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Effect of Immunotherapy on Seasonal Changes in Serum-Specific IgE and IgG4 in Patients With Pollen Allergic Rhinitis

[Independent Papers]

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Abstract

Serum specific IgE and IgG4 in 70 patients with seasonal rhinitis caused by Japanese cedar pollens were determined before and during the pollen season. Seasonal increase rate in specific IgE was significantly smaller in the immunotherapy patients than the pharmacotherapy patients, and seasonal increase in specific IgG4 was significant in the immunotherapy patients only. Seasonal increase rate in specific IgE was not significantly different between the patients who responded markedly to short-term

immunotherapy and those who did not. On the other hand, seasonal increase rate in specific IgG4 was significantly different between them. In contrast, seasonal increase rate in specific IgE was significantly smaller in the patients who showed marked response to the long-term immunotherapy than those who did not show marked response to the long-term immunotherapy, but seasonal increase rate in specific IgG4 was not significantly different between them. In conclusion, our results suggest that modulation of specific IgG4 response and specific IgE response might be involved in the early and late symptom relief during immunotherapy, respectively. However, further studies might be necessary to definitively establish the clinical roles of specific IgE and specific IgG4 in immunotherapy.

INTRODUCTION

Immunotherapy is an effective form of treatment for pollen-induced seasonal allergic rhinitis,^{1,2} but the mechanism behind clinical benefit of immunotherapy is still unclear. In recent years, there is increasing evidence that T lymphocytes and their products, cytokines, play a central role for coordination and persistence of airway allergic disorders. Recent knowledge indicates that allergic pathogenesis is caused by a preferential activation of a special subset of T-helper lymphocytes (TH-2 cells) in predisposed atopic individuals.³ Recent work has also devoted increasing attention to the possible effect of immunotherapy on T-cell cytokine profiles and suggested that clinical improvement might be orchestrated by modulation of hyperactivity of helper T cells and alteration from predominant TH-2 response to TH-1 response.⁴⁻⁷ However, the in vivo modulation of T-cell cytokine profiles by immunotherapy has little evidential support.

Considerable attention was previously devoted to changes in serum allergen-specific antibodies, especially specific IgE and specific IgG4, in relation to clinical effects of immunotherapy during the last two decades, because specific IgE and IgG4 were believed to be of key importance in respiratory allergic diseases. However, the role of changes in serum specific IgE and IgG4 during immunotherapy might be out of the limelight by recent progress in the knowledge of T-cell cytokine profiles using modern molecular biology. Nevertheless, changes in serum specific IgE and IgG4 are, at least in part, assumed to be involved in the working

mechanisms of immunotherapy. Seasonal elevations in serum specific IgE in pollen-sensitive patients have been well established. We have investigated, therefore, the seasonal dynamics of serum specific IgE and IgG4 in patients who were receiving immunotherapy for seasonal allergic rhinitis caused by Japanese cedar (*Cryptomeria japonica*) pollens, with special reference to the clinical outcome.

PATIENTS AND METHODS

Patients

This study included 70 adult patients (42 women and 28 men, age range, 18 to 55 years) with seasonal allergic rhinitis caused by Japanese cedar (*C japonica*) pollens who gave informed consent to participation in the present study. All the patients were selected from our outpatients who completely satisfied the following conditions before treatment: 1. well-documented history of typical Japanese cedar pollinosis but no history of asthma and no nasal symptoms out of the cedar pollen season; 2. positive skin test to Japanese cedar pollens; and 3. positive nasal provocation to the pollens. The patients were divided into the pharmacotherapy group (16 women and 10 men) and the immunotherapy group (26 women and 18 men) according to their treatment background. None of the patients of the pharmacotherapy group had previously been treated with immunotherapy and were not receiving steroid treatment. The patients of the immunotherapy group had variable periods (mean, 4.7 ± 4.4 years; range, 1 to 15 years) of immunotherapy using the Japanese cedar pollen antigens (Torii Co, Ltd., Tokyo, Japan). Patients on immunotherapy were further divided into two groups, according to the duration of immunotherapy: short-term immunotherapy group who had been treated for 2 or fewer years with immunotherapy, and long-term immunotherapy group who had been treated for 3 or more years with immunotherapy.

