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Is There Any Parameter Helpful for Predicting a Suitable Candidate for Mite Immunotherapy?

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ABSTRACT

Few biomarkers that can predict the clinical response to allergen immunotherapy (AIT) have been identified. The aim of the present study was to investigate parameters that could be used "in predicting the clinical response to AIT" in children with asthma caused by house dust mites.

We evaluated 107 children with mild persistent asthma who were sensitised only to mite aeroallergens. The study group included 47 patients who underwent a 4-to-5-year course of subcutaneous immunotherapy with standardised mite allergenic extract. Sixty patients who had not undergone AIT but were allergic to house mites were included in the control group. The clinical features and laboratory parameters of patients who did and did not sustain remission were compared.

Remission was achieved in 74.5% of the 47 patients in the study group and in 20% of those in the control group. In the study group, one parameter predictive of a clinical response to AIT was identified by multivariate logistic analysis. This parameter was the serum total IgE level (tIgE) at the time of diagnosis (OR 131.64 and CI 0.858–20193; $p = 0.032$). Serum tIgE levels ≤ 339 kU/L at diagnosis were associated with an effective clinical response to AIT, with a sensitivity of 64.5% and specificity of 88.9%.

We conclude that measurement of the serum tIgE level can be used as a predictive test prior to AIT in patients sensitized to mite aeroallergens.

Keywords: Allergen immunotherapy; Asthma; Children; Immunoglobulin E; Mite

INTRODUCTION

Allergen immunotherapy (AIT) is an effective treatment for respiratory allergic disease. To date, AIT has primarily involved subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT); it is a suitable treatment for both children and adults with regard to allergies to pollen, pet dander, house dust mites, mould, and venom. The disease modification effect leads to decreased disease severity, less drug usage, prevention of future allergen sensitisations, and a long-term curative effect. It may

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be particularly preventive in children because AIT can change the course of allergic disease.[1,3] The ability to predict success before starting this treatment would be beneficial, as the treatment is prolonged and can lead to severe side effects. Changes in the levels of several cytokines, such as interleukin (IL)-4, IL-10, IL-12, interferon-γ, and transforming growth factor-β have been associated with successful AIT, although their measurement is not recommended in clinical practice.[4] Several studies have attempted to identify predictive tests for a clinical response to AIT in children, but these have met with limited success.[5]

Therefore, we performed a retrospective study of candidates undergoing mite immunotherapy. The aim was to identify parameters predictive of a response to AIT.

MATERIALS AND METHODS

This study included a total of 107 children sensitised to mite allergens who were followed after diagnosis of mild persistent asthma at the Department of Paediatric Allergy, Dr. Behçet Uz Children's Hospital, between June 2003 and June 2013 (the follow-up period). Data were analysed retrospectively after approval of the study by the local research ethics board of Dr. Behçet Uz Children's Hospital (date: 11.12.2014, protocol code: 2014/50). All children fulfilled the criteria for persistent mild asthma according to the global initiative for asthma (GINA) guidelines.[6] Inclusion criteria were as follows: (a) documented diagnosis of allergic asthma based on patient-reported symptoms, physical examination and the results of a pulmonary function test (including bronchodilation test); (b) documented sensitisation to mites (a positive skin prick test result); (c) clinically relevant allergic symptoms (e.g. perceptiblr and bothersome symptoms); d) diagnosis of persistent mild asthma; e) history of a consistent relationship between mite allergen and occurrence of asthma symptoms; and f) follow-up at our department for at least 6 years (5 years for SCIT plus 1 year of follow up confirm remission). Similarly, the control group was followed for at least 6 years.

The study group consisted of 47 patients who met the inclusion criteria and who had undergone SCIT (Alutard; ALK-Abello) for 4 to 5 years and completed SCIT at least 1 year previously. The control group consisted of 60 patients who met the inclusion criteria and who had not undergone AIT due to socioeconomic and cultural factors (e.g. income, prolonged treatment duration, receiving treatment from parents, distrust of the effects of AIT, or distance from the treatment centre).

