INTRODUCTION

Allergic rhinitis (AR) is the most common respiratory allergic disease across the globe. Its prevalence, in common with other allergic diseases, such as allergic asthma (AA), has increased over the past few decades. In Asia, 10% to 32% of the general population has AR; it is estimated to be 17% to 29% in Europe and 15% in the United States have AR. Allergy to house dust mites (HDM) is one of the most common causes of allergic disease. One recent study reported a rate of HDM sensitization of 89.1% in Korean children and adolescents with AR. For managing HDM-induced AR, both avoidance measures and pharmacological treatment are used. Pharmacologic treatment for AR mainly includes H1-antihistamines and leukotriene receptor antagonists (LTRA), and an intranasal corticosteroid is given to patients with more severe symptoms of AR.

Allergen-specific immunotherapy (AIT) is considered in patients whose symptoms are not adequately controlled with medication, in individuals experiencing side effects from medication, and those who want to avoid regular use of medication. Compared with pharmacologic agents that merely offer symptomatic relief, AIT has been found to be effective in preventing sensitization to new allergens, in reducing the risk of developing asthma, and in maintaining its therapeutic effects upon treatment completion. Subcutaneous immunotherapy (SCIT), 1 mode of AIT, which has been used for more than 100 years, is a promising therapeutic option for patients with AR sensitized to HDM. However, AIT is not a cure for AR and the results of many clinical trials have been inconsistent. Thus, the aim of this study was to describe the efficacy and safety of SCIT in routine clinical practice in Korean adults with AR sensitized to HDM.

Methods: We reviewed medical records of 304 patients with AR treated at an allergy clinic of a tertiary hospital using SCIT with aluminum hydroxide-adsorbed allergen extract targeting HDM alone or with pollens for at least 1 year from 2000 to 2012. Patients with asthma were excluded. Rates of remission, defined as no further requirement of maintenance medication, over time were determined by means of life tables and extension of survival analysis. Specific immunoglobulin E (IgE) levels to HDM were categorized into 6 classes.

Results: The mean time until achieving remission was 4.9 ± 0.1 years, and the cumulative incidence of remission from AR was 76.6%. Severe AR (odds ratio [OR], 0.40; 95% confidence interval [CI], 0.23-0.69; \( P = 0.001 \)), specific IgE levels to HDM \( \geq 17.5 \) kU/L (OR, 1.85; 95% CI, 1.01-3.37; \( P = 0.045 \)), and duration of immunotherapy \( \geq 3 \) years (OR, 7.37; 95% CI, 3.50-15.51; \( P < 0.001 \)) were identified as significant predictors of clinical remission during SCIT for patients with AR sensitized to HDM. Overall, 73 patients (24.0%) experienced adverse reactions to SCIT, and only 1 case of anaphylaxis (0.3%) developed.

Conclusions: SCIT with HDM was found to be effective and safe for patients with AR. Specific IgE levels to HDM and a duration of SCIT \( \geq 3 \) years may be predictors of clinical responses to SCIT in AR patients.

Key Words: Allergen-specific immunotherapy, house dust mites, remission, rhinitis, allergic
years, is effective against seasonal AR, as well as perennial AR, and its efficacy is supported by several systematic reviews. Compared with sublingual immunotherapy (SLIT), another mode of AIT, SCIT has been found to be more efficacious and to introduce fewer safety concerns.

Notwithstanding, there are several unmet needs in SCIT, especially for clinical predictors and laboratory biomarkers of efficacy. In addition, the efficacy of SCIT would be unlikely to be identical in geographically different regions. Therefore, in a retrospective cohort covering 12 years, we sought to investigate clinical outcomes and prognostic factors of SCIT in Korean adults with AR.

MATERIALS AND METHODS

Study design and population
This retrospective cohort study analyzed 304 patients who visited a university hospital from 2000 to 2012 and received SCIT with HDM with or without pollen allergens for AR for more than 1 year, but less than 7 years. The diagnosis of AR was made according to clinical symptoms, physical examination, and a skin prick test (SPT).