Study Design

The period for pollination of Japanese cedar in 1995 was from the first week of February to the second week of April. The 26 patients

The remaining 44 patients of the immunotherapy group continued their scheduled maintenance dose subcutaneous injection. The patients of the immunotherapy group were allowed to take rescue medications(nonsedating antihistamine tablets) during the pollen season, if necessary.

Venous blood was collected twice from each patient, before the cedar pollen season of 1995 (from December 1994 to January 1995) and during the pollen season of 1995 (first week of April 1995). These serum samples were separated and stored at -80°C for the determination of serum cedar pollen-specific IgE and IgG4. All the serum samples were tested in the same batch. Japanese cedar pollen-specific IgE in serum was determined by the Pharmacia CAP system(Pharmacia, Japan) and the results were expressed as U/mL. Japanese cedar pollen-specific IgG4 in serum was determined by the enzyme-linked immunosorbent assay (ELISA) as previously described by Engvall and Perlmann [8](#) with some modification: methodology and justification of the method employed in the present study have been described elsewhere.[9,10](#) The result of specific IgG4 was expressed as arbitrary U/mL against a positive serum pool.

The seasonal increase rate in specific IgE or IgG4 in response to the cedar pollen exposure was calculated using the following formulae:[Equation](#)

$$\text{seasonal increase rate in specific IgE (\%)} = \frac{\text{specific IgE during pollen season} - \text{specific IgE before pollen season}}{\text{specific IgE before pollen season}} \times 100;$$

Equation
1

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Mode of Immunotherapy

The patients of the immunotherapy group started immunotherapy exclusively outside the pollen season. They were given subcutaneous injection using the Japanese cedar pollen antigens (Torii Co, Ltd., Tokyo, Japan), with prior informed consent. The individual initial dose was determined as indicated by the end-point concentration determined by the threshold skin test. Doses were increased by 50% at weekly intervals until the individual maximum tolerated dose was reached. The maximum tolerated dose was attained in 4 to 8 months with the once weekly program. A weekly injection of this dose was administered for the first 3 to 5 months after attainment of the maintenance dose, and then patients received injections of this dose on a biweekly basis for the next 3 to 5 months, followed by a monthly schedule. Finally, the interval between injections was gradually increased up to 2 months. However, during the pollen season, each patient was recommended to receive biweekly injections of the maintenance dose. After each injection, the patient was asked to remain under our supervision for a minimum of 30 min and to report any symptoms that they may have experienced.

Clinical Evaluation of Immunotherapy

Clinical evaluation of pollen immunotherapy was performed during the first week of April in 1995 and rated as follows: marked response = no nasal symptoms without rescue medication; moderate response = nasal symptoms appeared slight but there was no need of rescue medication; and poor response = need for rescue medication to control nasal symptoms.

Statistical Analysis

For comparison of data between the groups, Mann-Whitney *U*-test was used. For comparison of the paired values within a group, Wilcoxon signed-rank test was used. Significant differences were accepted in each analysis when $P < 0.05$. Spearman's correlation coefficient (r_s) was calculated to analyze possible correlation between two different parameters, and significant correlation was accepted when $P < 0.05$ according to the Spearman's rank correlation analysis.

RESULTS

Pharmacotherapy Group

Seasonal increase in specific IgE was significant ($P < 0.0001$) (Table I), but seasonal increase in specific IgG4 was not significant ($P = 0.2215$) (Table II).

