

# Clinical Efficacy of Autologous Plasma Therapy for Atopic Dermatitis

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## Key Words

Atopic dermatitis · Autologous blood therapy · Autologous plasma therapy

## Abstract

**Background:** The clinical efficacy of autologous blood therapy (ABT) in patients with atopic dermatitis (AD) was demonstrated by a randomized double-blind placebo-controlled study. To characterize the blood component mediating the therapeutic efficacy of ABT for AD, we evaluated the clinical efficacy of autologous plasma therapy (APT) and autologous high-molecular-weight plasma protein fraction therapy (AHPT) in patients with AD in this study. **Methods:** A total of 22 patients with recalcitrant AD were treated with 8 weekly intramuscular injections of either autologous plasma (n = 11) or autologous high-molecular-weight plasma protein fraction (n = 11) for 7 weeks. **Results:** The clinical severity score of AD (SCORAD value) of 11 patients who completed AHPT significantly decreased from  $79.7 \pm 17.0$  (mean  $\pm$  SD) at baseline to  $65.8 \pm 16.4$  at 6 weeks and  $60.1 \pm 16.0$  at 7 weeks (Wilcoxon signed-rank test,  $p < 0.05$ ). There were no significant differences among the SCORAD values measured at baseline ( $74.2 \pm 19.6$ ), at 6 weeks ( $66.3 \pm 23.6$ ) and at 7 weeks ( $67.5 \pm 20.8$ ) in 10 patients who completed APT ( $p > 0.05$ ). **Conclusion:** This result suggests that the

blood component mediating the therapeutic efficacy of ABT in patients with AD might be present in the high-molecular-weight plasma protein fraction. © 2013 S. Karger AG, Basel

## Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by itching, dry skin, inflammation and exudation. AD is frequently associated with a personal or familial history of allergic diseases [1]. Hypersensitivity reaction to environmental agents has been suggested as the pathogenetic mechanism responsible for the development and maintenance of chronic skin inflammation in patients with AD [2]. The pathogenetic mechanism of AD seems to be complex and associated with genetic abnormalities, environmental triggering factors, skin barrier dysfunction, and immunological abnormalities [2, 3]. However, the precise pathogenetic mechanism of AD is not yet completely understood.

Current standard medical therapies for AD, including topical corticosteroids and/or topical calcineurin inhibitors, are focused mainly on symptomatic relief, and their clinical efficacy is frequently disappointing to both pa-

tients and physicians [1]. Although a significant number of patients with recalcitrant AD can be improved by treatment with systemic corticosteroids, cyclosporine or mycophenolate mofetil, there is a possibility of toxicity from long-term treatment with these compounds. Recent clinical trials with monoclonal antibodies (anti-IgE antibody, anti-activated T cell antibody, and anti-B cell antibody) reported conflicting results in terms of clinical efficacy and safety [4–6]. Further development of an additional therapeutic modality for patients with severe or recalcitrant AD is thus needed.

Various complementary and alternative medicine modalities have been used for the treatment of AD in many countries, including Europe [7]. Autologous blood therapy (ABT) is reportedly the most commonly used complementary and alternative medicine modality for AD by physicians in Germany [7]. ABT involves the repeated administration of small amounts of autologous blood (1–5 ml) by intramuscular injection immediately after sampling of venous blood [8]. The positive clinical efficacy of ABT in patients with AD has been demonstrated by a randomized double-blind placebo-controlled study [8]. ABT also induced significant clinical improvements in patients with chronic urticaria and a positive autologous serum skin test in a randomized placebo-controlled study [9]. Interestingly, autologous serum therapy (repeatedly administering small amounts of serum separated from clotted autologous venous blood of patients by intramuscular injection) is also reportedly effective in patients with chronic urticaria [10].

We hypothesized that the blood component mediating the therapeutic efficacy of ABT in patients with AD is a plasma protein present in the venous blood. To characterize the active blood component, we evaluated the clinical efficacy of autologous plasma therapy (APT) and autologous high-molecular-weight plasma protein fraction therapy (AHPT) in patients with recalcitrant AD in this study.

