A multicenter study of leukocytapheresis in rheumatoid arthritis

Y. Ueki[1], A. Sagawa[2], K. Tanimura[3], A. Yamada[4], K. Yamamoto[5], H. Tsuda[6], S. Tohma[7], K. Suzuki[8], M. Tominaga[9], Y. Kawabe[10], M. Mine[11], S. Honda[12], M. Tsukano[13], T. Nakamura[13], T. Hidaka[14], K. Eguchi[15]

[1]Rheumatic and Collagen Disease Center, Sasebo Chuo Hospital; [2]Sagawa Akira Rheumatology Clinic; [3]Center for Rheumatic Diseases, Tokeidai Memorial Hospital; [4]Department of Internal Medicine, Division of Rheumatology, The Jikei University School of Medicine; [5]Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo; [6]Department of Geriatric General Medicine, Juntendo Tokyo Koto Geriatric Medical Center; [7]Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization; [8]Internal Medicine I, National Defense Medical College; [9]Department of Internal Medicine, Nijigaoka Hospital; [10]Department of Rheumatology, Ureshino Medical Center, National Hospital Organization; [11]Department of Rheumatology, Suga Orthopedic Hospital; [12]First Department of Internal Medicine, Kurume University School of Medicine; [13]Section of Internal Medicine and Rheumatology, Kumamoto Center for Arthritis and Rheumatology; [14]Institute of Rheumatology, Zenjinkai Shimin-no-mori Hospital; [15]First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Japan.

Abstract

Objective

To evaluate the efficacy and safety of leukocytapheresis (LCAP) in patients with rheumatoid arthritis (RA) that is refractory to disease modifying antirheumatic drugs (DMARDs), we conducted a prospective, multicenter, open-label clinical trial.

Methods

We enrolled 38 active RA patients, including 32 patients who showed an inadequate response to ≥ 2 DMARDs and 6 patients with rapidly progressive RA. All patients continued drug therapy and were treated with 5 LCAP sessions conducted at 1-week intervals. The clinical response was evaluated at baseline before starting LCAP and at 4 weeks after the completion of all the LCAP sessions using the American College of Rheumatology (ACR) criteria and the 28-joint disease activity score (DAS28) of the European League Against Rheumatism (EULAR).

Results

Of the 35 patients who fulfilled the study's eligibility criteria, 24 (69%), 10 (29%), and 23 (66%) patients achieved 20% (ACR20), 50% (ACR50), and DAS28-C-reactive protein (CRP) EULAR improvement, respectively. The mean DAS28-CRP score of the 35 patients decreased significantly from 5.99 ± 0.92 at baseline to 4.54 ± 1.39 after treatment. Comparison analysis of the ACR20 responders and non-responders to LCAP revealed that 22 of 24 responders (92%) concomitantly received methotrexate, whereas significantly fewer, that is, 6 of 11 non-responders (55%) received methotrexate. Less frequent and transient mild-to-moderate adverse events, including nausea and headache, were seen in 12 of 189 LCAP sessions (6.3%).

Conclusion

These results demonstrate the usefulness of LCAP in combination with DMARDs, particularly methotrexate, as an effective and safe treatment for refractory RA.

Key words

Leukocytapheresis, rheumatoid arthritis, clinical trial, multicenter, methotrexate.

Yukitaka Ueki, MD; Akira Sagawa, MD; Kazuhide Tanimura, MD; Akio Yamada, MD; Kazuhiko Yamamoto, MD; Hiroshi Tsuda, MD; Shigeto Tohma, MD; Kimihiro Suzuki, MD; Masahiro Tominaga, MD; Yojiro Kawabe, MD; Masanobu Mine, MD; Seiyo Honda, MD; Michishi Tsukano, MD; Tadashi Nakamura, MD; Toshihiko Hidaka, MD; Katsumi Eguchi, MD.