	Before Pollen Season (U/mL)	During Pollen Season (U/mL)	Seasonal Increase Rate (%)
Pharmacotherapy group (n = 28)	19.3 ± 18.1	20.3 ± 28.9	172.6 ± 153.1
Immunotherapy group (n = 44)	22.2 ± 24.2	27.2 ± 26.5	43.2 ± 79.1
Marked response (n = 18)	17.6 ± 21.8	17.7 ± 18.2	18.1 ± 65.2
Moderate response (n = 16)	25.3 ± 22.7	32.4 ± 28.2	41 ± 68.2
Poor response (n = 10)	25.5 ± 21.3	35.8 ± 31	59 ± 186.3
Short-term immunotherapy group (n = 22)	21.9 ± 21	26.8 ± 28.1	73.8 ± 97.6
Marked response (n = 5)	14 ± 12.8	18 ± 15.5	77.2 ± 195.9
Moderate response (n = 8)	27.3 ± 30	26.7 ± 26.5	57.6 ± 103.1
Poor response (n = 9)	26.6 ± 32.8	36.7 ± 33.8	86.3 ± 112.8
Moderate + poor (n = 17)	24.5 ± 29.8	31 ± 31.7	72.7 ± 97.6
Long-term immunotherapy group (n = 22)	22.5 ± 21.8	33.8 ± 24.2	13 ± 28.2
Marked response (n = 10)	19.2 ± 24.4	17.8 ± 21.2	-4.8 ± 6.2
Moderate response (n = 8)	28.4 ± 17	30.3 ± 26.3	24.4 ± 15.1
Poor response (n = 4)	11	28	154.5
Moderate + poor (n = 12)	27.3 ± 17	37.1 ± 34.9	36.8 ± 45.6

TABLE I. Serum-Specific IgE Level.

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	Before Pollen Season (U/mL)	During Pollen Season (U/mL)	Seasonal Increase Rate (%)
Pharmacotherapy group (n = 28)	37.3 ± 25.3	41.1 ± 24.7	18.8 ± 93
Immunotherapy group (n = 44)	176.1 ± 185.7	223.2 ± 235.5	42 ± 49.9
Marked response (n = 18)	216.8 ± 176.3	262.7 ± 221.4	53.4 ± 50.9
Moderate response (n = 16)	186.4 ± 206.8	243.5 ± 275.6	52 ± 124.9
Poor response (n = 10)	88.8 ± 152	98.9 ± 141.9	5.7 ± 12.9
Short-term immunotherapy group (n = 22)	87.3 ± 127.1	138 ± 162.1	49.8 ± 52
Marked response (n = 5)	39.4 ± 129.2	166.6 ± 225.5	185.5 ± 193.7
Moderate response (n = 8)	133.8 ± 98.7	167.6 ± 144.1	83.3 ± 28.2
Poor response (n = 9)	96 ± 159.8	94.8 ± 148.9	-4.7 ± 12.6
Moderate + poor (n = 17)	96.8 ± 130.4	125.9 ± 146.1	31.8 ± 57.1
Long-term immunotherapy group (n = 22)	243 ± 208.3	313.5 ± 269	24.3 ± 24.4
Marked response (n = 10)	285.8 ± 170.6	325.5 ± 212.1	31.8 ± 28.7
Moderate response (n = 8)	229 ± 266	319.9 ± 357.9	40.7 ± 13.6
Poor response (n = 4)	28	30	20
Moderate + poor (n = 12)	208.9 ± 251	257.1 ± 348.1	36.4 ± 14.5

TABLE II. Serum-Specific IgG4 Level.

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Immunotherapy Group

Seasonal increase in specific IgE was significant ($P = 0.0003$)(Table I) and the seasonal increase rate in specific IgE was inversely correlated with the duration of immunotherapy ($r_s = -0.513, P = 0.0002$). Seasonal increase in specific IgG4 was also significant ($P < 0.0001$) (Table II), but the seasonal increase rate in specific IgG4 was not significantly correlated with the duration of immunotherapy ($r_s = -0.143, P = 0.2238$). Both the specific IgG4 level before the season and the specific IgG4 level during the season were significantly correlated with the duration of immunotherapy (before the season: $r_s = 0.671, P < 0.0001$; during the season: $r_s = 0.636, P < 0.0001$).

Short-Term Immunotherapy Group

Seasonal increase in specific IgE as well as specific IgG4 was significant(IgE, $P = 0.0005$; IgG4, $P = 0.0012$) (Tables I and II). The respective numbers of patients in this group who showed marked, moderate, and poor responses were 5, 8, and 9 (Table III). The seasonal increase rate in specific IgG4 was significantly different between the marked response patients and the remaining patients of this group ($P = 0.0042$) (Table II), but the seasonal increase rate in specific IgE was not significantly different between them ($P = 0.8755$) (Table I).

