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# Effects of Intramuscular Injection of Autologous Immunoglobulin on Clinical Severity and Serum IgE Concentration in Patients with Atopic Dermatitis

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**Key Words**

Atopic dermatitis · Immunoglobulins · Immunomodulation · Therapy · Immunoglobulin E

**Abstract**

***Background/Objective:*** The management of patients with atopic dermatitis (AD) is often difficult for both patients and physicians. We hypothesized that repeated intramuscular injections of autologous immunoglobulin can induce clinical improvement in patients with AD by correcting immune dysfunction. ***Methods:*** Seventeen adult patients with severe AD were treated by intramuscular injection of 50 mg autologous immunoglobulin (mainly IgG with a purity ≥97%) twice a week for 4 weeks. The standardized clinical severity scoring system for AD (SCORAD) value and serum IgE concentration were measured at baseline and at 4, 8, and 12 weeks. ***Results:*** SCORAD values and serum IgE concentrations significantly decreased at 4, 8, and 12 weeks compared to baseline ($p < 0.05$). No significant side effects were observed. ***Conclusions:*** Repeated intramuscular injections of autologous immunoglobulin significantly decreased the clinical severity and serum IgE concentration in patients with severe AD. Further studies are required to evaluate the clinical significance of these findings.



## Introduction

Atopic dermatitis (AD) is a common chronic relapsing inflammatory skin disease characterized by itching, dry skin, inflammation, and exudation frequently associated with a personal or familial history of allergic diseases [1]. The precise pathogenetic mechanism of AD is not completely understood. Hypersensitivity reaction to environmental agents has been suggested as a pathogenetic mechanism responsible for the development of AD [2]. A skin barrier defect originating from a filaggrin gene mutation has also been suggested as an important pathogenetic factor inducing chronic skin inflammation in AD [2]. However, the pathogenetic mechanism of AD seems to be associated with complex interrelationships among genetic abnormalities, environmental triggering factors, skin barrier defects, and immune dysfunction [2].

Current standard medical therapies for AD, including topical corticosteroids and/or topical calcineurin inhibitors, are focused mainly on symptomatic relief, and their clinical efficacies are often disappointing to both patients and physicians [1]. Although a significant number of patients with AD can experience improvement via systemic treatment with corticosteroids, cyclosporine, or mycophenolate mofetil, there is a possibility of toxicity from



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long-term treatment with these compounds [1]. Various approaches to modulate the immune system using monoclonal antibodies (anti-IgE and anti-IL-4 receptor antibodies) have been tried in patients with AD [3, 4]. Further development of an additional therapeutic modality for patients with AD is required.

An interesting puzzle regarding the nature of AD is that a significant number of children with AD (up to 70%) experience natural remission of their disease before puberty [5]. The natural remission observed in children with AD might be due to a natural induction of immune tolerance. Induction of an anti-idiotypic immune response (immune response to the antigen-binding site of the antibody) has been suggested as the mechanism responsible for the development of immune tolerance based on animal studies [6]. However, limited clinical data supporting anti-idiotypic immunomodulatory therapy in human subjects with allergic diseases are available. Recently, the clinical efficacy of a recombinant idiotype vaccine resulting in prolongation of disease-free survival was demonstrated in patients with B cell lymphoma in a randomized placebo-controlled clinical trial [7]. This result suggests that anti-idiotypic immunomodulatory therapy may also be effective clinically in patients with AD.

We hypothesized that repeated intramuscular injections of autologous immunoglobulin (autologous immunoglobulin therapy; AIGT) could induce clinical improvements in patients with AD by stimulating active immune responses to the antigen-binding sites of pathogenic antibodies, thereby correcting immune dysfunction. Recently, we reported a preliminary result of AIGT on clinical severity in 3 patients with severe recalcitrant AD [8]. In this study, we further evaluate the effect of AIGT on clinical severity and serum IgE concentrations in 17 patients with severe AD.

