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Granulocyte and Monocyte Adsorption Apheresis Therapy for Ulcerative Colitis Patients：A Useful Tool for Surgical Indication Assessments

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Abstract：No optimal treatment regimen for ulcerative colitis (UC) has yet been established, and approximately one third of all such patients undergo operative treatments. Recently, granulocyte and monocyte adsorption apheresis (GCAP) has been shown to be a safe and effective treatment for active UC. Our objective was to investigate whether the outcome of GCAP therapy can help to determine the surgical indications for patients with UC. GCAP was performed on 18 patients with active UC, of whom 5 had relapsing–remitting UC and 13 had chronic continuous UC. The patients received up to 10 apheresis sessions over a 12–week period. All patients with UC received 5 apheresis sessions during a 5–week period. Sixteen of 18 patients showed an improvement in symptoms (abdominal pain, rectal bleeding, and diarrhea) after GCAP, thereby avoiding the re-administration of steroids. The mean dose of prednisolone before GCAP was 32.7 mg/day per patient, which decreased to 17.2 mg/day after 5 sessions of GCAP. Of the 18 patients treated with GCAP, 7 obtained remission, 6 showed a clinical response, 4 remained unchanged, while one patient demonstrated an aggravation of the disease. Two patients who hardly showed any improvement in the symptoms or UCDAI score even after additional GCAP therapy underwent a colectomy. GCAP therapy was well tolerated and no serious side-effects were observed. The findings of this study suggest that GCAP therapy may therefore be a useful alternative therapy for patients with UC and that the outcome of GCAP therapy may also be useful for determining the indications for surgery.

Key words：**Granulocyte and monocyte adsorption apheresis, Surgical indication, UCDAI, Ulcerative colitis**

Introduction

Ulcerative colitis (UC) is a nonspecific inflammatory bowel disease involving the mucosa of the colon and rectum. The cause of UC has not yet been clearly elucidated, but the current hypothesis is that external agents such as microbial, viral, and dietary factors, host immune responses, and genetic immunologic influences interact in the pathogenesis of such inflammatory bowel disease.[1)] It is possible that UC and Crohn's disease are different manifestations of a single disease process.[1)] Once the immunologic priming of the gut is established, perhaps during the early period of microbial colonization, any insult that increases the mucosal permeability to these antigens can initiate an inflammatory reaction in the bowel wall. The types of antigens and many other factors determine the nature of such inflammatory processes

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(e.g., Crohn's disease or ulcerative colitis).[2] On the other hand, some lines of evidence suggest that the clinical relapse of UC is mediated by an increase in mucosal permeability, thus resulting in an uncontrolled influx of granulocytes and monocytes/macrophages to the mucosa in response to the mucosal exposure of luminal antigens.[3)4)]

The initial therapy for UC in patients with mild to moderate symptoms has been a combination of oral mesalazine 5–aminosalicylic acid (5–ASA) /sulfasalazine and topical 5–ASA or corticosteroid enema. Mild or insidious UC limited to the rectum and sigmoid can usually be managed on an outpatient basis, while severe or fulminating UC requires hospitalization. Corticosteroids are given intravenously initially as hydrocortisone or predonisolone, which may lead to remission in up to 60% of all patients.[5)–7)] For many years, patients who failed to respond to intensive steroid therapy have formerly tended to undergo a colectomy.[7)] Cyclosporine A (CsA) is an effective treatment for severe colitis refractory to steroid therapy. CsA therapy has been used to induce remission in corticosteroid–refractory patients in order to avoid a colectomy.[8)–11)] However, these conventional therapies tend to be ineffective in some patients. Recently, granulocyte and monocyte adsorption apheresis (GCAP) has been introduced for the therapy of active UC in Japan.[12)] Shimoyama et al.[12)] reported that 58.5% of patients with active UC demonstrated either a remission or a clinical improvement following a course of GCAP therapy. They concluded that GCAP therapy is a useful adjunct to conventional therapies for patients with active severe UC who are refractory to conventional drugs.[12)] On the other hand, surgical therapy is recommended for UC patients who failed to respond to several conservative treatments. Some UC patients required an operation after GCAP therapy in order to ensure their survival.[13)–15)]

In the present study, we investigated whether the outcome of GCAP therapy can be a useful surgical indication for patients with UC.

Patients and Methods

This study was approved by the institutional review board of the Faculty of Medicine, Fukuoka University. All patients agreed to receive GCAP therapy and signed the informed consent forms after they were informed about the purpose and nature of the procedures involved. They were selected for GCAP therapy based on the fact that they had been treated by conventional medication alone.