All patients were sensitized to HDM (Dermatophagoides pteronyssinus [Dp] and Dermatophagoides farinae [DI]) allergens (Allergopharma Joachim Ganzer KG, Reinbek, Germany) on a SPT and/or had serum specific immunoglobulin E (IgE) levels higher than 0.35 kU/L. With respect to pollens, tree (Alder, Birch, Hazel, Beech, and Oak), grass (Orchard, Rye, Bermuda, Timothy, Kentucky, and Meadow), and weed (Ragweed and Mugwort) were considered combined causative allergens of AR according to seasonal variations in rhinitis symptoms and SPT results. Positivity to allergens on SPTs was determined when the size of wheals caused by an allergen was greater than or equal to the size of wheals induced by histamine. We measured serum total and specific IgE levels to the allergens using the ImmunoCAP system (Thermo-Fisher, Uppsala, Sweden). A cutoff value of 0.35 kU/L for specific IgE was regarded as a positive result (class 1, 0.35-0.7 kU/L; class 2, 0.7-3.5 kU/L; class 3, 3.5-17.5 kU/L; class 4, 17.5-50 kU/L; class 5, 50-100 kU/L; and class 6, >100 kU/L).

Patients who were sensitized only to animal dander, mold, or pollen and who were not sensitized to HDM in SPT were excluded. Patients with asthma were also excluded in the present study. Symptom severity was classified according to medical charts, physical examination, and a skin prick test (SPT). All patients were sensitized to HDM (Dermatophagoides pteronyssinus [Dp] and Dermatophagoides farinae [DI]) allergens (Allergopharma Joachim Ganzer KG, Reinbek, Germany) on a SPT and/or had serum specific immunoglobulin E (IgE) levels higher than 0.35 kU/L. With respect to pol...
ters, such as mode of immunotherapy, target allergens, initial disease severity, and the occurrence of AE, time to remission were analyzed by Kaplan-Meier estimate and multiple logistic regression models, accommodating for both continuous and binary variables. Odds ratios (OR) are presented with 95% confidence intervals (CI). A generalized estimating equation was used to analyze temporal correlations between total IgE and specific IgE levels to HDM according to SCIT outcomes. Since serum levels of total and specific IgE did not follow normal distribution, they were converted to logarithmic values for statistical analyses. All statistical analyses were performed with SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). P values less than 0.05 were considered statistically significant.

RESULTS

Demographics of the study subjects
The mean age of the patients was 27.8 ± 11.2 years, with 52.6% being male. The mean time interval between the diagnosis of AR and the commencement of SCIT at our university hospital among the study subjects was 4.8 ± 9.7 months. Of the total subjects, 91.1% were classified as having moderate (54.3%) to severe (36.8%) AR. The mean duration of immunotherapy was 3.8 ± 1.6 years (Table 1).

Overall, 201 (66.1%) received SCIT for HDM and 103 (33.9%) for mixed allergens (at least 1 pollen with HDM). Rush SCIT was administered to 89 (29.3%) patients, while the other 215 patients received conventional SCIT. Target allergens, modes of immunotherapy, and clinical outcomes at final visit are described in Fig. 1 in detail.

Outcomes of immunotherapy
The cumulative incidence of clinical remission from AR was 76.6% (Fig. 2). However, only 2.0% of patients achieved remission during the first year of SCIT. The cumulative incidence of AR remission increased annually up to 61.0% in the fifth year. The mean time until achieving remission from AR was 4.9 ± 0.1 years, with a median of 5 years.

AE were recorded in 73 patients (24.0%). Most AE (98.6%) occurred during the build-up phase. Of the 215 patients who un-

| Characteristics | Total study subjects (N=304) |
|-----------------|-----------------------------|
| Age (year)      | 27.8 ± 11.2                 |
| Sex             | Male 160 (52.6)             |
| Initial severity of AR | Mild 27 (8.9)         |
|                 | Moderate 165 (54.3)         |
|                 | Severe 112 (36.8)           |
| Targeting allergens | HDM 201 (66.1)            |
|                 | HDM+pollen 103 (33.9)       |
| Mode of immunotherapy | Rush 89 (29.3)           |
|                 | Conventional 215 (70.7)     |
| AIT duration (year)* | 3.8 ± 1.6                 |
| Disease duration (mon) | 4.8 ± 9.7                 |
| Total IgE level (kU/L) | 1227.0 ± 1586.8            |
| Specific IgE class to HDM† | Class 3 (30.6)       |
|                 | Class 4 (76.0)              |
|                 | Class 5 (55.1)              |
|                 | Class 6 (80.2)              |