## Methods

*Patients*

Seventeen adult patients with severe AD (13 males and 4 females) were enrolled (table 1) according to the following inclusion criteria: (1) typical clinical features of AD compatible with the diagnostic criteria for AD suggested by Hanifin and Rajka [9]; (2) age ≥16 years; (3) a positive result for serum-specific IgE antibody to *Dermatophagoides farinae* or *Pityrosporum orbiculare* (≥0.7 kU/l) using the ImmunoCAP assay (Phadia, Uppsala, Sweden); (4) severe AD with a clinical severity score of AD >50 measured using the standardized clinical severity scoring system for AD (SCORAD), as described previously [10, 11], and (5) difficult-to-treat AD in which the clinical condition has not been effectively controlled by medical treatments (topical moisturizers, topical corticosteroids, topical calcineurin inhibitors, and oral antihistamines, among others) for more than 2 months. Nine patients were treated with cyclosporine for more than 2 months upon enrollment into this study. Eight patients were treated with intermittent administration of low-dose oral corticosteroids for more than 2 months (≤10 mg prednisolone/day or an equivalent dose of another corticosteroid) upon enrollment into this study. This study was approved by the institutional review board. All patients provided written informed consent for participation in this study and underwent a sampling of 400 ml venous blood at the initial visit. An observation period of 4 weeks was established for each patient to prepare the autologous immunoglobulin before the initiation of AIGT. Medical therapies were maintained in all patients throughout the study period from the initial visit without dose changes (table 2).

**Table 1.** Baseline clinical characteristics of the 17 patients with severe AD who participated in this study

| | |
|---|---|
| Age, years | 24 (20–33.5) |
| Gender | |
| Male | 13 (76.5) |
| Female | 4 (23.5) |
| Disease duration, years | 20 (12.5–23.0) |
| Clinical severity score (SCORAD value) | 67.5 (60.3–77.2) |
| Concomitant atopic diseases | |
| Asthma | 3 (17.6) |
| Allergic rhinitis | 10 (58.8) |
| Allergic conjunctivitis | 2 (11.8) |
| Allergic sensitization[a] | |
| *D. farinae* | 16 (94.1) |
| *P. orbiculare* | 15 (88.2) |
| Systemic treatment upon enrollment | |
| Cyclosporine | 9 (52.9) |
| Intermittent low-dose oral corticosteroid[b] | 8 (47.1) |

Data are expressed as medians (IQR; 25th to 75th percentiles) or n (%). [a] Defined as a positive result (≥0.7 kU/l) on a serum allergen-specific IgE antibody test. [b] Defined as administration of ≤10 mg prednisolone/day or an equivalent dose of another corticosteroid.

*Preparation of Autologous Plasma Using the Double Blood Bag System*

Venous blood (400 ml) was collected using a double blood bag system (Green Cross PBM, Seoul, Korea) containing 56 ml citrate phosphate dextrose as an anticoagulant. The venous blood in the double blood bag was separated into packed red blood cells and plasma by centrifugation of the double blood bag at 3,500 rpm and 4°C for 10 min. The separated autologous plasma (~200 ml) was stored at –20°C.

*Preparation of Autologous Immunoglobulin*

Autologous immunoglobulin was aseptically purified from autologous plasma by affinity chromatography using Protein A as described previously [12, 13]. Briefly, autologous plasma was applied to Protein A-coupled beads, and the beads were washed with sterile saline. Immunoglobulin was then eluted from Protein A

**Table 2.** Clinical severity and previous treatments of the 17 patients with severe AD upon initial enrollment into this study

