Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8428-16
Intern Med 56: 2705-2710, 2017
http://internmed.jp

【 ORIGINAL ARTICLE 】

Long-interval Cytapheresis as a Novel Therapeutic Strategy Leading to Dosage Reduction and Discontinuation of Steroids in Steroid-dependent Ulcerative Colitis

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Abstract:

Objective This study was performed to confirm the efficacy of long-interval cytapheresis on steroid-dependent ulcerative colitis (UC).

Methods To discontinue steroids in patients with steroid-dependent UC, we previously designed a novel regimen of cytapheresis (CAP), which we termed "long-interval cytapheresis (LI-CAP)", in which CAP was performed as one session every two or three weeks and continued during the whole period of tapering steroid dosage. In this study, we performed LI-CAP therapy 20 times (11 male and 9 female; mean age 41.8 years) between April 2010 and April 2015 for 14 patients with steroid-dependent UC. We evaluated the effectiveness of LI-CAP by examining the improvement in Lichtiger's clinical activity index (CAI), the rate of clinical remission, and the rate of steroid discontinuation. We further examined the rate of sustained steroid-free clinical remission at 6 and 12 months after LI-CAP in patients who successfully discontinued steroid-use after LI-CAP. The primary endpoint was the rate of discontinuation of steroids after LI-CAP.

Results The mean CAI score before LI-CAP (7.550) significantly decreased to 1.65 after LI-CAP ($p< 0.0001$). The rate of clinical remission after LI-CAP was 80%. The rate of steroid discontinuation after LI-CAP was 60.0%. The mean dose of daily prednisolone was significantly decreased after LI-CAP (2.30 mg) compared with that before therapy (17.30 mg) ($p=0.0003$). The rate of sustained steroid-free clinical remission after LI-CAP was 66.7% at 6 months and 66.7% at 12 months.

Conclusion We confirmed that LI-CAP has therapeutic effects on reducing the dosage and discontinuing steroids in patients with steroid-dependent UC.

Key words: ulcerative colitis, inflammatory bowel disease, cytapheresis, granulocyte and monocyte adsorptive apheresis, leukocytapheresis, steroid-dependent

(Intern Med 56: 2705-2710, 2017)
(DOI: 10.2169/internalmedicine.8428-16)

Introduction

Ulcerative colitis (UC) is an intractable chronic inflammatory bowel disease of unknown etiology that can affect the entire colon. Most patients with UC are treated with medications, but 7-20% develop chronically active or steroid-dependent disease (1-3). Immunomodulatory agents such as azathioprine (AZA) are generally used for patients with steroid-dependent UC (4-7). A recent study showed that significantly more patients receiving AZA had clinical and endoscopic remission and discontinued steroid therapy than those receiving 5-aminosalicylic acid (5-ASA) (4). However, it has also been reported that a proportion of patients with steroid-dependent UC do not respond to AZA (5), and 5-10% of patients do not tolerate thioprines due to the associated adverse effects, such as a flu-like illness, a fever, and abdominal pain (6). In addition, a proportion of patients do

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Received: October 21, 2016; Accepted: March 2, 2017; Advance Publication by J-STAGE: September 15, 2017
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not continue AZA due to severe adverse events, such as myelotoxicity and hepatotoxicity (6).

Recent advances in the treatment of UC, including biological therapy using anti-tumor necrosis factor-α (TNF-α) antibodies, can ameliorate the disease activity in many patients with active UC. Among these treatments, cytapheresis (CAP), which was developed in Japan, has been shown to be an effective strategy for patients with active UC with a lower rate of adverse effects (8-13). CAP is performed via one of two methods: [1] granulocyte and monocyte adsorptive apheresis (GMA), which uses cellulose acetate beads (Adacolumn, JIMRO, Takasaki, Japan); and [2] leukocytapheresis (LCAP), which uses polyethylene phthalate fibers (Cellsorba., Asahi Kasei Medical, Tokyo, Japan) (14). CAP is conventionally performed as a single session per week and repeated 5-10 times. A recent study showed that intensive GMA (i.e. two sessions per week) was more effective than routine weekly GMA treatment in patients with active UC (15).

