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Intramuscular Injection of Autologous Serum in Adolescent and Adult Patients with Atopic Dermatitis: A Preliminary Randomized Clinical Trial

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Purpose: The favorable clinical efficacies of intramuscular injection of autologous blood in patients with atopic dermatitis (AD) and intramuscular injection of autologous serum in patients with chronic urticaria have been demonstrated by randomized clinical trials. In this study, we assessed the clinical effectiveness and safety of the intramuscular injection of autologous serum in patients with AD.

Materials and Methods: In this randomized, placebo-controlled, and double-blind trial, 23 adolescent and adult patients with moderate-to-severe AD were enrolled. The patients were randomized to receive eight intramuscular injections of 5 mL of autologous serum (n=11) or saline (n=12) over 4 weeks, and were followed up until week 8. Changes in the clinical severity scores of AD assessed by SCORing Atopic Dermatitis (SCORAD), patient-reported Dermatology Life Quality Index (DLQI) score, and incidence of adverse events were assessed from baseline to week 8.

Results: One patient in the treatment group and two patients in the placebo group were lost to follow-up before week 8. The intramuscular administration of autologous serum, compared with saline, decreased the SCORAD clinical severity score (-14.8% vs. 10.7%, p=0.006) and improved the DLQI score (-32.6% vs. 19.5%, p=0.01) from baseline to week 8. Serious adverse events were not observed.

Conclusion: Intramuscular injection of autologous serum may be effective in treating AD. Further studies are needed to evaluate the clinical usefulness of this intervention for AD (KCT0001969).

Key Words: Clinical trial; dermatitis, atopic; serum

INTRODUCTION

Atopic dermatitis (AD) is a chronic and inflammatory skin disorder characterized by intensely pruritus and relapsing eczematous skin condition, and is associated with a personal or familial history of allergic diseases.[1-3]

Current medical therapies for moderate-to-severe AD, including topical corticosteroids, topical calcineurin inhibitors, systemic corticosteroids, oral cyclosporine, and oral methotrexate, only provide temporary symptomatic relief.[1] Monoclonal antibodies and small molecules (Janus kinase inhibitors) inhibiting Th2 cytokine-mediated immune response could provide clinical improvements in significant portions of patients with moderate-to-severe AD.[4-7] Despite the use of new biologic medications, the clinical effectiveness of these medications in moderate-to-severe AD is still insufficient.[1-3] The currently available treatment modalities for AD can only provide transient clinical improvements during regular maintenance treatments and are not effective in a certain portion of patients with AD

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who receive treatment with dupilumab or JAK inhibitor.[6,7] Therefore, further research is needed to develop a new therapeutic modality for patients with AD. Consequently, there exists an unmet need for the development of a new therapeutic modality for AD.

We have searched an alternative therapy with a significant clinical efficacy for AD that could be easily applied to the treatment of patients with AD in real clinical practice. Autologous blood therapy (ABT) and autologous serum therapy (AST) involve repeated administrations of autologous blood or autologous serum (1–5 mL) to the same subjects by intramuscular injections, immediately after venous blood sampling.[8-12] These therapies have been used for the treatment of AD and chronic urticaria by physicians in many countries since they were first reported in 1913.[8-12] ABT was reported as the most commonly practiced complementary and alternative medicine modality for AD by physicians in Germany.[13] A randomized, placebo-controlled, and double-blind study showed a significant clinical effectiveness of ABT in adolescent and adult patients with AD.[10] Interestingly, another randomized, placebo-controlled, and double-blind study also showed a significant clinical effectiveness of AST in adult patients with chronic urticaria.[11] However, the clinical effectiveness of AST for AD has not yet been evaluated by either pilot or randomized clinical study.

In this study, we conducted a randomized clinical trial to assess the clinical effectiveness and safety of the intramuscular injection of autologous serum in patients with AD.

MATERIALS AND METHODS

Study design

A randomized, placebo-controlled, and double-blind, parallel-group clinical trial was performed at Ajou University Hospital (Suwon, Republic of Korea). Patients were enrolled from December 2015 to April 2016. A 4-week screening and washout period was followed by a 4-week intervention period and a 4-week follow-up period (Fig. 1A).

This clinical trial was performed in compliance with the guidelines for the Good Clinical Practice and Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Ajou University Hospital (AJIRB-BMR-SMP-15-331). All of the study participants provided their written informed consent. This study has been registered in the Clinical Research Information Service of Korea (KCT0001969).