Please address correspondence to: Yukitaka Ueki, MD, Rheumatic and Collagen Disease Center, Sasebo Chuo Hospital, Yamato-cho 15, Sasebo 857-1195, Japan.
E-mail: u-yuki@hakujyujikai.or.jp

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease clinically characterized by destructive synovitis and extra-articular immunologic abnormalities (1, 2). Although the etiology of RA is not completely understood, a large amount of research in the last 20 years has revealed that immunocompetent cells such as lymphocytes and macrophages play pivotal roles in the pathogenesis and progression of RA (3, 4). As a treatment to remove lymphocytes, thoracic duct drainage was previously attempted and its effectiveness for refractory RA has been reported (5, 6). However, the treatment has not been widely accepted because it involves surgery.

Leukocytapheresis (LCAP) was subsequently developed as a more convenient treatment that removes immunocompetent cells in the peripheral blood with a filter by extra-corporeal circulation (7). Hidaka *et al*. and Ueki *et al*. conducted clinical trials of LCAP in patients with RA that was refractory to disease modifying antirheumatic drugs (DMARDs) and in patients in whom DMARDs cannot be used because of their side effects; they presented evidence demonstrating the clinical benefit of LCAP (8, 9). However, in these studies only a small number of subjects were administered methotrexate (MTX) because the drug had not yet been approved for RA in Japan when these studies were conducted, although MTX is currently recommended as the first-line treatment for refractory RA (10). MTX was subsequently approved in Japan in 1999, and the efficacy of LCAP was reported in a small series of patients with RA that was refractory to MTX therapy in a single center study (11, 12).

Since LCAP involves an extra-corporeal procedure, there was a concern that the therapeutic outcome of LCAP could differ among centers. Therefore, we conducted a prospective study in which 15 centers participated. Here, we report the results concerning the efficacy and safety of LCAP in patients with RA that was refractory to therapy with DMARD, particularly MTX.

Methods and materials

Patients

The following were the eligibility criteria for this study: RA patients fulfilling the classification criteria of the 1987 American College of Rheumatology (ACR) (13), patients in the age range of 20–75 years, and duration of RA of ≥ 6 months. Furthermore, patients had to have: (i) active RA that was refractory to drug therapy, with an inadequate response to ≥ 2 DMARDs administered for ≥ 3 months (the applicable drugs were MTX, salazosulfapyridine, actarit, injectable gold, D-penicillamine, lobenzarit disodium, bucillamine, mizoribine, auranofin); or (ii) rapidly progressive RA with systemic symptoms such as fever and severe multi-articular synovitis that was refractory to drug therapy and in whom the disease activity could not be suppressed with steroids. In addition, 3 indices of RA disease activity had to be fulfilled: tender joint count ≥ 6 (among 49 joints), swollen joint count ≥ 6 (among 46 joints), C-reactive protein (CRP) level ≥ 3.0 mg/dl, or the erythrocyte sedimentation rate (ESR) ≥ 50 mm/h).

The exclusion criteria were leukopenia (WBC count < 3500/μl) or thrombocytopenia (platelet count < 10 x 10^4/μl). Patients with heart disease, cerebrovascular disease, hypotension (maximum blood pressure of ≤ 80 mmHg), pregnancy, dementia, active infection, or other serious diseases were also excluded from the study.

Prior to treatment, to confirm their eligibility the patients' demographics (age, disease history, coexisting illnesses, etc.), concurrent medications, disease activity, body weight, blood pressure, etc., were recorded. DMARDs were continued at the same dose until the completion of the study, without changing the dosage.

LCAP procedure

Leukocytapheresis was performed using the Cellsorba® column (CS-100, Asahi Kasei Medical Co., Ltd., Japan) (9). During treatment 16–20 gauge needles were cannulated into the peripheral veins, and outgoing and incoming extra-corporeal circuit lines were maintained. The column was installed

in an extra-corporeal machine, and blood was processed for 60–90 min using a blood pump at a speed of 35–50 ml/min. The anticoagulant nafamostat mesilate (Futhan, Torii Pharmaceutical Co., Ltd., Japan) was infused continuously into the incoming circuit line at 50 mg/h. LCAP was performed once a week for 5 weeks. The objective blood volume to be treated was 2000–3000 ml per treatment session.