Regarding treatment of steroid-dependent UC, only a few studies have shown therapeutic efficacy of CAP for inducing clinical remission or steroid-free clinical remission (16-22). When administrating CAP therapy in patients with UC, we have noticed that some steroid-dependent UC cases who responded to CAP subsequently relapsed after the completion of CAP on tapering the steroid dosage. Based on these unsuccessful experiences, we designed a novel regimen of CAP in order to allow for the discontinuation of steroids in steroid-dependent UC patients, which we termed "long-interval CAP (LI-CAP)". In this regimen, CAP was performed once every two or three weeks and was continued throughout the period of steroid dosage tapering. We reported the efficacy of LI-CAP in three patients with steroid-dependent refractory UC (23). Thus, LI-CAP was originally designed to allow for dosage reduction and discontinuation of steroids in patients with steroid-dependent UC. We have since continued this clinical study to confirm the efficacy of LI-CAP in more steroid-dependent UC patients, including those who responded poorly to immunomodulatory agents.

In this paper, we confirmed the efficacy of LI-CAP in patients with steroid-dependent UC, especially with regard to reducing the dosage and discontinuing steroids, and discuss a novel therapeutic strategy for patients with steroid-dependent UC.

Materials and Methods

This clinical study of LI-CAP was conducted in accordance with the Declaration of Helsinki and approved by the Institute Review Board of Akita Red Cross Hospital (Approval No: 115). We provided sufficient explanation of the aim, methods, expected efficacy, and potential side effect of LI-CAP to the patients in a document. In addition, we gave them sufficient information, including regarding the risks and benefits, concerning not only LI-CAP but also other therapies for steroid-dependent UC. Informed consent was subsequently acquired from all of the patients involved in this study. Patients who chose therapies other than LI-CAP were not enrolled in this study.

LI-CAP regimen

In this LI-CAP regimen, CAP was performed once every two or three weeks in principle, and this pattern was continued throughout the entire period during which the prednisolone dosage was being tapered. The prednisolone dosage was tapered at the timing of CAP in patients who showed clinical improvement during LI-CAP but was not tapered in those who did not improve or worsen after several CAP sessions; instead, other conventional medications were considered. The number of LI-CAP sessions performed in this study was 5 to 15 (mean 10.2 times), and the treatment period was 11 to 30 weeks (mean 19.7 weeks). Under the Japanese health insurance treatment system, the 11th CAP session was performed at one month after the 10th CAP session in patients who received more than 10 CAP sessions.

Patients and times of LI-CAP

We performed LI-CAP therapy 20 times (LI-CAP with GMA: 14 times, LI-CAP with LCAP: 6 times) with patients' informed consent between April 2010 and April 2015 in 14 patients with steroid-dependent refractory UC. Four patients who previously failed to discontinue steroids by conventional CAP were included in this study. In this study, LI-CAP was performed two times in six patients. Among these six patients, we performed the second LI-CAP in three due to the relapse of UC and in the other three due to the failure of discontinuation of steroids after the previous LI-CAP.

The detailed clinical profiles of the patients enrolled in this study are shown in Table 1. These patients had unsuccessful clinical histories with respect to tapering the dosage and discontinuing steroids before LI-CAP therapy. The dosage of prednisolone [5-50 mg (mean±(SE): 17.3±2.85 mg)], and the concomitant therapies at apheresis commencement are also shown in Table 1. Concomitant medications except for prednisolone were continued at the same dosage. Patients with granulocytopenia (granulocyte cell count $<2{,}000/mm^3$); serious heart, kidney, or liver diseases; coagulation disorders; infections; a history of hypersensitivity to heparin; severe dehydration; anemia (hemoglobin <9.0 g/dL); thrombocytopenia (platelet count $<10\times10^4/mm^3$); and using angiotensin-converting enzyme inhibitors were excluded.

Evaluation of the efficacy of LI-CAP

The severity of UC was assessed using Lichtiger's clinical activity index (CAI), with a value ≥11 defined as severe and <11 as moderate/mild (24). In this study, we evaluated the effectiveness of LI-CAP in steroid-dependent patients with UC at 1 month after the last apheresis session (initial efficacy) by examining the following points: [1] The improvement in the CAI and the rate of clinical remission using Li-

Table 1. Patients' Profiles.

