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Safety and efficacy of leukocytapheresis in elderly patients with ulcerative colitis: The impact in steroid-free elderly patients

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Key words
elderly patients, leukocytapheresis, safety, ulcerative colitis.

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Declaration of conflict of interest:
K. Matsuoka, T. Kobayashi, Y. Yokoyama, Y. Suzuki, and T. Hibi have served as speakers of Asahi Kasei Medical. K. Matsuoka, T. Kobayashi, Y. Yokoyama, and T. Hibi have served as advisory board members for Asahi Kasei Medical. K. Matsuoka received honoraria for AbbVie GK and Mitsubishi Tanabe Pharma Corporation; T. Kobayashi received honoraria for Asahi Kasei Medical; Y. Suzuki received honoraria for Mitsubishi Tanabe Pharma Corporation, AbbVie GK, Zeria Pharmaceutical Co. Ltd., and KYORIN Pharmaceutical Co., Ltd.; and T. Hibi received honoraria for Asahi Kasei Medical.

Abstract

Background and Aim: The number of elderly patients with ulcerative colitis (UC) is increasing. Several new therapies for UC have improved patient outcomes. Leukocytapheresis (LCAP) is an extracorporeal therapy for UC. However, its efficacy and safety for elderly UC patients has not been reported.

Methods: We conducted a *post hoc* analysis of data from a large, prospective, observational study of LCAP, conducted at 116 medical facilities in Japan between May 2010 and December 2012. Of 847 patients included in this analysis, LCAP was used in 75 (8.9%) elderly patients (≥ 65 years) and 772 (91.1%) non-elderly patients.

Results: There were no serious adverse events in the elderly, and the rate of adverse events between the non-elderly and elderly was not different. Overall rate of remission was also not different between the two groups. In patients who were not on concomitant treatment with corticosteroids, the rate of remission was significantly higher in the elderly group than in the non-elderly group (90.9% [20/22] *vs* 64.6% [135/209], $P = 0.02$).

Conclusions: Real-world data demonstrate that the safety and tolerability of LCAP were comparable in the elderly and non-elderly groups, indicating that it is well tolerated by elderly UC patients.

Author contribution: The authors had full access to all the data and take responsibility for the integrity of the data and the analysis. All the authors were involved in critical revisions of the manuscript and approved the final manuscript.

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory condition of the gastrointestinal tract. While it usually affects young adults, UC can present at any age, including old age. About 25–35% of the population with inflammatory bowel disease (IBD) are above the age of 60 years.[1]

During the disease course, elderly UC patients have a higher risk for hospitalization, particularly during the first flare.[1] Patients above the age of 65 years account for about 25% of all IBD-related hospitalizations. These patients have a higher morbidity and mortality than non-elderly patients. Elderly IBD patients treated with oral corticosteroids have a high rate of overall, as well as serious infections.[2–6] Tumor necrosis factor (TNF) inhibitors in the elderly IBD patients lead to a high rate of severe infections and mortality, compared with non-elderly patients or patients of the same age who did not receive this therapy.[7] In addition, we must consider the high risk of drug interactions because of multiple medications.

Over the last decade, several new therapies for IBD (immunosuppressors and biologics) have improved patient outcomes, but there are limited data on their effectiveness and safety

in elderly IBD patients. It is difficult to obtain data for elderly IBD patients, because the old population is often excluded from clinical trials. To date, there have been no controlled clinical trials to evaluate treatment efficacy, specifically in the elderly population with UC. Thus, real-world data from a large, prospective, observational study would be very useful to evaluate treatment efficacy in such patients.

Leukocytapheresis (LCAP) using a Cellsorba E column (Asahi Kasei Medical Co., Ltd., Tokyo, Japan), which is filled with nonwoven polyester fiber, is a blood purification therapy that produces anti-inflammatory effects by removing activated leukocytes or platelets from the peripheral blood, through an extracorporeal circulation.[8–10] In a multicenter, double blind, prospective, case–control study with sham apheresis as placebo treatment, the response rate with LCAP was 80% in 19 patients with active UC, which was significantly higher than that in the sham group.[11] Because LCAP does not induce immunosuppression, adverse events or adverse events related to infection were extremely rare and it was considered a safe therapy.[12,13] Thus, LCAP is a promising candidate for treatment of UC in the elderly. However, data about its efficacy and safety in the elderly patients are not available.

