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Leukocytapheresis (LCAP) for Management of Fulminant Ulcerative Colitis with Toxic Megacolon

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Leukocytapheresis (LCAP) is a method of therapeutic apheresis to remove patients' peripheral leukocytes by extracorporeal circulation. Previous studies showed that LCAP for the treatment of ulcerative colitis (UC) was more effective and had fewer adverse effects compared to high-dose steroid therapy. However, there are no reports on the application of LCAP for UC patients with toxic megacolon (TM). This study reports the effectiveness and safety of LCAP in treating patients with severe or fulminant UC with TM. Six patients were enrolled in this study and LCAP sessions were performed three times per week for 2 weeks, followed by four further times in the next 4 weeks. After completion of therapy, four patients improved in TM and went into the remission stage of UC. The average Rachmilewitz clinical activity index of these four patients improved from 19.5 to 1. The remaining two patients had to undergo colectomy, however, the symptoms had been mitigated by LCAP and the operations were completed without any problems. These results suggest that LCAP is an additional effective and safe option for TM management in preventing colectomy or for bridging to a safer operation.

KEY WORDS: leukocyte apheresis; ulcerative colitis; toxic megacolon; bacterial translocation; inflammatory bowel disease.

Toxic megacolon (TM) is a life-threatening complication of intestinal conditions and is defined as a severe episode of colitis with segmental or total dilatation of the colon with systemic toxicity (1, 2). TM is typically a complication of ulcerative colitis (UC) and sometimes a complication of other inflammatory bowel diseases (IBDs), such as Crohn's disease and other of the numerous forms of colonic inflammation. Common symptoms are pain, distention of the abdomen, fever, rapid heart rate, and dehydration. Once TM is diagnosed, the patient must be immediately admitted to an intensive care unit where monitoring by a team of experienced gastroenterologists and surgeons is possible (3). Generally, for primary care, the patients should be placed under complete bowel rest and should receive adequate supplementation with intravenous fluids. Previous reports have introduced some techniques involving decompression of the megacolon such as the knee–elbow position (4), rolling (5), endoscopic colonic decompression (6), and hyperbaric oxygen (7). Steroid therapies including oral, intra-arterial injection (8), and pulse therapy (9) have generally been selected for initial medication. If bacterial translocation is specifically indicated, antibiotics should also be administered. Recently, immune-suppressant medications such as cyclosporine (10) and tacrolimus (11) were tried for management of TM. However, medical management or decompression therapy for TM is not always effective. These facts lead to early-stage surgery, shortly after diagnosis of TM (12, 13),

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even though such a policy may also lead to some unnecessary emergency colectomies. Hence, a new therapy to treat TM without surgery is eagerly sought.

Leukocytapheresis (LCAP) is a method of therapeutic apheresis to remove the patient's peripheral leukocytes by extracorporeal circulation. The therapy has been established as an effective treatment for patients with UC (14–17). Therefore, we applied LCAP for the treatment of TM complicating UC. In this paper, we report the first application of LCAP to TM and demonstrate the effectiveness and safety of the therapy.

MATERIALS AND METHODS

This study was conducted at the Department of Gastroenterology, Hyogo College of Medicine. During the study, the Second Department of Surgery at the college hospital prepared the team for emergency surgery (colectomy) for all enrolled patients throughout the study. Patients who became toxic at our hospital or patients who became toxic at another hospital and were then transferred to our hospital were the subjects of the study. Informed consent was obtained from all patients after explanation of the purpose, procedures, expected effectiveness, and possible adverse effects of the study. It was also stated that enrolled patients could withdraw from the study at any time without prejudice to subsequent care and treatment.

Patients. Patients with severe or fulminant UC not responding to conventional steroid therapy who then developed TM were enrolled in this study. TM was defined as a clinical entity characterized by fever, tachycardia, abdominal pain, abdominal distension, decreased bowel sounds, other toxic symptoms, and dilation of the transverse or ascending colon of more than 6 cm diagnosed by X-ray examination (1, 2). Conventional steroidal therapies for treatment of UC include oral and venous administration of steroids at a dose of 1 to 1.5 mg/kg/day, arterial administration of more than 1000 mg hydrocortisone, and intravenous hydrocortisone pulse therapy at a dose higher than 1000 mg. There was no limitation or exclusion criterion regarding the use of antibiotics or salicylic acid, such as salazosulfapyridine (SASP) and 5-aminosalicylic acid (5-ASA). A γ-globulin product infusion and/or a blood transfusion were also allowed for suspected serious bacterial infection and/or severe anemia (less than 8 mg/dl hemoglobin). Patients with severe cardiovascular disease, hypotension of less than 80 mm Hg systolic pressure, dementia, suspected perforation, complications of cancer, or massive bleeding were excluded from the study.

