Original Article

Combined effects of granulocyte and monocyte adsorption apheresis and corticosteroids on ulcerative colitis

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Several new treatments for ulcerative colitis have been developed recently. The depletion of leukocytes by granulocyte and monocyte adsorption apheresis (GMA) was developed and adapted for patients with ulcerative colitis with rare adverse events. We investigated whether treatment with GMA and prednisolone (GMA + PSL) is more effective than PSL alone for patients with moderate to severe ulcerative colitis. Forty-seven patients with moderate to severe ulcerative colitis were retrospectively analyzed. Among the 47 patients, 27 received PSL, while 20 received GMA + PSL. The clinical activity of ulcerative colitis was evaluated using the Lichtiger clinical activity index (CAI) and serum levels of C-reactive protein. Mayo endoscopic score (MES) was used to examine endoscopic activity. The clinical remission rate was significantly higher in the GMA + PSL group than in the PSL group (65% vs 29.6%, $p = 0.0206$). The mucosal healing rate was also significantly higher in the GMA + PSL group than in the PSL group (60% vs 26%, $p = 0.0343$). The combination of GMA and steroids may be more effective than steroids alone for inducing clinical remission and mucosal healing in patients with moderate to severe ulcerative colitis.

Key Words: **ulcerative colitis, granulocyte and monocyte absorption apheresis, corticosteroids, mucosal healing, Lichtiger clinical activity index**

The number of patients getting diagnosed with ulcerative colitis (UC) is increasing in Western countries, and yet its etiology remains unknown.[1] However, treatment strategies have been established using the guidelines provided by public research groups and the Japanese Society of Gastroenterology.[2] The baseline treatments for UC are 5-amynosalysilic acid (5-ASA), corticosteroids (CSs), and immunosuppressants (IM). In addition, several biologics and low-molecular-weight compounds have been developed and administered to patients with UC in clinical practice.[2] However, periodic administration of these medications sometimes induces serious adverse events, including infection.[3] Among the treatments described in the guidelines, granulocyte and monocyte apheresis (GMA) with Adacolumn® (JIMRO, Gunma, Japan) was developed and adapted for patients with UC as an inflammatory cytokine-producing immune cell depletion therapy, and adverse events are rare with this treatment.[4,5] GMA reduces leukocytes, which are a source of inflammatory cytokines.[6]

GMA has been reported to be effective in several clinical trials. Among the large-scale clinical trials, Yokoyama *et al.*[7] reported that the overall clinical remission rate was 68.9% and that the mucosal healing rate was 62.5%. In terms of long-term prognosis, GMA is effective in maintaining remission.[8] According to the inflammatory bowel disease (IBD) treatment guidelines in Japan, GMA is officially approved by Japanese health insurance for patients with moderate to severe UC.

Moreover, GMA has been shown to have a dose-sparing effect on steroids in steroid-dependent UC.[9] Recently, it was reported that GMA is effective in UC, both as a single therapy and combination therapy with prednisolone (PSL).[10] In addition, GMA has been reported to be effective as an adjunctive treatment with primary treatment regimens in the induction and maintenance of remission in UC, especially when compared to conventional therapy alone.

However, whether GMA combined with PSL is more effective than PSL alone in moderate to severe UC has not been investigated. To monitor the effects of the treatments, a treat-to-target strategy has been adopted for UC.[11] Clinical remission and mucosal healing are the key parameters for this strategy.

Therefore, in this study, we retrospectively examined whether GMA combined with PSL induced clinical remission and mucosal healing when compared to PSL alone in steroid-naïve patients with moderate to severe UC.

Materials and Methods

Study design and objectives. The study protocol complied with the tenets of the revised Declaration of Helsinki (1989) and was approved by the ethics committee of the Institutional Review Board of Saitama Medical University (approval number 19062. 01). The requisite for an informed consent was waived due to the retrospective nature of this study. The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Forty-seven patients with moderate to severe UC treated with either GMA combined with CSs or with CSs alone in our hospital between June 2017 and September 2020 were analyzed. The physicians in charge of the enrolled patients decided on the treatment regimen: GMA + PSL or PSL alone. Systemic or oral PSL was administered to all 47 patients; of which, 27 received PSL alone, while 20 received GMA + PSL. During the treatment, the PSL dosage was reduced by 10 mg every 1–2 weeks in patients receiving PSL >30 mg and by 5 mg in patients receiving PSL <30 mg, based on its effectiveness. In addition, the total dosage of corticosteroids was calculated for both groups. Other

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treatments, including probiotics, 5-ASA, and biologics, were continued during this study. Adverse events were observed during the entire course of treatment.