We previously conducted a large-scale, prospective, observational study to evaluate the safety and efficacy of LCAP for active UC.[14] In this study, 75 patients were ≥ 65 years of age and 772 were < 65 years of age. Therefore, we analyzed the results of this study to evaluate the safety and tolerability of LCAP for UC in the elderly.

Methods

Study design. The present study used data from a large-scale, prospective, observational study of LCAP, which included 847 patients with active UC.[14] The study was conducted in accordance with the Good Post marketing Study Practice ordinance of the Japanese Ministry of Health, Labor, and Welfare. All patients in this study underwent LCAP at one of the 116 participating medical facilities, between May 2010 and December 2012. The treatment strategy for each patient, including the course of LCAP, was determined by the attending physician. The period of observation was from 2 weeks prior to the initiation of LCAP, up to 2 weeks following treatment completion. The treating physicians filled out case report forms after the observation period. Elderly group was defined as patients with the age of 65 years or older. Non-elderly group was defined as patients below 65 years of age.

Leukocytapheresis treatment. Leukocytapheresis was performed using Cellsorba E, a column filled with nonwoven polyester fiber to remove leukocytes. LCAP was performed 5–10 times during the treatment period with a blood flow rate of 30–50 mL/min and a blood processing volume ≥ 30 mL/kg bodyweight. Intensive LCAP was defined as performing ≥ 4 LCAP treatments within the first 2 weeks.

Assessment of treatment outcomes. The surveyed patient demographic data included age, weight, gender, UC disease duration, response to corticosteroids, and concomitant medications. The information from each LCAP session included the date that LCAP was performed, the amount of processed blood, the anticoagulant used, and the reason for discontinuation of LCAP where applicable.

The Lichtiger clinical activity index (CAI)[15] was used to determine efficacy and was assessed before the start of LCAP and 2 weeks after the last LCAP session. Clinical remission was defined as a CAI score ≤ 4 at 2 weeks after the last LCAP session. In addition, clinical improvement was defined as clinical remission or a final CAI score at least 50% lower than that obtained before the start of LCAP. Mucosal healing was assessed in all patients with an endoscopic index within the disease activity index[16] and was defined as an endoscopic index of ≤ 1 or 0 at 2 weeks after the last LCAP session.

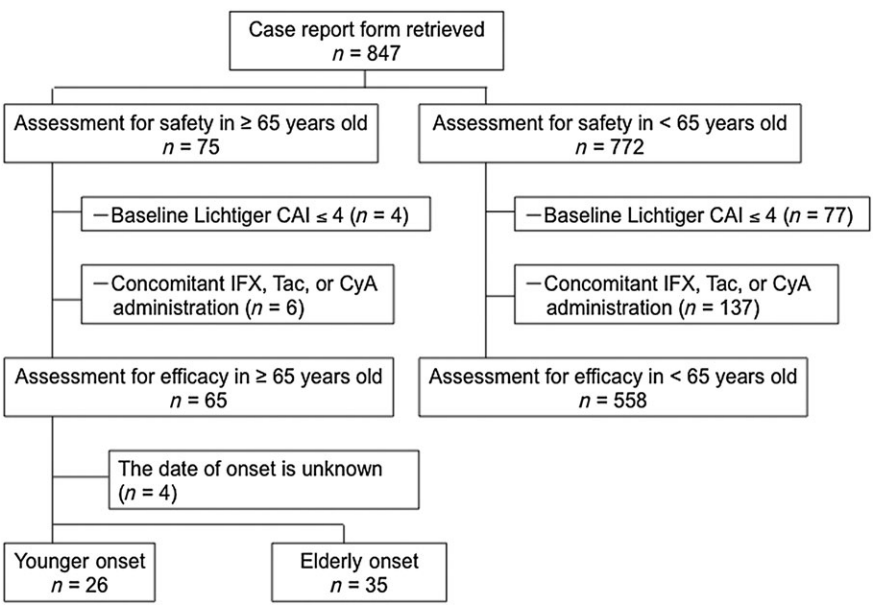

Figure 1 Study design. CAI, clinical activity index; CyA, cyclosporine; IFX, infliximab; Tac, tacrolimus.

Statistical analysis. Patient demographic data and treatment efficacy were compared by analyzing continuous data using Wilcoxon rank sum tests and categorical data using Fisher's exact test. Any missing data were excluded. In all the analyses, $P < 0.05$ (two sided) was considered to be statistically significant.

