INTRODUCTION
Atopic dermatitis (AD) is a common chronic allergic inflammatory skin disease characterized by itching, dry skin, inflammation, and exudation, and is frequently associated with a personal or familial history of allergic diseases. Hypersensitivity reaction to environmental agents has been suggested as a pathogenetic mechanism responsible for the development and maintenance of chronic skin inflammation in AD patients. However, the pathogenetic mechanism of AD seems to be more complexly associated with genetic abnormalities, environmental factors, skin barrier defects, and immune dysfunction. The precise pathogenetic mechanism underlying AD is not completely understood.

Current standard medical therapies for AD, including the use of topical corticosteroids and/or topical calcineurin inhibitors, focus mainly on transient symptomatic relief, and their clinical efficacies are often disappointing for both patient and physician. Although a significant number of patients with severe AD find improvement upon systemic treatment with cyclosporine, mycophenolate, methotrexate or azathioprine, there is a possibility of toxicity from long-term treatment with these compounds. Recently, a randomized clinical trial showed significant clinical improvements in patients with moderate-to-severe AD after treatment with monoclonal antibody to interleukin (IL)-4 receptor alpha. This result suggested that immune dysfunction and hypersensitivity reaction play key roles in the pathogenesis of AD and could be the critical therapeutic targets for AD. Further development of a new therapeutic modality is required to change the long-term clinical course of AD.

Subcutaneous allergen immunotherapy (SCIT) is a treatment modality for patients with AD sensitized to house dust mite (HDM). SCIT is a therapeutic option that desensitizes patients with AD sensitized to HDM. Early initiation of SCIT might provide a favorable clinical outcome in patients with severe AD sensitized to HDM.
method of administering gradually increasing doses of allergen to decrease hypersensitivity to the allergen and eventually reduce allergic symptoms resulting from exposure to the allergen. The clinical efficacy of SCIT has been proven by multiple randomized, placebo controlled studies for the treatment of allergic rhinitis, allergic asthma, and bee venom hypersensitivity. A recent meta-analysis of randomized clinical trials on SCIT with house dust mite (HDM) preparation in patients with AD provided a moderate-level evidence of the efficacy for AD. However, the clinical usefulness of SCIT for AD is still controversial. This controversy is partly due to the lack of the knowledge on the degree of clinical efficacy, predictive factor for a favorable clinical response, and selection criteria of patients for the treatment.

In this study, we analyzed the clinical efficacy of SCIT in 251 patients with AD sensitized to HDM and the clinical characteristics of patients showing a favorable clinical response to the treatment.

MATERIALS AND METHODS

Patients

Two hundred and fifty one patients with AD (103 females and 148 males) between 5 and 55 years of age (19.9±10.1; mean±SD) with AD who fulfilled all of the criteria below were included in this study (Table 1). The patients showed the typical clinical features of AD compatible with the diagnostic criteria for AD suggested by Hanifin and Rajka. All included patients showed a positive result for serum-specific IgE antibody to Dermatophagoides pteronyssinus (D. pteronyssinus) or Dermatophagoides farinae (D. farinae) (≥3.5 kU/L) using the ImmunoCAP assay (Phadia US, Portage, MI, USA). The exclusion criteria for SCIT in patients with AD were 1) patients with concomitant significant systemic diseases, such as autoimmune disorders, malignancy, cardiovascular diseases, chronic infections, immunodeficiencies, mental diseases, or other chronic inflammatory disorders; 2) children of age less than 5 years; 3) pregnancy; and 4) patients with poor compliance to long-term therapy. All of the patients provided written informed consent for SCIT, and this study was performed in accordance with local clinical practice guidelines. This study was approved by Institutional Review Board.

Study design

This study was conducted as an observational cohort study to assess the clinical efficacy of SCIT and clinical characteristics of patients with AD showing a favorable clinical response to SCIT. Systemic immunosuppressants, including cyclosporine, were not administered during the SCIT. All patients received premedication with fexofenadine or levocetirizine to minimize allergic side effects of SCIT. The use of topical corticosteroids and topical calcineurin inhibitors were adjusted according to the clinical condition of the patients by physicians.