The exclusion criteria were as follows: (a) allergic diseases (e.g. atopic dermatitis),[7] except allergic rhinitis and IgE-mediated type-I food allergy; (b) clinically relevant anatomic impairment (e.g. diaphragma eventration, pectus excavatum); (c) acute or chronic disorders that contraindicate AIT (e.g. autoimmune disease and malignancy); and (d) allergy to multiple allergens.

All patients were informed about protecting against mite allergens, as described in the GINA guidelines, to achieve asthma control. They were followed up for 3 months and administered medication (leukotriene receptor antagonists, short acting β_2 agonists, inhaled steroids, and long-acting β_2 agonists) as needed.

A medical history of preschool wheezing (episodic viral wheeze or multiple-trigger wheeze),[8] a family history of atopy, the onset of respiratory symptoms, and accompanying allergic diseases was obtained from each patient. Patients with a history of food allergy and positive specific IgE (sIgE) levels for the suspected food were considered to have food allergy; patients with a positive food sIgE reading but no history of food allergy were considered food sensitized.

Allergy Tests

Skin prick tests were conducted using a standard aeroallergen panel consisting of the following: house dust mites (*Dermatophagoides farinae and Dermatophagoides pteronyssinus*), cat and dog epithelia, Alternaria alternata, cockroach and pollen [grass, weed, grain and tree (olive, pine)] (ALK-Abello, Madrid, Spain). A drop of each allergen extract was introduced via lancets into the skin on the volar side of the forearm. Histamine (10 mg/mL) and glycerinated saline were used as positive and negative controls, respectively. After 15 min, the mean of the largest diameter of the resulting wheal and its perpendicular diameter were recorded as the response. A response of at least 3 mm greater than the saline control was deemed positive.

At the time of diagnosis, serum total IgE (tIgE) levels and blood eosinophil counts were assessed in all patients. Mite sIgE (*Dermatophagoides pteronyssinus and Dermatophagoides farinea*) and IgE specific to a panel of food allergens were also measured. The panel included the following allergens: egg white, cow's milk, fish, wheat,

peanuts, and soybeans. Serum tIgE and sIgE levels were determined using the UniCAP 100 system fluorescein-enzyme immunoassay (Phadia, Uppsala, Sweden) from 2003 to 2009. The limit for the sIgE cut-off was <0.35 kU/L. The test values were expressed as classes 0–6. A class of ≥1 was recognized as positive. Subsequently, serum tIgE and sIgE levels were assessed by the fluoroimmunoassay technique (Pharmacia CAP System, MultiCap fx5, Pharmacia and Upjohn Diagnostics, Uppsala, Sweden), so the mite IgE level could not be included as a parameter. When a panel of food allergens was positive and a specific food allergen test could not be performed, a skin prick testing was conducted for each allergen in the panel. In the event of a positive skin test, an oral provocation test was performed.

Sustained Remission

Sustained remission was defined as no current use of asthma medication, no asthma-like symptoms (wheezing, tightness in the chest, shortness of breath) and no asthma attacks in the last 12 months.[9] Additionally, pulmonary function testing yielded normal values.

In the study group, patients who entered remission did not receive any medical treatment for asthma symptoms after completion of the AIT procedure.

Statistical Analysis

Statistical analysis was performed using the SPSS version 21 and Medcalc 9 (Acacialaan 22, B-8400 Ostend, Belgium) software. The normality of the distribution of the data was analysed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The variability coefficient and parametric methods were used for analysis of normally distributed variables and non-parametric methods were used for analysis of variables not normally distributed. An independent-samples *t*-test and Mann–Whitney U-test (Exact) were used to compare two independent groups. Spearman's rho test was used to analyse correlations betwen variables. Pearson chi-square and linear-by-linear association tests were performed using the Exact technique for comparison of categorical variables. A logistic regression test was used to determine the causality of categorical variables with respect to binomial and multinomial explanatory variables. Sensitivity and specificity between the classifications were determined using cut-off values calculated fom the group variables and analysed using a receiver operating curve (ROC). Quantitative data were expressed as means ± standard deviation and medians ± IQR (interquartile ranges). Data were analysed at the 95% confidence level. A level of $p<0.05$ was accepted as indicative of statistical significance.