Treatment Procedure. The LCAP treatment was performed using a Cellsorba leukocyte removal column (Asahi Medical Co., Ltd., Tokyo). The column contains a fine polyester nonwoven fabric filter, which has the capability of trapping leukocytes from whole blood (17, 18). It mainly traps granulocytes and monocytes (more than 90%) and partially traps lymphocytes and platelets, whereas it traps only a minimal percentage of erythrocytes. Before therapy, 50 mg of Nafamostat mesilate (Torii Pharmaceutical Co., Tokyo) (19) was dissolved in 20 ml of 5% glucose and then added to 500 ml of saline to make an anticoagulant-added saline solution. One hundred milliliters of the solution was then used to fill the column at the end of the rinsing procedure, and the remaining 400 ml of solution was continuously infused at the inlet line of the column during apheresis. The patient's whole blood from a cubital vein was pumped out at 30 to 50 ml/min, mixed with the anticoagulant-added saline solution, and then introduced into the column. The processed blood was then returned to the patient via the cubital vein of the contralateral arm. The short half-life (about 6 min) of Nafamostat mesilate reduces the patient's bleeding risk compared to other anticoagulants such as heparin. Usually, 2.0 ± 0.5 liters of the patient's whole blood was processed and a session was completed within approximately 1 hr. The sessions were conducted three times per week for 2 weeks, followed by an additional four sessions, once per week, in the next 4 weeks (Figure 1).

Medication. Before entry into the study, the patients were medicated with typical regimes including steroids, and so on, for the treatment of UC. The details for each patient are described in the Results. After entry into the study, concomitant steroid therapy was initially set at 1.0 to 1.5 mg/kg/day (60 to 80 mg/day) of prednisolone intravenously and the same dosage was continued throughout the initial 2 weeks of the study. In accordance with the improvement in symptoms and manifestations, the dosage was reduced to 30 mg/day in a stepwise manner in 10-mg decrements over the following 10 to 14 days. Administration was then changed from intravenous to oral when the dosage was less than 30 mg/day. The use of antibiotics and/or salicylic acid (SASP or 5-ASA) was allowed to continue during the study, however, increases in dosage and/or new medications were prohibited.

Evaluation. Assessments of LCAP were evaluated by a UC scoring system reported by Rachmilewitz (20) as the clinical activity index (CAI). Plain abdominal X-ray examination was also compared with baseline and post–first LCAP session. Endoscopy, based on the Matts endoscopic index (EI) (21), and effectiveness of the study were evaluated within 2 weeks after completion of all LCAP sessions. In any case where all the LCAP sessions could not be completed for some reason, the data within 2 weeks after the last LCAP session were used to assess effectiveness. Adverse effects were also monitored until 2 weeks after the completion of LCAP sessions.

Laboratory Tests. Conventional blood laboratory tests were performed to monitor each patient's condition and assess the adverse effects. As a precaution against shock, disseminated intravascular coagulation or multi-organ failure due to bacterial translocation, serum endotoxin was also measured before enrollment using the endotoxin- specific chromogenic limulus test (22).

RESULTS

Six patients were enrolled in this study to be treated with LCAP. One patient (Case 2) developed TM during the UC follow-up period at our hospital and the other five patients had been transferred to our hospital for TM with UC. The baseline characteristics of the patients are summarized in Tables 1 and 2. Two patients (Cases 1 and 3) had acute fulminant first attack–type UC, while the other four patients had the relapsing–remitting type and had a long medical history of UC. No patients had a family history of IBD or autoimmune-related diseases. The enrolled patients were inpatients during the study under total parenteral nutrition (TPN), as they could not eat and