Preparation of allergen extract for SCIT

Standardized allergen extract containing a mixture of D. pteronyssinus and D. farinae extract (50%:50%) adsorbed to aluminum hydroxide (Novo-Helisen Depot; Allergopharma Joachim Ganzer KG, Reinbeck, Germany) was used for SCIT. The HDM allergen extract for SCIT was composed of three vials (labeled as No. 1, 2, and 3) with ten-fold increases in allergen concentrations. The schedule of SCIT was divided into an initial build-up phase and a maintenance phase. According to the schedule for initial build-up phase, we choose either a cluster schedule or an accelerated schedule to reach a maximal maintenance dose of HDM extract. In a cluster schedule for initial build-up phase, two increasing doses of HDM extract (in order of 0.1, 0.2, 0.4, and 0.8 mL of each vial) were injected subcutaneously to 181 of 251 patients (72.1%) at 30-minute intervals between two injections weekly for 6 weeks. In an accelerated schedule for initial build-up phase, subcutaneous injections of increasing doses of HDM extract were completed with a 1-day protocol (ultra-rush) or a 3-day protocol (rush) upon admission to a hospital for safety reasons, as previously described. Selection of the schedule for the initial build-up phase was determined by a physician considering the distance of each patient’s living place from the hospital, ability to make frequent hospital visits, and the patients’ occupations. In the maintenance phase of SCIT, 0.8 mL of the highest maintenance concentration of HDM extract (labeled as No. 3; 5000 TU/mL) was directly mixed with histamine-immunoglobulin complex (Histobulin®; Green Cross Co., Seoul, Korea), containing 12 mg of human immunoglobulin

Table 1. Baseline Clinical Characteristics of 251 Patients With Atopic Dermatitis Who Received Subcutaneous Allergen Immunotherapy with House Dust Mite Extract

| Characteristic | Value |
|----------------|-------|
| Age, yrs       | 19.9±10.1 |
| Gender, n (%)  |       |
| Male           | 148 (59.0) |
| Female         | 103 (41.0) |
| Duration of disease, yrs | 11.4±9.2 |
| Age at onset of disease, yrs | 8.3±9.5 |
| Clinical severity score, SCORAD value | 44.4±19.3 |
| Mild (≤25), n (%) | 34 (13.5) |
| Moderate (25–50), n (%) | 123 (49.0) |
| Severe (>50), n (%) | 94 (37.5) |
| Total IgE (kU/L) | 2218.0±1936.3 |
| Specific IgE to D. pteronyssinus (kU/L) | 52.0±39.6 |
| Specific IgE to D. farinae (kU/L) | 61.8±39.1 |
| Peripheral blood eosinophil count (/μL) | 578.4±565.8 |
| Schedule of initial build-up phase for immunotherapy, n (%) | Cluster/rush/ultra-rush 181 (72.1)/14 (5.6)/56 (22.3) |

SCORAD, standardized clinical severity scoring system for atopic dermatitis; D. pteronyssinus, Dermatophagoides pteronyssinus; D. farinae, Dermatophagoides farinae.

Data are expressed as means±SD or numbers with percentages.
lin and 0.15 µg of histamine dichloride, and injected subcutaneously at monthly intervals as described in previous reports.12,13

**Assessment of clinical efficacy and side effects**

The primary efficacy outcome was change in clinical severity measured using standardized clinical severity scoring system for AD (SCORAD) values at 12 months in comparison with the values at baseline in patients with AD who received SCIT.14 In this study, severe AD was defined as a baseline total SCORAD value above 50 as previously described.15 A favorable clinical response to SCIT was defined as a decrease in total SCORAD value at 12 months greater than 50% compared to baseline value. To assess the safety of the SCIT, details of systemic reactions were recorded according to European Academy of Allergy and Clinical Immunology (EAACI) criteria for the classification and grading of systemic reactions associated with SCIT, as previously reported.16

**Laboratory parameters**

Serum concentrations of total IgE, specific IgE antibody to *D. pteronyssinus*, and specific IgE antibody to *D. farinae* were measured using ImmunoCAP assay (Phadia US, Portage, MI, USA). This measurement system has limitations of detection levels for total IgE (2–5000 kU/L) and for the allergen-specific IgE (0.1–100 kU/L). If the result of measurement was above the upper detection limit, serum concentration of total IgE was regarded as 5000 kU/L and serum concentration of allergen-specific IgE was regarded as 100 kU/L for statistical analysis. Peripheral blood eosinophil count was measured using an automated hematology analyzer (Coulter Counter STKS; Beckman Coulter, Fullerton, CA, USA).