## Patients and Methods

### Patients

A total of 22 adult patients with recalcitrant AD who fulfilled all of the criteria below were included in the study. The patients showed typical clinical features of AD compatible with the diagnostic criteria for AD suggested by Hanifin and Rajka [11]. In this study, recalcitrant AD was defined when the clinical conditions of patients had not been effectively controlled by current standard medical therapies (topical moisturizers, topical corticosteroids, topical calcineurin inhibitors and oral antihistamines) for more than 3 months. After providing a detailed explanation of the pro-

cedure to obtain autologous venous blood using a double blood bag system for APT and the procedure of double-filtration plasmapheresis (DFPP) to obtain a high-molecular-weight plasma protein fraction for AHPT, we gave patients the option of receiving either APT or AHPT. In total, 11 patients with recalcitrant AD (8 male and 3 female patients) aged 17–42 years (mean  $\pm$  standard deviation, SD: 26.6  $\pm$  7.3 years) were assigned to the APT group and 11 patients with recalcitrant AD (8 male and 3 female patients) aged 19–32 years (mean  $\pm$  SD: 26.5  $\pm$  4.7 years) were assigned to the AHPT group. There were no significant differences in the baseline characteristics of patients (age, sex and clinical severity) between the APT and AHPT groups (table 1). Of note, 5 patients in the APT group and 3 patients in the AHPT group were treated with cyclosporine (100–200 mg/day) for more than 3 months before enrollment in this study. In addition, 5 patients in the APT group and 4 patients in the AHPT group were treated with intermittent administration of low-dose oral corticosteroids for more than 3 months ( $\leq$ 10 mg of prednisolone/day or an equivalent dose of another corticosteroid for fewer than 7 days/month) before enrollment in this study. Medical therapies were maintained in all 22 patients with recalcitrant AD throughout the study period without changes in dose. This study was approved by the institutional review board. All patients provided written informed consent.

### Preparation of Autologous Plasma Using a Double Blood Bag System

Approximately 400 ml of venous blood was collected into a double blood bag system (Green Cross PBM, Seoul, Republic of Korea) containing citrate phosphate dextrose as an anticoagulant. The whole venous blood was aseptically separated into packed red blood cells and plasma by centrifuging the double bag at 3,500 rpm and 4°C for 10 min. The separated autologous plasma (approx. 200 ml) was divided among sterile glass vials and stored at –20°C.

### Preparation of Autologous High-Molecular-Weight Plasma Protein Fraction by the DFPP Procedure

The high-molecular-weight plasma protein fraction was separated from the venous blood of the patients with DFPP, using a plasma separator (Plasmaflo, OP-05W; Asahi Kasei Kuraray Medical, Tokyo, Japan) and a plasma fractionator (Cascadeflo, EC-40W; Asahi Kasei Kuraray Medical) as previously described [12]. The plasma separator separates plasma from blood cells, and the plasma fractionator selectively separates the high-molecular-weight plasma protein fraction, including immunoglobulins, from the low-molecular-weight plasma protein fraction, including albumin, in a molecular-weight-dependent manner based on the pore size of the capillary filter [12]. Single-lumen vinyl catheters were inserted into the antecubital veins of the patients in both arms for the DFPP procedure. During the DFPP procedure, the high-molecular-weight plasma protein fraction was aseptically collected from the draining outlet, and the low-molecular-weight plasma protein fraction was mixed with blood cells and returned to the patients. The separated autologous high-molecular-weight plasma protein fraction (approx. 100 ml) was divided among sterile glass vials and stored at –20°C.

### Analysis of Plasma Protein Concentrations

Total protein and albumin concentrations were measured by the biuret method using an ADVIA 2400 analyzer (Siemens Healthcare Diagnostics Ltd., Camberley, UK). IgA, IgG, and IgM

**Table 1.** Baseline characteristics of patients with recalcitrant AD who received APT or AHPT

	APT (n = 11)	AHPT (n = 11)	p
Age, years	26.6±7.3	26.5±4.7	0.717
Age at onset of disease, years	17.5±8.5	14.8±7.0	0.339
Duration of disease, years	13.3±7.7	16.9±6.8	0.306
Clinical severity score, SCORAD value	74.2±19.6	79.7±17.0	0.412
Percentage of patients with severe AD (SCORAD value >50)	10 (90.9%)	10 (90.9%)	
Gender			
Male	8 (72.7%)	8 (72.7%)	
Female	3 (27.3%)	3 (27.3%)	
Serum protein concentrations			
Total protein, g/dl	7.2±0.7	6.9±0.6	0.575
Albumin, g/dl	4.5±0.4	4.3±0.3	0.305
IgG, mg/dl	1,358.4±298.9	1,330.7±269.6	0.922
IgA, mg/dl	283.9±122.4	206.4±55.2	0.108
IgM, mg/dl	128.5±92.1	125.5±39.1	0.393
IgE, kU/l	12,988.0±13,979.1	14,137.5±19,428.5	0.922

Data are expressed as means ± SD or numbers with percentages. p values were calculated by Mann-Whitney U test.

were assayed by turbidimetric immunoassay using a COBAS Integra analyzer (F. Hoffmann-La Roche, Basel, Switzerland). IgE was assayed by ImmunoCAP (Thermo Scientific Inc., Kalamazoo, Mich., USA).