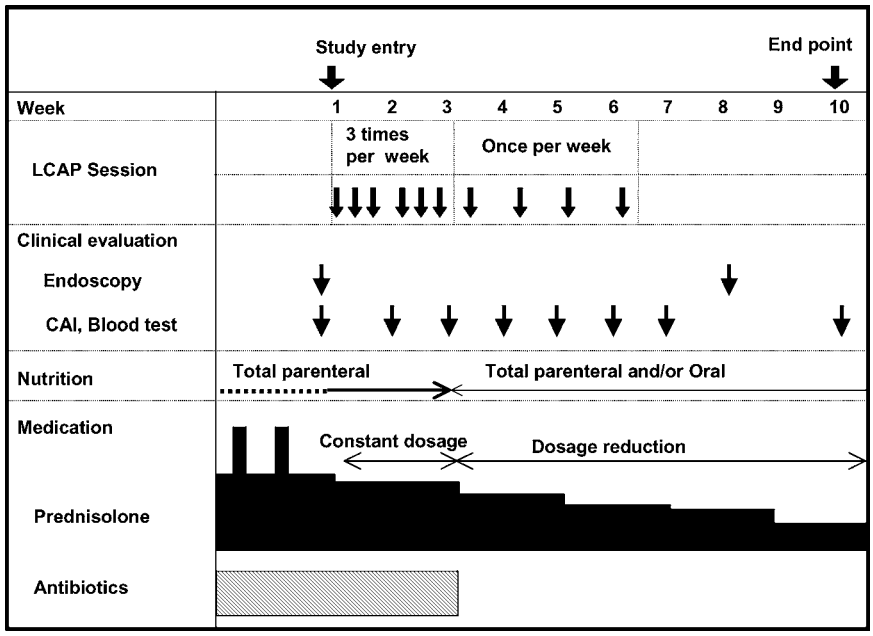

Fig 1. Schematic drawing of the study protocol. Closed arrows in the session and clinical evaluation rows indicate the time of the corresponding events. In the medication row, closed and hatched boxes indicate the medication periods and dosages of prednisolone and antibiotics, respectively.

drink due to severe abdominal pain. Plain abdominal X-ray showed that Case 1 had more than 7.5 cm dilatation of the sigmoid colon and a large amount of gas in the transverse colon and ileum, and the other cases had more than 7 cm dilatation of the transverse colon. The patients had a 7 to 20 times/day incidence of watery and bloody diarrhea, a fever of more than 38°C, and tachycardia of 88 to 110 beats/min. All patients had been treated with high-dose prednisolone (1 to 1.5 mg/kg/day, 60 to 80 mg/day) and antibiotics before enrollment in the study. Three patients, Cases 1, 4, and 5, also had been administered steroid pulse therapy (1000 mg/day hydrocortisone three times per week) before entry into the study. In addition, Case 1 had received a total of 12,500 mg/day γ-globulin products (human IgG treated with pepsin). Case 3 had been administered 3.0 g/day SASP, however, this was terminated

TABLE 1. PATIENTS' BASELINE SYMPTOMS AND CHARACTERISTICS

Case No.	*Sex*	*Age*	*Admission date*	*Extent of lesion*	*Clinical course*	*Time since onset of UC*	*Location of dilated colon*	*Diameter of colon (cm)**	*Treatments†*
1	M	58	3/24/1995	Left sided	Acute fulminating	13 days	Sigmoid and transverse	7.5	Steroid (1 mg/kg/day), antibiotics, TPN, steroid pulse, γ-globulin products
2	M	26	10/09/1995	Entire colitis	Frequent relapse	10 years	Transverse	9.0	Steroid (1 mg/kg/day), antibiotics, TPN
3	M	49	11/14/1997	Entire colitis	Acute fulminating	7 weeks	Transverse	7.5	Steroid (1 mg/kg/day), antibiotics, TPN, blood transfusion, SASP
4	M	24	2/15/1998	Entire colitis	Relapsing–remitting	42 months	Transverse	7.2	Steroid(1 mg/kg/day) antibiotics, TPN, steroid pulse
5	M	28	1/24/1999	Entire colitis	Relapsing–remitting	51 months	Transverse	7.5	Steroid (1.5 mg/kg/day), antibiotics, TPN, steroid pulse
6	M	53	5/15/2002	Entire colitis	Relapsing–remitting	50 months	Transverse	7.0	Steroid (1.5 mg/kg/day), antibiotics, TPN

*The largest diameter of the dilated colon segment.
†TPN, total parenteral nutrition; SASP, salazosulfapyridine.

TABLE 2. PATIENTS' BASELINE CHARACTERISTICS AND LABORATORY DATA

Case No.	*Nature of stool*	*Stool /day*	*Fever (°C)*	*HR (bpm)*	*Other symptoms*	*CAI*	*EI*	*WBC (/μl)*	*CRP (mg/dl)*	*ESR (mm/hr)*	*Hb (g/dl)*	*Alb (g/dl)*	*K (Eq/l)*
1	Watery and bloody diarrhea	7	38.5	102	Abdominal distention, severe abdominal pain	20	3	11,000	11	55	8.7	2.9	3.1
2	Watery and bloody diarrhea	20	40.5	110	Abdominal distention, severe abdominal pain	19	4	10,900	7.4	41	10.2	2.0	3.5
3	Watery and bloody diarrhea	10	37.0	88	Abdominal distention, severe abdominal pain	18	4	16,000	17.8	35	16.5	3.6	3.6
4	Watery and bloody diarrhea	15	38.2	97	Abdominal distention, severe abdominal pain	19	3	8,500	10.5	40	10.6	3.1	3.3
5	Watery and bloody diarrhea	16	39.2	104	Abdominal distention, severe abdominal pain	19	3	9,200	10.8	42	10.5	3.0	3.2
6	Watery and bloody diarrhea	14	38.5	100	Abdominal distention, severe abdominal pain	20	4	9,300	12.2	45	9.5	2.8	3.0

