Acta Med. Nagasaki 47 : 145−148

Effectiveness and Safety of Leukocytapheresis Therapy for Ulcerative Colitis

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Leukocytapheresis (LCAP) was performed in seven patients with moderate or severe active ulcerative colitis (UC) at the Koga Hospital. LCAP was considered as having been effective in all seven patients (excellent clinical response in five and moderate clinical response in two patients). The excellent or moderate clinical response continued throughout maintenance LCAP in three of seven patients. None of the patients required discontinuation of LCAP, despite the appearance of some side effects, including facial redness, low-grade fever, discomfort, headache and hypotension during the therapy. The results of this study indicate that LCAP may be a safe and effective intensive and maintenance therapy for UC.

ACTA MEDICA NAGASAKIENSIA 47 : 145−148, 2002

Key Words: leukocytapheresis, ulcerative colitis.

Introduction

Corticosteroids are effective for inducing clinical remission in patients with ulcerative colitis (UC) (1,2). However, in severely relapsed cases, corticosteroids are not always effective, even when a high dosage is administered (3,4). In addition, the long-term use of corticosteroids often causes serious side effects, including hormonal derangements, peptic ulcers and psychological problems (5,6). Therefore, an alternative treatment for active ulcerative colitis is desirable in order to avoid these clinical problems.

Recently, the efficacy of leukocytapheresis (LCAP) was reported for inflammatory bowel disease, using a leukocyte removal filter or centrifugal method (7-10). In our hospital, LCAP was performed in seven patients with severe UC, and in this report we present the effects of this therapy.

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Patients and Methods

LCAP was performed in seven patients with UC (four males and three females) between November 1995 and June 1998 in Koga Hospital. Three patients had moderate active UC and four had severe active UC, and showed insufficient response to conventional therapy. Informed consent was obtained from all patients prior to inclusion in the study. Table 1 provides the clinical profile of the participating patients. Imugard (Terumo Corporation, Tokyo, Japan) was used as a leukocyte removal filter (Fig. 1 A,B). Heparin or nafamostat mesilate was used as anticoagulant and 1575 ml of whole blood were processed with a blood flow rate of 35 ml/min for each procedure for a duration of 45 min.

LCAP was usually performed once each week for five weeks in severely affected UC patients requiring intensive therapy. For maintenance therapy, LCAP was usually performed once every four to six weeks until steroids were discontinued or the dose tapered, or for up to six months. LCAP was discontinued and the clinical course of the patient was followed after steroids were discontinued or tapered to a maintenance dose of 5-10 mg. For the evaluation, we classified the response to the LCAP using the criteria of Egashira et al. (11); excellent, moderately improved, no change, or deterioration.

Table 1. Demography of patients with ulcerative colitis treated by LCAP

Age (mean ± SEM)	51.4 ± 12.3
Male/Female	4 / 3
Duration of disease (years)	5.5 ± 3.5
Severity of UC	
severe	4
moderate	3
pancolitis	5
left-side colitis	2
Types of clinical course	
one only attack type	1
relapse-remitting type	4
chronic persistent type	2

Data are number of patients

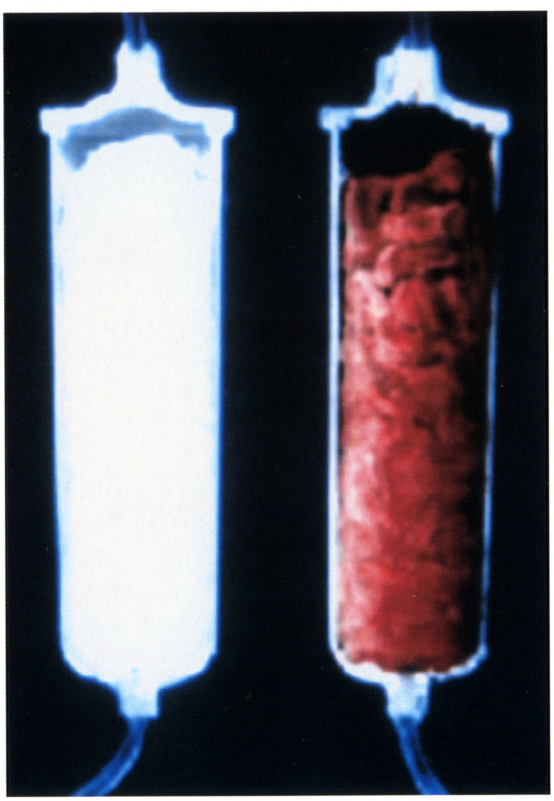

Figure 1. Imugard leukocyte removal filter before (A) and after (B) LCAP.

