Jpn J Apheresis **14** (1): 48-50, 1995

Efficacy and Safety of Leukocytapheresis Therapy with Leukocyte Removal Filter for Patients with Inflammatory Bowel Disease

K. Sawada, K. Amano, K. Ohnishi, T. Kosaka, S. Fukui, K. Yamada, M. Yamamura, K. Amano, M. Okabayashi, M. Wada, M. Satomi, and T. Shimoyama

4th Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya 663, Japan

Regardless of the cause of inflammatory bowel disease (IBD) involving environmental, genetic, immune, and microbiological agents,[1] the final pathway of tissue damage in IBD is mediated by the cellular immune response in the intestinal mucosa with white blood cells. Therefore, we examined its efficacy and the safety of leukocytapheresis therapy (LCAP)[2] with a leukocyte removal filter for patients with IBD such as UC and CD as LCAP had been used successfully in the treatment of rheumatoid arthritis,[3] Behçet's disease,[3] and pemphigus vulgaris.[3]

Patients and Methods

Eight patients with recurred active UC and 5 with CD were included in this study. Disease severity of UC patients were 4 with severe, 2 with moderately severe and 2 with mild grade.[4] Four of 5 CD patients had recurrent concomitant colonic and ileal lesions with moderately severe and one had a first episode of severe transmural colitis.[5] We obtained informed consent from all patients who participated in this clinical trial. LCAP was performed with a leukocyte removal filter, Cellsorba (Asahi Medical Co., Ltd.)[2,3] and Nafamostat mesilate (Torii Pharmaceutical Co., Tokyo)[6] was used as an anticoagulant. Three thousands milliliters of whole blood were processed at a blood flow rate of 50 ml/min and cubital or femoral veins were used to connect to the access and return lines.[2] LCAP was performed once weekly for 5 weeks as an intensive therapy and once every 4 weeks for 5 times as maintenance therapy. Drugs that had been given to the patients before LCAP were gradually withdrawn then stopped when possible.

Clinical manifestations, conventional routine laboratory tests, and endoscopic evaluation and/or barium enema examination were followed up before and after 5 procedures for each intensive and maintenance therapy. In addition, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and flow cytometry of T, B, OKT3+, OKT4+, OKT8+, HLADR+, HLADR+ CD3+, HLADR+CD4+, and HLADR+CD8 cells (%) were monitored before and after LCAP.

We classified the responses to the LCAP into 4 groups: 1) excellent improvement group, where clinical symptoms disappeared and endescopical examination showed remission for UC, IOIBD score showed more than 50% improvement for CD, during the intensive or maintenance therapy; 2) moderate improvement group, the clinical symptoms improved and objective examination showed improvement during the intensive or maintenance therapy, however, remission was not ascertained for US. IOIBD score showed 25% to 50% improvement for CD; 3) no change group, no clinical and no objective improvement was found during the intensive and maintenance therapy, nor deterioration was found; and 4) deterioration group, subjective and/or objective deterioration was found during the therapy.

Patients who showed no improvement at the end of either intensive or maintenance therapy were dropped out and given conventional treatments such as an increase of drug dosage, new medication, and/or operation.

Results

LCAP procedures were well tolerated by all patients. There was no side effect regarding LCAP therapy and routine laboratory tests for liver and renal functions were normal during the therapy. During the intensive therapy, clinical and objective improvements were found in 11 (84.6%) out of 13 patients, including 6 with excellent improvement and 5 with moderate improvement status. However, 2 mild UC patients (15.4%) with a disease history of longer than 10 years showed no change (Table 1). Clinical and objective improvements maintained in 8 of 13 patients (61.5%) in the maintenance therapy, including 6 with maintained remission status and 2 with maintained moderate improvement status. Furthermore, all these 8 patients have been showing remission status with LCAP once a month for more than 10 months without any other medications (Table 1). One of the 2 UC patients with moderate

Table 1 Clinical feature of patients with ulcerative colitis (UC) and Crohn's disease (CD).