Note. HR, heart rate; CAI, Rachimilewitz clinical activity index; EI, Matts endoscopic index; WBC, white blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Alb, albumin; K, potassium; bpm, beats per minute.

after transfer to our hospital because of severe pain after administration. The patient had also been administered a massive blood transfusion (1600 ml) just before arrival at our hospital.

The clinical conditions of UC at baseline were estimated by CAI and EI. These values were between 18 and 20 and between 10 and 12, respectively, which indicate severe or fulminant conditions. Laboratory examinations of leukocytosis, C-reactive protein, and erythrocyte sedimentation rate also showed elevated inflammation. Moreover, low hemoglobin, low serum albumin, and hypokalemia were found in all patients except Case 3. These parameters might be temporarily improved by blood transfusion. The stool culture tests for all patients showed no pathogenic bacteria such as enteropathogenic *Escherichia coli*, *Salmonella*, *Shigella*, and *Clostridium* or amoebic dysentery, etc. Colonic biopsy specimens showed no cytomegalic inclusions from cytomegalovirus infection. Arterial blood pH, serum creatinine, serum lactate dehydrogenase, and creatine phosphate were in the normal range in all patients, so we concluded that the patients' megacolons were not complicated by metabolic acidosis, necrosis of the colonic muscular layer, or kidney dysfunction even though their symptoms indicated a very toxic condition. In Cases 1 and 2, the endotoxin levels were elevated to 13 and 22 pg/dl, respectively. They also showed low systolic pressures of 90 and 86 mm Hg, respectively, however, the symptoms were resolved by the administration of vasopressors. Consequently, their studies were performed without any problem related to their elevated endotoxin levels.

Clinical Effectiveness. The first LCAP procedure for each patient was performed on the evening of the first day of enrollment and within 6 hr of diagnosis of megacolon except for Case 3. For this patient, the first LCAP procedure was performed 24 hr after diagnosis of megacolon. The alteration of UC condition evaluated by CAI for each patient is shown in Table 3. All patients' symptoms improved after the first LCAP session. For Cases 1, 2, 4, and 5, their megacolons resolved by the morning following the first LCAP session. For Cases 3 and 6, it disappeared about 40 hr after the first LCAP session but still before the second LCAP session.

Improvement continued in four patients (Cases 1, 4, 5, and 6), and the CAI was reduced to 1 for each of them at week 10 (Table 3). Endoscopy for these patients was also performed. The EI was improved from grade 3 to grade 1 in Cases 1, 4, and 5 and from grade 4 to grade 1 in Case 6. Steroid dosage could be reduced gradually and only 5 mg/day of prednisolone was being administered to these patients before their release from the hospital. Administration of 5-ASA to these patients was then started as a chronic-phase treatment for UC after the study. They could drink and eat without any abdominal pain after the seventh LCAP session at Week 3 (less than 3 weeks after admission) and were discharged at Week 8 after completion of the 10th LCAP session. At this point their UC was in remission and they were followed up as outpatients. The megacolon did not appear again by the end of the study and their remission has continued for at least the following periods: 7 years 8 months for Case 1, 4 years for Case 4, 2 years, 11 months for Case 5, and 8 months for Case 6. Case 5 had a relapse of UC at about 2 years, without megacolon, and LCAP was effective in settling the active UC condition again.

In contrast, in the other two patients (Cases 2 and 3) TM reappeared during the study. For Case 2, the patient had achieved remission for UC, however, TM appeared about 2 weeks after completion of the final LCAP session. The CAI was reduced from 19 to 2 at week 7 but increased to 10 at week 10. Case 3 improved temporarily, however TM reappeared a week after the third LCAP session. Total colectomies were then performed for these patients after the diagnosis of TM reappearance. They had received preoperative examinations for respiratory, cardiac, renal, and hepatic functions during the LCAP trial period, to prepare for this contingency, and their operations were thus safe. In the surgical findings for Case 3, dilatation of the transverse colon was 13 cm and the splenic flexure of the transverse colon was adhered to the major omentum, but no perforation was found. Case 2 showed an extirpated colon: thin, weak, and close to perforation. Endoscopic examination