Patients and samples

From 2001 to 2003, 18 patients with moderate to severe UC were treated with GCAP in our institute. The diagnosis of UC was based on established endoscopic and histological criteria.[16)] The demographic features of the patients and the history of drug therapy up to the time of colonoscopy are summarized in Table 1. The diagnosis of UC was made according to the accepted criteria.[16)17)]

Table 1. Demographic features of the patients with UC.

No. of patients	18
Sex (male ; female)	10 ; 8
Age (yr) /mean	13–66 / 40.6
Disease duration (yr) /mean	1–9.4 / 4.5
Disease extent	
Total colitis	8
Left–sided colitis	10
BMI /mean	12–25.8 / 20.1
Treatment	
(a) SASP+5–ASA only	1
(b) SASP/5–ASA+PSL	10
(c) (b)+Immunosuppressive agents	7

BMI : body mass index, SASP : salicylazosulfapyridine,
5–ASA : mesalazine, PSL : predonisolone

At the time of diagnosis, we excluded any patients with infectious colitis, radiation colitis, ischemic colitis, Crohn's disease, and intestinal Bechet's disease. Intestinal mucosal biopsy samples were obtained from the inflamed areas in 18 patients with steroid-refractory and -dependent UC. Medical treatment was not altered during the 2 weeks prior to the start of GCAP treatment. Likewise, there was no change in the dosage of mesalazine or immunosuppressants during the treatment. The corticosteroid dosage was allowed to be tapered with an improvement of symptoms, and the dosage of corticosteroids was decreased by 5 to 10 mg every week after the second GCAP session. Azathioprine therapy was administerd to 7 patients from 7 to 20 months before the start of GCAP. Any antidiarrheal drugs that patients had been receiving prior to the initiation of this study were continuously given, but no new therapy was provided. No patient was shown to be infected with colonic cytomegalovirus before GCAP therapy.

GCAP treatment

GCAP using the G-1 column (G-1 Adacolumn Japan Immunoresearch Laboratories, Takasaki, Japan) was performed as previously described.[12] The G-1 column is composed of spherical and adsorbent cellulose diacetate beads, measuring 2 mm in diameter with a slightly roughened surface. Two hundred twenty-two grams of beads are packed in a polycarbonate/polypropylene column. The patient's blood is usually drained from a cutaneous vein in one arm, passed though the G-1 column from the bottom upwards, and returned to another vein in the contralateral arm. These beads selectively adsorb granulocytes and monocytes/macrophages from the blood in the column. The rate of perfusion is 30 ml/min, and the duration of treatment is 60 min per session. All patients received 5 GCAP sessions over 5 consecutive weeks, with GCAP therapy being performed once per week, except for one steroid-refractory patient with severe symptoms who received GCAP sessions twice in the first week and thereafter once a week for the following 4 weeks.

Measurement of the clinical disease activity

A 12-point UC disease activity index (UCDAI) that measured the frequency of bowel movements, blood in stool, endoscopic severity, and the overall well-being was used as the primary endpoint for determining patient improvement.[18] The frequency of bowel movement and the amount of rectal bleeding were determined based on a symptom diary maintained by each patient. The UCDAI score was calculated for a 3-day baseline period before GCAP treatment, and at the endpoint evaluation of GCAP therapy. The response to the treatment was defined as a decrease in the UCDAI score ≥ 3 points.

Statistical analysis

The results are expressed as the mean$\pm$SD or frequencies. A data analysis was performed using Wilcoxon signed ranks test at a statistical significance level of 5%.

Results

Changes in the patient's clinical symptoms by GCAP therapy

A total of 18 patients were included in the study (Table 1). Seven of 18 patients had previously been treated with immunomodulators such as azathioprine, but not with infliximab. All patients had abdominal pain and mucous and bloody stool, while 16 patients had diarrhea before GCAP treatment. Abdominal pain disappeared in 17 of 18 patients (94.4%), and the clinical symptoms and diarrhea stopped in 15 of 16 patients (93.8%) after GCAP therapy. In addition, in 15 of 18 patients (83.3%), both mucous and bloody stool disappeared (Figure 1). All clinical symptoms therefore improved significantly after GCAP therapy (<0.005).