	Duration (d)	Marked Response	Moderate Response	Poor Response
Immunotherapy group (n = 44)	4.6 ± 4.4	5 (11.4%)	18 (40.9%)	10 (22.7%)
Marked response (n = 5)	7.3 ± 5			
Moderate response (n = 18)	3.4 ± 3			
Poor response (n = 10)	1.4 ± 0.7			
Short-term immunotherapy group (n = 22)	1.2 ± 0.4	8 (36.4%)	8 (36.4%)	6 (27.3%)
Long-term immunotherapy group (n = 22)	8.1 ± 3.4	1 (4.5%)	8 (36.4%)	1 (4.5%)

TABLE III. Duration of Immunotherapy and Clinical Response.

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Long-Term Immunotherapy Group

Seasonal increase in specific IgE was not significant ($P = 0.1526$), but seasonal increase in specific IgG4 was significant ($P = 0.0002$) (Table II). The respective numbers of patients in this group who showed marked, moderate, and poor responses were 13, 8, and 1 (Table III). The seasonal increase rate in specific IgG4 was not significantly different between the 13 patients who showed marked response to long-term immunotherapy and the remaining nine patients who showed moderate or poor response to long-term immunotherapy ($P = 0.2164$) (Table II), but the seasonal increase rate in specific IgE was significantly different between them ($P = 0.0001$) (Table I).

Comparison Between Pharmacotherapy Group and Immunotherapy Group

Specific IgE level before the season was not significantly different between the two groups ($P = 0.9177$), whereas specific IgE level during the season was significantly higher in the pharmacotherapy group than the immunotherapy group ($P = 0.0286$) (Table I). The seasonal increase rate in specific IgE was also significantly larger in the pharmacotherapy group than the immunotherapy group ($P < 0.0001$) (Table I). Specific IgG4 level before as well as during the season was significantly higher in the immunotherapy group than the pharmacotherapy group ($P < 0.0001$) (Table II). In addition, the seasonal increase rate in specific IgG4 was significantly larger in the immunotherapy group than the pharmacotherapy group ($P = 0.0001$) (Table II).

Comparison Between Short- and Long-Term Immunotherapy Groups

Specific IgE level before the season was not significantly different between the two groups ($P = 0.5034$) (Table I). However, the seasonal increase rate in specific IgE was significantly smaller in the long-term immunotherapy group than the short-term immunotherapy group ($P = 0.0031$) (Table I).

Specific IgG4 level before the season as well as during the season was significantly higher in the long-term immunotherapy group

short-term immunotherapy group (before the season, $P = 0.0005$, during the season, $P = 0.0005$) (Table II). However, the seasonal increase rate in specific IgG4 was not significantly different between them ($P = 0.5494$) (Table II).

DISCUSSION

Two opposite roles, an anaphylactic and a blocking antibody, for specific IgG4 have been presented. A possible relationship between the IgG4 subclass and so-called IgG short-term sensitizing antibodies was considered.¹¹ In addition, delayed asthma was induced in response to inhaled allergens in patients whose serum specific IgE was negative but specific IgG4 to these allergens was positive.¹² A doctrine was advocated that a rise in specific IgG4 was strongly associated with failure and an early increase in specific IgG4 could predict a poor clinical outcome of immunotherapy.¹³ These authors concluded that specific IgG4 plays an anaphylactic part in allergic diseases, especially in severe asthma.

However, a number of studies directed attention to the role of IgG4 as a protective factor.¹⁴ These investigations suggest that specific IgG4 could compete with specific IgE at sites on the surface of mast cells as a so-called blocking antibody to inhibit IgE-mediated immunologic reactions. The protective role of specific IgG4, as a blocking antibody, has been supported by increasing evidence that serum specific IgG4 is increased in patients receiving immunotherapy for bee venom and house dust mite allergies,^{9,10,15,16} and that this increase is not the result of an immunotherapy-independent and age-related phenomenon but the result of active immunologic modulation by immunotherapy.¹⁷ However, critics are skeptical of a clinical role for specific IgG4 based on the idea that the increase in specific IgG4 is simply a marker of antigen exposure following subcutaneous injection and probably represents an epiphenomenon unrelated to the underlying working mechanism of clinically successful immunotherapy.¹⁸ To definitely establish the clinical significance of specific IgG4, a significant correlation should be established between clinical response to immunotherapy and changes in specific IgG4. Few studies have paid attention to the role of specific IgG4 in seasonal allergy caused by pollens, although specific IgG4 was well studied in bee venom and house dust mite immunotherapy.^{9,10,15,16}