TABLE 3. CHANGE OF CLINICAL ACTIVITY INDEXES AND FOLLOW-UP RESULTS

Case No.	*Baseline*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 10*	*Disappearance of TM*	*Results in follow-up period*
1	20	11	4	3	2	1	1	1	Next morning	Remission for 7 years 8 months
2	19	13	10	6	3	2	2	10	Next morning	Total colectomy at Week 10
3	18	10	13	—	—	—	—	—	41 hr later	Total colectomy at Week 3
4	19	11	3	2	1	1	1	1	Next morning	Remission for 4 years
5	19	10	4	3	1	1	1	1	Next morning	Remission for 2 years 11 months
6	20	11	3	2	1	1	1	1	43 hr later	Remission for 8 months

for evaluation of effectiveness was not performed for these patients.

In conclusion, four of six patients achieved remission and LCAP was judged as causing "excellent improvement" for these cases, confirmed both clinically and endoscopically. The other two patients were finally judged as "negligible change" because they underwent total colectomy. However, LCAP provided some improvement in these two patients and could be inferred to be a useful therapy for bridging to nonurgent surgery.

Adverse Events. One patient (Case 3) had a headache during the LCAP procedure. In total, the patient had a headache during three sessions and refused to continue the following sessions. The headache was not severe, thus no medication was necessary. The patient became TM again a week after the third LCAP session. The other patients had no adverse effects resulting from LCAP. Therefore, a total of 3 of 53 LCAP sessions (5.7%) incurred adverse effects.

DISCUSSION

The original applications of LCAP using Cellsorba for the treatment of UC were reported by our group (14–17). The results demonstrated that LCAP was an effective and safe therapy for the treatment of severe UC, resulting in remission. A similar therapy, called granulocyte/monocyte apheresis (GCAP), using an Adacolumn, which contains cellulose acetate beads as an adsorbent, also was shown to be effective for UC treatment (17, 23–25). According to this evidence, LCAP and GCAP have been approved for treatment of UC in Japan. In addition, these apheresis therapies have been reported to possess effectiveness for autoimmune diseases such as Crohn's disease (17, 26), rheumatoid arthritis (27–30), and progressive glomerulonephritis (31).

The therapeutic mechanisms of LCAP for these diseases are not well established at this stage. However, some reports describe that the cytokine levels in patients' blood were modulated by LCAP as follows. The concentrations of pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1β, IL-2, IL-8, and interferon-γ were reduced, whereas the levels of immunoregulatory cytokines such as IL-4 and IL-10 increased after LCAP (15, 32). In addition, circulating activated leukocytes, which are the major source of inflammatory cytokines, are elevated, with an increased survival time, in active IBD (33, 34). These leukocytes then accumulate in the inflamed mucosa (35) and the cells' infiltration in particular not only defines the disease activity but also relates quantitatively to the severity of the clinical relapse (36). LCAP removes such activated leukocytes from the peripheral blood circulation. These results suggest that the effectiveness of LCAP is achieved by remedial action on the cytokine network within the disease condition, returning it to a normal level.

The symptoms of megacolon caused by severe inflammation of UC are thought to occur via cessation or weakness of bowel movement. Then the symptoms deteriorate to TM due to excess distension by colonic gas and stool contents and as a result of microcirculatory failure leading to necrosis. In this situation, patients' leucocytes are considered to play an important role in the pathway of colonic mucosal damage caused by UC (37). Therefore, we supposed that patients with fulminant or severe UC with megacolon might respond clinically to the removal of leukocytes as an adjunct to conventional medications. In other words, the inflammatory process is temporarily shut down and this settles the inflammation in the colonic lesion by removing the peripheral immunocompetent cells. The colonic mucosa can regenerate during this period, meaning that recovery of the colonic mucosa exceeds its rate of damage. Intestinal movements then normalize and colonic gas can be evacuated after tissue swelling improves. Microcirculation in these regions also would be improved. From the results of this study, LCAP treatment truly showed a superb improvement in TM with UC.

The authors emphasize the importance of early diagnosis of the disease and early introduction of conservative treatment. In this study, LCAP was started within 6 hr of diagnosis of megacolon except for one patient, and megacolon disappeared by the following morning in four of six cases, and within 2 days in the remaining two cases, so that we did not need to consider emergency surgery. This is the first report mentioning the application of LCAP to TM with UC. The results, rapid improvement of TM with minimal adverse effects, indicate that LCAP should be considered as one option for the management of TM or as a bridging therapy to surgery, thereby avoiding high-risk emergency colectomy. Further controlled studies with larger numbers of patients should be performed to confirm our findings and to establish a standard for management incorporating LCAP in the treatment of TM.

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