#### Treatment Procedure of APT and AHPT

The treatment procedure was started 2 months after venous blood sampling for preparation of autologous plasma or the DFPP procedure for the preparation of the high-molecular-weight plasma protein fraction. The frozen autologous plasma or autologous high-molecular-weight plasma protein fraction in a glass vial was thawed at room temperature for each injection. The patients in both the APT and AHPT groups were treated with 8 weekly intramuscular injections of either the autologous plasma or high-molecular-weight plasma protein fraction, respectively, for 7 weeks. The injection volume was 2 ml for the initial 4 injections (from 0 to 3 weeks) and 5 ml for the subsequent 4 injections (from 4 to 7 weeks).

#### Clinical Assessment

The primary efficacy outcome was the change in the clinical severity of AD, measured using the standardized clinical severity scoring system for AD (SCORAD) [13]. The Dermatology Life Quality Index (DLQI) [14] and patient ratings of pruritus, quality of sleep and global severity on a 100-mm visual analog scale (VAS) were defined as secondary outcome measures. The primary and secondary outcome measures were assessed at baseline (week 0), weekly during the 7 weeks of APT or AHPT, and at 11 weeks.

#### Statistical Analysis

Data are expressed as means ± SD. The statistical significance of changes in values before and after treatment was analyzed using the Wilcoxon signed-rank test. Differences in parameters between

the two groups were analyzed using the Mann-Whitney U test. The  $\chi^2$  test was used to compare the response rates of treatments between the two groups. A p value <0.05 was regarded as statistically significant.

## Results

### Compliance and Side Effects

Among the 11 patients of the APT group, 1 patient dropped out after the 6th injection due to noncompliance. The other 10 patients of the APT group and all 11 patients of the AHPT group completed the 8 weekly injections of autologous plasma or autologous high-molecular-weight plasma protein fraction, respectively, for 7 weeks and a follow-up evaluation at 11 weeks. None of the patients in either group experienced significant side effects from the treatment or any significant exacerbation of AD during the treatment period, with the exception of transient mild soreness at the injection site.

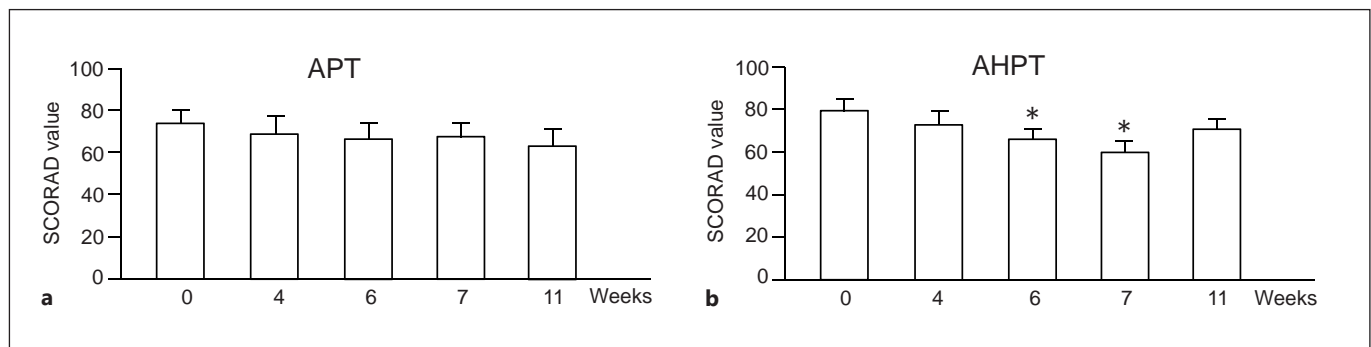
### Primary Clinical Efficacy Outcome

In the 11 patients who completed AHPT, the SCORAD values decreased significantly from  $79.7 \pm 17.0$  (mean ± SD) at baseline to  $65.8 \pm 16.4$  at 6 weeks and  $60.1 \pm 16.0$  at 7 weeks (Wilcoxon signed-rank test,  $p < 0.05$ ) (table 2; fig. 1). However, there were no significant differences in