Change in the white blood cell number by GCAP therapy

Table 2 shows the changes in the number of white blood cells (WBC) in patients with UC after GCAP therapy. In 14 of 18 patients, the number of WBC decreased after GCAP therapy, while they

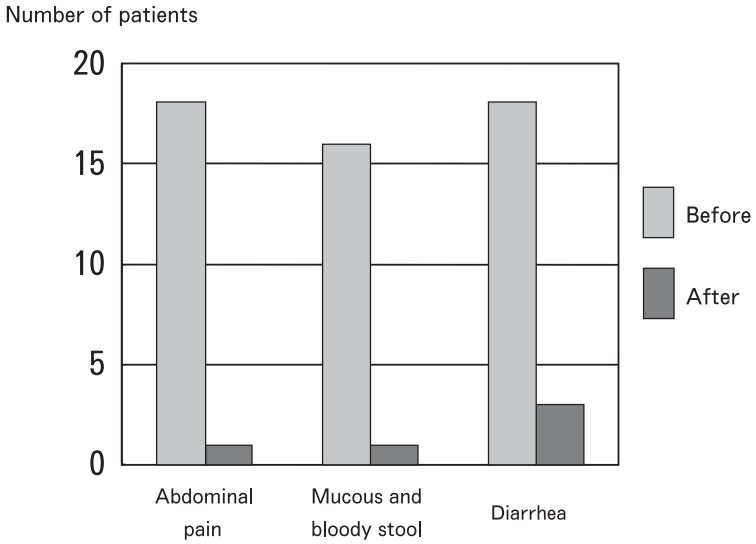

Figure 1. Comparison of the clinical symptoms in patients with UC before and after treatment with GCAP.

Table 2. Comparisons of the clinical symptoms, white blood cells (WBC), c-reactive protein (CRP), daily steroid dose (prednisolone) and UCDAI in patients with UC before and after treatment GCAP (n=18).

	Before	After	p<0.05
Diarrhea (times/ day)	8.8±5.8	0.1±0.4	*
Bloody stool (−〜4+)	1.8±0.6	0.1±0.3	*
WBC (/μl)	8,272±2,762	7,288±2,574	
CRP (mg/dl)	1.47±3.5	0.72±1.33	
PSL (mg/day)	32.6±25.6	17.1±15.0	*
UCDAI	9.6±1.5	2.8±2.2	*

increased in 4 patients. The mean WBC number did not significantly decrease (8,300 to 7,300/μL) in 18 patients.

Changes in C-reactive protein by GCAP therapy

Table 2 shows the changes in the C-reactive protein (CRP) in the patients with UC by GCAP therapy. The mean CRP did not significantly decrease (1.5 to 0.7 mg/dl) in 18 patients.

Changes in daily steroid dose by GCAP therapy

In Table 2, some of the changes in the daily steroid dose in the patients with UC who underwent GCAP therapy are shown. In these patients, the mean dose of corticosteroids after the treatment with GCAP was tapered to 17.2 mg of PSL/day, which was significantly less than the dose (32.7 mg/day) before GCAP therapy ($p<0.005$).

Clinical efficacy based on UCDAI

Patients were treated with GCAP therapy instead of receiving intensive conventional medication. The clinical evaluations were based on Sandborn's UCDAI.[18] Table 3 and Figure 2 show the changes in the UCDAI in the patients with UC who were treated by GCAP therapy. The mean UCDAI decreased to 2.83, which was significantly less than the score (9.61) before GCAP therapy ($p<0.05$). The response to the treatment was defined as a decrease in the UCDAI score ≥3 points. Seventeen of 18 patients (94.4%) showed a decreased score ≥3 points in UCDAI. In addition, six of 18 patients (33.3%) achieved remission and 7 patients (38.8%) showed a clinical response, whereas

Table 3. Comparison of the UCDAI in 18 patients based on GCAP therapy.

	UCDAI		
Patient No.	Before	After	Reduction
1*	6	1	5
2*	10	3	7
3	11	1	10
4	9	2	7
5	11	1	10
6	10	1	9
7*	9	2	7
8*#	8	4	4
9	10	3	7
10*	6	1	5
11#	12	10	2
12*	11	3	8
13	10	4	6
14*	10	3	7
15	10	5	5
16	10	4	6
17	10	1	9
18	10	2	8

underwent a colectomy
* Immunosuppressive agents

5 patients (27.7%) were nonresponders (unchanged, 4; aggravated, 1). In 5 nonresponders group, the mean UCDAI score was not defined as a significant decrease (Figure 2). Of these 5 nonresponders, three were effectively treated by an additional 5 to 16 sessions of re-apheresis during the 5 weeks to 4 months of treatment as described below.