Patients

We enrolled adolescent and adult patients (aged 13 years or older) diagnosed with moderate-to-severe AD that was not adequately controlled by topical corticosteroids and/or topical calcineurin inhibitors for more than 2 months, with typical clinical features compatible with the diagnostic criteria for AD according to Hanifin and Rajka,[14] and body surface area affected by AD ≥10% at the initial screening and baseline.

Key exclusion criteria included ultraviolet radiation or systemic immunomodulatory therapy (corticosteroids, cyclosporine, methotrexate, etc.) within 4 weeks before randomization, use of topical corticosteroids or topical calcineurin inhibitors within 7 consecutive days before randomization, other active skin diseases that could interfere with study assessments, pregnancy, lactation, addiction to alcohol, and concomitant severe systemic diseases.

Preparation of autologous serum

We obtained 100 mL of autologous blood from patients antecubital vein with a sterile BD Vacutainer® (Becton Dickinson, Franklin Lakes, NJ, USA) at the screening visit (week -4), as previously described for an autologous serum skin test.[15] Approximately, 50 mL of autologous serum was aseptically collected by centrifugation for 10 minutes at room temperature. Then, the autologous serum was immediately aliquoted into sterile glass vials (5 mL per vial) and stored at -20°C.

Randomization

The randomization list was made by an independent statistician using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA), with a block size of four. Patients were randomly assigned (1:1) to receive the autologous serum (treatment group) or saline (placebo group) at the baseline visit (week 0).

The un-blinded nurse, who was not in contact with the patients, prepared 5 mL of either saline or autologous serum thawed at room temperature in plastic syringes that were made completely opaque using adhesive paper tape for concealment of the content according to the randomization list. During the intervention period, the blinded nurse received the syringes for injection from the un-blinded nurse and administered intramuscular injections to the patients. Patients, investigator, laboratory personnel, and the blinded nurse were masked to intervention assignments.

Interventions

Patients were randomized to receive eight intramuscular injections of either autologous serum (5 mL) or saline (5 mL) over a 4 weeks, and were followed up for 4 weeks until week 8 (Fig. 1A). During the entire study period (total of 12 weeks), all drugs and procedures used for the treatment of AD were discontinued, except for the topical moisturizers. Systemic corticosteroids were provided to the patients as a rescue therapy to control intolerable symptoms of AD at the discretion of investigator.

Outcomes

The efficacy outcomes included changes in the clinical severity scores of AD from baseline to week 8 assessed by using following parameters: the SCORing Atopic Dermatitis (SCORAD) score,[16] which ranges from 0 to 103, with higher scores indicating greater clinical severity of AD; the Eczema Area and

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Severity Index (EASI),[17] which ranges from 0 to 72, with higher scores indicating greater severity; the patient-reported Dermatology Life Quality Index (DLQI) score,[18] which ranges from 0 to 30, with higher scores indicating a lower quality of life; the Investigator's Global Assessment (IGA) score;[19] visual analogue scale (VAS) for pruritus; and VAS for quality of sleep.

Assessments of clinical severity scores of AD (SCORAD, EASI, IGA, DLQI, VAS for pruritus, and VAS for quality of sleep) were made at the initial screening visit (week -4) and weekly from week 0 (baseline) to weeks 4 and 8.

Laboratory assessments, including a complete blood cell count and liver and renal function tests, were made at baseline and week 8. Adverse events and clinical conditions were assessed during the study periods.

Data were collected by the investigator, and statistical analysis was performed by independent statisticians.

Laboratory biomarkers

Venous blood was collected from the median cubital vein at the initial screening visit (week -4), baseline (week 0), and weeks 4 and 8. Serum samples were stored at -20°C. The serum levels of interleukin (IL)-10 and interferon-gamma (IFN-γ) were analyzed by enzyme-linked immunosorbent assay sets (BD PharMingen, San Diego, CA, USA). The peripheral blood eosinophil count and serum lactate dehydrogenase (LDH) level were measured using an automated hematology analyzer (Coulter Counter STKS; Beckman Coulter, Fullerton, CA, USA) and a Cobas c702 analyzer (Roche Diagnostics, Basel, Switzerland), respectively.

Statistical analysis

By our calculation on generalized estimating equation analysis, a sample size of nine patients per group would provide the study with 90% power to detect 20% difference of mean percentage changes in the clinical severity score from baseline to week 8 between the two study groups (assuming working correlation=0.5 and variance=1.5). Based on an expected drop-out rate of 10%, the sample size was determined as 10 patients per group.