**Statistical analysis**

The data are expressed as mean±SD. The statistical significance of changes in SCORAD values before and after SCIT were analyzed using Wilcoxon signed-rank test. Differences in parameters between the two groups were analyzed using the Mann-Whitney U test. The χ²-test was used to compare the clinical efficacy of SCIT between the two groups. A p value <0.05 was regarded as statistically significant.

**RESULTS**

**Compliance**

Overall compliance rate for SCIT was 66.5% (167 of 251 patients) at 12 months. There was no significant difference in the compliance rate for SCIT between patients with mild to moderate AD and patients with severe AD (p>0.05). In addition, there was no significant difference in the compliance rate for SCIT between cluster schedule group and accelerated schedule group for the initial build-up phase of SCIT (p>0.05).

**Clinical efficacy**

Overall, SCORAD values were measured in 144 of 167 patients (86.2%) who received SCIT for 12 months and the clinical efficacy of SCIT over 12 months was calculated in these patients. SCORAD values significantly decreased from 44.4±19.3 at baseline to 13.7±9.2 at 12 months (Wilcoxon signed-rank test, p<0.001) (Fig. 1A). The mean decrease in SCORAD value at 12 months, compared to baseline values, after SCIT was 62.5% in patients with AD. In patients with severe AD, the SCORAD value significantly decreased from 64.9±12.4 at baseline to 14.6±10.9 at 12 months (p<0.001). In patients with mild to moderate
AD, the SCORAD value significantly decreased from 32.1±9.9 at baseline to 13.2±8.1 at 12 months (p<0.005). There was a significant difference in the mean percentages of decreases in SCORAD values at 12 months, compared to baseline, between patients with severe AD (77.2±17.2%) and patients with mild to moderate AD (53.9±31.7%) (Mann-Whitney U test, p<0.001) (Fig. 1B). However, there was no significant difference in the mean percentages of decreases in the SCORAD values at 12 months, compared to baseline, between the accelerated schedule group (64.1±23.1%) and cluster schedule group (59.9±41.6%) (p=0.741). A favorable clinical response to SCIT with a decrease in SCORAD value at 12 months greater than 50%, compared to baseline value, was observed in 106 (73.6%) of 144 patients (Table 2). The proportion of patients with a favorable clinical response was significantly higher in patients with severe AD (90.6%, 48/53) than patients with mild to moderate AD (63.7%, 58/91) at 12 months after SCIT (p<0.001). The proportion of patients showing a decrease in SCORAD value at 12 months greater than 75%, compared to baseline value, was significantly higher in patients with severe AD (66.0%, 35/53) than patients with mild to moderate AD (29.7%, 27/91) (p<0.001) (Table 2).

**Clinical characteristics of patients showing a favorable clinical response to SCIT**

Baseline clinical and laboratory parameters were compared between patients showing a favorable clinical response to SCIT (responders) and patients showing no significant clinical response to SCIT (non-responders) among the 144 patients with AD who received the 12 months of SCIT. Baseline SCORAD values were significantly higher in the 106 responders (48.4±18.3) than 38 non-responders (31.6±16.8) (p<0.001) (Table 3). In 53 patients with severe AD who received 12 months of SCIT, 48 responders showed a significantly shorter duration of AD (12.3±8.5 years) than five non-responders (20.6±10.9 years) (p<0.05) (Table 4). In 53 patients with severe AD who received 12 months of SCIT, age of onset of AD was significantly higher in the 48 responders (9.1±10.5 years) than the five non-responders (1.2±2.2 years) (p<0.001) (Table 4).

**Changes in laboratory parameters**

Laboratory parameters, including serum total IgE, specific IgE antibody to *D. pteronyssinus*, specific IgE antibody to *D. farinae*, and peripheral blood eosinophil count, were measured in 131 of 167 patients (78.4%) with AD at baseline and 12 months.