Table 1. Demographic and clinical characteristics of the study subjects

*Time interval between diagnosis of AR and commencement of AIT. †Specific IgE levels to either Dp or Df were divided into 6 classes: 0.35 ≤ class 1 < 0.7 kU/L; 0.7 ≤ class 2 < 3.5 kU/L; 3.5 ≤ class 3 < 17.5 kU/L; 17.5 ≤ class 4 < 50 kU/L; 50 ≤ class 5 < 100 kU/L; 100 kU/L ≤ class 6.

Fig. 1. Target allergens and treatment status in patients with AR. AR, allergic rhinitis; HDM, house dust mites.
derwent conventional immunotherapy, 40 (18.6%) had AE, a significantly smaller proportion than the 32 of 89 (36.0%) individuals who underwent rush immunotherapy \((P=0.001)\). Local AE occurred in 49 (16.1%), and systemic AE occurred in 72 (23.7%). The severities of the systemic AE reached grade I in 63 (20.7%), grade II in 8 (2.6%), and grade IV in 1 patient (0.3%). No patient died from an immunotherapy-related AE.

Baseline levels of total IgE and specific IgE to HDM were compared in 304 patients who received SCIT with HDM. Overall, total IgE and specific IgE levels to Dp and Df were decreased with immunotherapy. A generalized estimating equation model revealed a significant temporal correlation for total IgE levels over the SCIT period between the remission and non-remission groups of AR patients \((P=0.038)\); significance was not recorded for specific IgE levels to Dp or Df (Fig. 3).

Changes in skin reactivity were evaluated according to differences in the A/H ratio (the ratio of mean wheal diameters in produced by HDM allergens and histamine [1 mg/mL] on the SPT) at baseline and upon completion of AIT in 121 patients with HDM-sensitized AR. A/H ratios at the completion of AIT were significantly decreased for both Dp \((3.9 \pm 2.2 \text{ vs } 2.3 \pm 1.6, P<0.001)\) and Df \((3.3 \pm 2.2 \text{ vs } 1.9 \pm 1.1, P=0.002)\). Mean reductions in the A/H ratio for HDM allergens were not different between the remission and non-remission groups \((38.2\% \pm 43.65\% \text{ vs } 23.9\% \pm 60.9\%, P=0.185)\).

**Predictive factors for clinical responses to immunotherapy**

Age, mode of immunotherapy, target allergens, and occurrence of AE did not affect remission rates or the duration of immunotherapy until remission from AR (Table 2). Male patients had more favorable results than females in terms of remission rate and duration of immunotherapy until remission \((43.8\% \text{ vs } 34.0\%, 4.6\% \pm 0.2 \text{ vs } 5.3\% \pm 0.2 \text{ years}, P=0.018)\). When patients were divided into 2 groups according to specific IgE levels to HDM, those with IgE levels \(\geq 17.5 \text{ kU/L} \) were found to have benefited
null

Table 2. Remission rate and mean duration until remission in patients with AR treated with allergen specific SCIT

| Characteristics                  | Remission (%) | Mean duration (yr) | P value* |
|----------------------------------|---------------|--------------------|----------|
| Age group (year)                 |               |                    |          |
| ≤30                              | 73/181 (40.3) | 4.5 ± 0.1          | 0.208    |
| >30                              | 46/123 (37.4) | 5.1 ± 0.2          |          |
| Sex                              |               |                    |          |
| Male                             | 70/160 (43.8) | 4.6 ± 0.2          | 0.018    |
| Female                           | 49/144 (34.0) | 5.3 ± 0.2          |          |
| Mode of immunotherapy            |               |                    | 0.602    |
| Rush                             | 33/89 (37.1)  | 5.0 ± 0.2          |          |
| Conventional                     | 86/215 (40.0) | 4.9 ± 0.2          |          |
| Target allergens                 |               |                    | 0.257    |
| HDM only                         | 89/201 (44.3) | 4.8 ± 0.2          |          |
| HDM + pollen                     | 30/103 (29.1) | 5.3 ± 0.3          |          |
| Specific IgE to HDM (kU/L)       |               |                    | 0.007    |
| ≥17.5                            | 90/211 (42.7) | 4.6 ± 0.2          |          |
| <17.5                            | 29/93 (31.2)  | 5.5 ± 0.2          |          |
| Rhinitis severity                |               |                    | 0.003    |
| Severe                           | 30/112 (28.8) | 5.5 ± 0.2          |          |
| Mild to moderate                 | 88/192 (46.4) | 4.7 ± 0.2          |          |
| Occurrence of AE                 |               |                    | 0.999    |
| AE (+)                           | 23/72 (31.9)  | 4.6 ± 0.2          |          |
| AE (-)                           | 96/232 (41.4) | 4.9 ± 0.1          |          |