We performed an efficacy analysis using the intention-to-treat population, including all randomized patients who were administered at least one study intervention. Categorical variables were analyzed using the chi-squared test (Fisher's exact test was used when more than 20% of cells in the contingency table had expected frequencies less than 5). Continuous endpoints were analyzed using a generalized estimating equation model with an exchangeable correlation matrix to estimate the least-squares (LS) means. In this model, no imputation for missing data was applied. The model included fixed effects for treatment, week, and treatment-by-week interaction. Inter-group comparisons of the treatment effects by the generalized estimating equation model repeated measures were based on the LS mean changes [with 95% confidence interval (CI)] from baseline to week 8.

The Wilcoxon signed-rank test and the Mann-Whitney U test were used to analyze the within-group differences and inter-group differences in laboratory parameters. All analyses were two-sided. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the R software, version 4.1.0 (R Development Core Team, 2021, R Foundation for Statistical Computing, Wien, Austria).

RESULTS

Study patients

Among 132 adult patients with AD who were assessed for eligibility, 23 patients with AD were found to be eligible for study participation at the initial screening visit. A total of 23 patients (age range, 16–36 years) were randomized to receive eight weekly intramuscular injections of 5 mL of autologous serum (n=11) or saline (n=12) over 4 weeks at the baseline visit (Fig. 1A and B).

One patient in the treatment group and one patient in the placebo group were lost to follow-up due to acute severe exacerbation of AD (at week 0.5 and 1, respectively). One patient in the placebo group was lost to follow-up due to non-compliance without an identifiable reason (at week 1.5) (Fig. 1B). Twenty randomized patients (10 patients in each groups) completed all of the interventions and scheduled follow-ups.

The baseline clinical and laboratory characteristics were similar between the treatment group and the placebo group (Table 1).

Clinical efficacy outcomes

There was a significant difference in changes in the SCORAD score from baseline to week 8 between the treatment group and the placebo group (p=0.006). The mean percentage change in the SCORAD score from baseline to week 8 was -14.8% (95% CI, -30.1 to 0.6) in the treatment group and 10.7% (95% CI, 0.7 to 20.6) in the placebo group (p=0.006) (Table 2 and Fig. 2A). There was a significant difference in the changes in the objective SCORAD score from baseline to week 8 between the treatment group and the placebo group (p=0.004). The mean percentage change in the objective SCORAD score from baseline to week 8 was -14.5% (95% CI, -31.2 to 2.3) in the treatment group and 13.3% (95% CI, 4.1 to 22.5) in the placebo group (p=0.004) (Table 2 and Fig. 2B). There was no significant difference in the changes in the EASI score from baseline to week 8 between the treatment group and the placebo group (p>0.05). The mean percentage change in the EASI score from baseline to week 8 was 12.9% (95% CI, -39.3 to 65.2) in the treatment group and 25.9% (95% CI, 4.6 to 47.2) in the placebo group (p= 0.652) (Table 2). The mean percentage change in the DLQI score from baseline to week 8 was -32.6% (95% CI, -59.2 to -5.9) in the treatment group and 19.5% (95% CI, -9.6 to 48.5) in