GMA procedures. Twenty patients from the GMA + PLS group received GMA therapy with Adacolumn® twice a week (intensive GMA), as described previously.[12] Conventional medications including 5-ASA and an immunomodulator [azathioprine (AZA)] were continued during GMA therapy.

Depending on its effectiveness, either five or ten rounds of GMA therapy were administered. When the first five rounds of GMA were deemed effective but not enough for remission, patients underwent another five rounds upon admission. Conversely, only five rounds of GMA were performed if they were effective enough for patients to be discharged or if patients were shifted to another treatment due to refractory events. In summary, eight patients underwent five rounds, while 12 patients underwent 10 rounds of treatment.

Evaluation of efficacy. During GMA treatment sessions, the patients' vital signs were monitored. Routine blood samples were taken before and after GMA treatment and during the observation period that lasted 3–6 months. UC activity was evaluated using the Lichtiger CAI with C-reactive protein (CRP) as a biomarker.[13] MES was used to determine endoscopic severity.[14] The patients were assessed before and after the administration of their 5–10 GMA rounds. A CAI of ≤4 after treatment was defined as *clinical remission*, and *mucosal healing* was defined as MES of 0 or 1 after treatment.

Statistics. Numerical data are presented as the mean ± SD. Baseline characteristics were compared using either the Wilcoxon test as a non-parametric test, Student's *t* test, or Fisher's exact test. All statistical analyses were performed using the JMP statistical package (ver. 2020, SAS Institute, Vary, NC). *P* value <0.05 is defined as statistically significant. The statistical methods of this study were reviewed by Takeru Kusano from the Saitama Medical University, Saitama, Japan.

Results

Baseline characteristics of patients with UC. The baseline characteristics of the patients are shown in Table 1. The patients in the GMA + PSL group were significantly older than those in the PSL group (45.7 ± 17.2 years vs 34.4 ± 17.1 years, $p = 0.016$). There were no significant differences in sex ratio, disease duration, and disease extent between the two groups. The total dosage of corticosteroids was 1,845 ± 683 mg (mean ± SD) in the PSL + GMA group and 1,728 ± 625 mg in the PSL group. There was no significant difference between the total dosages of the two groups ($p = 0.627$). The MES before GMA administration was significantly higher in the GMA + PSL group than in the PSL group (2.75 ± 0.55 vs 2.33 ± 0.62, $p = 0.012$). There were no significant differences in the Lichtiger CAI, CRP levels, or treatment with 5-ASA, PSL, AZA, or biologics before GMA administration in either group.

No serious adverse events were observed in the 20 patients during the GMA treatment sessions. The evaluation time for the efficacy of GMA for CAI and CRP was 0–2 weeks after the last GMA session. The evaluation time for the efficacy of GMA by endoscopy (MES) was 1–10 weeks after the last GMA session. The large variation in evaluation time was due to the retrospective nature of the study, especially in the timing of endoscopy for effective cases. However, there were no significant differences in the evaluation times between the two groups (data not shown).

Efficacy of GMA + PSL on clinical remission. The clinical efficacy of GMA + PSL and exclusive PSL on CAI before and after GMA treatment is shown in Fig. 1. There was no significant difference in CAI before GMA administration between the two groups (10.9 ± 3.4 vs 11.1 ± 3.6, $p = 0.70$). The individual changes are shown in Fig. 1A. The average CAI after treatment was 5.9 ± 4.2 in the GMA + PSL group and 6.7 ± 4.2 in the PSL group. The average reduction of Lichtiger CAI was −5.7 ± 4.0 in the GMA + PSL group and −4.4 ± 4.0 in the PSL group ($p = 0.153$, Fig. 1B). In addition, the number of GMA sessions varied across patients in the GMA + PSL group because of the retrospective nature of this study. More specifically, 12 of 20 patients were treated with two sessions of GMA; treatment effectiveness was observed in seven patients (58%). In contrast, eight patients were treated using one session of GMA, which was effective in six patients (75%). The treatment effectiveness was evaluated using CAI improvement. There was no significant difference between the effectiveness of having one or two sessions ($p = 0.363$). However, the clinical remission rate in the GMA + PSL group was significantly higher than that in the PSL group (65% vs 29.6%, $p = 0.0206$, Fig. 1C).