Results

All patients included in the study had active UC (pancolitis [n=5], left-side colitis [n=2]). Six (87.5%) of the seven patients achieved clinical remission within four weeks of undergoing apheresis, and remained in remission for an average of eight months without any additional corticosteroid therapy. As intensive therapy, LCAP was effective in all seven patients (excellent [n=5] and moderately effective [n=2]; effectiveness rate = 100%). Maintenance LCAP was also effective in three patients, who progressed to a remission stage (Table 2). Side effects, such as facial redness, low grade fever, discomfort and headache occurred in some cases, but none of the patients required discontinuation of LCAP (Table 3). Blood biochemical parameters did not change significantly between before and after LCAP. No ef-

Table 2. Effectiveness of LCAP.

A. Intensive therapy	n (%)
excellent clinical response	5 (71.4)
moderate clinical response	2 (28.6)
no clinical response	0 (0)
change for the worse	0 (0)
B. Maintenance therapy	
continuous remission	3 (100)
change for the worse	0 (0)

Table 3. Side effects of LCAP

Side effect	n (%)
Facial redness	5 (71.4)
Fever	5 (71.4)
Discomfort	3 (42.8)
Headache	3 (42.8)
Hypotension	2 (28.6)
Abdominal pain	1 (14.3)
Arthralgia	1 (14.3)
Nausea, vomiting	1 (14.3)

fects of the therapy were noted on hepatic or renal function.

Case

A 41-year-old male was admitted to our hospital in April, 1998 with a history of melena. On admission, he had bloody stools 5-6 times/day, abdominal pain, slight fever and hypoproteinemia. Prior to admission, the condition had not improved for about nine months, despite various drug therapies. Physical examination on admission revealed mild tenderness of the left lower abdomen. Laboratory studies showed moderate anemia (hemoglobin 9.8 g/dl) and an elevated CRP (15.0 mg/dl). Colonoscopy showed hyperemia, oozing of blood, and diffuse mucosal ulcerations. The diagnosis was established as severe pancolitis (Fig. 2A). After admission, IVH and steroid therapy (40 mg methylprednisolone) was performed for two weeks, but both were ineffective. LCAP was performed once a week for five courses. The patient became asymptomatic after two LCAP courses, and laboratory data reverted to within normal limits after five LCAP treatments. Colonoscopy after LCAP confirmed that he had entered remission (Fig. 2B).