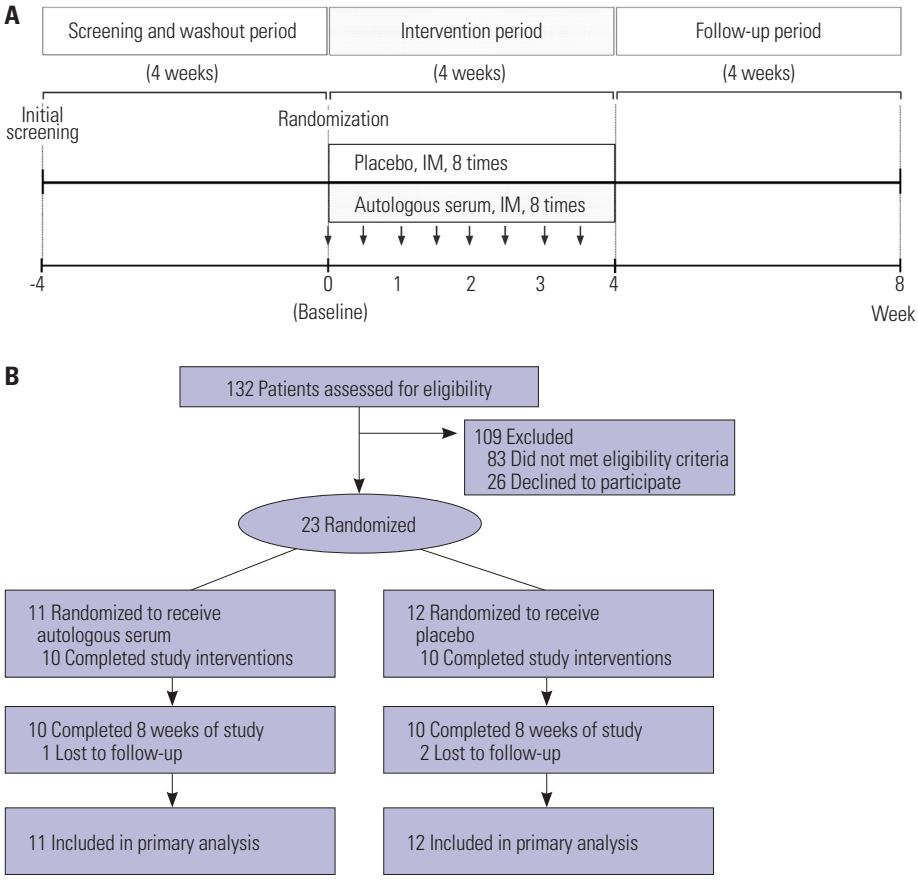

Fig. 1. The study design (A) and numbers of patients enrolled and included in the primary analysis (B). Arrows indicate the timing of intramuscular injection. IM, intramuscular injection.

the placebo group (p=0.010).

There were no significant differences in the changes of IGA score, VAS for pruritus, and VAS for quality of sleep between the treatment group and the placebo group (p>0.05) (Table 2).

Safety

No serious adverse event was reported in this study. Overall, 43.5% (10/23 patients) of the randomized patients reported at least one adverse event (Table 3). The most common adverse event was herpes simplex virus infection, which was reported in 9.1% (1/11 patients) in the treatment group and 25.0% (3/12 patients) in the placebo group (p=0.590). Other common adverse events included exacerbation of AD, eczema herpeticum, and bacterial skin infection, which were reported in similar frequencies in the treatment group and the placebo group. Although the patients experienced exacerbations of AD, none of the patients used systemic corticosteroids or topical corticosteroids during the study period.

None of the patients had significant changes in the laboratory parameters of complete blood cell counts and liver and renal function test (data not shown).

Changes in the serum levels of IL-10 and IFN-γ

There were no significant differences in IL-10 or IFN-γ levels at baseline and at weeks 4 and 8 between the treatment group and the placebo group (p>0.05) (Table 4). There were no significant changes in IL-10 or IFN-γ levels at weeks 4 and 8 compared to those levels at baseline in the treatment group and the placebo group (p>0.05) (Table 4).

Changes in the peripheral blood eosinophil count and serum level of LDH

No significant differences were observed in the peripheral blood eosinophil count or serum LDH level at baseline and at weeks 4 and 8 between the treatment group and the placebo group (p>0.05) (Table 4). There were no significant changes in the peripheral blood eosinophil count or serum LDH level at weeks 4 and 8 compared to those values at baseline in the treatment group and the placebo group (p>0.05) (Table 4).

DISCUSSION

This study is the first randomized clinical trial in patients with AD to assess the clinical effectiveness of the intramuscular in-

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Table 1. Clinical and Laboratory Characteristics at Baseline

