)	2 (50)	3 (42.9)	1.000
Disease activity at entry				
CDAI	median (IQR)	182.9 (147.2-215.1)	165.7 (132.7-173.2)	0.571
Laboratory data at entry				
WBC count	median (IQR)	6240 (5930−7450)	6820 (5200−8505)	0.850
Hemoglobin, g/dL	median (IQR)	9.6 (8.7−10.6)	11.2 (9.9−12.1)	0.185
Platelet count	median (IQR)	19.8 (18-23.4)	23.8 (16.7−35.8)	0.571
TP, g/dL	median (IQR)	6.9 (6.6−7.2)	7.2 (6.9−7.3)	0.635
ALB, g/dL	median (IQR)	3.1 (2.7−3.6)	3.1 (2.9−3.6)	0.925
CRP, mg/dL	median (IQR)	0.23 (0.1−0.43)	0.51 (0.24−0.96)	0.286
Enteral nutrition	N (%)	4 (100)	5 (71.4)	0.491
Concomitant medication with biologics				
5-aminosalicylic acid	N (%)	1 (25)	3 (42.9)	1.000
Corticosteroid/Budesonide	N (%)	0 (0)	1 (14.3)	1.000
Immunomodulators	N (%)	1 (25)	3 (42.9)	1.000
Biologics				
Anti-TNF-alpha agent (loss of response)	N (%)	4 (100)	6 (85.7)	1.000
Vedolizumab (primary non-response)	N (%)	0 (0)	1 (14.3)	1.000

Discussion

This multicenter retrospective cohort study evaluated the clinical efficacy and safety, including subsequent clinical progression, after GMA in patients with active CD. Our findings indicate that GMA is associated with a high RR and favorable safety profile, underscoring that serum ALB and CRP levels may serve as valuable biomarkers for predicting clinical efficacy. Notably, GMA demonstrated efficacy even in patients who have experienced a LOR to biologic, indicating that GMA enables long term continuous use of the same biologics to restore their efficacy.

This study enrolled 173 patients with active IBD who underwent GMA with Adacolumn from seven independent institutes, but only 17 (9.8%) patients had active CD. The analysis included 16 cases with a median CDAI (IQR) of 255 (235.5–327.9) and a median SES-CD of 10 (9–19). All these patients presented with active lesions in the small intestine, and most cases received concomitant medication, including steroids/budesonide, immunomodulators, and biologics. Furthermore, these patients exhibited ineffectiveness in response to biologics, including both primary non-response and LOR to biologics. The overall ReR and RR were 25.0% and 68.8%, respectively, even in such refractory cases. GMA combined with biologics has been reported to be effective in a small number of refractory CD cases.[9,10] These indicate that GMA is a considerable treatment even in combination with biologics for patients with moderately active disease although GMA utilization for active CD in real world clinical practice remains limited.

ReR for twice a week and 10 sessions of GMA was higher than that for once a week and five sessions of GMA although with no significant difference in RR between groups regarding the frequency and total session of GMA. All of the AEs observed in this study were attributed to issues related to blood access, and physical symptoms were not reported. These cases were all mild and recovered soon; however, GMA was discontinued in two cases. Fukuda et al. first reported significant improvements from baseline to week seven in the CDAI ($p = 0.0005$) in 21 patients with mild to moderate active CD who received GMA as an adjunct to ongoing medication for five sessions.[11] In contrast, Sands et al. conducted a randomized double-blind control study, involving 235 patients with moderate to severely active CD, and demonstrated no clinical efficacy for 10 sessions of GMA (RR, GMA vs. sham; 28.0% vs. 26.9%).[12] A validation study of the GMA protocol by Yoshimura et al. revealed that intensive GMA (10 sessions, twice a week) was not superior to weekly GMA (10 sessions, once a week), but the time to clinical remission was significantly shorter in the former without an increase in AEs.[13] Fukuchi et al. reported high rates of clinical remission (81.8%) at 52 weeks in 22 corticosteroid and biologics-naive patients with early diagnosed CD who received intensive GMA (10 sessions, twice a week) and immunomodulators without serious AEs.[14] Conversely, a small number of consecutive patients with refractory CD who received intensive GMA (10 sessions, twice a week) combined with biologics achieved clinical remission at week 10.[9,10] Additionally, GMA has been widely recognized as a safe and well-tolerated treatment for UC.[15,16] Thus, intensive GMA is considered an effective treatment in patients with CD with mild to moderately active disease although clinical efficacy of GMA for patients with CD was controversial. GMA has also demonstrated a safe profile in patients with CD; however, securing blood vessels is considered the most important issue to complete intensive GMA, especially in patients with dehydration, undernourishment, and anemia.