Clinical and laboratory assessments

The following parameters of disease activity were evaluated prior to each of the 5 LCAP sessions and at 4 weeks after the completion of the LCAP treatment: the tender joint count, swollen joint count, patient assessment of pain (visual analog scale, VAS), patient assessment of global disease activity (VAS), physician assessment of global disease activity (VAS), patient assessment of physical function (m-HAQ) (14), CRP level, and ESR. Clinical hematological tests were conducted prior to LCAP sessions 1, 3, and 5 and at 4 weeks after the completion of treatment, while blood biochemistry tests were conducted prior to LCAP session 1 and at 4 weeks after the completion of the treatment.

Measurement of the clinical response

As the evaluation criteria for clinical efficacy, ACR improvement (15, 16), the 28-joint disease activity score (DAS28-ESR) (17), and the derivative DAS28-CRP (18) were used.

ACR20 and ACR50 are defined as 20% and 50% improvement, respectively, in the tender joint count and the swollen joint count, as well as 20% and 50% improvement, respectively, in 3 of the 5 remaining indices in the ACR core set (patient assessment of pain (VAS), patient assessment of global disease activity (VAS), physician assessment of global disease activity (VAS), patient assessment of physical function (m-HAQ), and acute phase reactant (CRP or ESR).

The DAS28-ESR and DAS28-CRP scores are calculated by an equation based on the following 4 parameters: the tender joint count for 28 joints (TJC28), the swollen joint count for 28 joints (SJC28), patient assessment of global disease activity (VAS), and the CRP or ESR level. The formulas are as follows: DAS28-ESR = 0.56 x $\sqrt{}$ (TJC28) + 0.28 x $\sqrt{}$ (SJC28) + 0.7 ln (ESR) + 0.014 x (VAS), DAS28-CRP = 0.56 x $\sqrt{}$ (TJC28) + 0.28 x $\sqrt{}$ (SJC28) + 0.36 x ln (CRP + 1) + 0.014 x (VAS) + 0.96. The EULAR improvement criteria classifies efficacy based on the DAS28 scores before and after treatment into 3 levels: "good response," "moderate response," and "no response" (18). A "good response" is defined as a patient in whom the DAS28 improves by > 1.2 and who has a DAS28 < 3.2 at the time of evaluation. A "moderate response" is defined as a patient who has either an improvement of DAS28 of 0.6 – 1.2 and a DAS28 < 3.2; or an improvement of DAS28 > 0.6 and a current DAS28 of 3.2 – 5.1; or who has an improvement of DAS28 > 1.2 and a current DAS28 > 5.1. Patients who do not fulfill these criteria are considered to show "no response."

The primary endpoint for efficacy was the proportion of patients achieving ACR20 at 4 weeks after the completion of the LCAP treatment. The ACR50 rate, both DAS28 values over time, and the EULAR criteria were evaluated as secondary endpoints (19).

Ethics

The clinical trial protocol was approved by the Human Ethics Review Committee of each center. Informed consent was obtained from all patients.

Statistical analysis

Continuous data was indicated as the mean ± standard deviation (SD). For changes within groups, non-standard distribution and rank data were analyzed using the Wilcoxon rank-sum test, while continuous data with standard distribution was analyzed using the Student's t-test. Comparisons between groups were analyzed using the Mann-Whitney U test. The bivariate chi-square test was used as a non-parametric test of statistical significance. P values less than 0.05 were considered statistically significant.

Results

Patient characteristics

Thirty-eight patients with RA refractory to drug therapy (7 men and 31 women, mean age 53.8 ± 10.9 years, age range 23–76 years) were enrolled in the study. The patient characteristics are summarized in Table I. At baseline the disease was very active, and the mean values for the tender joint count, swollen joint count, CRP level, and ESR were 16.4 ± 10.4, 12.1 ± 8.8, 4.1 ± 2.2 mg/dl, and 68.7 ± 25.7 mm/h, respectively.