Efficacy of GMA + PSL on CRP. The clinical efficacy of GMA + PSL and PSL alone on CRP before and after GMA treatment is shown in Fig. 2. There was no significant difference in CRP before GMA administration between the two groups (4.6 ± 4.2 vs 4.5 ± 7.2, $p = 0.48$). The individual changes are shown in

Table 1. Baseline characteristics of 47 patients with ulcerative colitis

	PSL + GMA (*n* = 20)	PSL (*n* = 27)	*p* value
Age (years, mean ± SD)	45.7 ± 17.2	34.4 ± 17.1	0.016
Sex (male:female)	13:07	14:13	0.39
Disease duration (months, mean ± SD)	28.9 ± 13.0	33.0 ± 9.4	0.6
Disease extent (total:left-sided)	19:01	22:05	0.22
Lichtiger CAI-pretreatment	10.6 ± 3.1	11.1 ± 3.6	0.7
CRP-pretreatment (md/dl)	4.57 ± 4.18	4.50 ± 7.18	0.48
MES-pretreatment	2.75	2.33	0.0096
Treatment			
5-ASA	18/20	18/27	0.75
PSL (0.5 mg/kg:1 mg/kg)	8:12	17:10	0.072
Total dosage of PSL (mg)	1,845 ± 683	1,728 ± 625	0.272
Azathioprine	2/20	2/27	0.75
Biologics	0	1 (adalimumab)	0.466

Data are presented as ratios or means ± SD, as appropriate. *P*<0.05 was considered statistically significant. 5-ASA, 5-aminosalicylic acid; CAI, clinical activity index; CRP, C-reactive protein; GMA, granulocyte and monocyte adsorption apheresis; MES, Mayo endoscopic score, PSL, prednisolone.