Patient	Age, sex, & disease	Duration of disease (years)	Drugs administered before LCAP	Severity and classification	Response for LCAP		Duration of improvement
					Intensive	Maintenance	
#1	26 M, UC	1.5	PI: 60 mg/day	Severe Entire colon	Excellent	Excellent	13 months
#2	27 F, UC	2.5	PI: 60 mg/day	Severe Entire colon	Excellent	Excellent	10.5 months
#3	27 F, UC	2.3	PI: 60 mg/day	Severe Entire colon	Excellent	Excellent	10 months
#4	22 M, UC	3.5	PO: 50 mg/day S: 3.0 g/day	Severe Entire colon	Excellent	Excellent	15 months
#5	19 M, UC	5.0	PO: 50 mg/day S: 3.0 g/day	Moderate Entire colon	Moderate	Moderage	14 months
#6	32 M, UC	6.0	PO: 40 mg/day S: 3.0 g/day	Moderate Entire colon	Moderate	No change	Drop out
#7	40 F, UC	10.0	PO: 20 mg/day S: 3.0 g/day	Mild Entire colon	No change	Drop out	—
#8	47 M, UC	15.0	PO: 30 mg/day S: 3.0 g/day	Mild Proctitis	No change	Drop out	—
#9	19 F, CD	(1 week)	None IVH	Severe TC	Excellent	Excellent	14 months
#10	28 M, CD	11.0	S: 3.0 g/day IVH	Moderate EC	Excellent	Excellent	10 months
#11	18 F, CD	4.5	None IVH	Moderate EC	Moderate	Moderate	12 months
#12	19 F, CD	2.5	None IVH	Moderate EC	Moderate	No change	Drop out (operation)
#13	37 M, CD	8.0	ED	Moderate EC	Moderate	No change	Drop out (operation)

PI: prednisolone intravenously, PO: prednisolone orally, S: salazosulfapyridine, IVH: intravenous hyperalimentation, ED: elemental diet, TC: transmural colitis, EC: enterocolitis.

Table 2 Results of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and flow cytometries performed in the both effective and ineffective responders.

	Normal range	Effective responders Excellent and moderate improvement (n=7)			Ineffective responders No change (n=3)		
		Pre	Post intensive	Maintenance	Pre	Post intensive	Maintenance
CRP (mg/dl)	0–0.3	6.1±5.3[a)]	0.32±0.1[a,b)]	0.21±0.1[a,b)]	2.0±1.1[a)]	1.35±0.6[a)]	1.3±0.6[a)]
ESR (1 hour)	<10	52.5±30[a)]	12.5±12.3[b)]	12.3±6.3[b)]	14.1±5.1[a)]	13.2±7.1	11.2±8.5
T cell (%)	66–89	83.1±6.2	84.2±6.3	81±7.5	83.2±4.8	82.2±6.8	80.3±10
B cell (%)	4–17	12.9±3.1	15.9±4.8	16.2±6.2	15.7±3.9	14.5±5.1	14.9±4.1
OKT3+cells (%)	58–84	64.8±11.5	66.7±8.3	63.8±7.9	63.1±9.2	62.4±8.8	64.1±7.5
OKT4+cells (%)	25–56	37.3±8.5	43.1±6.3	48.4±3.5[a,b)]	41±2.2	42.1±3.2	37.3±3[a)]
OKT8+cells (%)	17–44	41.6±7.1	33.7±7.3[b)]	31.1±4.1[b)]	37±4.2	34.4±4.1	37.2±6.8
HLADR+cells (%)	8–33	48.5±11.7[a)]	38.6±6.4[a,b)]	33.7±7.1[b)]	32±10.5[a)]	33.2±11[a)]	31.2±8
HLADR+CD3+ (%)	<8	27.3±2.7[a)]	17.2±2.1[a,b)]	16.6±2.8[a,b)]	6.5±10.3[a)]	7.1±2.3[a)]	7.4±2.9[a)]
HLADR+CD4+ (%)	<6	5.4±2.2[a)]	5.2±1.6[a)]	5.1±1.9[a)]	1.5±2.1[a)]	1.4±3.1[a)]	1.6±2.1[a)]
HLADR+CD8+ (%)	<10	20.1±5.2[a)]	15.2±3.9[a)]	10±2.2[a,b)]	9.2±3.1[a)]	6.8±2.2[a)]	6.6±2.8[a)]