| Patient No. | Age, years | Sex | SCORAD value (at the initial visit) | Previous systemic therapies (dose, duration[a]) | Topical therapies (duration[a]) |
|---|---|---|---|---|---|
| 1 | 20 | M | 51.3 | – | TCI (55) |
| 2 | 30 | F | 88.5 | cyclosporine (1.4–3.6 mg/kg/day, 20), prednisolone[b] (5 mg/day, 18) | TCI (16), TCS (10) |
| 3 | 44 | M | 58.5 | cyclosporine (1.5–2.9 mg/kg/day, 20), prednisolone[b] (5 mg/day, 20) | TCI (29) |
| 4 | 28 | M | 72.0 | – | TCI (48) |
| 5 | 22 | M | 73.2 | – | TCI (24) |
| 6 | 24 | M | 83.8 | – | TCS (6) |
| 7 | 20 | M | 79.0 | cyclosporine (1.9–3.8 mg/kg/day, 60) | TCS (62) |
| 8 | 18 | M | 50.2 | – | TCS (24) |
| 9 | 24 | F | 66.0 | – | TCI (59), TCS (50) |
| 10 | 23 | M | 63.5 | cyclosporine (0.7–2.8 mg/kg/day, 66), prednisolone[b] (5 mg/day, 29) | TCI (43) |
| 11 | 20 | F | 63.5 | deflazacort[b] (6 mg/day, 33) and then prednisolone[b] (5 mg/day, 6) | TCI (71), TCS (4) |
| 12 | 40 | M | 52.4 | cyclosporine (1.5–3.0 mg/kg/day, 50) | TCS (51) |
| 13 | 32 | M | 88.5 | cyclosporine (1.4–2.8 mg/kg/day, 20), prednisolone[b] (5 mg/day, 20) | TCI (17), TCS (18) |
| 14 | 35 | M | 53.0 | cyclosporine (1.6–3.2 mg/kg/day, 67), deflazacort[b] (6 mg/day, 37) and then prednisolone[b] (5 mg/day, 44) | TCI (85), TCS (85) |
| 15 | 20 | F | 89.0 | cyclosporine (1.0–3.0 mg/kg/day, 3) | TCI (58), TCS (60) |
| 16 | 23 | M | 51.8 | prednisolone[b] (5 mg/day, 43) | TCI (24), TCS (40) |
| 17 | 40 | M | 69.4 | cyclosporine (1.0–2.0 mg/kg/day, 91), deflazacort[b] (6 mg/day, 60), then methylprednisolone[b] (4 mg/day, 13), and then prednisolone[b] (5 mg/day, 7) | TCS (122) |

M = Male; F = female; TCI = topical calcineurin inhibitors; TCS = topical corticosteroid. [a] In months. [b] Oral corticosteroids were administered intermittently at a low dose (≤10 mg prednisolone/day or an equivalent dose of another corticosteroid).

with 100 mM sodium citrate buffer (pH 3.5), and the buffer of the eluted immunoglobulin was changed with sterile saline. The immunoglobulin solution was filtered using a 0.45-μm sterile syringe filter (Satorius AG, Goettingen, Germany). The autologous immunoglobulin solution was then aliquoted into sterile glass vials and stored at –20°C. The purified autologous immunoglobulin solution was tested for the absence of bacterial contamination using an endotoxin assay kit (Associates of Cape Cod Inc., Falmouth, Mass., USA).

*AIGT Procedure*

AIGT was started 4 weeks after venous blood sampling to prepare autologous plasma. The frozen autologous immunoglobulin solution in the glass vial was thawed at room temperature for each injection. Patients received intramuscular injections of 50 mg autologous immunoglobulin (mainly IgG with a purity ≥97%) twice a week for 4 weeks (for a total of 8 injections).

*Assessment of Clinical Severity*

The SCORAD value, the Dermatology Life Quality Index (DLQI) [14], and patient ratings of pruritus, quality of sleep, and global clinical severity on a 100-mm visual analogue scale (VAS) were assessed at the initial visit (–4 weeks), at baseline (0 weeks), every week during the 4 weeks of AIGT, at 8 weeks, and at 12 weeks.

*Laboratory Parameters*

Serum concentrations of IgA, IgG, and IgM were assayed by turbidimetric immunoassay using a COBAS Integra analyzer (F. Hoffmann-La Roche, Basel, Switzerland). The serum IgE concentration was measured using enzyme-linked immunosorbent assays as described previously [15, 16]. Peripheral blood eosinophil, neutrophil, monocyte, and lymphocyte counts were measured using an automated hematology analyzer (Coulter Counter STKS; Beckman Coulter, Fullerton, Calif., USA).

*Statistical Analysis*

Data are expressed as medians and interquartile ranges (IQR; 25th to 75th percentiles). The statistical significance of differences in values before and after AIGT was analyzed using the Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant.

**Table 3.** Changes in the clinical severity of AD in 17 patients with severe AD who received intramuscular injections of 50 mg autologous immunoglobulin twice a week for 4 weeks