The medications used by the 38 patients are summarized in Table II. Of the 38 RA patients, 32 were receiving NSAIDs, 35 were receiving DMARDs,

Table I. Baseline characteristics of 38 patients enrolled in the study.

Number of patients	38
Age, years (range)	53.8 ± 10.9 (23-76)
Male : female	7 : 31
Disease duration, years	8.8 ± 6.8
Tender joint count, 0-49 joints	16.4 ± 10.4
Swollen joint count, 0-46 joints	12.1 ± 8.8
Patient's assessment of pain, 0-100 mm VAS	67.1 ± 19.0
Patient's global assessment of disease activity, 0-100 mm VAS	65.2 ± 18.4
Physician's global assessment of disease activity, 0-100 mm VAS	64.6 ± 19.5
Patient's assessment of physical function, 0-24 m-HAQ	9.4 ± 4.5
C-reactive protein level, mg/dl	4.1 ± 2.2
ESR, mm/h	68.7 ± 25.7
Stage	2.9 ± 0.9
I, II, III, IV	2, 11, 15, 10
Class	2.3 ± 0.5

Values are presented as the mean ± SD. All other data represent the number of patients.
ESR: erythrocyte sedimentation rate; VAS: visual analog scale; m-HAQ: modified Health Assessment Questionnaire.

Table II. Medication taken by the 38 patients enrolled in the study.

Medication	Previous medication	Current medication
NSAIDs		32 (84%)
DMARDs	37 (97%)	35 (92%)
methotrexate	34 (89%)	29 (76%)
salazosulfapyridine	24 (63%)	10 (26%)
bucillamine	23 (61%)	5 (13%)
sodium aurothiomalate gold	11 (29%)	3 (8%)
actarit	9 (24%)	5 (13%)
auranofin	9 (24%)	0 (0%)
cyclosporine	7 (18%)	3 (8%)
penicillamine	5 (13%)	0 (0%)
mizoribine,	3 (8%)	2 (5%)
azathioprine	2 (5%)	0 (0%)
Corticosteroids		37 (97%)
Number of DMARDs	3. 3 ±1.7	1.5 ± 1.1
Dosage of methotrexate, mg/week		7.6 ± 2.7
Dosage of corticosteroids, mg/day		8.1 ± 3.5

Values are presented as the mean ± SD. All other data represent the number of patients. Values between parentheses represent percentages.
NSAIDs: nonsteroidal antiinflammatory drugs; DMARDs: disease-modifying antirheumatic drugs.

and 37 were receiving corticosteroids (2–15 mg/day; prednisolone equivalent 8.1 ± 3.5 mg/day). Thirty-four of the 38 patients had been treated in the past with MTX, and 29 were currently receiving MTX. The MTX dose was 4–12.5 mg/week (7.6 ± 2.7 mg/week). In Japan, the approved MTX dose is only up to 8 mg/week; RA in these subjects was considerably refractory to MTX therapy, because the disease activity could not be controlled despite treatment with almost the maximum allowed dose of MTX.

One patient who did not present for evaluation at 4 weeks after the completion of the treatment was considered to have dropped out, while 2 patients who did not fulfill the eligibility criteria were excluded from the efficacy analysis, but included in the safety analysis. Of the 35 patients included in the efficacy analysis, 30 were cases of DMARD-refractory RA and 5 were cases of rapidly progressive RA.

Clinical response

To evaluate the clinical efficacy of LCAP in RA, the data were analyzed using the ACR core set of measures at baseline prior to conducting LCAP and at 4 weeks after the last LCAP session. Table III shows the patients' responses according to the ACR core set. The mean tender joint count and swollen joint count scores decreased significantly, and ≥ 20% improvement was seen in 86% of the patients. The patient- and physician-assessed scores improved significantly as well. Table III also shows the mean DAS28-CRP and DAS28-ESR scores at baseline and at 4 weeks after the last LCAP session. Both of these scores decreased significantly.