P value <0.05. [a)] Effective group vs ineffective group, [b)] pre vs post intensive or maintenance therapy.

improvement during the intensive therapy dropped out because the endoscopic finding showed no further improvement after the maintenance therapy. In CD, 2 of the 3 patients who had shown moderate improvement dropped out during the maintenance therapy period because the stenosis ileum was not resolved and surgery was necessary to remove the stenotic area. However, patient #10 with CD who had had operations to remove stenotic area twice previously showed excellent improvement during both the intensive and the maintenance therapy. Dosage of the drugs such as prednisolone and salazosulfapyridine was gradually decreased and stopped during the intensive therapy in only the patients with improvement.

The flow cytometry results showed high initial values of HLADR+, HLADR+CD3+, and HLADR+

CD8+ cells % decreased and approached the normal range, OKT8+ cells % deceased, and OKT4+cells % and the ratio of OKT4/OKT8 increased after LCAP therapy significantly as well as the improvements of CRP and ESR in the only effective responders (Table 2). However, these cells % before LCAP therapy for the ineffective responders were generally near or within the normal range and their initial values of CRP and ESR were lower than those of the effective responders, and no significant changes were noted for them during LCAP therapy. There were no significant changes for T, B, OKT3+, HLADR+CD4+ cells % and T/B ratio for both groups.

Discussion

The results indicated that this therapy was effective for the UC patients with relatively short disease history regardless of the disease severity although it seems to be ineffective for the patients with a long disease history. LCAP was ineffective towards CD patients with a stenotic lesion, however the patient with operations to remove the stenotic lesions may benefit from LCAP therapy. It has been reported that the number of active WBC had increased in the patients with active UC and CD.[7] In the results of flow cytometry, high initial values of HLADR+, HLADR+CD3+, and HLADR+CD8+ cells % before the initiation of LCAP decreased and approached the normal range only in the patients with effective response and they were almost within the normal range in the ineffective responders (Table 2). These results of CRP, ESR, flow cytometry, and relatively mild disease severity in the ineffective responders suggest that the inflammation of the intestine may have been burnt out already in them.

The clinical improvement in the absence of any additional medical treatment suggests that LCAP had an effect on the causal mechanism(s) of IBD and that the cause of IBD is strongly associated with cell-mediated immune responses.[8] The present results showed that LCAP is a safe and effective treatment for patients with IBD. These promising results may justify conducting a larger scale controlled study for testing the effect of LCAP for IBD.

References

1) Podolsky DK: Inflammatory bowel disease (First of two parts). N Engl J Med **325**: 928-937, 1991
2) Sawada K, Malchesky PS, Nosé Y: Available removal system: State of the art. In Therapeutic Hemapheresis in the 1990s. Current Studies in Hematology and Blood Transfusion, vol. 57, Nydegger UE, ed, Karger, Basel, 1990, p. 51-113
3) Amano K, Ezaki H, Fujimoto K, et al: Leukapheresis for autoimmune diseases. Therapeutic Plasmapheresis **IX**: 423-425, 1991
4) Bockus HL, Roth JLA, Buchman E, et al: Life history of nonspecific ulcerative colitis; Relation of prognosis to anatomical and clinical varieties. Gastroenterologia **86**: 549-581, 1956
5) Krause U, Bergman K, Norlen BJ: Crohn's disease. A clinical study based on 186 patients. Scand J Gastroenterol **6**: 97-108, 1971
6) Aoyama T, Ino Y, Ozeki M, et al: Pharmacological studies of FUT-175, Nafamostat Mesilate. I. Inhibition of protease activity in *in vitro* and *in vivo* experiments. Jpn J Pharmacol **35**: 203-227, 1984
7) McCarthy DA, Rampton DS, Liu Y-C: Peripheral blood neutrophils in inflammatory bowel disease: Morphological evidence of *in vivo* activation in active disease. Clin Exp Immunol **86**: 489-493, 1991
8) Matsuura T, West GA, Youngman KR, et al: Immune activation genes in inflammatory bowel disease. Gastroenterology **104**: 448-458, 1993