The analysis of factors associated with response to GMA revealed a significantly longer disease duration in the responder group (336 vs 44 months, p = 0.036). Additionally, the responder group exhibited a relatively lower rate of intestinal strictures and a median score of SES-CD (9.1 vs 60%, p = 0.063 and 10 vs 21.5, p = 0.091, respectively). Our previous study regarding patients with UC revealed that the clinical remission group had a significantly longer disease duration compared to the non-clinical remission group[17] while no previous reports have described clinical factors related to GMA response in patients with CD. Moreover, several large cohort studies have indicated that GMA does not respond well to severe endoscopic activity in patients with UC.[6,15,16] The results of the present study align with these previous studies conducted on patients with UC and may apply to select the patient suitable for GMA. However, objective biomarkers are necessary to predict GMA responsiveness because disease activity and endoscopic activity scores are subjective assessments. We have previously reported that fecal calprotectin is a useful biomarker for estimating the clinical efficacy of GMA in patients with UC.[17] The present study revealed a significantly higher ALB level after GMA than that before GMA in all patients who did not receive albumin products. Moreover, the CRP level after GMA was significantly higher than that before GMA only in non-responders. These items may serve as biomarkers for GMA clinical efficacy evaluation. Among these, CRP is known to be upregulated in IBD, especially CD, compared to UC,[18] and maybe a potential biomarker for predicting the effectiveness of GMA in patients with active CD.

Furthermore, we investigated the sustained clinical efficacy after GMA up to 52 weeks. All patients who responded to GMA were administrated biologics, and these patients continued the same biologics as before GMA. The same biologics were continued in four of the 11 (36.4%) patients up to 52 weeks. Notably, all patients who continued the same biologics had previously experienced LOR to anti-TNF-α agents. Yokoyama et al. revealed that GMA therapy decreased serum anti-infliximab antibody levels in patients with IBD who had LOR to infliximab.[8] These results suggest that GMA may contribute to restoring a therapeutic effect in a proportion of patients with CD who lost response to biologics, allowing for long term continuous use of the same biologics. Limited information is available on the subsequent clinical progression after GMA. Fukuchi et al. reported 81.8% in sustained clinical remission at 52 weeks with corticosteroid- and biologic-naive early diagnosed CD receiving intensive GMA and immunomodulators.[11] The usefulness of immunomodulators as maintenance therapy after GMA is controversial in patients with UC. Ishiguro et al. reported the effectiveness of GMA in corticosteroid-naive patients, and the sustained efficacy was greater in those who did not receive immunomodulators during GMA.[19] Our previous report revealed that immunomodulators after GMA contributed to sustaining clinical remission up to 52 weeks in patients with UC receiving biologics as maintenance therapy.[6] This study revealed that concomitant use of immunomodulators did not affect the long term efficacy of biologics. A substantial number of cases are needed to assess the additional effect of immunomodulators on biologics after GMA in patients with active CD.

Our findings, as well as previous studies, suggest that GMA may exhibit more effectiveness in cases with moderate active disease without severe endoscopic activity. It could potentially serve as a therapeutic option for refractory CD, particularly in individuals who have not adequately responded to biologics.

However, certain limitations associated with our study should be acknowledged. Specifically, this was a retrospective cohort study with a small number of patients whose clinical information was not perfectly collected on some points. Moreover, treatment plans are separately determined by each physician, and assessing the disease and endoscopic activity of the patients varied. Furthermore, concomitant medications were collected only during admission, thereby excluding the medications initiated during GMA. Furthermore, the dose and the frequency of each concomitant medication during and after GMA were not investigated. Further investigations employing prospective observational studies on a larger scale are warranted to establish a comprehensive therapeutic strategy.