### Table 2. Degree of Clinical Improvement in 144 Patients with Atopic Dermatitis Who Received Subcutaneous Allergen Immunotherapy with House Dust Mite Extract for 12 Months, at 12 Months Compared to Baseline

|                      | Total            | Mild to moderate (n=91) | Severe (n=53) | p value    |
|----------------------|------------------|-------------------------|--------------|------------|
| SCORAD-50 (clinical improvement >50%) | 106 (73.6%)      | 58 (63.7%)              | 48 (90.6%)   | <0.001*    |
| SCORAD-75 (clinical improvement >75%) | 62 (43.1%)       | 27 (29.7%)              | 35 (66.0%)   | <0.001*    |

SCORAD, standardized clinical severity scoring system for atopic dermatitis. *p<0.05 is less than 0.05, †SCORAD-50: decrease of SCORAD values at 12 months compared to baseline >50%, ‡SCORAD-75: decrease of SCORAD values at 12 months compared to baseline >75%.

### Table 3. Comparison of Baseline Clinical and Laboratory Parameters between Patients Showing a Favorable Clinical Response (Responders) and Patients Showing No Significant Clinical Response (Non-Responders) at 12 Months among Patients with Atopic Dermatitis Who Received Subcutaneous Allergen Immunotherapy with House Dust Mite Extract for 12 Months

|                          | Responders (n=106)* | Non-responders (n=38) | p value |
|--------------------------|---------------------|-----------------------|---------|
| Age, yrs                 | 20.1±9.3            | 18.2±9.3              | 0.291   |
| Gender, n (%)            |                     |                       |         |
| Male                     | 62 (58.5)           | 24 (63.2)             |         |
| Female                   | 44 (41.5)           | 14 (36.8)             |         |
| Duration of disease, yrs | 12.1±8.9            | 12.4±8.6              | 0.850   |
| Age at onset of disease, yrs | 8.0±9.0            | 5.8±7.4               | 0.185   |
| Clinical severity score, SCORAD value | 48.4±18.3          | 31.6±16.8             | <0.001* |
| Total IgE (kU/L)         | 2480.0±1955.1       | 1995.8±1828.0         | 0.186   |
| Specific IgE to *D. pteronyssinus* (kU/L) | 54.7±39.2          | 52.5±39.1             | 0.762   |
| Specific IgE to *D. farinae* (kU/L) | 64.4±38.4          | 65.8±39.1             | 0.851   |
| Peripheral blood eosinophil count (/μL) | 626.3±730.9        | 579.8±428.3           | 0.713   |

SCORAD, standardized clinical severity scoring system for atopic dermatitis; *D. pteronyssinus, Dermatophagoides pteronyssinus; D. farinae, Dermatophagoides farinae.*

Data are expressed as means±SD or numbers with percentages. *p<0.05 is less than 0.05, †Responders: patients with atopic dermatitis showing a favorable clinical response to subcutaneous allergen immunotherapy as a decrease clinical severity score at 12 months greater than 50% compared to baseline value.
after SCIT. Serum total IgE concentrations significantly decreased from 2379.4±1956.2 kU/L at baseline to 2165.7±1837.8 kU/L at 12 months (p=0.012) (Table 5). In patients with severe AD, serum total IgE concentrations significantly decreased from 3387.0±1788.8 kU/L at baseline to 3017.9±1773.9 kU/L at 12 months (p<0.005). There was no significant difference of serum total IgE concentrations between baseline (1777.4±1806.7 kU/L) and 12 months (1656.4±1698.4 kU/L) in patients with mild to moderate AD (p>0.05). Peripheral blood total eosinophil counts significantly decreased from 610.0±681.4 µL at baseline to 398.1±332.0 µL at 12 months (p<0.001) (Table 5). In patients with severe AD, peripheral blood total eosinophil counts significantly decreased from 895.4±961.7 µL at baseline to 500.0±398.3 µL at 12 months (p<0.001). In patients with mild to moderate AD, peripheral blood total eosinophil counts significantly decreased from 439.5±344.3 µL at baseline to 335.3±267.7 µL at 12 months (p<0.001). However, there was no significant difference in serum concentrations of specific IgE anti-