	Placebo (n=12)	Autologous serum (n=11)	*p* value
Age (yr)	24.0 (16.0–36.0)	26.0 (16.0–35.0)	0.829
Male, sex	10 (83.3)	10 (90.9)	>0.999
Duration of disease (yr)	20.0 (12.0–35.0)	17.0 (1.0–29.0)	0.622
IGA score			0.417
3 (moderate)	1 (8.3)	3 (27.3)	
4 (severe)	11 (91.7)	8 (72.7)	
5 (very severe)	0 (0)	0 (0)	
SCORAD score	60.2 (47.4–75.3)	62.4 (40.4–85.9)	0.758
Objective SCORAD score	44.7 (32.4–55.3)	49.0 (27.4–67.9)	0.622
VAS for pruritus	8.5 (4.0–10.0)	7.0 (3.0–10.0)	0.256
VAS for sleep loss	8.0 (4.0–10.0)	7.0 (2.0–10.0)	0.288
Body surface area affected (%)	34.8 (20.5–65.5)	37.0 (14.5–77.0)	0.667
EASI score	17.2 (9.2–26.1)	18.4 (5.0–43.4)	0.854
DLQI score	17.0 (5.0–30.0)	14.0 (5.0–27.0)	0.338
Concomitant atopic diseases			
Allergic rhinitis	5 (41.7)	4 (36.4)	>0.999
Allergic conjunctivitis	2 (16.7)	2 (18.2)	>0.999
Asthma	0 (0)	1 (9.1)	0.478
Laboratory parameters			
Peripheral blood eosinophil counts (/μL)	728.1 (371.7–1830.0)	800.8 (288.0–1623.6)	0.622
Total IgE (kU/L)	2392.0 (63.0–5000.0)	5000.0 (184.0–5000.0)	0.279
LDH (U/L)	328.5 (194.0–885.0)	274.0 (193.0–413.0)	0.176

IGA, Investigator's Global Assessment; SCORAD, SCORing Atopic Dermatitis; VAS, visual analogue scale; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; LDH, lactate dehydrogenase.
Data are presented as number (%) or medians (range).

jection of autologous serum. The intramuscular injection of autologous serum, compared with saline injection, provided a significant clinical improvement showing decreased objective clinical severity score (SCORAD and objective SCORAD) and improvement of patient-reported subjective DLQI score in patients with moderate-to-severe AD in this study. In addition, no serious adverse event was observed after intramuscular injection of autologous serum in patients with AD. These results suggests the clinical usefulness of this intervention in patients with AD.

These findings could be clinically meaningful since ABT and AST have been reported as the commonly practiced complementary and alternative medicine modalities for AD and chronic urticaria by physicians in many regions, including Europe, Russia, Japan, India, China, and South America, for more than 100 years since they were first reported in 1913.[8-13] ABT was also reported to be clinically effective in three patients with pruritic urticarial papules and plaques of pregnancy in Korea.[20] Recently, a case report on successful treatment of severe recalcitrant AD by ABT at acupoint (intramuscular injection of autologous whole blood at acupuncture site) was also reported in China.[21]

Interestingly, there were no significant differences in the changes of clinical severity assessed by the EASI score from baseline to week 8 between the treatment group and the placebo group (p=0.652) in this study. Discrepancies in changes of SCORAD, EASI, IGA, and VAS scores between the treatment group and placebo group were observed in this study. There were important differences between EASI and SCORAD in the methods of calculating the extent of the affected area, number of parameters assessing the intensity of skin lesions, and inclusion of patient's subjective symptoms.[22] Mismatching of changes in EASI and SCORAD scores was also reported in a recent randomized clinical trial on the clinical efficacy of sublingual allergen immunotherapy in patients with AD.[23] Unfortunately, there is still no gold standard for evaluating the clinical severity of AD, and this may be the reason for using multiple clinical severity scoring systems to assess the clinical efficacy in clinical trials on new therapeutic modalities for AD.[22]

In this study, none of the 10 patients with moderate-to-severe AD in the AST treatment group achieved an EASI-50 clinical response at week 8. This EASI-50 clinical response rate of AST is evidently lower than the EASI-50 response rates of dupilumab (61%–83% at week 16) and upadacitinib (82%–87% at week 16) reported in randomized clinical trials in patients with moderate-to-severe AD.[5,6,24,25] These results suggest a relatively poor clinical efficacy of AST in patients with moderate-to-severe AD, and further studies are needed to evaluate its clinical usefulness in patients with mild-to-moderate AD.