Progrnosis of 18 patients

The prognosis of 18 patients is shown in Table 4. Five nonresponders (unchanged, 4 ; aggravated, 1) were added 5 to 16 sessions of GCAP treatment during the 5 weeks to 4 months of treatment. Three of 4 patients who were unchanged after 5 session of GCAP therapy achieved remission with conventional medication within 3 months after GCAP therapy. In addition, 2 patients (11.1%) underwent a colectomy. One patient demonstrated aggravated symptoms while another patient remained unchanged after 10 sessions of GCAP therapy. One 13-year-old female, who showed an aggravation of symptoms, often relapsed during a two-year period and eventually required colectomy due to the side effects of steroid against her growth. Immunomodulators such as azathioprine did not affect the prognosis of 18 patients (Table 3).

Treatment safety

GCAP therapy was very well tolerated and only minor side effects were registered in a few patients. During the study protocol, one patient reported a mild headache. While another patient who presented with a mild infectious problem (tonsillitis) was treated with oral antibiotics. No patient experienced any serious adverse effects.

Discussion

UC is an inflammatory bowel disease of unknown etiology that involves a severe inflammation of the colonic mucosa. The goals of the therapy for UC are to terminate the acute attack as rapidly as possible and to prevent a relapse. However, 15–25% of patients do not respond to conservative therapy such as the treatment with steroids, thus resulting in the need to perform operative treatment. The chronic use of steroids should be avoided because of the systemic side effects even if the drug is only administered topically. The indications for surgical treatments

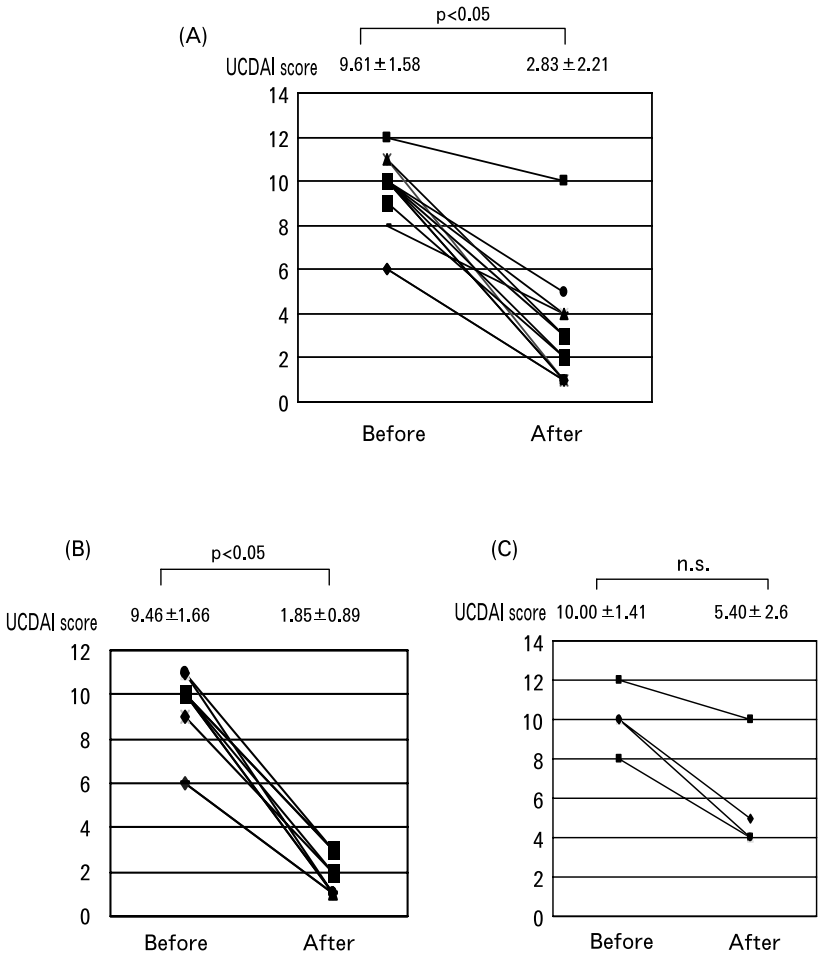

Figure. 2. Comparison of the UCDAI in patients with UC before and after treatment with GCAP. (A) All 18 patients. (B) Patients with remission and clinical response (n=13). (C) Nonresponders (n=5 ; 4 unchanged and 1 aggravated).