Results

Patients' background. Of the 847 patients enrolled in this study, 75 (8.9%) were 65 years or older (elderly group) and 772 (91.1%) were below 65 years of age (non-elderly group) and eligible for safety assessment. Of the 847 patients enrolled in this study, 81 who had a baseline CAI ≤ 4 and 143 who were concomitantly treated with infliximab, tacrolimus, or cyclosporine were excluded. The remaining 623 patients (65 of them belonged to the elderly group and 558 to the non-elderly group) were eligible for the efficacy outcome assessment. Of 65 patients in the elderly group, 26 had been diagnosed with UC when they were below 65 years of age, 35 cases were diagnosed at the age of 65 years or above, and the age at diagnosis was unknown in 4 (Fig. 1).

The patients' baseline data and concomitant medications of patients in the elderly and non-elderly groups are shown in Table 1. CAI score or extent of the disease was not different between the two groups. However, leukocyte counts, erythrocyte count, platelet count, and hemoglobin levels were significantly lower in the elderly group. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were significantly higher in the elderly group. The concomitant use of 5-aminosalicylic acid or corticosteroids were not different between the two groups. The use of thiopurines (azathioprine or 6-mercaptopurine) was 20.0% in the elderly group and 32.8% in the non-elderly group and significantly higher in the non-elderly group.

Table 1 Comparison of the baseline demographic data, concomitant medications, and LCAP treatment status between < 65-year-old (n = 558) and ≥ 65-year-old (n = 65) groups for the efficacy assessment

Item	≥ 65-year-old group (no. of patients)	< 65-year-old group (no. of patients)	*P* value
Age (years)	72.4 ± 5.5 (65)	38.2 ± 13.0 (558)	< 0.01†
Body weight (kg)	55.3 ± 9.2 (60)	57.5 ± 11.3 (511)	0.20†
Sex (male/female) (%)	70.8/29.2 (65)	57.9/42.1 (558)	0.05‡
UC duration (years)	7.9 ± 7.2 (61)	6.8 ± 7.6 (542)	0.14†
Lichtiger CAI	9.7 ± 2.9 (65)	10.3 ± 3.1 (558)	0.12†
Clinical activity			
Mild (CAI = 5–6) (%)	12.3	11.6	
Moderate (CAI = 7–11) (%)	58.5	55.2	0.82‡
Severe (CAI ≥ 12) (%)	29.2	33.2	
Disease extent			
Total/left sided/others (%)	61.5/33.8/4.6 (65)	54.0/40.5/5.6 (556)	0.51‡
Response to corticosteroid			
Resistant/dependent/nonrefractory (%)	40.0/27.7/32.3 (65)	26.3/38.0/35.7 (555)	0.06‡
Laboratory data			
Leukocyte count (per mm^3)	7672.1 ± 2872.6 (63)	9065.9 ± 3902.1 (533)	0.01†
Erythrocyte count ($\times 10^4/mm^3$)	387.3 ± 66.9 (63)	435.3 ± 60.0 (532)	< 0.01†
Platelet count ($\times 10^4/mm^3$)	26.7 ± 10.5 (63)	33.9 ± 11.8 (532)	< 0.01†
Hemoglobin level (g/dL)	11.8 ± 2.2 (63)	12.4 ± 2.1 (532)	0.04†
CRP level (mg/dL)	2.7 ± 3.8 (62)	2.3 ± 4.4 (530)	0.02†
Erythrocyte sedimentation rate (mm/h)	43.3 ± 28.4 (39)	35.3 ± 29.6 (294)	0.03†
Concomitant medications			
5-ASA (%)	92.3 (60)	95.9 (535)	0.20‡
Corticosteroids (%)	66.2 (43)	62.5 (349)	0.59‡
Thiopurine (%)	20.0 (13)	32.8 (183)	0.04‡
LCAP treatment status			
Number of LCAP sessions	9.0 ± 2.1 (65)	8.5 ± 2.4 (558)	0.38†
Weekly/intensive LCAP (%)	32.3/67.7 (62)	29.3/70.7 (519)	0.66‡
Blood processing volume per weight (mL/kg)	47.2 ± 12.8 (59)	43.9 ± 13.6 (508)	0.04†

The data shown are percentages (%) or mean ± standard deviation values.