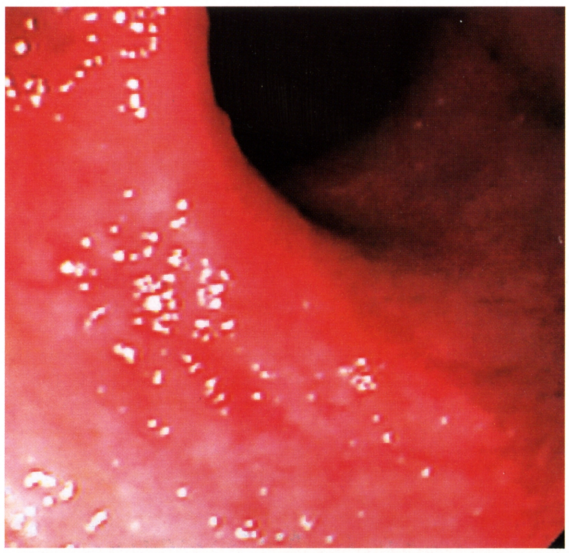

Fig 2-A

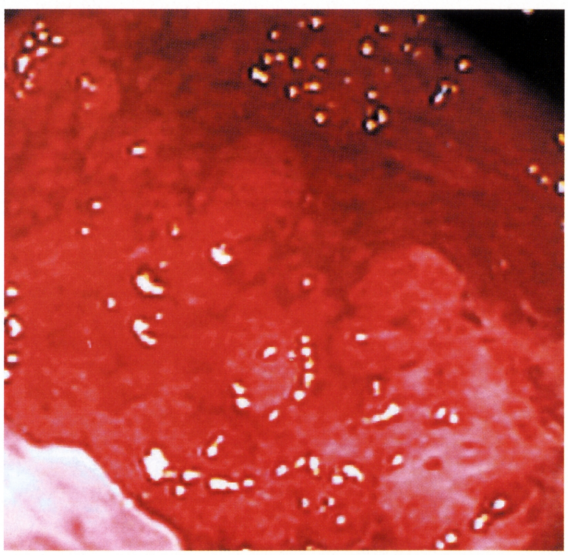

Fig 2-B

Figure 2. Endoscopic appearance of the sigmoid colon. A. Colonoscopy on admission revealed hyperemia, oozing of blood, and diffuse mucosal ulceration. B. Colonoscopy after five LCAP treatments revealed almost normal mucosa without ulceration.

Discussion

Ulcerative colitis is characterized by infiltration of inflammatory cells such as monocytes, lymphocytes and neutrophils. Immune effector mechanisms are central to the disease process in inflammatory bowel disease, but it is not clear whether the mucosal or systemic immunological abnormalities are primary phenomena, or are secondary to disease activity (12). Activated neutrophils, as well as lymphocytes, are thought to play an important role in the pathogenesis of UC. The exact mechanism by which LCAP reduces severe colonic inflammation in active UC is obscure. One possible mechanism using the Imugard filter may be the removal of leukocytes. About 70% of leukocytes are removed in a single pass through this filter, and 3 x 10^9 leukocytes are calculated to be removed in a single procedure (13). A few reports have suggested that in cases where LCAP is effective, production of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF)-a, decreased, whereas this did not occur in cases where treatment was ineffective (14,15).

LCAP is reported to be beneficial in other diseases, including rheumatoid arthritis, erythroderma, and Crohn's disease, in which it can halt the "vicious immune cycle" and relieve local inflammation (16-18). One report, based on flow cytometric analysis stated that among UC patients with repeated recurrences, LCAP tended to be effective in those with elevated activated leukocyte counts, but not in those with low counts with minimal active inflammation (7). Since our study included only patients with severe and active UC, the effect of LCAP in patients with mild UC could not be determined. This is probably because of repeated recurrences and progression to chronic UC,

with secondary activation of leukocytes and triggering of the so-called "vicious immune cycle" (9).

LCAP had a dramatic effect in many cases in an uncontrolled study, although clinical evaluation was performed as early as just before the fourth treatment (9). Sawada et al. (19) proposed that the major inclusion criterion for LCAP therapy was insufficient response to conventional drug therapy, and that LCAP could be a treatment for UC that falls between drug therapies and surgery. The results of the present study indicate that LCAP may be useful as a therapy both in acute disease and during maintenance. However, no definite consensus has been reached with regard to the required duration of therapy. Several issues remain unresolved, including whether permanent or semi-permanent LCAP is required to maintain remission, and the optimum duration of LCAP therapy. In our hospital, LCAP is usually performed once every four to six weeks until steroids are discontinued or their dose tapered, or for up to six months. LCAP is discontinued and the clinical course of the patient is followed when steroids are discontinued or tapered to a maintenance dose of 5-10 mg. To date, there are no reports of recurrence of UC in any patient during or after LCAP. However, the follow-up period in our study is only 12 months at most, and longer follow-up will be necessary in future studies.

With respect to safety, none of the patients required discontinuation of LCAP, despite the appearance of side effects during therapy; LCAP had to be discontinued prematurely in two patients due to the development of severe malaise. LCAP may have serious side effects such as hypotension in patients who are in poor general condition (19,20). It would be prudent to avoid LCAP in patients in poor general condition, patients with a systolic blood pressure of 80 mmHg or lower, patients under 10 or over 75 years of age, patients with serious hepatic or renal disorders, and patients with bleeding tendencies (19).

In conclusion, LCAP therapy is useful for patients with severe attacks of ulcerative colitis, including those who fail to respond to glucocorticoid therapy.

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