Twenty-two of the 30 patients with DMARD-refractory RA and 2 of the 5 patients with rapidly progressive RA achieved ACR20 (Table IV). Overall, of the 35 patients, 24 (69%) achieved ACR20 and showed overall improvement after LCAP, and 10 (29%) achieved ACR50. By the EULAR improvement criteria based on DAS28-CRP, 23 of the 35 patients (66%) achieved EULAR improvement; of these 23 patients, 16 (46%) and 7 (20%)

Table III. Changes in individual components of the ACR core set and the DAS28 scores for the 35 eligible patients.

	Prior to LCAP (Baseline)*	4 weeks after the 5th LCAP session*	*P*-value†	≥ 20% response (ACR20)‡	≥ 50% response (ACR50)‡
Tender joint count	19.3 ± 11.2	9.1 ± 9.0	< 0.001	30 (86%)	17 (49%)
Swollen joint count	13.7 ± 9.1	6.8 ± 7.5	< 0.001	30 (86%)	22 (63%)
Patient's assessment of pain§	64.5 ± 19.0	42.7 ± 27.1	< 0.001	25 (71%)	12 (34%)
Patient's global assessment of disease activity§	65.1 ± 19.2	43.1 ± 27.4	< 0.001	22 (63%)	13 (37%)
Physician's global assessment of disease activity§	64.8 ± 19.4	35.6 ± 23.1	< 0.001	26 (76%)	19 (54%)
Patient's assessment of physical function¶	9.4 ± 4.9	7.2 ± 4.8	< 0.01	16 (46%)	9 (26%)
CRP level, mg/dl	3.8 ± 2.5	3.1 ± 3.3	NS	22 (65%)	14 (41%)
ESR, mm/h	67.3 ± 29.3	61.0 ± 31.5	NS	8 (25%)	3 (9%)
ACR overall improvement				24 (69%)	10 (29%)
DAS28-CRP score	5.99 ± 0.92	4.54 ± 1.39	< 0.001		
DAS28-ESR score	6.68 ± 0.85	5.29 ± 1.32	< 0.001		

*Values are presented as the mean ± SD.
†*P*-values were analyzed by the Wilcoxon rank-sum test.
‡Data represent the number of patients. Values between parentheses represent percentages.
§VAS score, range 0-100.
¶m-HAQ, range 0-24.
ACR: American College of Rheumatology; LCAP: leukocytapheresis.

Table IV. ACR and DAS28 EULAR responses at 4 weeks after the 5th LCAP session.

	DMARD-refractory RA	Rapidly progressive RA	All patients
No. of enrolled patients	32	6	38
No. of patients who completed the study	30	5	35
ACR20 response	22/30 (73%)	2/5 (40%)	24/35 (69%)
ACR50 response	9/30 (30%)	1/5 (20%)	10/35 (29%)
DAS28-CRP EULAR improvement	20/30 (67%)	3/5 (60%)	23/35 (66%)
Moderate response			23/35 (46%)
Good response			7/35 (20%)
DAS28-ESR EULAR improvement	19/30 (63%)	3/5 (60%)	22/35 (63%)
Moderate response			20/35 (57%)
Good response			2/35 (6%)

Data represent the number of patients. Values between parentheses represent percentages.
DAS28: 28-joint disease activity score; EULAR: European League Against Rheumatism.

Table V. Comparison of the ACR20 responders with the non-responders.