AR, allergic rhinitis; SCIT, subcutaneous immunotherapy; HDM, house dust mites; IgE, immunoglobulin E; AE, adverse events. *P values were calculated using the Kaplan-Meier method.

Table 3. ORs of characteristics related with clinical remission after immunotherapy by means of logistic regression analysis in AR patients

| Characteristics                  | OR (95% CI) | P value |
|----------------------------------|-------------|---------|
| Age ≤30 years                    | 0.97 (0.55-1.71) | 0.910   |
| Male sex                         | 1.56 (0.93-2.61) | 0.092   |
| Specific IgE to HDM ≥17.5 kU/L   | 1.85 (1.01-3.37) | 0.045   |
| Severe AR                        | 0.40 (0.23-0.69) | 0.001   |
| Duration of immunotherapy ≥3 years | 7.37 (3.50-15.51) | <0.001  |
| HDM only                         | 1.36 (0.77-2.42) | 0.293   |

OR, odds ratio; AR, allergic rhinitis; CI, confidence interval; IgE, immunoglobulin E; HDM, house dust mites.

DISCUSSION

In the present retrospective study, SCIT with aluminum hydroxide-adsorbed allergen extract facilitated remission in 76.6% of patients with AR within 4.9 years on average. IgE levels specific to HDM were identified as significant predictors of favorable responses to SCIT. Moreover, in multi-sensitized patients, clinical responses did not differ significantly between patients undergoing SCIT with multiple allergens and those undergoing SCIT with HDM alone.

Previous guidelines have recommended that an age of at least 5 years is safe for immunotherapy, with no upper limit for age. In our study, age at starting SCIT had no significant influence on clinical outcomes, although a tendency toward more favorable responses was noted in younger patients at ages ≤30 years. Corresponding with our results, previous studies have reported no significant difference between treatment response and age. In another study, the clinical efficacy of treatment in patients older than 54 years was not different from that in patients younger than 54 years. On the contrary, a recent study has indicated that patients with a shorter symptom duration of AR experience greater efficacy from AIT. Since data with which to conclude this relationship are insufficient, it remains to be investigated.

In the present study, we noted that the effect of AIT decreased in severe AR patients. Schmitt et al. previously described the preventive effects of immunotherapy from AR to AA in a large retrospective cohort study of antihistamine prescriptions and health care use as a surrogate marker of severity, similar to how...
we classified patients in our study. Although the primary end-
point was different from our study, patients with more severe
AR tended to progress to AA more frequently despite receiving
immunotherapy.\textsuperscript{11} Meanwhile, however, other studies have
suggested that highly symptomatic patients appear to benefit
more from AIT than their counterparts.\textsuperscript{16,17} These conflicting re-
ports in regards to the effects of AIT in relation to severity might
be based on adoption of different ways of classifying severity
(i.e., by either medication use or symptoms).

Predicting individuals who will respond favorably to immu-
notherapy has been a major concern and unmet need.\textsuperscript{18} Specific
IgE levels seem to be a promising biologic marker to fulfill
this demand. Ciprandi and Silvestri\textsuperscript{19} suggested a cutoff value of
>9.74 kU/L for \textit{Parietaria judaica}, HDM, and birch to discrimi-
nate between responders and non-responders among patients
with rhinitis and/or asthma. In addition, Tosca \textit{et al.}\textsuperscript{20} described
that allergic children with specific IgE to HDM >10 kU/L showed
more favorable results than those with levels <10 kU/L.