RESULTS

We examined data from a total of 107 patients who met the inclusion criteria. The study group was composed of 47 patients (31 males and 16 females), and the control group included 60 patients (38 males and 22 females). The mean age symptom onset and at diagnosis were 56.9±38.0 and 86.9±35.1 months, respectively, in the study group and 47.8±32 and 80.6±29.1 months, respectively, in the control group ($p>0.05$). A total of 14 patients in the study group (29.8%) had preschool wheezing and 13 (27.6%) had a family history of atopy. In the control group, 24 (40%) had preschool wheezing and 21 (35%) had a family history of atopy. The differences between groups were not statistically significant ($p>0.05$).

Allergic rhinitis was detected in 23 (48.9%) cases in the study group, and in 21 (35%) cases in the control group ($p>0.05$). Food sensitivity was detected in six (12.5%) cases in the study group (one egg white, one fish, two wheat, and two peanut) and four (6.7%) cases in the control group (one egg white, two wheat, and one peanut) ($p>0.05$). The mean duration of SCIT was 49.6±5.6 months in the study group. Positive mite sIgE was detected in 42 (89.3%) cases in the study group, and in 52 (86.6%) cases in the control group. The rate of sustained remission was 74.5% in the study group and 20% in the control group. Table 1 shows the demographic and clinical characteristics of both groups.

Univariate Analysis

When patients in the study group were compared with respect to sustained remission, significant differences were detected in two parameters: the presence of food sensitivity before AIT ($p<0.004$) (i.e. absence of food sensitivity was more favourable) and increased levels of serum tIgE at the time of diagnosis [i.e. low levels were more favourable ($p<0.005$)].

Conversely, we found no differences in gender distribution, age of asthma diagnosis, age of first wheezing, family history of atopy, history of preschool wheezing, asthma accompanied by allergic rhinitis, age of initiation of AIT or blood eosinophil count at the

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time of diagnosis. The control group was divided into two subgroups: sustained remission and symptomatic patients. No statistically significant differences were detected in any parameter when the patients in the control group were compared with regard to the same parameters (age, age at time of diagnosis, age of asthma onset, family history of atopy, history of wheezing, asthma accompanied by allergic rhinitis , accompanying food sensitivity, total IgE level and blood eosinophil count) (Table 2).

Multivariate Analysis

Our ROC curve analysis identified 339 kU/L as the optimal cut-off value for serum tIgE to discriminate a clinical response to AIT, with a sensitivity of 64.5% and a specificity of 88.9% (Figure 1). A multivariate unconditional logistic regression model was used to determine the factors independently predictive of a clinical response to AIT. Of the independent predictive factors analyzed by a multivariate unconditional logistic regression model, only serum tIgE level (OR

Table 1. General characteristics of 107 patients

	The Study Group (N=47)	The Control Group (N=60)	*p* value
Diagnosis age*	86.9±35.1	80.6±29.1	0.357
Male gender, No (%)	31 (%66)	38 (%63)	0.393
Atopic family history, No	13	21	0.110
Asthma, No	24	27	0.356
Asthma plus rhinitis, No	23	33	0.356
Age of first wheezing*	56.9±38.0	47.8±32.3	0.180
AIT duration*	49.6±5.6	-	-
Serum tIgE level, kU/l**	413.3±354.2	328.5±375.2	0.257
Blood eosinophils counts (cells X 10^{-3} µL)**	543.1±384.0	560.3±390.8	0.786
Sustained remission, No (%)	35 (%74.5)	12 (%20)	0.001***
Presence of food sensitivity, No (%)	6 (%12.5)	4 (%6.7)	0.313
Preschool wheezing No (%)	14 (%29.8)	24 (%40)	0.297

* month, mean ±SD ** mean ± SD *** $p<0.05$=significant

Table 2. Demographic and clinical characteristics of groups according to sustained remission status by univariate analysis