The Japanese cedar pollinates heavily during early spring, and there is no significant interference by other pollens.¹⁹ In particular, the pollen season in 1995 was the most intensive, with unusually high pollen counts, of the last two decades. Therefore, Japanese cedar pollination of 1995 provides a supreme in vivo model to investigate the effect of immunotherapy on natural changes in specific IgE and IgG4 in response to natural provocation by the allergen. Our study therefore aimed at elucidating the specific IgG4 level in seasonal allergic rhinitis caused by Japanese cedar pollens, and also at documenting possible modulation of seasonal changes in specific IgG4 and IgE by the pollen immunotherapy.

In patients not treated with immunotherapy, pollen-specific IgE was significantly increased in response to natural exposure to the pollen. Also, specific IgE increased in the immunotherapy group, but the seasonal increase in specific IgE was significantly smaller in the immunotherapy group than the pharmacotherapy group. The seasonal increase in specific IgE was inversely correlated with the duration of immunotherapy, suggesting that the longer immunotherapy is continued, the more it apparently attenuates seasonal increase in specific IgE. Indeed, the seasonal increase in specific IgE in the long-term immunotherapy group was significantly smaller than that in the short-term immunotherapy group, and specific IgE did not significantly change in the long-term immunotherapy group. On the other hand, seasonal increase in specific IgG4 was significant in the immunotherapy group but not significant in the pharmacotherapy group. Therefore, our data suggest that immunotherapy is capable of attenuation of the usual rise in specific IgE in the pollen season and additionally switches seasonal preferential IgE production to IgG4 production. This antibody switch may result in part from immunotherapy-induced decline in serum interleukin-4, because interleukin-4 plays a critical role in switching B lymphocytes from IgG to IgE production ²⁰ and immunotherapy can afford a reduced serum interleukin-4 in the long term.⁴

Effects either of the specific antibody responses by immunotherapy seem theoretically to develop a good clinical course. However, seasonal increase in specific IgE in the patients who showed marked response to the short-term immunotherapy was not different

from that in the patients who did not show marked response to the short-term immunotherapy. In contrast, seasonal increase in specific IgG4 was significantly different between them. These data could be therefore interpreted to mean that in patients on short-term immunotherapy, the magnitude of clinical improvement is not dependent on the magnitude of specific IgE response but is exclusively dependent on the magnitude of specific IgG4 response. On the contrary, seasonal increase in specific IgE was significantly smaller in the patients who showed marked response to the long-term immunotherapy than those who did not show marked response to the long-term immunotherapy, but seasonal increase in specific IgG4 was not significantly different between them. Therefore, the magnitude of clinical improvement in patients on long-term immunotherapy is mainly influenced by the magnitude of seasonal changes in specific IgE. Taken together, this evidence suggests that the effect of immunotherapy on IgE response is involved in the early mechanisms behind the clinical efficacy and the effect of immunotherapy on IgG4 response is involved in the late mechanisms, although immunotherapy can provide modulation of both the IgE and IgG4 responses throughout the course of immunotherapy.

Our study has elucidated that immunotherapy-induced changes in serum specific IgE and IgG4 are not epiphenomena unrelated to the working mechanism of immunotherapy, but have significant relevance to clinical improvement. In contrast, several of our previous studies have argued against an important role of specific IgE reduction in house dust mite immunotherapy for perennial allergic rhinitis.[4,9,10,21](#) We therefore assume that pollen immunotherapy and mite immunotherapy may produce clinical improvement through different mechanisms, or that the nature of the diseases may be somewhat different between perennial allergic rhinitis and seasonal allergic rhinitis, because the former is a disease formed by perennial exposure to small amounts of allergens, whereas the latter is caused by vast amounts of allergens for a restricted period.