ABT and AST have been approved as clinically valid therapeutic procedure for the treatment of chronic urticaria by the

Table 2. Changes in Clinical Severity Parameters of Atopic Dermatitis

	Placebo			Autologous serum			Difference in percentage change for autologous serum vs. placebo, LS mean (95% CI)	*p* value
	Baseline, mean (SD) (n=12)	Week 8, mean (SD) (n=10)	Percentage change from baseline to week 8, LS mean (95% CI)	Baseline, mean (SD) (n=11)	Week 8, mean (SD) (n=10)	Percentage change from baseline to week 8, LS mean (95% CI)		
Continuous parameters								
SCORAD score	59.0 (8.3)	62.0 (8.7)	10.7% (0.7 to 20.6)	59.6 (13.9)	51.7 (15.9)	-14.8% (-30.1 to 0.6)	-25.4% (-43.7 to -7.2)	0.006
Objective SCORAD score	43.2 (6.8)	46.3 (7.2)	13.3% (4.1 to 22.5)	45.7 (11.9)	39.7 (13.6)	-14.5% (-31.2 to 2.3)	-27.8% (-46.9 to -8.7)	0.004
VAS for pruritus	8.2 (1.7)	7.7 (1.3)	5.9% (-21.3 to 33.1)	7.1 (2.4)	6.0 (2.1)	-12.8% (-32.3 to 6.8)	-18.7% (-52.2 to 14.8)	0.274
VAS for sleep loss	7.7 (1.8)	7.9 (1.7)	17.4% (-13.5 to 48.3)	6.8 (2.1)	6.0 (2.3)	-14.2% (-28.6 to 0.2)	-31.6% (-65.7 to 2.5)	0.069
EASI score	17.3 (5.8)	19.0 (6.4)	25.9% (4.6 to 47.2)	18.2 (10.0)	18.3 (11.6)	12.9% (-39.3 to 65.2)	-13.0% (-69.4 to 43.4)	0.652
DLQI score	16.8 (7.2)	16.9 (6.3)	19.5% (-9.6 to 48.5)	14.1 (6.4)	9.7 (4.7)	-32.6% (-59.2 to -5.9)	-52.0% (-91.4 to -12.6)	0.010
Body surface area affected (%)	38.1 (13.8)	42.7 (11.6)	28.6% (8.2 to 49.0)	40.5 (16.5)	42.6 (19.6)	8.3% (-22.0 to 38.6)	-20.3% (-56.9 to 16.2)	0.275
Categorical parameters								
SCORAD-30		0 (0)			3 (30.0)			0.211
SCORAD-50		0 (0)			0 (0)			-
EASI-30		0 (0)			4 (40.0)			0.087
EASI-50		0 (0)			0 (0)			-
Reduction in IGA score ≥2 points from baseline		1 (10.0)			3 (30.0)			0.582
Reduction in VAS for pruritus ≥3 points from baseline		2 (20.0)			2 (20.0)			>0.999
Reduction in VAS for quality of sleep ≥3 points from baseline		1 (10.0)			1 (10.0)			>0.999

SD, standard deviation; LS, least squares; CI, confidence interval; SCORAD, SCORing Atopic Dermatitis; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; IGA, Investigator's Global Assessment; VAS, visual analogue scale; SCORAD-30, proportion of patients achieving at least a 30% reduction in the SCORAD score from baseline; SCORAD-50, proportion of patients achieving at least a 50% reduction in the SCORAD score from baseline; EASI-30, proportion of patients achieving at least a 30% reduction in the EASI score from baseline; EASI-50, proportion of patients achieving at least a 50% reduction in the EASI score from baseline.

P values were calculated by using a generalized estimating equation model with an exchangeable correlation matrix to estimate the LS means for continuous parameters and by Fisher's exact test for categorical parameters.