In the present study, specific IgE to HDM \(\geq\) class 4 or specific
IgE levels to HDM \(\geq\) 17.5 kU/L at the start of SCIT were signifi-
cantly associated with clinical remission of AR in adult patients
who were sensitized to HDM and/or pollens. Generally, levels
of specific IgE in serum reflect the degree of exposure to partic-
ular allergens. The dose-dependent association between HDM-
specific IgE levels and allergen-related symptoms has been re-
ported in a prior study.\textsuperscript{21,22} Therein, the odds of dust-related
symptoms increased by 5-fold from subjects not sensitized to
HDM to subjects with HDM-specific IgE levels \(\geq\) 17.5 kU/L.\textsuperscript{23}
They also found that subjects with higher levels of specific IgE
more frequently reported using inhalers.\textsuperscript{23} Thus, it is believable
that the higher the specific IgE level, the more clinically relevant
the allergen is for a particular individual. The more clinically as-
associated the allergens for AIT, the more effective outcomes will
be acquired. In the same context, Di Lorenzo \textit{et al.}\textsuperscript{24} demon-
strated that both serum specific IgE level and specific IgE to to-
tal IgE ratio are significantly correlated with clinical responses
to AIT. A possible mechanism is that the induction of regulatory
T cells specific to the dominant allergen of a particular patient
can help suppress IgE responses to relevant allergens during
AIT, resulting in an overall decrease in allergenic inflamma-
tion.\textsuperscript{25} Thus, baseline levels of specific IgE to HDM may be an
acceptable predictor of effective immunotherapy in AR pa-
tients, although more validation and a clear cutoff level are still
needed.

A previous study estimated that approximately 80% of allergic
patients are polysensitized, which makes it difficult to select al-
lergen extracts for immunotherapy.\textsuperscript{26} Although the US has fa-
vored multi-allergen immunotherapy and European countries
have preferred immunotherapy with a single or a few relevant
allergens, it is impossible to directly compare which is more ef-
efective because of regional differences in clinically relevant al-
lergens and the lack of standardization of allergen extracts.\textsuperscript{6} Sin-
gle-allergen immunotherapy for seasonal grass pollen and pe-
rennial HDM has been found to be equally effective in mono-
sensitized and polysensitized patients.\textsuperscript{27} However, few studies
have attempted to investigate efficacy between single-allergen
and multi-allergen AIT within polysensitized patients. Although
we could not draw a definitive conclusion on this concern, our
results showed that single-allergen immunotherapy with HDM
only was enough to achieve remission or at least better than
multi-allergen AIT when treating patients polysensitized to
HDM and pollens. In support of our results, a recent study de-
scribed that multi-allergen immunotherapy with seasonal and
 perennial allergens failed to prevent AR from progressing to AA,
whereas single-allergen immunotherapy did.\textsuperscript{11} Taken together,
these results suggest that multi-sensitized patients with AR can
be effectively treated with immunotherapy targeting only HDM
rather than multiple allergens. Indeed, when mixing allergens,
unnecessary dilution or proteolysis of allergens can occur, po-
tentially reducing the efficacy thereof in AIT.\textsuperscript{3}

The present study has several limitations. In our retrospective
cohort analysis, the severity of AR was defined by medication
requirements not by clinical symptoms. In general, clinical tri-
als to prove the efficacy of AIT in AR patients have adopted total
symptom scores and total medication scores as primary end-
points. However, it is difficult for clinicians to evaluate these pa-
tient-oriented outcome measures prospectively in routine clin-
ical practice. Also, the lack of a control group that did not re-
ceive SCIT made it difficult to estimate the true effectiveness of
AIT. The present study, nonetheless, also has some merit in that
clinical outcomes (remission and control states) were applied
as primary endpoints in a relatively large population and ana-
alyzed in terms of remission rate over time. Also, the study cov-
ers maintenance durations of up to 7 years in patients from a
single institution.

In conclusion, this large retrospective cohort expounded on
previous results by demonstrating that AIT facilitates remission
in 76.6% of adult AR patients sensitized to HDM with rare seri-
osous AE. Finally, specific IgE levels to HDM were found to influ-
ence clinical responses to SCIT in Korean patients with AR.

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