Some investigators argue against a vital role of changes in specific IgE or IgG4 for the working mechanisms of immunotherapy,

because the onset of clinical improvement usually occurs well before changes in specific IgE or IgG4.¹⁸ We also agree that changes in specific IgE or IgG4 may occur only after a considerable period of immunotherapy and can hardly explain the very early clinical efficacy. In our opinion, allergic rhinitis is an extremely complex disease, in which a variety of immunologic as well as other pathogenetic mechanisms are involved in a complicated manner. It appears that no single pathogenetic phenomenon can account for the whole nature of the disease. It is therefore probable that immunotherapy modulates and influences many different immunologic as well as nonimmunologic phenomena ²² to produce clinical efficacy and that the clinical effect is a consequence of different working mechanisms with time. Therefore, it is no wonder that changes in specific IgE or IgG4 cannot account for the very early clinical improvement. The clinical importance of changes in specific IgE and IgG4 should not be downplayed for this reason alone.

CONCLUSION

Changes in both specific IgE and IgG4 might play some clinical roles in pollen immunotherapy. Although immunotherapy can modulate both the IgE and IgG4 responses throughout the treatment course, specific IgG4 response is likely to be involved in symptom relief in the early phase of immunotherapy, and specific IgE response is likely to be involved in symptom relief in the late phase of immunotherapy. However, clinical roles of specific IgE and specific IgG4 responses during pollen immunotherapy remain to be definitively established.

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Equation 1

seasonal increase rate in specific IgE (%) =

$$\frac{\text{specific IgE during pollen season} - \text{specific IgE before pollen season}}{\text{specific IgE before pollen season}} \times 100;$$

Equation 1

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TABLE II

	Before Pollen Season (U/mL)	During Pollen Season (U/mL)	Seasonal Increase Rate (%)
Pharmacotherapy group (n = 26)	37.2 ± 25.3	41.7 ± 24.7	18.8 ± 50
Immunotherapy group (n = 44)	170.1 ± 185.7	223.2 ± 236.5	42 ± 40.9
Marked response (n = 18)	216.8 ± 176.3	282.7 ± 221.4	53.4 ± 50.8
Moderate response (n = 16)	168.4 ± 206.8	240.5 ± 275.8	52 ± 24.9
Poor response (n = 10)	88.9 ± 152	88.3 ± 141.9	5.7 ± 12.9
Short-term immunotherapy group (n = 22)	97.3 ± 127.1	136 ± 162.1	49.6 ± 52
Marked response (n = 5)	89.4 ± 129.2	168.8 ± 225.5	109.5 ± 53.7
Moderate response (n = 8)	103.8 ± 98.7	161.8 ± 144.1	63.3 ± 29.2
Poor response (n = 9)	96 ± 159.5	94.8 ± 148.9	4.1 ± 12.6
Moderate + poor (n = 17)	99.6 ± 130.4	126.3 ± 146.1	31.9 ± 37.1
Long-term immunotherapy group (n = 22)	243 ± 208.3	310.5 ± 269	34.5 ± 24.4
Marked response (n = 13)	265.8 ± 170.6	326.5 ± 212.1	31.8 ± 29.7
Moderate response (n = 9)	222 ± 260	310.5 ± 257.0	40.7 ± 40.0

Moderate response (n = 8)	233 ± 209	319.3 ± 357.9	40.7 ± 13.0
Poor response (n = 1)	25	30	20
Moderate + poor (n = 9)	209.9 ± 261	287.1 ± 348.1	38.4 ± 14.5

TABLE II. Serum-Specific IgG4 Level.

From: Ohashi: Laryngoscope, Volume 107(9).September 1997.1270-1275

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TABLE III

	Duration (y)	Marked Response	Moderate Response	Poor Response
Immunotherapy group (n = 44)	4.6 ± 4.4	18 (40.9%)	16 (36.4%)	10 (22.7%)
Marked response (n = 18)	7.5 ± 5			
Moderate response (n = 16)	3.4 ± 3			
Poor response (n = 10)	1.4 ± 0.7			
Short-term immunotherapy group (n = 22)	1.2 ± 0.4	5 (22.7%)	8 (36.4%)	9 (40.9%)
Long-term immunotherapy group (n = 22)	8.1 ± 3.4	13 (59.1%)	8 (36.4%)	1 (4.5%)

TABLE III. Duration of Immunotherapy and Clinical Response.

From: Ohashi: Laryngoscope, Volume 107(9).September 1997.1270-1275