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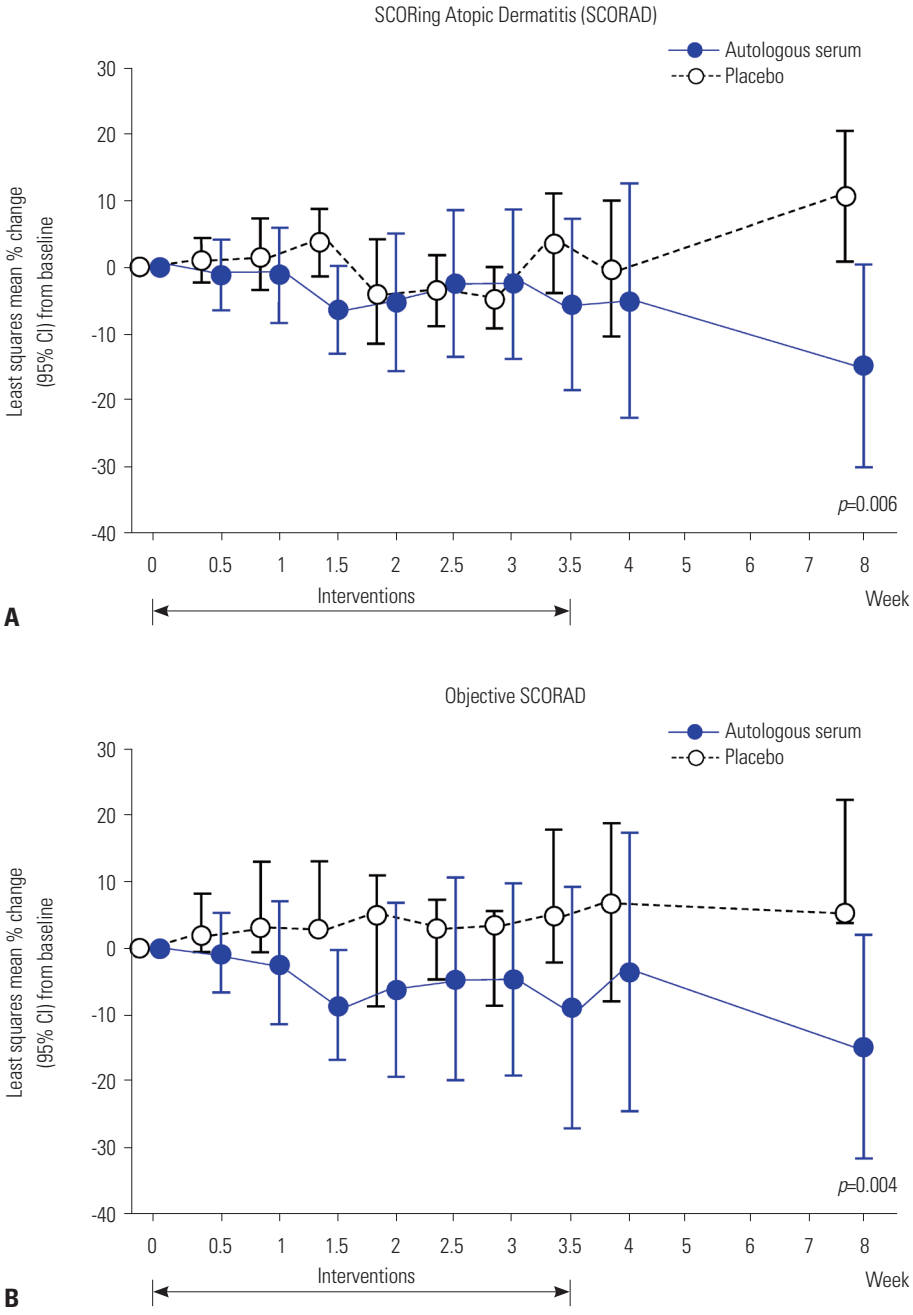

Fig. 2. Changes in clinical severity scores of atopic dermatitis (SCORAD and objective SCORAD). Changes in the clinical severity scores of atopic dermatitis assessed by SCORing Atopic Dermatitis (SCORAD) (A) and objective SCORAD (B). Error bars indicate 95% confidence intervals (CI). The *p*-value comparisons are for week 8, and were determined based on a generalized estimating equation model with an exchangeable correlation matrix to estimate the least squares means.

New Health Technology Assessment System entrusted by the Ministry of Health and Welfare of Korean Government in 2015 (https://nhta.neca.re.kr/nhta/publication/nhtaU0601V.ecg?pub_seq=322). However, the clinical usefulness of ABT and AST for the treatment of AD was not approved due to the insufficiency of objective evidence for clinical efficacy supported by the randomized controlled study. In this study, we provided a result of the first randomized clinical trial evaluating the clinical effectiveness and safety of AST for moderate-to-severe AD. Further studies are needed to evaluate the clinical usefulness of AST and ABT in patients with AD.

In a previous randomized controlled study on ABT in patients with AD, autologous whole venous blood (1–3 mL) was intramuscularly injected to the patients immediately after sampling.[10] In this study, 5 mL of frozen stored autologous serum thawed at room temperature was intramuscularly injected to the patients. AST has several advantages compared to ABT in real clinical practice.[26] Intramuscular injection of autologous

serum is less painful than the intramuscular injection of whole venous blood in patients. Autologous serum can be stored in the frozen state for a long-time, and this can be useful as a sampling of 100 mL of venous blood can provide at least eighgt vials of 5 mL of frozen autologous serum, avoiding multiple venous blood samplings for AST.[26]