Conclusion

To our best knowledge, this is the first study demonstrating the effectiveness of GMA, even in patients with refractory CD with LOR to biologic therapy. GMA may facilitate the continuous and long term use of the same biologics to restore their efficacy in selected cases. We propose that GMA may exhibit heightened effectiveness in patients with moderately active CD without significant endoscopic activity. Moreover, it represents a potential novel therapeutic option for refractory CD, particularly among those with insufficient response to biologic treatments.

Abbreviations

CD: Crohn's disease; anti-TNF-α: anti-tumor necrosis factor α; LOR: loss of response; GMA: granulocyte and monocyte adsorptive apheresis; IBD: inflammatory bowel disease; UC: ulcerative colitis; CDAI: Crohn's disease activity index; SES-CD: simple endoscopic score for Crohn's disease; WBC: white blood cell; TP: total protein; ALB: albumin; CRP: C-reactive protein; 5-ASA: 5-aminosalicylic acid; AEs: adverse events; RR: response rate; IQR: interquartile ranges; ReR: remission rate

Declarations

Ethics approval and consent to participate

The need for informed consent was waived by ethics committee of Asahikawa Medical University (approval no. 21004) because it is a study which uses only information such as medical records without using samples.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

NU developed study design. All authors treated inflammatory bowel disease patients in each hospital. SeS, MS, YS, YK, YM, KS, AS, KaT, ShS, KA, MM, and YI collected all clinical data and calculated partial Mayo score. TS, KeT, KaT, ShS, KA, SK, YI, KM, and HT performed endoscopy and calculated MES. NU and MF analyzed and interpreted all clinical data. NU, TO and MF drafted manuscript and all author revised it. All authors have approved the final version of this manuscript.
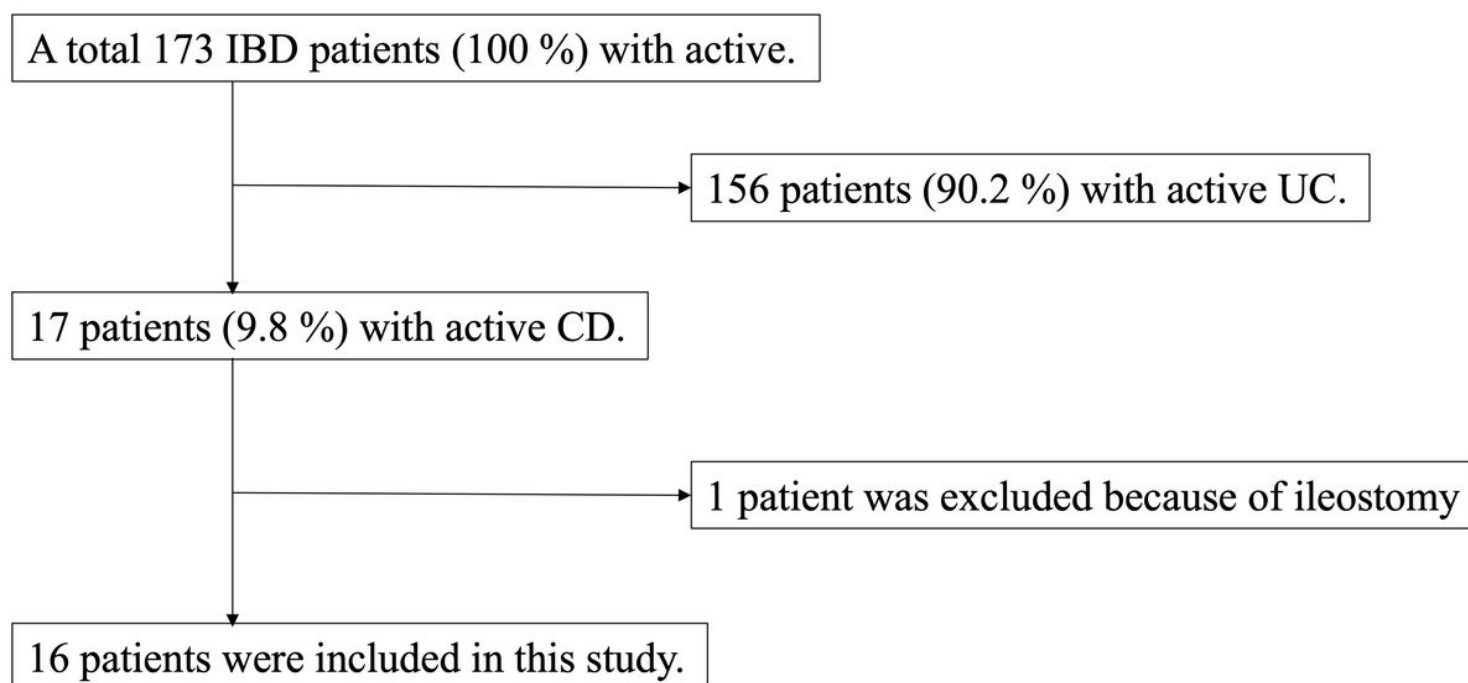
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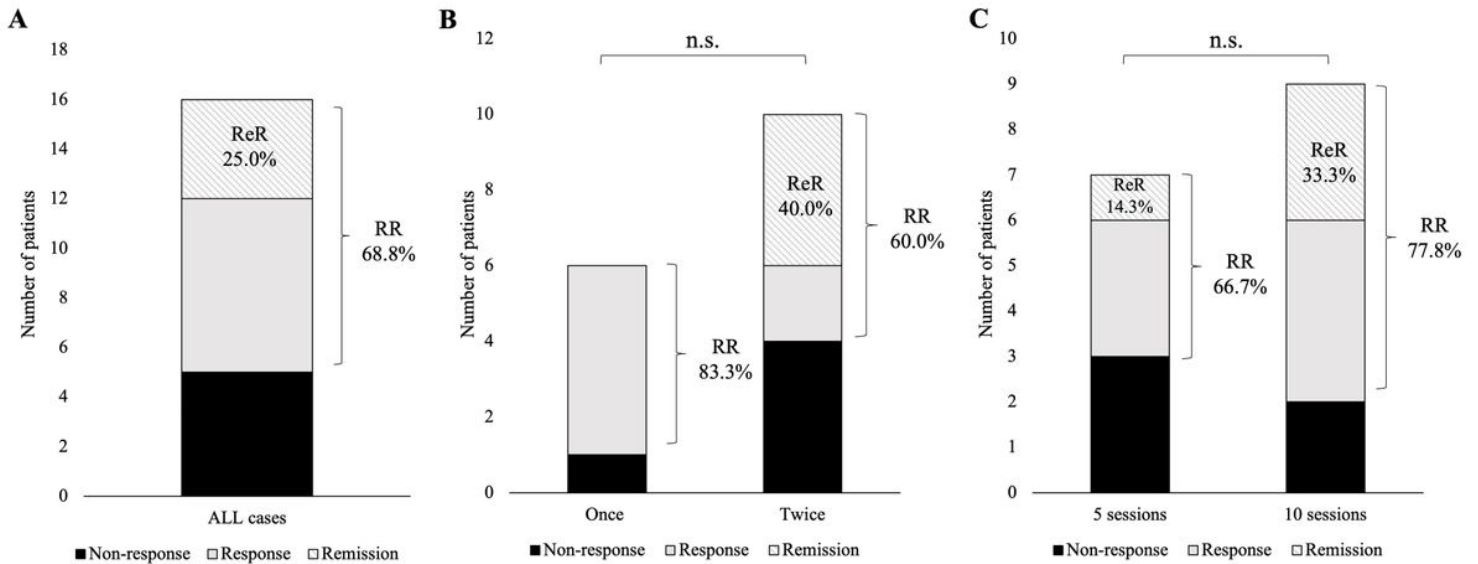
Figures

A total 173 IBD patients (100 %) with active.

→ 156 patients (90.2 %) with active UC.

17 patients (9.8 %) with active CD.