| | Week –4 (initial visit) | Week 0 (baseline) | Week 1 | Week 2 | Week 3 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|---|---|---|---|
| SCORAD | 66.0 (52.7–81.4) | 67.5 (60.3–77.2) | 59.3 (55.9–66.3)[a] | 58.2 (50.8–70.0) | 58.9 (49.6–62.8) | 49.8 (41.4–61.4)[b] | 48.8 (39.8–58.0)[b] | 50.0 (36.2–64.2)[b] |
| Objective SCORAD | 49.5 (41.3–68.9) | 53.0 (44.3–60.3) | 49.6 (43.3–53.3)[a] | 46.2 (38.8–58.5) | 47.0 (39.2–49.5) | 37.3 (33.3–47.9)[b] | 35.6 (28.6–48.0)[b] | 40.9 (25.8–51.5)[b] |
| DLQI | 17.0 (12.5–25.0)[a] | 15.0 (12.5–18.5) | 13.0 (7.0–16.5)[a] | 11.0 (9.0–16.5)[a] | 12.0 (6.0–14.5)[a] | 12.0 (5.5–15.5)[a] | 11.0 (7.0–15.0)[a] | 9.0 (5.5–17.0)[a] |
| VAS for pruritus | 8.0 (6.5–8.0) | 7.0 (6.0–8.0) | 7.0 (6.0–7.0) | 6.0 (6.0–7.0)[a] | 7.0 (6.0–8.0) | 6.0 (5.0–7.0)[a] | 7.0 (4.5–7.5) | 6.0 (3.0–7.0)[a] |
| VAS for quality of sleep | 7.0 (5.0–8.0) | 7.0 (5.0–8.0) | 6.0 (5.5–7.0) | 6.0 (5.0–7.0) | 6.0 (5.0–7.0) | 6.0 (4.5–7.0) | 7.0 (4.5–7.5) | 6.0 (2.5–7.5) |
| VAS for global severity | 8.0 (7.0–9.0) | 7.0 (6.5–7.5) | 6.0 (5.5–7.0)[a] | 6.0 (6.0–7.0)[b] | 6.0 (5.0–7.0)[b] | 6.0 (5.0–7.0)[b] | 6.0 (4.5–7.0)[a] | 5.0 (2.5–7.0)[a] |

Data are expressed as medians (IQR; 25th to 75th percentiles). [a] $p < 0.05$. [b] $p < 0.005$ compared to baseline using Wilcoxon's signed-rank test.

## Results

*Compliance and Side Effects*

All 17 patients with severe AD who participated in this study completed AIGT. None of the patients experienced significant side effects as a result of the treatment or significant exacerbation of AD during the treatment period, with the exception of transient mild soreness at the injection site.

*Changes in Clinical Severity*

SCORAD values significantly decreased from 67.5 (IQR 60.3–77.2) at baseline to 49.8 (IQR 41.6–61.4) at 4 weeks, 48.8 (IQR 39.8–58.0) at 8 weeks, and 50.0 (IQR 36.2–64.2) at 12 weeks (Wilcoxon's signed-rank test, $p < 0.005$; table 3; fig. 1). Objective SCORAD values also significantly decreased from 53.0 (IQR 44.3–60.3) at baseline to 37.3 (IQR 33.3–47.9) at 4 weeks, 35.6 (IQR 28.6–48.0) at 8 weeks, and 40.9 (IQR 25.8–51.5) at 12 weeks ($p < 0.005$; table 3). A decrease in SCORAD value ≥30% from the baseline value was observed in 5 (29.4%) of 17 patients at 4 weeks, in 10 (58.8%) of 17 patients at 8 weeks, and in 8 (47.1%) of 17 patients at 12 weeks. A decrease in SCORAD value ≥30% from the baseline value was observed in 13 (76.5%) of 17 patients during the follow-up period after the initiation of AIGT. DLQI scores significantly decreased from 15.0 (IQR 12.5–18.5) at baseline to 12.0 (IQR 5.5–15.5) at 4 weeks, 11.0 (IQR 7.0–15.0) at 8 weeks, and 9.0 (IQR 5.5–17.0) at 12 weeks ($p < 0.05$; table 3; fig. 1). VAS scores for global clinical severity significantly decreased at 1, 2, 3, 4, 8, and 12 weeks compared to baseline ($p < 0.05$). In addition, VAS scores for pruritus significantly decreased at 2, 4, and 12 weeks compared to baseline ($p < 0.05$). However, there were no significant changes in VAS scores for quality of sleep before and after AIGT ($p > 0.05$). There were no significant differences in SCORAD and VAS (pruritus, quality of sleep, global severity) scores between 4 weeks before the initiation of AIGT and baseline ($p > 0.05$; tables 3).