Age (years, mean±SE)	17-82 (41.8±3.52)
Sex (male:female)	11:9
Duration from diagnosis (months, mean±SE)	6-408 (80.0±20.7)
Concomitant therapies at the initiation of apheresis (%)	
Prednisolone	100
5-ASA	90
Thioprines	35
Metronidazole	25
Severity of UC (%)	
Severe	15
Moderate/Mild	85
Dose of prednisolone at the initiation of apheresis (mg, mean±SE)	5-50 (17.3±2.85)
UC extent (%)	
Total colitis	85
Left-sided colitis	15
Proctitis	0

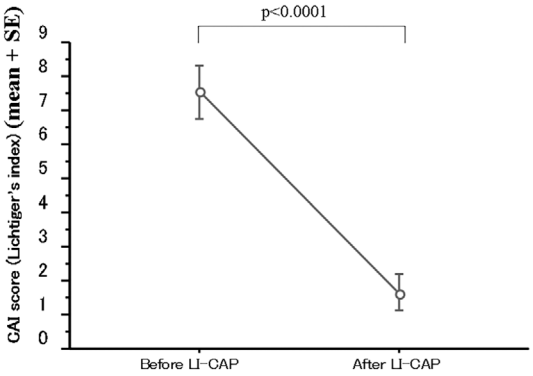

Figure 1. Mean CAI score before and after LI-CAP: The CAI score (mean±SE) before and after LI-CAP is shown. The mean CAI score was significantly lower after LI-CAP than before (pre-CAI: 7.550 vs. post-CAI: 1.650, p<0.0001).

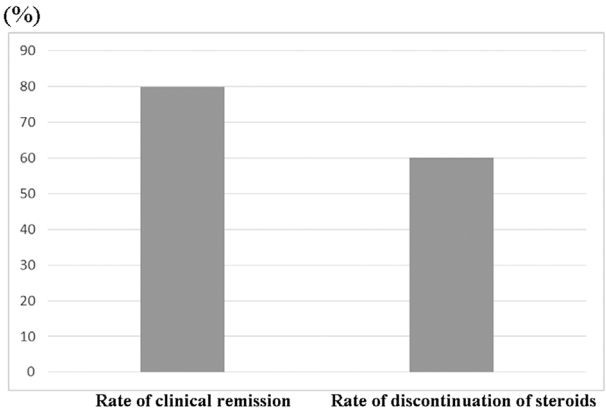

Figure 2. The rate of clinical remission and discontinuation of steroids after LI-CAP: The rate of clinical remission after LI-CAP was 80.0% (16/20), and the rate of discontinuation of steroids after LI-CAP was 60.0% (12/20).

chtiger's CAI, with clinical remission defined as CAI of ≤ 4 (24); [2] The rate of discontinuation of steroids after LI-CAP; [3] The rate of clinical remission and of the discontinuation of steroids in the patients who responded insufficiently to thioprines; and [4] The improvements in the laboratory data [C-reactive protein (CRP) level, white blood cell count (WBC), hemoglobin (Hb) level, and serum albumin concentration]. In addition, we also evaluated the rate of sustained steroid-free clinical remission at 6 and 12 months after the last apheresis of LI-CAP to assess the long-term effectiveness in the patients who successfully discontinued steroids after LI-CAP.

The primary endpoint of this study was the rate of discontinuation of steroids after LI-CAP.

We defined the "discontinuation of steroids" as the point at which both oral steroids and enemas including steroids were discontinued. However, suppositories including small amounts of steroid were permitted, as an exception. The statistical analyses were performed using the paired t test, and a p value of <0.05 was considered statistically significant.

Results

Rate of clinical remission

The CAI scores (mean±SE) before and after LI-CAP are shown in Fig. 1. The mean CAI score before LI-CAP was 7.550, which decreased significantly to 1.650 after treatment (p<0.0001). As shown in Fig. 2, the rate of clinical remission after LI-CAP was 80.0% (16/20).