**Table 2.** Changes in primary and secondary outcome measures of clinical severity in the APT and AHPT groups

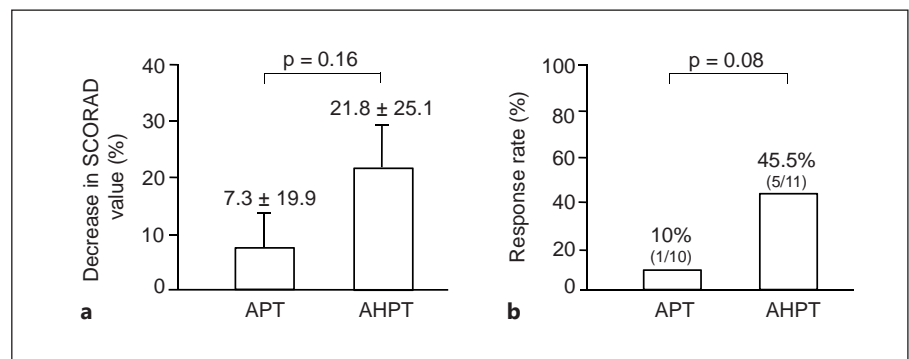
Measure	Baseline (week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 11
<b>SCORAD</b>									
APT	74.2±19.6	77.5±26.1	72.3±22.8	72.6±23.1	68.9±25.1	71.3±24.8	66.3±23.6	67.5±20.8	63.2±25.5
AHPT	79.7±17.0	73.3±17.4	73.5±20.7	69.6±18.1	72.6±21.1	70.9±20.6	65.8±16.4*	60.1±16.0*	71.0±14.2
<b>Objective SCORAD</b>									
APT	59.9±16.5	61.4±25.6	57.1±23.3	59.9±24.4	55.5±22.5	57.0±24.2	54.0±25.3	54.1±23.5	49.9±22.9
AHPT	65.7±15.1	59.6±15.7	60.7±17.3	56.9±14.7	60.1±16.8	58.9±15.7	53.4±13.9*	49.5±12.3*	58.9±11.0
<b>DLQI</b>									
APT	17.7±4.8	18.3±6.6	17.6±6.7	17.7±7.6	16.9±8.6	18.8±8.3	17.6±8.2	17.8±7.9	16.8±7.6
AHPT	18.5±7.8	17.5±9.4	17.4±8.9	16.4±8.7	14.5±9.8	15.7±9.2	13.5±6.9*	14.8±8.4	14.7±7.6
<b>VAS for pruritus</b>									
APT	6.5±2.5	6.8±1.9	6.5±1.6	5.9±2.1	5.6±2.0	6.1±2.1	5.6±2.1	5.9±2.1	5.6±2.4
AHPT	7.2±2.3	6.6±2.2	6.6±2.4	6.3±2.4	6.1±2.5	6.4±2.8	6.2±2.4	5.7±2.5*	6.6±2.2
<b>VAS for quality of sleep</b>									
APT	4.9±3.2	6.5±2.6	5.6±2.4	5.7±2.6	5.2±2.3	5.9±2.3	5.3±2.2	5.7±2.5	4.9±2.5
AHPT	6.8±2.5	7.0±2.0	6.2±2.6	6.5±2.9	6.4±3.2	5.6±3.2	6.2±2.8	4.9±2.6*	5.5±2.9
<b>VAS for subjective severity</b>									
APT	6.9±1.9	6.5±1.6	5.9±1.5	5.5±2.0	5.3±1.9*	6.0±1.7	5.5±2.1	5.9±2.2	5.3±2.2
AHPT	7.8±2.1	6.8±1.9	7.1±1.9	7.3±2.1	6.5±2.5	6.4±2.5	6.1±2.1*	5.3±2.2*	6.2±2.2*

Data are expressed as means ± SD. \* p < 0.05 compared with baseline by Wilcoxon signed-rank test.



**Fig. 1.** SCORAD values (measured at baseline, weekly during the 7 weeks of treatment, and at 11 weeks) in the APT (a) and AHPT (b) groups. \* p < 0.05, Wilcoxon signed-rank test. Data are expressed as means ± SEM.

**Fig. 2.** Decrease in SCORAD values (a) and response rate to treatment (b) in the APT and AHPT groups. The response rate to treatment is the percentage of patients who showed a decrease in the clinical severity score of ≥30% from baseline at 7 weeks after initiation of treatment.