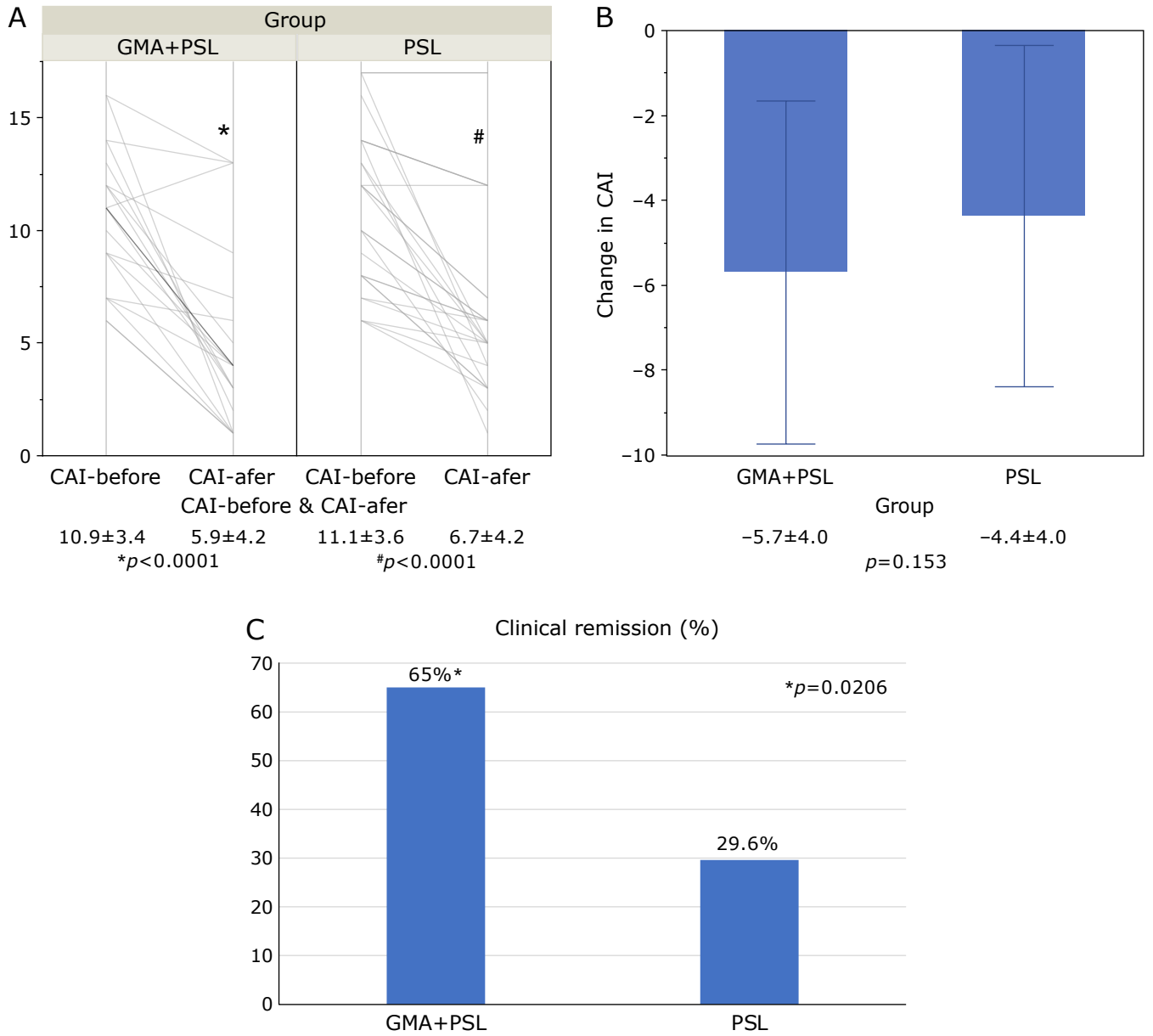

Fig. 1. The clinical efficacy of GMA + PSL and PSL on Lichtiger CAI. (A) The efficacy of GMA + PSL and PSL on individual changes in Lichtiger CAI evaluated before and after each GMA treatment. (B) The efficacy of GMA + PSL and PSL on the reduction in Lichtiger CAI evaluated before and after each GMA treatment. Data are presented as the reduction of CAI. (C) The remission rate of GMA + PSL and PSL. Data are presented as the ratio of CAI of ≤4 per number of patients in each group (%). GMA, granulocyte and monocyte adsorption apheresis; PSL, prednisolone; MES, Mayo endoscopic score; CAI, clinical activity index.

Fig. 2A. The average CRP after treatment was 0.5 ± 0.7 in the GMA + PSL group and 1.2 ± 3.9 in the PSL group. The average reduction of CRP was −4.1 ± 4.0 in the GMA + PSL group and −3.3 ± 4.7 in the PSL group, with no significant difference between them (p = 0.2615, Fig. 2B).

Efficacy of GMA + PSL on MES. The clinical efficacy of GMA + PSL and PSL alone on the changes in MES before and after GMA treatment is shown in Fig. 3. MES before GMA administration in the GMA + PSL group was significantly higher than that in the PSL group (2.75 ± 0.55 vs 2.33 ± 0.62, p = 0.012). The individual changes are shown in Fig. 3A. The average MES after treatment was 1.5 ± 1.3 in the GMA + PSL group and 2.06 ± 0.76 in the PSL group. There was a significant difference in the reduction of MES between the two groups (−1.25 ± 1.21 in the GMA + PSL group vs −0.30 ± 0.72 in the PSL group, p = 0.0056, Fig. 3B). In addition, the mucosal healing rate in the GMA + PSL group was significantly higher than that in the PSL group (60% vs 26%, p = 0.0343, Fig. 1C). The rate of mucosal healing with GMA + PSL and PSL in patients with MES 2 and 3 before treatment also showed a similar trend (57.9% vs 24%, p = 0.0311).

Discussion

Patients with UC need certain medications, such as oral and/or topical 5-ASA, thiopurines, and oral steroids, for the induction and maintenance of remission in active UC.[15,16] In our study, all 47 patients had active disease despite receiving baseline medica-