Table 4. Prognosis of 5 patients who did not respond to the first session of GCAP and received additional GCAP sessions.

Patient No.	Age (yr)	Remission	Colectomy
Unchanged			
13	53	Yes (after 5 GCAP)	No
15	27	Yes (after 5 GCAP)	No
16	42	Yes (after 5 GCAP)	No
8	60	No (after 10 GCAP)	Yes
Aggravated			
11	13	No (after 16 GCAP)	Yes

of UC patients have so far included intractability, dysplasia–carcinoma, massive bleeding, and toxic megacolon.[1] The largest number of colectomies for UC, however, tend to be performed for less dramatic indications, such as the disease enters an intractable phase and becomes both a physical and social burden to the patients.[19] In the present study, we showed that the unresponsiveness to the GCAP therapy may be useful as a surgical indication in patients with steroid–refractory and –de-

pendent UC. To our knowledge, this is the first report in which the response to GCAP therapy has been suggested to be a useful factor for determining the surgical indications.

CsA has been administered to patients with sever UC with the intention of avoiding a colectomy.[8)-11)] In Japan, however, CsA therapy for UC is currently not covered by the National Health Insurance Program in Japan, partly because CsA therapy often yields undesirable outcomes due to its adverse effects.[13)] On the other hand, GCAP therapy has already been authorized for UC therapy in Japan. Therefore, GCAP therapy may be an alterative therapy for patients with UC in Japan.

Granulocytes and monocytes/macrophages are major sources of inflammatory cytokines.[20)21)] Several studies have indicated active UC to be associated with the activation of granulocyte and nomocyte/macrophage.[20)22)-25)] Ohara et al.[26)] demonstrated that 67% of granulocytes, 55% of monocytes, and 2% of lymphocytes depleted from the blood stream by adsorbing to the G-1 column. Accordingly, patients with active UC should benefit from a reduction in these inflammation leukocytes which are closely associated with inflammation in the colon. Shimoyama et al. showed that the production of proinflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-1β, and IL-6, by peripheral blood leukocytes was markedly suppressed after GCAP therapy.[12)] In addition, a dramatic down-regulation of L-selectin was also observed, which plays a key role in the initiation of leukocyte extravasations. These actions should reduce the inflammation and remission in patients with moderately active UC. Our results suggested that GCAP is an efficient and safe therapeutic treatment for UC patients. Almost all UC patients showed improvements in their symptoms and the results of a blood test after GCAP therapy. Furthermore, GCAP improved the clinical symptoms without the use of steroids in 16 of 18 patients who refused to undergo a re-administration of steroids at the time of relapse. The symptoms of the patients improved after GCAP therapy and it was accordingly possible to decrease the quantity of steroids, thus resulting in a reduction of side effects. As a result, GCAP therapy may be a novel alterative therapy for UC patients. However, a small number of patients exhibited little or no improvement even after they received repetitive GCAP treatment. The frequency of the patients who revealed no response to repetitive GCAP treatments has been reported to range from 10% to 20%,[13)-15)27)] and in our study, two patients (11.1%) showed no significant improvement in their symptoms and UCDAI scores after repetitive GCAP treatments. For these patients, operative treatment should thus be considered.

An operation after GCAP therapy seems to be superior to an operation without attempting GCAP because : 1) inflammation is decreased, 2) the quantity of steroids given can be reduced, and 3) it may be easier for patients to consent to an operation when GCAP has proven to be ineffective. These points are also important for decreasing surgical-related complications. In fact, 2 of 18 patients, who underwent surgical treatment after GCAP, did not show any complications following the operation in our study. The treatment of UC patients with steroids can negatively affect the growth of children. Surgical therapy is also recommended for children who fail to mature at an acceptable rate.

In conclusion, our present study suggests that GCAP can help UC patients avoid a colectomy or the adverse effects associated with corticosteroid therapy while, in addition, the ineffectiveness of this therapy may also be useful as an indication for operative treatment. As a result, GCAP therapy is therefore considered to be beneficial to both those UC patients, who respond and those who do not respond to this therapy. Our results also indicate that outcome of GCAP therapy may have a useful clinical application as a major marker of evaluation of UC, particularly an in corticosteroid-refractory patients with UC. Although the determination of the outcome of GCAP therapy cannot be currently used to determine the indications for surgery, it might help to define a subgroup of patients with UC, who may require a more aggressive therapeutic strategy to prevent the appearance of complications. Confirmation of these results in future studies is necessary before interventional studies based on outcome of GCAP can be designed.

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