*Changes in Serum Immunoglobulin Concentrations*

Serum IgE concentrations significantly decreased from 8,613 kU/l (IQR 5,378–22,775) at baseline to 8,100 kU/l (IQR 4,868–16,000) at 4 weeks, 7,050 kU/l (IQR 3,785–20,905) at 8 weeks, and 6,990 (IQR 4,172–14,050) at 12 weeks ($p < 0.05$; table 4). However, there were no significant differences in serum concentrations of IgG, IgA, or IgM at 4, 8, or 12 weeks compared to baseline values ($p > 0.05$; table 4).

*Changes in Peripheral Blood Eosinophil, Neutrophil, Monocyte, and Lymphocyte Counts*

There were no significant differences in peripheral blood eosinophil counts at 4 weeks (median 739, IQR

**Table 4.** Changes in serum immunoglobulin concentrations in 17 patients with severe AD who received intramuscular injections of 50 mg autologous immunoglobulin twice a week for 4 weeks

| | Week 0 (baseline) | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|
| IgG, mg/dl | 1,438.0 (1,271.8–1,603.0) | 1,470.5 (1,288.0–1,605.5) | 1,507.0 (1,268.0–1,646.5) | 1,453.0 (1,245.5–1,575.8) |
| IgA, mg/dl | 301.0 (227.0–368.0) | 308.0 (266.0–371.5) | 307.0 (244.5–380.0) | 310.0 (241.5–352.5) |
| IgM, mg/dl | 82.0 (62.0–147.5) | 84.0 (58.0–150.5) | 84.0 (56.0–147.5) | 81.0 (51.5–151.5) |
| IgE, kU/l | 8,613 (5,378–22,775) | 8,100 (4,868–16,000)[a] | 7,050 (3,785–20,905)[a] | 6,990 (4,172–14,050)[a] |

Data are expressed as medians (IQR; 25th to 75th percentiles). [a] $p < 0.05$ compared to baseline using Wilcoxon's signed-rank test.

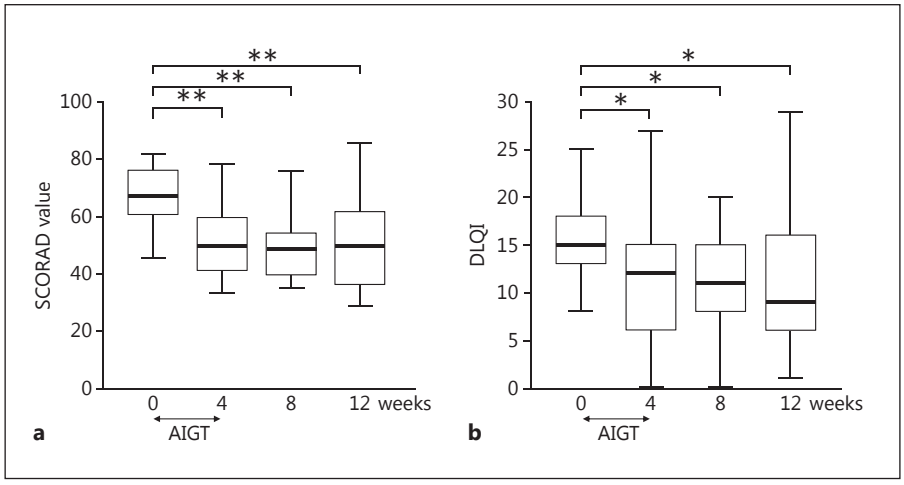


**Fig. 1.** Changes in SCORAD values (**a**) and the DLQI (**b**) in 17 patients with severe AD who received intramuscular injections of 50 mg autologous immunoglobulin twice a week for 4 weeks (AIGT). Thick lines represent medians, boxes represent IQR, and error bars indicate minimum/maximum values. * $p < 0.05$; ** $p < 0.005$ compared to baseline using Wilcoxon's signed-rank test.

396–1,663/μl), 8 weeks (median 715, IQR 336–1,070/μl) or 12 weeks (median 726, IQR 267–1,364/μl) compared to baseline values (median 599, IQR 440–1,491/μl; $p > 0.05$). In addition, there were no significant differences in peripheral blood neutrophil, monocyte, and lymphocyte counts at 4, 8, or 12 weeks compared to baseline values ($p > 0.05$; data not shown).