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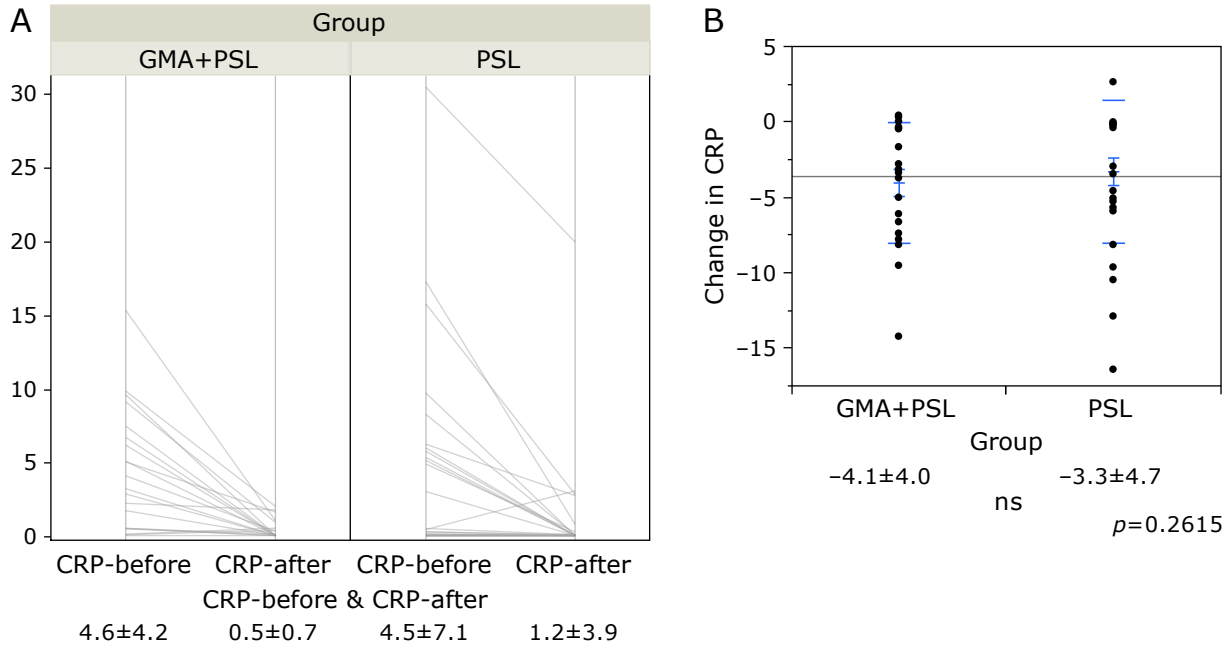

Fig. 2. The clinical efficacy of GMA + PSL and PSL on CRP. (A) The efficacy of GMA + PSL and PSL on individual changes in CRP evaluated before and after each GMA treatment. (B) The efficacy of GMA + PSL and PSL on reduction of CRP evaluated before and after each GMA treatment. Data are presented as the reduction of CAI. GMA, granulocyte and monocyte adsorption apheresis; PSL, prednisolone; MES, Mayo endoscopic score; CRP, C-reactive protein; CAI, clinical activity index.

tions (5-ASA and IM). In general, approximately half of the patients with moderate to severe UC require systemic PSL, biologics including anti-Tumor Necrosis Factor alpha (TNF-α) antibody, vedolizumab, and ustekinumab, or low molecular agents for years.[17] These medications may lead to drug dependency and/or loss of response (LOR). The concomitant use of immunomodulators, such as thiopurines, may reduce drug dependency and LOR.[18] However, patients with mutant Nudix hydrolase 15 (NUDT15) may experience adverse events, such as myelosuppression and hair loss.[19,20]

Nonpharmacological treatment, such as GMA, may be suitable for minimizing the adverse events of drugs, especially corticosteroids. Suzuki *et al.*[12] reported that GMA had an efficacy of 85% without severe adverse events in steroid-naïve patients with UC. In fact, the patients in the PSL + GMA group were older than those in the PSL group. There is no apparent reason for this age difference; however, it must be noted that GMA is typically chosen as an additional treatment for older patients because of its low rate of adverse events.

Fukunaga *et al.*[21] reported the efficacy of GMA in preventing relapse in corticosteroid-refractory active UC patients. Although studies on the efficacy of GMA and steroid reduction effects have been published, the effect of GMA combined with steroids in steroid-naïve UC patients has never been investigated.

The outcome of our study demonstrated significant efficacy of GMA + PSL treatment in the induction of clinical remission of UC and mucosal healing compared with PSL alone. Specifically, GMA adds to the therapeutic effects of steroids in patients with moderate to severe UC without an increase in adverse events, showing that GMA + PSL is a more effective treatment regimen than PSL alone.

In this study, GMA + PSL tended to be effective in older patients and patients with severe endoscopic conditions (MES: 2.75 ± 0.55 for GMA + PSL vs 2.33 ± 0.62 for PSL alone). Taken together, although there was a recruitment bias, GMA + PSL may be a more effective treatment; therefore, it is suitable even for elderly patients with other underlying diseases and those with severe UC.