†Calculated using the Wilcoxon rank sum test.

‡Calculated using the Fisher's exact test.

5-ASA, 5-aminosalicylic acid; CAI, clinical activity index; CRP, C-reactive protein; LCAP, leukocytapheresis; UC, ulcerative colitis.

Rate of completion of treatment. Completion of treatment was defined as 5 cycles or more of LCAP. Rate of completion of treatment was 90.7% (68/75) in the elderly group and 91.3% (705/772) in the non-elderly group, and they were not significantly different ($P = 0.83$). The reasons for discontinuation of LCAP in seven patients of the elderly group were adverse events in three, poor efficacy in one, increased intrafilter pressure or blood clotting in two, and satisfactory response in less than 5 cycles of LCAP in one.

Safety. The overall incidence of adverse events was 10.3% (87/847). The main adverse events observed were headache, nausea, and fever, which are commonly associated with extracorporeal circulation. Adverse events related to infections were observed only in three patients (0.4%). Almost all adverse events were mild to moderate, and all patients either recovered from the events or showed a significant improvement. The rate of adverse events in the elderly group was 8.0% (6/75), while that in the non-elderly group was 10.5% (81/772), and they were not significantly different (Fig. 2). Six severe adverse events were reported in five patients (0.6%), and all patients were in the non-elderly group. All the patients recovered from these events after appropriate treatment. All adverse events observed in the elderly group are listed in Table 2. There were no specific adverse events that were observed only in the elderly group. Importantly, there were no severe infection or thrombosis cases in the elderly group.

Efficacy outcomes. Among 623 patients, the overall rate of clinical improvement was 73.8% (460/623), and the rate of clinical remission was 68.9% (429/623), 2 weeks after the last LCAP session. The rate of improvement was higher in the elderly group than in the non-elderly group (83.1% [54/65] *vs* 72.8% [406/558], $P = 0.08$). The remission rate in the elderly group was also higher than that in the non-elderly group (78.5% [51/65] *vs* 67.7% [378/558], $P = 0.09$) (Fig. 3a). The baseline disease activity indicated by CRP or ESR was significantly higher in the elderly group. The rate of mucosal healing was not different between the groups: 64.5% (20/31) in the elderly and 62.2% (125/201) in the non-elderly group ($P = 0.85$) (Fig. 3b).

In patients who were on concomitant treatment with corticosteroids, the remission rate between the non-elderly and the elderly groups was not different (72.1% [31/43] *vs* 69.6% [243/349], respectively). On the contrary, in patients who were not on concomitant corticosteroids therapy, the rate of clinical improvement was significantly higher in the elderly group than in the non-elderly group (90.9% [20/22] *vs* 69.4% [145/209], respectively, $P = 0.04$). The rate of remission was also significantly higher in the elderly group than in the non-elderly group (90.9% [20/22] *vs* 64.6% [135/209], $P = 0.02$) (Fig. 4).

Comparison of efficacy with respect to the age at disease onset. We divided the elderly group into two subgroups, based on the age at disease onset: patients diagnosed at younger than 65 years of age (non-elderly-onset group) and patients diagnosed at 65 years or older (elderly-onset group). The patients' baseline parameters and concomitant medications for the non-elderly-onset and elderly-onset groups are shown in Table 3. Extent of the disease or CAI was not different between the two groups. However, the CRP level was significantly higher in the elderly-onset group ($P = 0.02$). The remission rate between the elderly-onset and non-elderly-onset groups was not different (76.9% *vs* 77.1%) (Fig. S1). We compared the remission rates between the steroid-free elderly-onset and non-elderly-onset groups. Remission rate in the steroid-free elderly-onset group was 100% (6/6) and that in the steroid-free non-elderly-onset group was 86.7% (13/15), and they were not significantly different ($P = 1.00$).