	Study Group			Control Group		
	Remission (N=35)	Symptomatic (N=12)	*p* value	Remission (N=12)	Symptomatic (N=48)	*p* value
Male/females, No	24/11	7/5	0.725	9/3	29/19	0.507
Males, %	68.6	58.3		75	60.5	
Females, %	31.4	41.7		25	39.6	
Age at diagnosis**	84.3±30.6	93.3±46.7	0.504	86.4±7.7	79.2±4.3	0.187
Age of first wheezing**	54.3±31.4	64.6±53.8	0.542	46.6±7.4	48.0±4.9	0.411
Preschool wheezing, No (%)	10 (28.6)	4 (33.3)	1	3 (25)	21 (43)	0.329
Atopic family history, No (%)	11 (36.7)	2 (18.2)	0.451	5 (41)	16 (33)	0.737
Asthma/ plus rhinitis, No	20/15	4/8	0.193	5/7	22/26	0.632
Asthma, %	57.1	33.3		41.6	45.8	
Asthma + rhinitis %	42.9	66.7		58.4	54.2	
Food sensitivity, No (%)	1 (3.4)	5 (45.5)	0.004*	1 (9)	3 (6.6)	1
Age at AIT onset**	101.2±29.5	109.4±39.7	0.532			
Serum tIgE level, kU/L***	238.0±378.0	657.0±636.0	0.005*	343.5±117	324.2±53.6	0.683
Blood eosinophils count (cells x 10^{-3} µL)****	486.7±354.6	691.8±435.1	0.258	555.9±491	561.4±368.9	0.448

*$p<0.05$=significant, *month, mean ±SD, **median (IQR), *** mean ±SD

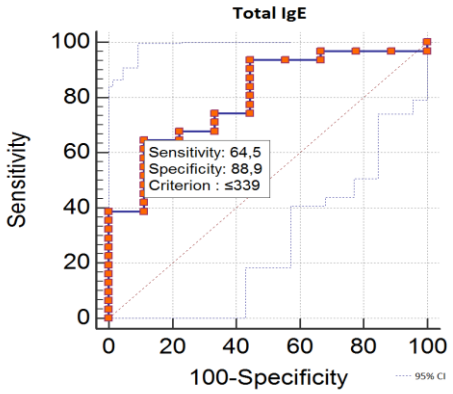

Figure 1. ROC curve for serum tIgE level (cut-off, ≤ 339 kU/L)

Table 3. Multivariate analysis of factors independently predictive of clinical response to AIT

Variable/predicting factor	OR	*p* value
Male/female	1.038	0.980
Age at diagnosis	0.92	0.079
Age at first wheezing	1.079	0.154
Preschool wheezing	2.189	0.743
Asthma/ plus rhinitis	49	0.051
Atopic family history	2.19	0.769
Age at onset of AIT	1.032	0.876
tIgE	131.64	0.032*
Food sensitivity	95.219	0.111
Blood eosinophils count	1.162	0.537

*p<0.05=significant

131.64 and 95% CI 0.85–20193; p = 0.032) was found to be significant (Table 3).

DISCUSSION

The availability of a biomarker capable of predicting the outcome of AIT would be extremely useful in clinical practice. Our findings show that mite sensitivity and serum tIgE levels > 339 kU/L at the time of diagnosis were associated with a less effective clinical response to AIT.

AIT reduced the symptoms of allergic asthma in children by modifying the underlying course of the disease and inducing long-term allergen-specific immune tolerance.[10-13] AIT treatment involves the administration of allergens to patients in repeated and increasing doses to induce immune tolerance.[14] Numerous double blind, placebo-controlled trials have ascertained that AIT is effective in reducing symptom scores and medication use, improving the quality of life for asthma patients, and inducing favourable changes in specific immunologic responses.[1,15] The evidence for AIT efficacy was analysed by the Cochrane study, which concluded that AIT reduces asthma symptoms and use of asthma medications while improving bronchial hyper-reactivity.[16]

A considerable number of studies have reported that mite immunotherapy is effective.[17] For example, Zhang et al. reported that 85% of their patients achieved complete control of asthma at the end of AIT.[18] Tabar et al. determined that 79.9% of their patients achieved clinical improvement following 3 years of AIT.[19] Determination of a marker predictive of the success of AIT would enable more effective use of this treatment. A recent preliminary report indicated that a cut-off level of serum sIgE could be used to define an AIT responder.[4]