Significant clinical remission was achieved in 65% of cases in the GMA + PSL group and in 29.6% of cases in the PSL group, which is comparable to a previous report that reported 85% and 67% remission rates, respectively.[12] The difference in the remission rates between our study and previous reports may be due to a difference in the average severity of the recruited patients and/or concomitant treatments.

CRP was measured as a representative biomarker in our study, and there was no significant difference in the change in CRP levels before and after GMA treatment between the two groups. Although the magnitude of mucosal inflammation in the GMA + PSL group was more severe than that in the PSL group, there was no significant difference in the CRP level before treatment. These data are comparable with previous reports showing that CRP does not reflect disease activity in UC.[22,23]

In contrast to the equivalence of CAI and CRP before GMA administration, MES in the GMA + PSL group was more severe than that in the PSL group. Despite the severity, significant efficacy was observed in the improvements of MES with GMA + PSL; therefore, this combination therapy is more effective in inducing mucosal healing. In active UC, circulating lymphocytes adhere to the vascular wall *via* adhesion molecules, migrate into the intestinal interstitium, and produce inflammatory cytokines. These cytokines, including TNF-α, play pivotal roles in mucosal damage.[24,25] Corticosteroids have powerful anti-inflammatory effects, leading to the detachment of lymphocytes from the vascular endothelium and prevention of inflammatory lymphocytes from migrating into interstitial spaces in the intestinal mucosa. In contrast, GMA removes these lymphocytes from systemic circulation. The mechanisms of each treatment may be attributed to the synergistic effects of GMA and steroids; therefore, GMA + PSL is a more effective treatment regimen (i.e., GMA has an add-on effect on steroids).

Since GMA has a a high response rate and lower rate of adverse events when compared to conventional drugs and biologics, it is considered to be a suitable treatment option for