→ 1 patient was excluded because of ileostomy

16 patients were included in this study.
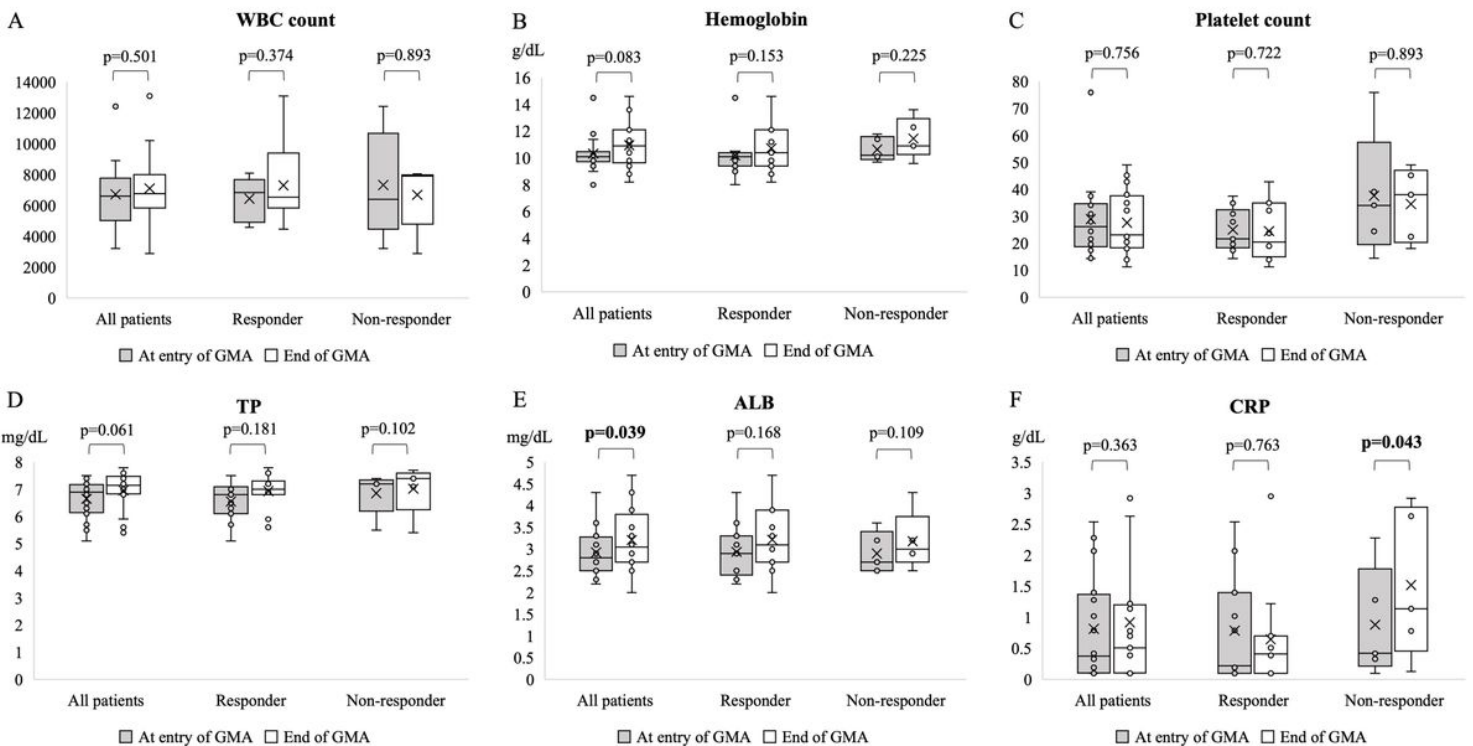
Figure 1

Patients enrolled in this study.

This retrospective cohort study enrolled 173 patients with active IBD who underwent GMA with Adacolumn. Among them, 156 with active UC and one with CD who underwent ileostomy were excluded, leaving a total of 16 patients for analysis.

Figure 2

Clinical efficacy and frequency and the total number of GMA sessions.

The overall remission rate (ReR) and response rate (RR) were 25.0% and 68.8%, respectively. RR for once a week and twice a week were 83.3% and 60.0%, and for 5 and 10 sessions of GMA were 66.7% and 77.8%, respectively. No significant difference was found in RR between groups concerning the frequency and total session of GMA.

Figure 3

Change in laboratory test values before and after GMA.