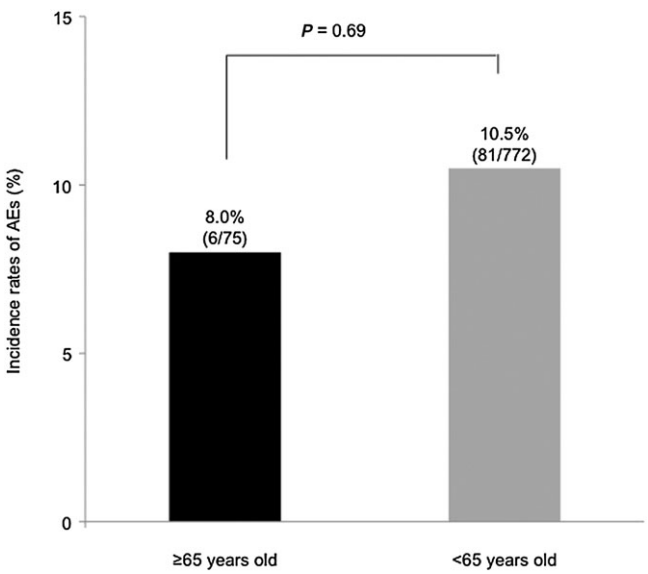

Figure 2 Comparison of incidence rates of adverse events (AEs) between ≥ 65-year-old ($n = 75$) and < 65-year-old ($n = 772$) groups.

Discussion

There are limited data on the efficacy and safety of therapy in elderly IBD patients, and this is the first report that compared the efficacy and safety of LCAP between non-elderly and elderly patients. The efficacy and remission rate between the two groups were not different. At baseline, the CAI score was not different between the groups, but indicators for active inflammation such as CRP level and ESR were significantly higher in the elderly group. In addition, in patients who were not on concomitant corticosteroid therapy, the rate of remission was significantly higher in the elderly group than in the non-elderly group. Finally, we compared the efficacy of LCAP between those diagnosed at 65 years of age or above and those diagnosed at an age below 65 years.

Table 2 Adverse events in elderly group patients (≥ 65)

No.	Age	Sex	Clinical activity	Disease extent	Anticoagulants	Adverse events	Severity	Treatment	Outcome
1	68	Male	Moderate	Total	Nafamostat mesilate	Rash	Slight	(−)	Recovery
2	83	Female	Moderate	Left sided	Nafamostat mesilate	Vomiting	Slight	(+)	Recovery
						Vomiting	Slight	(−)	
3	65	Female	Mild	Total	Nafamostat mesilate	Vomiting	Moderate	(−)	Recovery
						Epigastric distress	Moderate	(−)	Recovery
4	76	Male	Severe	Left sided	Heparin	Platelet count decreased	Slight	(−)	Recovery
						Platelet count decreased	Slight	(−)	Recovery
5	73	Female	Moderate	Total	Nafamostat mesilate	Blood pressure decrease	Moderate	(+)	Recovery
6	69	Male	Mild	Total	Nafamostat mesilate	Anaphylactic shock	Moderate	(+)	Recovery
						Anaphylactic shock	Moderate	(+)	Recovery

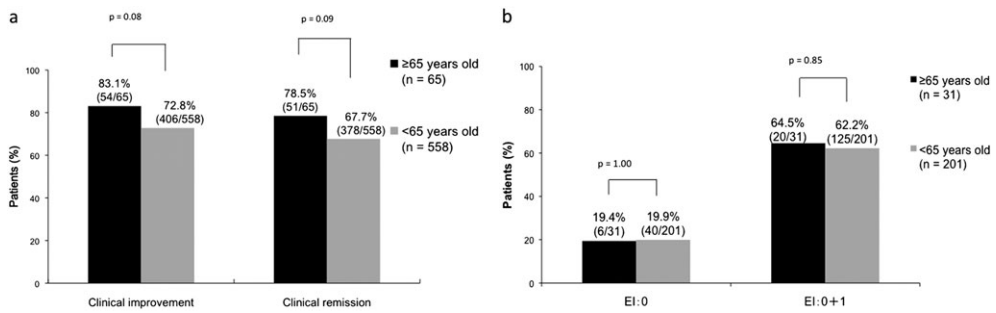

Figure 3 Comparison of efficacy between (■) ≥ 65-year-old (n = 65) and (■) < 65-year-old (n = 558) and between (■) ≥ 65-year-old (n = 31) and (■) < 65-year-old (n = 201) groups. (a) Clinical improvement and remission. (b) Mucosal healing rates.