The major scientific weakness of ABT and AST precluding an acceptance as standard treatment methods for AD by physicians is a lack of knowledge on the therapeutic component in blood or serum mediating their clinical efficacy and the mechanism of action. We and other investigators hypothesize that the blood component responsible for the therapeutic efficacy of ABT or AST is an autologous total immunoglobulin, and the therapeutic mechanism includes both anti-idiotypic immunomodulation and activation of regulatory T cells induced by intramuscular injection of autologous blood or serum.[27,28] To prove the concept, we conducted a randomized clinical trial in patients with moderate-to-severe AD, and demonstrated that intramuscular injection of autologous total immunoglobulin G (purified from autologous plasma using Protein A bead) could induce significant clinical improvements and increase serum IL-10 and IFN-γ levels compared to the placebo treatment (intramuscular injection of saline).[29] We also showed that intramuscular injection of autologous total immunoglobulin G could increase the percentage of IL-10 producing-$CD4^+$ T cells (regulatory T cells) in the peripheral blood samples of 13 healthy human subjects.[30] Further studies are needed to evaluate the immunomodulatory mechanism of ABT and AST.

This clinical trial has some limitations, including the disadvantages of a single-center design, small number of patients, and short study duration. Future clinical trials on the clinical efficacy of AST for AD in a larger number of patients (at least 25 or 50 patients in each treatment group and placebo group) with mild-to-moderate AD, study design of weekly intramuscular injections for at least 8 or 9 weeks, and follow-up period for at least 4 or 8 weeks after completion of the interventions might be needed to evaluate the clinical usefulness of AST in the treatment of AD.

In conclusion, intramuscular injection of autologous serum may be effective in treating AD. Further studies are needed to evaluate the clinical usefulness of this intervention for AD.

Table 3. Adverse Events

	Placebo (n=12)	Autologous serum (n=11)	*p* value
Total number of adverse events	7	4	
Atopic dermatitis exacerbation	2 (16.7)	2 (18.2)	>0.999
Herpes simplex	3 (25.0)	1 (9.1)	0.590
Eczema herpeticum	1 (8.3)	1 (9.1)	>0.999
Bacterial skin infection	1 (8.3)	0	>0.999
Patients with 1 ≥adverse event	6 (50.0)	4 (36.4)	0.680
Patients with an adverse event leading to withdrawal from intervention	1 (8.3)	1 (9.1)	>0.999
Total number of serious adverse events	0	0	

Data are presented as n (%).

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Table 4. Changes in Laboratory Parameters

	Placebo (n=12)		Autologous serum (n=11)		Inter-group *p* value†
	Median (range)	*p* value*	Median (range)	*p* value*	
IL-10 (pg/mL)					
Baseline	3.6 (3.1–5.8)		4.2 (3.2–6.6)		0.712
Week 4	4.4 (3.2–8.7)	0.066	3.8 (3.2–5.4)	0.327	0.336
Week 8	4.0 (3.3–7.6)	0.575	5.0 (2.9–6.7)	0.674	0.657
IFN-γ (pg/mL)					
Baseline	2.0 (0.04–43.8)		2.8 (0.2–12.9)		>0.999
Week 4	2.3 (0.07–23.7)	0.859	2.1 (0.1–27.8)	0.263	0.847
Week 8	3.1 (0.06–9.5)	0.721	5.8 (0.2–12.6)	0.093	0.248
Peripheral blood eosinophil counts (/μL)					
Baseline	728.1 (371.7–1830.0)		800.8 (288.0–1623.6)		0.622
Week 4	623.7 (331.5–1702.8)	0.515	918.9 (248.0–1524.6)	0.386	0.487
Week 8	644.4 (290.4–1999.2)	0.878	714.9 (108.8–1511.1)	0.646	0.821
LDH (U/L)					
Baseline	328.5 (194.0–885.0)		274.0 (193.0–413.0)		0.176
Week 4	287.0 (166.0–476.0)	0.286	290.5 (191.0–425.0)	0.678	0.744
Week 8	327.0 (175.0–464.0)	0.262	319.0 (210.0–389.0)	0.333	0.762

IL-10, interleukin-10; IFN-γ, interferon-gamma; LDH, lactate dehydrogenase.
*The *p*-value for within-group difference of the comparison with baseline (week 0) was analyzed by the Wilcoxon signed-rank test; †The *p*-value for inter-group comparison was analyzed by the Mann-Whitney U test.

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