The first study in this field was conducted by Di Lorenzo et al., who found that patients who benefited

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from AIT had lower tIgE and higher sIgE levels. Therefore, it was suggested that the serum sIgE/tIgE ratio was a stronger predictive marker than tIgE or sIgE levels alone. However the study a heterogeneous population composed of adults with allergic rhinitis and/or asthma who received treatments containing four allergens (*grass, Parietaria judaica, Olea europea, house dust mites*). The immunotherapy route was also heterogeneous─both SCIT and SLIT were used.[20] Our study was conducted in a more homogeneous group and in children only. All patients were sensitised only to mite allergens among aeroallergens and received SCIT with a single allergen extract. Our analysis showed a correlation between serum tIgE≤339 kU/l and an effective clinical response, with a sensitivity of 65.4% and a specificity of 88.9%.

Li et al. reported an example of the inverse relationship between the severity of atopy and the success of AIT. The success of AIT was investigated in children who received mite immunotherapy, as in our study, and AIT was effective in 69.7% of the patients. The serum tIgE level was ≥965 kU/L and sIgE/tIgE ratio was ≥ 6% in the patients who failed to respond to AIT. The serum tIgE measurement was superior to both the serum sIgE/tIgE ratio and sIgE level alone in terms of predicting clinical effectiveness. However, the cut-off value for tIgE (<965 kU/L) was higher than in our work. The other predictive markers identified by multivariate logistic analysis were tobacco smoke exposure and a family history of atopy, both of which were associated with increased effectiveness of AIT.[21]

However, the success of AIT has also been positively correlated with the severity of atopy. The study by Tosca et al. included children who received mite immunotherapy, as in our study. They showed that children with a mite sIgE>10 kU/L derived greater benefit from the therapy.[22] Similarly, Ciprandi et al. reported that an allergen sIgE level>9.74 kUA could be used as a biomarker of SLIT efficacy, with a sensitivity of 96.4% and specificity of 100.0%. In this study, the optimal cut-off value for serum tIgE to discriminate an effective from an ineffective clinical response to AIT was 130 kU/L. The difference may be attributable to the patient population studies, which consisted of adults suffering from allergic rhinitis with multiallergen sensitivity.[4]

The effectiveness of AIT has frequently been evaluated based on clinical response (reduction in nasal and pulmonary symptoms) and reduction in the medical therapy used on an as-needed basis (e.g. oral second-generation H1-antihistamines for rhinitis and inhaled short-acting β_2 agonists for asthma symptoms).[20] Recent studies have used a visual analog scale (VAS) for nasal symptoms and the Asthma Control Test for asthma to determine the success of AIT.[4,22] Li et al. added pulmonary function measurements to these factors.[21] In our study, we used sustained remission for 1 year as a measure of the effectiveness of AIT. However, spontaneous remission can occur in children with asthma and our results may have been affected by this phenomenon. Therefore, we investigated the extent of remission in a control group.

In our study, "sustained remission" was defined as "no current use of asthma medication, no asthma-like symptoms (wheezing, tightness in the chest, shortness of breath) and no asthma attacks in the last 12 months" with a normal spirometry. The Asthma Control Test score and visual analogue scale score were not used, as the asthma control test score was not in routine use at the time of data collection.

One important problem inherent in studies of predictive markers that purport to evaluate the success of AIT is that patients who have these predictive markers might have gone into remission even if AIT had not been applied. We overcame this problem by using a control group composed of patients who had the same clinical features but could not undergo AIT for socioeconomic reasons and compared this control group with the study group. No previous study has included a control group. The most important difference in our study is the use of this control group. No significant marker predictive of remission was detected in the control group. Another issue is the false positive sensitivity in allergy tests due to cross-reactions between food allergens and mite allergens. However, no such cross-reaction between food allergens and mite allergens has been reported.

As this study used a retrospective design, it was subject to the limitations inherent in such studies. Our study also enrolled only a small number of patients. Nevertheless, we believe that these limitations do not significantly confound the main findings.

In conclusion, we identified a predictive marker for the clinical response to AIT in children with mite allergy. The serum tIgE level may be used as a predictive marker for mite immunotherapy success in children with asthma.

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