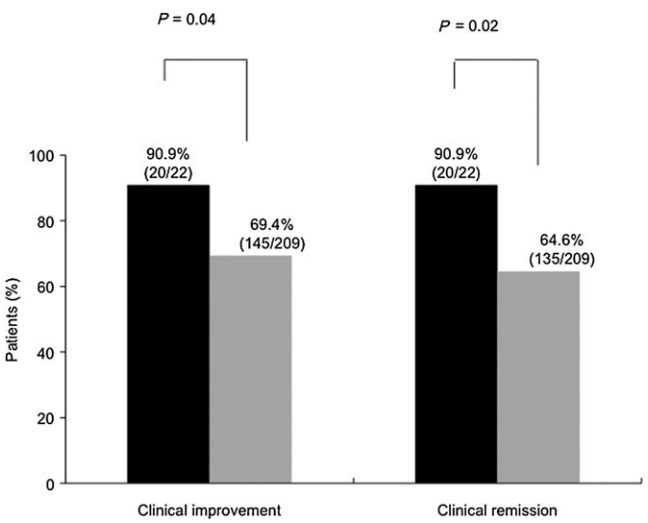

Figure 4 Comparison of efficacy between (■) ≥ 65-year-old (n = 22) and (■) < 65-year-old (n = 209) groups in patients not concomitantly treated with corticosteroids.

Table 3 Comparison of the baseline patient demographic data and concomitant medications between the non-elderly-onset group (diagnosed at younger than 65 years of age) (n = 26) and elderly-onset group (diagnosed at 65 years of age or older) (n = 35)

Item	Non-elderly-onset group (no. of patients)	Elderly-onset group (no. of patients)	P value
Age (years)	69.4 ± 4.5 (26)	74.3 ± 5.0 (35)	$< 0.01^{\dagger}$
Body weight (kg)	56.4 ± 10.4 (23)	54.8 ± 8.6 (34)	$0.67^{\dagger}$
Sex (male/female) (%)	65.4/34.6 (26)	74.3/25.7 (35)	$0.57^{\ddagger}$
UC duration (years)	13.4 ± 6.7 (26)	3.9 ± 4.3 (35)	$< 0.01^{\dagger}$
Lichtiger CAI	9.5 ± 2.8 (26)	10.1 ± 2.9 (35)	$0.45^{\dagger}$
Clinical activity			
Mild (CAI = 5–6) (%)	15.4	5.7	
Moderate (CAI = 7–11) (%)	53.8	65.7	$0.41^{\ddagger}$
Severe (CAI ≥ 12) (%)	30.8	28.6	
Disease extent			
Total/left sided/others (%)	53.8/42.3/3.8 (26)	62.9/31.4/5.7 (35)	$0.67^{\ddagger}$
Response to corticosteroid			
Resistant/dependent/nonrefractory (%)	42.3/34.6/23.1 (26)	37.1/22.9/40.0 (35)	$0.54^{\ddagger}$
Laboratory data			
Leukocyte count (per mm^3)	8247.6 ± 3001.3 (25)	7289.1 ± 2870.2 (34)	$0.21^{\dagger}$
Erythrocyte count ($\times 10^4/mm^3$)	413.8 ± 42.2 (25)	365.8 ± 73.8 (34)	$0.01^{\dagger}$
Platelet count ($\times 10^4/mm^3$)	28.1 ± 7.9 (25)	26.8 ± 12.0 (34)	$0.29^{\dagger}$
Hemoglobin level (g/dL)	12.3 ± 1.8 (25)	11.3 ± 2.4 (34)	$0.11^{\dagger}$
CRP level (mg/dL)	1.5 ± 2.8 (24)	3.6 ± 4.4 (34)	$0.02^{\dagger}$
Erythrocyte sedimentation rate (mm/h)	39.1 ± 23.4 (14)	48.1 ± 31.1 (23)	$0.48^{\dagger}$
Concomitant medications			
5-ASA (yes/no) (%)	88.5 (23)	97.1 (34)	$0.30^{\ddagger}$
Corticosteroids (yes/no) (%)	76.9 (20)	57.1 (20)	$0.17^{\ddagger}$
Thiopurine (yes/no) (%)	26.9 (7)	17.1 (6)	$0.53^{\ddagger}$

The data shown are percentages (%) or mean ± standard deviation values.

†Calculated using the Wilcoxon rank sum test.

‡Calculated using the Fisher's exact test.

LCAP, leukocytapheresis; UC, ulcerative colitis; CAI, clinical activity index; 5-ASA, 5-aminosalicylic acid; CRP, C-reactive protein.

Efficacy of LCAP was not different between the two groups. Based on these findings, we concluded that LCAP is as effective in elderly UC patients as that in non-elderly UC patients, especially in patients who are corticosteroid naïve.