## Discussion

The primary objective of this pilot study was to evaluate the effect of AIGT on clinical severity in patients with severe AD. In this study, AIGT significantly decreased clinical severity scores in 17 adult patients with severe AD whose clinical conditions were not effectively controlled by current medical therapies. In addition, AIGT was well tolerated and produced no significant side effects.

The concept of AIGT originated from our hypothesis on the active therapeutic component mediating the clinical efficacy of autologous blood therapy (ABT). ABT involves the repeated administration of small amounts of autologous blood (1–10 ml) by intramuscular injection immediately after sampling of venous blood [17]. ABT has been used as complementary and alternative medicine for AD and chronic urticaria (CU) by physicians in many countries, including those in Europe and Japan, since its first report in 1913 [18]. ABT is reportedly the most frequently used complementary and alternative medicine modality for AD by physicians in Germany [19]. The clinical efficacy of ABT has been demonstrated in patients with AD and CU based on randomized controlled studies [20, 21]. Recently, the clinical efficacy of autologous serum therapy (AST) consisting of repeated intramuscular injections of autologous serum was demonstrated in patients with CU in a randomized double-blind placebo-controlled study [22]. However, the blood or serum component mediating the therapeutic efficacy of ABT or AST in patients with AD or CU has not yet been identified [23]. Repeated intramuscular injections of autologous immunoglobulin significantly decreased the clinical severity and serum IgE concentrations in patients

with severe AD in this study. This result suggests that immunoglobulin is the main blood component mediating the therapeutic efficacy of ABT in patients with AD.

In this study, autologous immunoglobulin was purified by affinity chromatography using Protein A, and the immunoglobulin isotype used for AIGT was mainly IgG (purity ≥97%) with small amounts of IgM, IgA, and IgE, as reported previously [8, 12]. The clinical efficacy and anti-inflammatory properties of polyclonal human IgG purified from multiple healthy blood donors have been reported in various allergic and autoimmune diseases [24]. The precise therapeutic mechanism of polyclonal human IgG is still not completely understood [24]. Anti-idiotypic immunomodulation has been proposed as a therapeutic mechanism for polyclonal human IgG [24]. Significant long-term decreases in serum IgE concentrations have been reported in children with severe AD after intravenous administration of polyclonal human IgG [25]. We also observed significant decreases in serum total IgE concentrations in patients with AD after AIGT in this study. The clinical efficacy of intravenous immunoglobulin therapy in patients with AD persisted for about 4–5 weeks and required repeated monthly administrations of intravenous immunoglobulin (0.4–2.0 g/kg) to maintain clinical improvement [26]. However, we observed that the clinical efficacy of AIGT (8 intramuscular injections of 50 mg autologous IgG for 4 weeks) was maintained for at least 8 weeks in patients with AD in this study after completion of AIGT. There were clear differences in the origin of therapeutic materials, dose, administration route, and the duration of clinical efficacy between intravenous immunoglobulin therapy and AIGT in this study. These suggest that the therapeutic mechanisms of these two types of immunoglobulin therapy for AD could be different (such as passive immunization and active immunization). We speculate that intramuscular injections of autologous total IgG may actively induce anti-idiotypic suppression of pathogenic antibodies including IgE antibodies. Further studies on the detailed immunological mechanism of AIGT in patients with AD are necessary.

Single-step affinity purification is required for preparation of therapeutic material for AIGT. This methodological simplicity might be useful for the practical application of AIGT in patients with severe AD.

This study has several limitations. It was a nonrandomized pilot study on AIGT in patients with severe AD. Further randomized, placebo-controlled trials are required to evaluate the clinical usefulness of AIGT for AD. In this study, relatively short-term (12 weeks) changes in clinical severity and laboratory parameters after initiation of AIGT were evaluated. However, further long-term clinical improvements lasting more than 6 months after 4 weeks of AIGT were observed in 2 of 3 patients with severe AD in our previous report [8]. Decreases in peripheral blood eosinophil counts and serum total IgE concentrations could also be observed 6–12 months after initiation of AIGT in the 2 patients with severe AD who showed long-term clinical improvements in that previous report [unpubl. data]. Thus, long-term changes in clinical severity and laboratory parameters after long-term AIGT should be evaluated in future studies.

In conclusion, AIGT significantly decreased clinical severity and serum IgE concentrations in patients with severe AD. Further studies are required to evaluate the clinical significance of these findings.

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## Disclosure Statement

The authors have no conflicts of interests to declare.

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