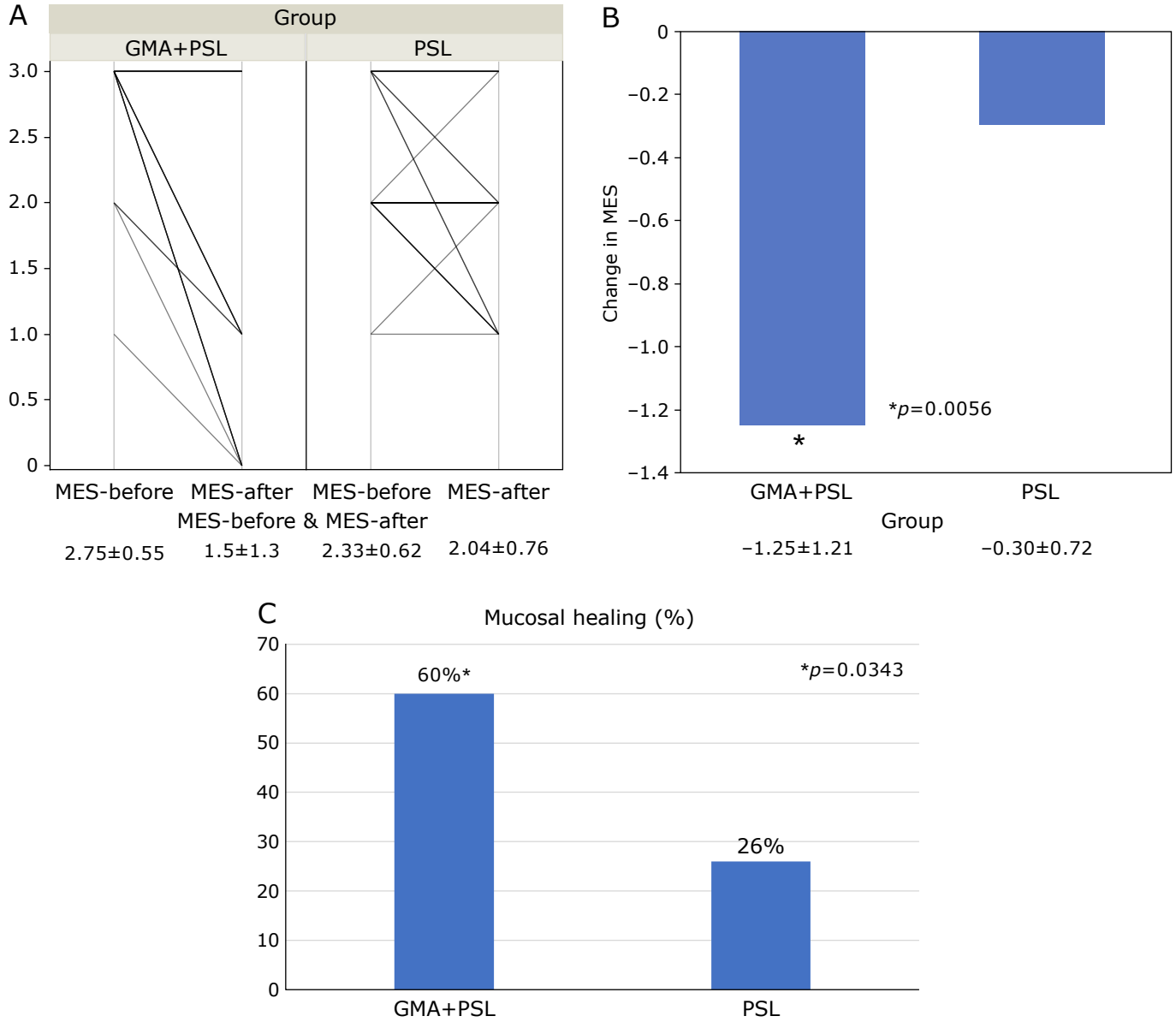

Fig. 3. The clinical efficacy of GMA + PSL and PSL on MES. (A) The efficacy of GMA + PSL and PSL on changes in MES evaluated before and after each GMA treatment. (B) The efficacy of GMA + PSL and PSL on reduction of MES evaluated before and after each GMA treatment. Data are presented as the reduction of MES. (C) The mucosal healing rate of GMA + PSL and PSL. Data are presented as the ratio of MES 0 and 1 per number of patients in each group (%). GMA, granulocyte and monocyte adsorption apheresis; PSL, prednisolone; MES, Mayo endoscopic score.

patients in the early stages of active UC.[4,6] In addition, our data demonstrated a higher rate of mucosal healing in patients with MES 2 and 3. Therefore, GMA + PSL may be a suitable treatment option for patients with more severe UC, especially for those with higher MES.

In addition to the short-term efficacy of GMA + PSL in the induction of clinical remission and mucosal healing, long-term prognosis by GMA alone has been reported to be effective in maintenance therapy.[8] Combining this information with our study's findings, the use of GMA + PSL as a strong induction therapy followed by periodical GMA as a maintenance therapy may be an ideal combination that has a low risk of adverse events.

The limitations of our study were the retrospective nature of the analysis, single-center involvement, and a small number of patients. In addition, since our results only show the efficacy of GMA combined with PSL compared to PSL alone, the threshold of disease severity for the selection of GMA + PSL as an initial strategy may be beneficial in the clinical setting. However, the patients' backgrounds could not be matched, and the optimal severity in clinical activity and/or endoscopic severity was not accurately calculated for the selection of GMA + PSL before GMA administration, partially because of the retrospective nature of this study. In addition, it is important to know the effect of GMA treatment alone in UC patients; however, no patients were treated using GMA alone for this study conducted in our facility. Moreover, recruitment bias and the influence of other underlying treatments cannot be excluded. Therefore, multicenter randomized controlled trials are necessary to further confirm and validate our findings.

Nevertheless, our data indicate that GMA + PSL is a powerful treatment with a low risk of adverse events; therefore, this

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combination may be selected as an initial treatment for patients with moderate to severe UC, especially in steroid-naïve and/or elderly patients.

In conclusion, the combination of GMA and steroids may be more effective than steroids alone for the induction of clinical remission and mucosal healing in patients with moderate to severe UC.

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Abbreviations

5-ASA	5-aminosalicylic acid
CAI	clinical activity index
CRP	C-reactive protein
CSs	corticosteroids
GMA	granulocyte and monocyte adsorption apheresis
IBD	inflammatory bowel disease
IM	immunosuppressants
MES	Mayo endoscopic score
NUDT15	Nudix hydrolase 15
PSL	prednisolone
TNF-α	tumor necrosis factor alpha
UC	ulcerative colitis

Conflict of Interest

No potential conflicts of interest were disclosed.

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