No significant difference was found in WBC count, hemoglobin level, platelet count, and TP level before and after GMA in all patients, responders, and non-responders. However, the ALB level after GMA was significantly higher than that before GMA in all patients, but not in responders and non-responders. Moreover, the CRP level after GMA was significantly higher than that before GMA only in non-responders, but not in all patients and responders.
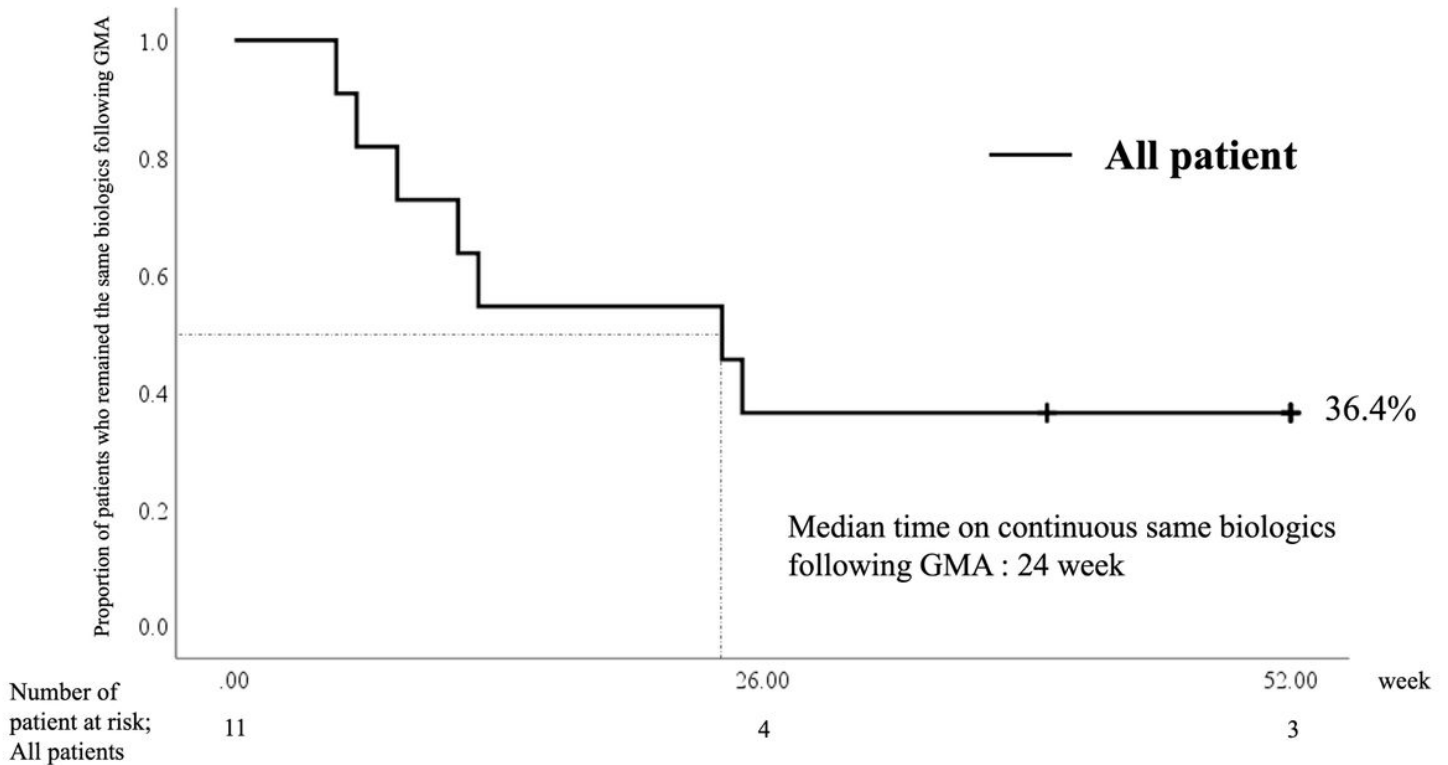
Figure 4

The proportion of patients who remained on the same biologics after GMA up to 52 weeks.

The same biologics were continued in three of the 11 patients up to 52 weeks. The proportion of patients who remained on the same biologics after GMA at 52 weeks was 36.4% and the median time of continuous same biologics following GMA was 30 weeks.