Table 4. Comparison of Baseline Clinical and Laboratory Parameters between Patients Showing a Favorable Clinical Response (Responders) and Patients Showing No Significant Clinical Response (Non-Responders) at 12 Months among Patients with Mild to Moderate Atopic Dermatitis and Patients with Severe Atopic Dermatitis Who Received Subcutaneous Allergen Immunotherapy with House Dust Mite Extract for 12 Months

| Table 5. Change in Laboratory Parameters in Patients with Atopic Dermatitis Who Received Subcutaneous Allergen Immunotherapy with House Dust Mite Extract from Baseline to 12 Months

| Clinical severity | Baseline (n=131) | 12 month (n=131) | p value |
|-------------------|------------------|------------------|---------|
| Total IgE (kU/L)  | 2379.4±1956.2    | 2165.7±1837.8    | 0.012*  |
| Specific IgE to D. pteronyssinus (kU/L) | 53.5±39.2 | 55.0±38.8 | 0.769 |
| Specific IgE to D. farinae (kU/L) | 64.0±38.5 | 65.2±38.1 | 0.481 |
| Peripheral blood eosinophil count (/µL) | 610.0±681.4 | 398.1±332.0 | <0.001* |

| Clinical severity | Baseline (n=82) | 12 month (n=82) | p value |
|-------------------|------------------|------------------|---------|
| Total IgE (kU/L)  | 1777.4±1806.7    | 1656.4±1698.4    | 0.354   |
| Specific IgE to D. pteronyssinus (kU/L) | 45.8±39.1 | 46.9±38.2 | 0.893 |
| Specific IgE to D. farinae (kU/L) | 57.5±39.6 | 58.4±39.2 | 0.561 |
| Peripheral blood eosinophil count (/µL) | 439.5±344.3 | 335.3±267.7 | <0.001* |

D. pteronyssinus, Dermatophagoides pteronyssinus; D. farinae, Dermatophagoides farinae.

Data are expressed as means±SD or numbers with percentages.

* p<0.05 is less than 0.05.

†Severe atopic dermatitis was defined as a baseline standardized clinical severity scoring system for atopic dermatitis (SCORAD) value above 50. Responders: patients with atopic dermatitis showing a favorable clinical response to subcutaneous allergen immunotherapy as a decrease clinical severity score at 12 months greater than 50% compared to baseline value.
tibody to *D. pteronyssinus* (*p*=0.77) and specific IgE antibody to *D. farinae* (*p*=0.48) between baseline and 12 months after SCIT (Table 5).

**Side effects**

Twenty six of the 251 patients (10.4%) showed systemic reactions during the initial build-up phase of SCIT. Localized or generalized urticaria was observed in 21 patients (8.4%) and mild bronchospasm (mild dyspnea without wheezing) was seen in 5 patients (2.0%). In 70 patients who received accelerated schedules for initial build-up phase of SCIT, localized or generalized urticaria was observed in 13 patients (18.6%), and mild bronchospasm (mild dyspnea without wheezing) was observed in 5 patients (7.1%). In 181 patients who received cluster schedules for initial build-up phase of SCIT, localized or generalized urticaria was observed in 8 patients (4.4%). Systemic reactions were significantly more frequently observed in patients who received accelerated schedules (16 of 70 patients, 25.7%) than the patients who received cluster schedules (8 of 181 patients, 4.4%), for the initial build-up phase (*p*<0.001). Grades of systemic reactions associated with SCIT ranged from grades 1 to 2 according to EAACI criteria. There was no case of patients who experienced anaphylaxis. Urticaria or bronchospasm rapidly resolved following intravenous administration of 4 mg of chlorpheniramine and 5 mg of dexamethasone and/or inhalation of short-acting bronchodilator.

**DISCUSSION**

In this study, a favorable clinical response to SCIT with HDM extract was observed in 73.6% of patients with AD sensitized to HDM at 12 months. A proportion of patients showing a favorable clinical response to SCIT was significantly higher in patients with severe AD (90.6%) than patients with mild to moderate AD (63.7%). This result is consistent with results from a previous randomized placebo-controlled clinical study of SCIT with HDM extract which showed significantly greater clinical improvements in patients with severe AD who received SCIT than patients with severe AD who received placebo treatment. These results suggest that SCIT is a clinically useful therapeutic option for patients with severe AD sensitized to HDM.