	ACR20 responders*	ACR20 non-responders*	*P*-value†
Number of patients	24	11	–
Age, years	52.5 ± 10.5	52.5 ± 9.4	0.958
Male/female	3 : 21	2 : 9	–
Disease duration, years	9.8 ± 7.1	5.7 ± 3.1	0.175
Stage	2.8 ± 0.8	2.9 ± 0.8	0.875
Class	2.2 ± 0.4	2.5 ± 0.5	0.267
Tender joint count	18.3 ± 11.4	21.5 ± 11.1	0.314
Swollen joint count	14.4 ± 9.6	12.0 ± 7.9	0.521
Patient's assessment of pain	61.7 ± 21.1	70.8 ± 11.7	0.127
Patient's global assessment of disease activity	64.7 ± 19.9	65.9 ± 18.5	0.861
Physician's global assessment of disease activity	64.7 ± 19.4	64.9 ± 20.4	0.819
Patient's assessment of physical function	9.7 ± 5.3	8.9 ± 4.2	0.916
CRP level, mg/dl	3.5 ± 2.3	4.3 ± 2.9	0.361
ESR, mm/h	64.7 ± 25.8	72.8 ± 36.6	0.587
White blood cell count, μl	9298 ± 2708	8336 ± 2758	0.675
Platelet count, 10^4/ μl	34.0 ± 11.9	33.2 ± 7.5	0.766
Number of concomitant DMARDs	1.7 ± 1.1	1.1 ± 0.7	0.145
Number of patients receiving MTX (%)‡	22 (92%)	6 (55%)	0.021¶
MTX dosage during study, mg/week§	7.8 ± 2.7	6.8 ± 2.2	0.122
Corticosteroid dosage, mg/day	7.8 ± 3.7	7.8 ± 3.8	0.889

*Values are presented as the mean ± SD. All other data represent the number of patients. Values between parentheses represent percentages.
†Statistically analyzed by the Mann-Whitney U-test, except for the parameter (‡), where the chi-square test was used.
§Excluding patients who were not concomitantly receiving MTX.
¶Significant < 0.05

Table VI. Incidence of adverse events.

	Patients†	Sessions‡
Overall	6 (15.8%)	12 (6.3%)
Nausea	3 (7.9%)	5 (2.6%)
Headache	1 (2.6%)	5 (2.6%)
Hypotension	2 (5.3%)	2 (1.1%)
Fever	1 (2.6%)	1 (0.5%)
Abdominal pain	1 (2.6%)	1 (0.5%)

Data represent the number of adverse events, whose relationship to LCAP cannot be denied. Values between parentheses represent percentages.
†Data from all 38 patients who underwent LCAP were analyzed for the incidence of adverse events.
‡Data from all 189 LCAP sessions were analyzed for the incidence of adverse events.

showed moderate and good responses, respectively. By the EULAR improvement criteria based on DAS28-ESR, 22 of the 35 patients (63%) achieved EULAR improvement; of the 22 patients, 20 (57%) and 2 (6%) showed moderate and good responses, respectively.

Comparison of the ACR20 responders with the non-responders

To investigate the background factors of patients whose clinical condition was improved by LCAP, we divided the patients into 2 groups — responders and non-responders; that is, those who achieved ACR20 and those who did not achieve ACR20, respectively. We compared the patients' characteristics at baseline between these groups. No significant differences were observed between the responders and non-responders with regard to any of the factors, except the percentage of patients who received MTX (Table V). In our study, 22 of the 24 responders (92%) were concomitantly receiving MTX, but only 6 of the 11 non-responders (55%) were receiving MTX. Excluding the patients who were not receiving MTX, no significant difference was observed in the mean dosage of MTX between the two groups. In the responder group, of the 2 patients who were not receiving MTX, 1 was MTX naive and the other had discontinued MTX due to side effects. On the other hand, in the non-responder group, of the 5 patients who were not receiving MTX, 1 was MTX naive, 1 discontinued MTX due to its side effects, and 3 discontinued MTX because of non-responsiveness to MTX.

Safety

Safety was evaluated in all 38 patients who underwent LCAP. A total of 14 adverse events, whose relationship to LCAP cannot be denied, were observed in 12 sessions of LCAP (total 189 sessions) in 6 patients (total 38 patients). The adverse events were as follows: 5 instances of nausea (3 patients); 5 of headache (1 patient); 2 of hypotension (2 patients); 1 of fever (1 patient); and 1 of abdominal pain (1 patient) (Table VI). Of the 14 adverse events, 10 events (4 patients) were mild and did

not require any intervention. The other 4 events (2 patients) were moderate in degree. One of the 2 patients experienced fever and abdominal pain prior to the fourth LCAP session, and the symptoms improved with the administration of fluid; however, the LCAP session was terminated at the patient's request. The other patient experienced hypotension and nausea, and the symptoms improved with the administration of intravenous fluids; and the subsequent LCAP sessions were conducted without encountering any problems. No serious adverse events were observed. None of the patients showed any adverse events during the period from the completion of LCAP to 4 weeks after the completion of LCAP.