Rate of the discontinuation of steroids

The rate of the discontinuation of steroids after LI-CAP was 60.0% (12/20) (Fig. 2). Three of the four patients who previously failed to discontinue steroids by conventional CAP discontinued steroids after LI-CAP. The dose of prescribed daily prednisolone (mean±SE) before and after LI-CAP is shown in Fig. 3. The mean dose of daily prednisolone was significantly lower after LI-CAP (2.30 mg) than

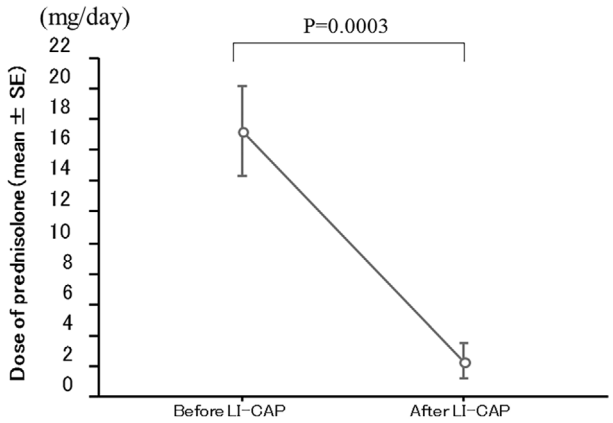

Figure 3. Mean daily dose of prednisolone before and after LI-CAP: The daily prescribed dose of prednisolone (mean±SE) before and after LI-CAP is shown. The mean daily dose of prednisolone was significantly lower after LI-CAP (2.30 mg) than before therapy (17.30 mg) (p=0.0003).

before therapy (17.30 mg) (p=0.0003).

Rate of clinical remission and of the discontinuation of steroids in patients who responded insufficiently to thioprines

Thioprines were prescribed in 7 cases [AZA 50 mg: 5 cases, 6-MP 30 mg: 2 cases; duration 10-116 weeks (mean 66 weeks)] before LI-CAP therapy. These cases responded insufficiently to thioprines. However, all seven cases achived clinical remission after LI-CAP therapy. In addition, 85.7% (6/7) of the patients prescribed thioprines discontinued steroids after LI-CAP.

Improvements in laboratory data

The laboratory data before and after LI-CAP are shown in Table 2. As shown in Table 2, the inflammatory parameters (CRP level, WBC count) and the nutritional parameters (serum albumin level) significantly improved after LI-CAP therapy. The Hb level tended to improve after LI-CAP therapy, but the improvement was not significant (Table 2).

Long-term effectiveness

The rate of sustained steroid-free clinical remission after LI-CAP in the patients who successfully discontinued steroids after LI-CAP was 66.7% at 6 months and 66.7% at 12 months.

Discussion

Steroids are effective for inducing remission in patients with active UC. However, it has been reported that a proportion of patients with UC (7-22%) develop chronically active or steroid-dependent UC (1-4). Since steroids are associated with serious systemic complications (25), it is very important for patients with steroid-dependent UC to achieve steroid-free remission. In this context, we designed a novel regimen of LI-CAP to allow for the discontinuation of steroids in patients with steroid-dependent UC (23). In this study, we confirmed our previous findings that LI-CAP has therapeutic effects on reducing the dosage of and facilitating the discontinuation of steroids in patients with steroid-dependent UC. We also showed that LI-CAP has good long-term efficacy.

Table 2. Laboratory Data Obtained (mean±SE) before and after LI-CAP.