**Table 3.** Protein concentrations in autologous plasma (APT group) and autologous high-molecular-weight plasma protein fraction (AHPT group)

	Autologous plasma (n = 10)	Autologous high-molecular-weight plasma protein fraction (n = 11)	p
Total protein, g/dl	6.5±0.7	8.8±2.1	0.005
Albumin, g/dl	3.9±0.4	4.8±1.1	0.112
IgG, mg/dl	1,207.0±272.2	1,959.9±654.1	0.002
IgA, mg/dl	235.6±97.3	389.5±224.8	0.072
IgM, mg/dl	116.8±86.1	267.2±88.8	0.002
IgE, kU/l	12,068.7±10,466.8	25,205.8±32,445.3	0.398

Data are expressed as means ± SD. p values were calculated by Mann-Whitney U test.

the SCORAD values between 11 weeks ( $71.0 \pm 14.2$ ) and baseline ( $79.7 \pm 17.0$ ) in these patients ( $p > 0.05$ ) (table 2; fig. 1). In the 10 patients who completed APT, there were no significant differences among the SCORAD values at baseline ( $74.2 \pm 19.6$ ), at 6 weeks ( $66.3 \pm 23.6$ ), at 7 weeks ( $67.5 \pm 20.8$ ) and at 11 weeks ( $63.2 \pm 25.5$ ,  $p > 0.05$ ) (table 2; fig. 1). A decrease in the SCORAD value of  $\geq 30\%$  from the baseline value after treatment was observed in 1 (10%) of 10 patients in the APT group and in 5 (45.5%) of 11 patients in the AHPT group at 7 weeks ( $\chi^2$  test,  $p = 0.08$ ) (fig. 2). A decrease in the SCORAD value of  $\geq 50\%$  from the baseline value was observed in none of the 10 patients in the APT group and in 1 (9.1%) of 11 patients in the AHPT group at 7 weeks. There were no significant differences in the mean percentages of the decreases in the SCORAD values between the APT ( $7.3 \pm 19.9\%$ ) and AHPT group ( $21.8 \pm 25.1\%$ ) at 7 weeks compared with baseline (Mann-Whitney U test,  $p > 0.05$ ) (fig. 2).

#### Secondary Efficacy Outcome

The mean DLQI scores decreased significantly from  $18.5 \pm 7.8$  (mean ± SD) at baseline to  $13.5 \pm 6.9$  at 6 weeks in the AHPT group (Wilcoxon signed-rank test,  $p < 0.05$ ) (table 2). There were no significant changes in the DLQI scores during the treatment in the APT group ( $p > 0.05$ ) (table 2). The VAS scores for pruritus and quality of sleep decreased significantly at 7 weeks compared with baseline in the AHPT group ( $p < 0.05$ ) (table 2). There were no significant changes in the VAS scores for pruritus and quality of sleep during treatment in the APT group ( $p > 0.05$ ) (table 2). The VAS scores for global severity decreased significantly at 6, 7 and 11 weeks compared with baseline in the AHPT group ( $p < 0.05$ ), and decreased significantly at 4 weeks compared with baseline in the

APT group ( $p < 0.05$ ) (table 2). There were no significant differences in the mean percentages of the decreases in the VAS values for pruritus, quality of sleep and global severity between the APT and AHPT groups after treatments compared with baseline ( $p > 0.05$ ) (table 2).

#### Protein Concentrations in Autologous Plasma and Autologous High-Molecular-Weight Plasma Protein Fraction

Concentrations of total protein, IgG, IgA, IgM and IgE were significantly higher in autologous high-molecular-weight plasma protein fraction than in autologous plasma in 11 patients with recalcitrant AD who completed 7 weeks of AHPT (Wilcoxon signed-rank test,  $p < 0.05$ ; data not shown). Concentrations of IgG and IgM in autologous high-molecular-weight plasma protein fraction from 11 patients with recalcitrant AD who completed 7 weeks of AHPT were significantly higher than those in autologous plasma from 10 patients who completed 7 weeks of APT (Mann-Whitney U test,  $p = 0.002$ ) (table 3). However, there were no significant differences in the concentrations of IgA and IgE between autologous high-molecular-weight plasma protein fraction from 11 patients with recalcitrant AD who completed 7 weeks of AHPT and autologous plasma from 10 patients who completed 7 weeks of APT (Mann-Whitney U test,  $p > 0.05$ ) (table 3).