Discussion

In this multi-center clinical study, 69% of refractory RA patients achieved ACR20 with LCAP treatment. Although this study targeted patients suffering from rapidly progressive RA or those with severe RA refractory to therapy with ≥ 2 DMARDs, and patients who met the 3 indices of (i) tender joint count ≥ 6, (ii) swollen joint count ≥ 6, and (iii) CRP level ≥ 3.0 mg/dl or ESR ≥ 50 mm/h, the therapeutic outcome of our study was similar to those found in previous single-center clinical studies (clinical outcomes reported: 79% by Hidaka *et al*. (8); 64% by Ueki *et al*. (9); 78% by Kempe *et al*. (11); and 73% by Izumi *et al*. (12)). Our outcome was also comparable to those of treatments with biological agents such as infliximab (20) and etanercept (21); the clinical trials of these agents targeted patients whose background was similar to that in our study.

Evaluation of the ACR core set revealed that the improvements in the joint symptoms and physician's global assessment of disease activity were remarkable; however, the mean CRP level and ESR did not change significantly. These therapeutic profiles were different from those obtained when DMARDs or biologicals were administered. Although little is known about the mechanism of action of LCAP, the following have been suggested as possiblities: (i) an immunomodulatory effect by removing lymphocytes from the peripheral circulation (22); (ii) redistribution of the activated T cells from the affected joints into the circulating blood (23); (iii) compensation of the cytokine levels in the serum and/or synovial fluid (24); or (iv) mobilization of immature hemocytes from the bone marrow pool (25). A pleiotropic mechanism of action may play a role in the therapeutic profiles of LCAP.

Comparison between the responders and non-responders to LCAP revealed that the number of patients who were concomitantly receiving MTX was significantly higher in the responder group (92%) than in the non-responder group (55%). MTX has been established as the anchor drug and probably should be the first DMARD used in the majority of RA patients (26). In addition, it has been reported that the use of MTX and, to a lesser extent, other DMARDs as a co-therapy with etanercept is associated with a higher likelihood of response (27). Thus, MTX rather than other DMARDs may have higher synergistic effects when combined with LCAP.

Furthermore, although the responder group did not include patients in whom MTX therapy was discontinued because of "no response to MTX", the non-responder group included 3 such patients. Since the patients currently receiving MTX in this study were those who showed an "insufficient response to MTX", their responsiveness to MTX was quite different from those with "no response to MTX". The maximum approved MTX dose is 8 mg/week in Japan, and as Table V indicates, the maximum dose was administered to almost all patients. This maximum was determined based on a study on Japanese RA patients (28), and a dose of MTX (6-8 mg/week) is generally believed to be sufficient for this ethnic group (29). Therefore, it is suggested that LCAP may be more effective in patients who show an "insufficient response to MTX despite receiving a sufficient dose of MTX" than in patients who show "no response to MTX".

The incidence of adverse events was low and transient, and no serious side effects were observed. Furthermore, unlike drug therapies – which require the factors of absorption, distribution, metabolism, and excretion of drugs to be taken into consideration – any long-term toxicity of LCAP administered through extra-corporeal circulation appears to be unlikely.

These results demonstrate the usefulness of LCAP in combination with DMARDs, particularly MTX, as an effective and safe treatment for refractory RA. Highly safe LCAP may be applicable to RA patients who are not eligible for an increase in the DMARD dose or for the administration of biologicals because of complications such as nephropathy, lung involvement, liver damage, and infection or due to advanced age.

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