	Before LI-CAP	After LI-CAP	Difference
CRP (mg/dL)	0.744±0.18	0.079±0.045	p=0.0027
WBC (μL)	8,585±751	6,740±648	p=0.0052
Hb (g/dL)	12.2±0.40	12.8±0.28	ns
Albumin (g/dL)	3.71±0.12	4.16±0.06	p=0.0012

CRP: C-reactive protein, WBC: white blood cell count, Hb: hemoglobin, ns: not significant

Several studies have suggested the steroid-sparing effects of CAP (16-19). Cabriada et al. (17) evaluated the short- and long-term effectiveness of LCAP in the management of patients with steroid-dependent UC. They showed that initial clinical remission with complete steroid withdrawal was achieved in 37% of cases. They also showed that the long-term clinical remission rates at 6 and 12 months were 41% and 36%, respectively. Ricart et al. evaluated the efficacy of 5 (group 1) and 10 (group 2) GMA sessions in patients with active steroid-dependent UC (19). They showed that 37.5% of patients in group 1 and 45.45% of those in group 2 were in clinical remission at 17 weeks. They also showed that 86% of patents achieving remission were steroid-free at 17 weeks. In the present study, the rate of clinical remission, rate of steroid discontinuation, and rate of sustained steroid-free clinical remission at 12 months of LI-CAP were 80%, 60%, and 66.7%, respectively. In addition, although the evaluation period and method were not identical to those parameters in this study, the rate of clinical remission and rate of steroid discontinuation of steroid-dependent UC treated with conventional CAP at our hospital between 2002 and 2009 were 71% and 46.6%, respectively (data not shown in the results section). Further, of note: three of the four steroid-dependent UC patients who previously failed to discontinue steroids by conventional CAP were ultimately able to discontinue steroids after LI-CAP. These results suggest that LI-CAP was more effective than conventional CAP in patients with steroid-dependent UC.

AZA and 6-MP have been generally used in the treatment of patients with steroid-dependent UC (4, 5, 26). Park et al. reported that 35.8% of patients with steroid-dependent UC maintained remission for a period of 3 years with AZA therapy (5). In addition, Chebli et al. reported that the proportion of patients maintaining steroid-free remission using AZA at 12, 24, and 36 months was 0.55, 0.52, and 0.45, respectively (26). However, as we mentioned before, a proportion of steroid-dependent UC patients reportedly do not respond or respond insufficiently to AZA (5). In this context, it is noteworthy that our study showed that LI-CAP had

therapeutic effects, even in the UC patients who responded insufficiently to thioprines.

The efficacy of anti-TNF-α antibodies, including infliximab (IFX) and adalimumab (ADA), for steroid-dependent UC has also been reported (27-30). Panaccione et al. (28) reported that corticosteroid (CS)-free remission at week 16 was achieved by 39.7% of UC patients receiving IFX + AZA. Sandborn et al. (29) showed that 49.6% of ADA-treated UC patients achieved clinical response at week 8 and that 21.1% of these responders achieved steroid-free remission at week 52. However, the use of anti-TNF antibody combined with thiopurine was reportedly associated with an increased risk of lymphoma in inflammatory bowel disease (IBD) patients (31). In contrast, to our knowledge, there have been no reports suggesting any association between CAP and lymphoma in IBD patients. LI-CAP might therefore be a safe, recommendable therapy for steroid-dependent UC.

Of particular note, some cases that achieved steroid-free remission with LI-CAP relapsed on completion of LI-CAP. In this context, Emmrich et al. showed that patients with UC who received monthly leukocytapheresis remained in remission more frequently than those receiving no further treatment (32). Fukunaga et al. also assessed the efficacy of monthly GMA as maintenance therapy to suppress relapse in patients with steroid-dependent UC (33). They concluded that monthly GMA may potentially prevent UC relapse in patients who initially achieved remission through weekly GMA. We therefore strongly hope that further clinical trials with larger numbers of patients will confirm whether or not scheduled maintenance therapy with CAP results in the maintenance of remission of steroid-dependent UC.

In conclusion, in the present study, we confirmed for the first time that LI-CAP has a therapeutic effect leading to the dosage reduction and discontinuation of steroids in patients with steroid-dependent UC. We believe that LI-CAP may be a useful therapeutic alternative for patients with steroid-dependent UC. However, we suggest that LI-CAP may not be an appropriate therapy for severely active UC patients, as LI-CAP usually does not work promptly and thus might exacerbate the condition of such UC patients. In addition, our study has limitations, such as the lack of any control group and the relatively small number of patients enrolled. Thus, further case-controlled studies with larger numbers of patients are awaited to validate our results.

The authors state that they have no Conflict of Interest (COI).

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