#### Discussion

In this study, AHPT resulted in significant clinical improvements in patients with recalcitrant AD. In addition, AHPT was well tolerated and produced no signifi-



cant side effects. These results are compatible with a previous report of the positive clinical efficacy of ABT in patients with mild-to-moderate AD in a randomized, double-blind, placebo-controlled clinical trial [8]. However, we did not observe significant clinical improvements in patients with recalcitrant AD who underwent APT. Because most patients with recalcitrant AD included in this study could be classified as having severe AD according to their baseline clinical severity score (SCORAD value >50) [15], the differences in the baseline clinical severity of the subjects in this study and those in the previous study of ABT may have influenced the results of the clinical efficacy of APT in this study.

ABT is used for the treatment of AD and chronic urticaria by physicians in many countries, including Europe and Japan, since first reported 100 years ago [16, 17]. ABT has advantages in terms of its simplicity, low cost and low risk of side effects. However, ABT also has several important disadvantages compared with current standard medical treatments for AD. Only one randomized placebo-controlled study has evaluated the clinical efficacy of ABT for AD [8]. Technically, ABT requires venous blood sampling for each injection, and the administration of whole venous blood by intramuscular injection is painful for patients due to the formation of artificial hematomas in the muscle. To overcome the above technical disadvantages of ABT in the treatment of AD, we evaluated the clinical efficacy of APT in patients with AD. The mechanism responsible for the therapeutic efficacy of ABT is not known because the blood component mediating the therapeutic efficacy of ABT has not yet been identified. To provide a clue for exploring the therapeutic mechanism of ABT, we attempted to characterize the blood component mediating the therapeutic efficacy of ABT by evaluating the clinical efficacy of AHPT in patients with recalcitrant AD. Our results suggest that the blood component mediating the therapeutic efficiency of ABT in patients with AD might be present in the high-molecular-weight plasma protein fraction of autologous blood.

We found that the high-molecular-weight plasma protein fraction of patients with recalcitrant AD was significantly enriched in immunoglobulin (especially IgG and IgM) compared with unprocessed plasma. This finding suggests that immunoglobulin could be the specific blood component mediating the therapeutic efficacy of ABT in patients with AD. Induction of an anti-idiotypic immune response (immune response to the antigen-binding portion of immunoglobulin) has long been suggested as the main mechanism of the develop-

ment of immune tolerance in allergic and autoimmune diseases [18, 19]. The possibility of involvement of an anti-idiotypic mechanism in the development of the therapeutic efficacy of ABT or AHPT should be further evaluated in future studies.

In this study, we showed that AHPT, but not APT, significantly reduced the clinical severity of recalcitrant AD. However, there was no significant difference in the response rates to treatment (percentages of patients showed a decrease in the clinical severity score of  $\geq 30\%$  from baseline after treatment) between the APT and AHPT groups (10.0 and 45.5%, respectively,  $p = 0.08$ ). This lack of an intergroup difference may have been due to the limited numbers of patients in each group. In addition, there was a tendency of progressive decrease in the SCORAD values and the VAS scores in patients with recalcitrant AD who completed APT, although these changes were not statistically significant. Further studies with greater numbers of patients with AD are needed to evaluate the clinical efficacy of APT and AHPT in AD.

This study had several limitations. It was a nonrandomized trial of the clinical efficacy of APT and AHPT in patients with recalcitrant AD. Further randomized, placebo-controlled trials of the clinical efficacy of APT or AHPT in patients with recalcitrant AD are needed. However, such studies on AHPT might be difficult because of the technical and ethical difficulties in conducting DFPP procedures in control patients. Thus, further investigation of the clinical efficacy of purified target plasma protein is needed to conduct a randomized controlled study for the development of the therapeutic principles of ABT in patients with AD. We evaluated clinical parameters only and did not examine laboratory parameters. Further studies on the changes in laboratory parameters in patients with AD during APT or AHPT might facilitate understanding of the therapeutic mechanisms of these treatments. In this study, the short-term clinical efficacy of APT and AHPT during 7 weeks of treatment and at follow-up evaluation at 11 weeks was determined. Thus, the clinical efficacy of long-term treatment with APT and AHPT in patients with AD should be further evaluated.

In conclusion, AHPT resulted in significant clinical improvements in patients with recalcitrant AD. This suggests that the blood component mediating the therapeutic efficiency of ABT in patients with AD is present in the high-molecular-weight plasma protein fraction. Further studies to identify the specific blood component responsible for the clinical efficacy of ABT in the high-molecular-weight plasma protein fraction are needed to clarify the therapeutic mechanism of ABT in patients with AD.

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## Disclosure Statement

The authors have no conflicts of interest to declare.

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