The reasons for the significantly higher rate of efficacy in the elderly group not concomitantly treated with corticosteroids compared with similar patients in the non-elderly group were not ascertained in this study. Difference in the pathophysiology of UC between non-elderly patients and elderly patients has not yet been extensively clarified. It has been recently proposed that age-related loss of regulatory subsets of T cells function increases the risk for autoimmunity.[17] It is possible that the immunological status between non-elderly and elderly patients with UC is different. Although the elderly have a high CRP level and ESR, they have a low leukocyte count. We presume that this is because baseline leukocyte counts decrease physiologically, as age advances. Because one of the mechanisms for the therapeutic effects of LCAP is increase in the regulatory subsets of T cells,[18] it might explain the significantly higher rate of effectiveness in the elderly group.

There is no evidence that the efficacy of any medical treatment in elderly IBD patients differs from that in the non-elderly.[19] Thus, it may not be surprising that the overall effectiveness of LCAP was not different between the non-elderly and elderly groups. However, it is noteworthy that the rate of adverse events between the groups was not different. The overall incidence of adverse events was very small 10.3% (87/847).[14] There were no serious adverse events such as severe infection in either group. All patients recovered from the adverse events after appropriate treatment. There was no serious infection or thrombosis in the elderly group.

All available data indicate a higher risk for serious adverse events with the use of corticosteroids in elderly patients with IBD, compared with non-elderly patients on corticosteroid therapy.[3–6] In a large study of elderly-onset IBD patients exposed to steroids, there was an increased risk for infections compared with steroid naive patients (relative risk 2.3; 95% confidence interval 18–2.9).[4] Those recently exposed (within the last 45 days) had a higher risk for infections (relative risk 2.8; 95% confidence interval 2.1–3.7).[4]

The use of thiopurines in the elderly increased the risk for lymphoma, non-melanoma skin cancer, and infections.[20,21] A prospective, observational cohort study showed that the multivariate-adjusted hazard ratio of lymphoproliferative disorders between elderly patients who received thiopurines *versus* those who did not was 5.28 (2.01–13.9, $P = 0.0007$).[22]

Elderly IBD patients treated with TNF inhibitors have an increased risk for severe infection compared with the non-elderly. Risk for tuberculosis increases with age and use of TNF inhibitors. Elderly patients treated with biologics had an increased risk for infections, malignancy, and mortality compared with the non-elderly or to elderly patients treated with other drugs.[7] The risk for severe adverse events was higher in patients above 65 years of age and taking anti-TNF (relative risk = 4.7; $P < 0.001$) with

both malignancy and infections.[23] In addition, some deaths were due to cardiovascular complications.

The exact reason as to why adverse events were not high in elderly patients treated with LCAP could not be ascertained in this study. One possible reason is that LCAP is a blood purification therapy, which removes activated leukocytes or platelets from the peripheral blood through an extracorporeal circulation, and does not involve administration of drugs. In this study, the blood processing volume by weight was larger in the elderly. It is partly because the rate of completion of treatment was higher in the elderly group because they experienced few side effects. It is considered that elderly patients on multiple drugs have a higher rate of adverse events. The potential for drug interactions is higher in elderly IBD patients. Because absorptive granulocyte and monocyte apheresis (GMA) is a similar non-pharmacological treatment for UC, GMA is also a promising treatment for elderly patients with UC. However, to the best of our knowledge, the safety and efficacy of GMA for elderly patients has not been reported and should be investigated in the future.

This study has some limitations. Because this was an observational post-marketing study, there was no common and predesigned treatment strategy. Thus, there was a limitation in evaluating the efficacy of treatment in this study. Moreover, not all the patients enrolled in this study underwent colonoscopy. However, the strength of this study is the large number of patients. Because enrolling elderly patients in randomized controlled study is difficult, a large observational study in elderly patients is necessary.

In conclusion, to the best of our knowledge, this large-scale, prospective study is the first to assess treatment outcomes of LCAP in elderly patients with UC. Based on the findings of our study, we conclude that LCAP is a safe and effective therapeutic option for UC in the elderly.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. Comparison of clinical remission between younger-onset (diagnosed at younger than 65 years of age) (n = 26) and elderly-onset (diagnosed at 65 years of age or older) (n = 35) groups.