In this study, patients with severe AD showing a favorable clinical response had a significantly shorter duration of AD (12.3±8.5 years) than patients with severe AD showing no significant clinical response (20.6±10.9 years). In patients with allergic rhinitis, patients showing a favorable clinical response to SCIT had a significantly shorter duration of symptom than patients showing no significant clinical response to SCIT in a previous study. In patients with AD, clinical outcomes for SCIT were better in patients younger than 12 years of age than patients older than 12 years in a previous study. These results suggest that early initiation of SCIT after onset of symp-

toms might provide a favorable clinical outcome in patients with severe AD sensitized to HDM.

The reason for the decreased therapeutic efficacy of SCIT in patients with severe AD with a long duration of disease might be associated with the natural course of AD. A hypothesis suggested a concept of natural evolution of AD from nonallergic AD in infants to allergic AD in children and young adults, and eventually to autoallergic AD in adults. In the acute stage of AD, Th2 immune responses are suggested to play a major role. However, Th1 immune responses and autoallergic reactions to self-protein have been suggested to play a role in the development of chronic AD. In this study, the significantly shorter duration of disease in patients with severe AD showing a favorable clinical response to SCIT, compared to patients with severe AD showing no significant clinical response to SCIT, is consistent with the above hypothesis. The natural course of AD seems to be a time-dependent evolutional process. Therefore, early initiation of SCIT in patients with severe AD at the stage of allergic AD might change the natural course of AD and improve long-term clinical outcome, as suggested by the data of this study.

The most important limitation of SCIT to be a standard treatment method for AD is a lack of objective clinical and laboratory parameters to predict the clinical efficacy of SCIT before the initiation of the treatment. Previous studies on the analysis of predictive factors for the clinical efficacy of SCIT in patients with allergic rhinitis and allergic asthma have suggested that levels of total serum IgE or allergen-specific IgE could be used as a predictive marker for clinical efficacy of SCIT. In this study, we could not find any differences in baseline laboratory parameters between patients with AD showing a favorable clinical response to SCIT and the patients with AD showing no significant clinical response to SCIT, similar to a previous study. Further studies to identify predictive biomarker for clinical efficacy of SCIT in patients with AD are needed.

Another important problem in the clinical application of SCIT for the treatment of patients with AD is a lack of knowledge on the expected degree of its clinical efficacy. This is a clinically important issue because clinicians should explain the chance of meaningful clinical improvement in patients with AD sensitized to HDM before the initiation of SCIT with HDM extract. In this study, we defined a favorable clinical response to SCIT as a decrease in SCORAD value at 12 months greater than 50% (SCORAD-50), compared to baseline, and a favorable clinical response were observed in 73.6% of patients with AD after SCIT for 12 months. Improvement of clinical severity at 12 months greater than 75% (SCORAD-75), compared to baseline, was observed in 66.0% of patients with severe AD who received SCIT with HDM extracts for 12 months. Treatment with anti-IL 4 receptor alpha monoclonal antibody has an advantage of early onset of clinical efficacy in patients with AD, and allergen immunotherapy has a possible advantage of long-term clinical efficacy in patients with AD, as shown.
in previous studies on allergic asthma and allergic rhinitis.\textsuperscript{4,7,8} Future clinical trials of combinations of allergen immunotherapy and monoclonal antibody therapy or polyclonal immunoglobulin therapy might improve the long-term therapeutic outcomes of patients with AD.\textsuperscript{3,4,12,13,24}

This study has an important limitation. This was an observational study on the clinical efficacy of SCIT in patients with AD. Therefore, our study is limited by the possible involvement of a placebo effect from the natural clinical course in patients with AD. Randomized placebo-controlled clinical studies are needed for precise evaluation of the degree of the clinical efficacy of SCIT over a placebo in patients with AD. Nevertheless, the results of our study provide useful information on the degree of long-term clinical efficacy of SCIT for AD and clinical characteristics of patients with severe AD showing a favorable clinical response to SCIT in a real clinical practice setting. Further studies are needed to evaluate the clinical usefulness of SCIT for AD.

In conclusion, SCIT could be a clinically useful therapeutic option for the patients with severe AD sensitized to HDM, and early initiation of SCIT might provide a favorable clinical outcome in patients with severe AD sensitized to HDM.

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