

Serum levels of specific IgE, soluble interleukin-2 receptor, and soluble intercellular adhesion molecule-1 in seasonal allergic rhinitis

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Background: There is increasing evidence that soluble interleukin-2 receptor (sIL-2R) might reflect T cell activation *in vivo* and soluble intercellular adhesion molecule-1 (sICAM-1) might reflect the ongoing inflammatory response in the inflamed site.

Objective: The aim of this study was to determine the effect of antihistamine tablets and allergen-specific immunotherapy on the seasonal changes in specific IgE, sIL-2R, and sICAM-1 in the serum of patients with seasonal allergic rhinitis.

Methods: This prospective study included 99 patients with seasonal allergic rhinitis due to Japanese cedar pollens and 27 nonatopic healthy volunteers. The patients were divided into an antihistamine-treated group and an immunotherapy group. Serum samples were collected before and during the pollen season from each patient to determine specific IgE, sIL-2R, and sICAM-1.

Results: Levels of sIL-2R before the pollen season did not differ significantly among the nonatopic group, the antihistamine-treated group, and the immunotherapy group. The levels of sICAM-1 before the pollen season were significantly higher in the antihistamine-treated group and in the immunotherapy group than in the nonatopic group. Seasonal increase in specific IgE was significant in the antihistamine-treated group regardless of their clinical outcomes. In contrast, significant increase in specific IgE was observed during the pollen season in poor responders but not in good responders to immunotherapy. Serum levels of sIL-2R and sICAM-1 were significantly increased during the pollen season in poor responders of the antihistamine-treated group and the immunotherapy group. On the other hand, neither seasonal increase in sIL-2R nor sICAM-1 was significant in good responders of the antihistamine-treated group and the immunotherapy group.

Conclusions: Serum levels of sICAM-1 are higher in patients with seasonal allergic rhinitis, even outside of the pollen season when the allergen does not naturally exist. Seasonal changes in serum sICAM-1 as well as sIL-2R and specific IgE are probably objective markers to indicate the clinical efficacy of antihistamines and immunotherapy on seasonal allergic rhinitis.

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INTRODUCTION

There is increasing evidence that T lymphocytes and eosinophils play a central role for coordination and per-

sistence of the allergic inflammatory process. The rate of release of the soluble form of interleukin-2 receptor (sIL-2R) reflects T cell activation *in vivo*.¹ The measurement of serum levels of sIL-2R might be useful in analyzing the disease state of allergic disorders. In our previous studies, sIL-2R levels in the serum of patients with perennial allergic rhinitis were higher than those of nonatopic individuals,

and decreased to the levels of nonatopic individuals after many years of immunotherapy.² In patients with seasonal allergic rhinitis due to Japanese cedar pollens, seasonal increase in sIL-2R was associated with poor clinical outcome, but not with good clinical course.³

Recently, soluble forms of intercellular adhesion molecule-1 (sICAM-1) have been identified in the peripheral blood of normal subjects⁴ and patients with various diseases. Elevated levels of sICAM-1 are observed in a variety of inflammatory conditions, including infections,⁵ systemic vasculitis,⁶ and neoplasia.⁷ The levels of sICAM-1 were also determined in allergic disorders, and sICAM-1 levels in asthmatics are higher during acute exacerbations than in stable conditions.⁸⁻¹¹ Levels of sICAM-1 in patients with seasonal allergic rhinitis were also reported to be increased during seasonal aggravation.¹² In addition, a significant increase in sICAM-1 levels was observed following bronchoprovocation.¹³ Taking these lines of evidence together, an increase in sICAM-1 may reflect the ongoing inflammatory response in the inflamed site. Detection of sICAM-1 could therefore, be useful in the investigation and monitoring of disease activity and inflammatory reactions in allergic disorders.

It is of clinical interest whether sICAM-1 levels could be modulated by appropriate treatments; however, modulation of serum concentrations of sICAM-1 by treatments remains to be unclear. The present study was designed to study whether antihistamine tablets and/or allergen-specific immunotherapy

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can modulate seasonal changes in serum sIL-2R and sICAM-1 in patients with seasonal allergic rhinitis due to Japanese cedar pollens.

PATIENTS AND METHODS

Patients

This study included 99 adult patients (mean: 31.8 ± 9.8 years; age range: 19 to 64 years) with seasonal allergic rhinitis due to Japanese cedar (*Cryptomeria japonica*) pollens who gave informed consent for participation. All the patients were selected from our outpatients who satisfied the following conditions before treatment: (1) well-documented history of typical Japanese cedar pollinosis, (2) no nasal symptoms outside the cedar pollen season, (3) no history of asthma, (4) positive intracutaneous skin test to Japanese cedar pollen according to Okuda's criteria,¹⁴ (5) positive nasal provocation to the pollens according to Okuda's criteria,¹⁴ and (6) eosinophilia in nasal smears during the cedar pollen season.

The patients were divided into an antihistamine-treated group and an immunotherapy group based on their treatment background. None of the patients of the antihistamine-treated group had previously been treated with immunotherapy or had received steroid treatment. The patients of the immunotherapy group had undergone variable periods (mean: 5.2 ± 4.1 years; range 1 to 15 years) of immunotherapy using Japanese cedar pollen (Torii Co, Ltd, Tokyo, Japan).

To serve as normal controls, 27 non-allergic healthy volunteers (mean: 33.6 ± 9.7 years; age range: 19 to 64 years, nonatopic group) were chosen on the basis of the following criteria: (1) no history of allergic disease; (2) no physical findings suggestive of atopic disease; and (3) negative serum IgE antibodies specific to the major allergens in Japan, such as house dust mites, Japanese cedar pollen, ragweed, Japanese cypress pollen, and molds.

Mode of Immunotherapy

The patients were given subcutaneous injections of Japanese cedar pol-

len extracts (Torii Co, Ltd, Tokyo, Japan), which are only commercially available in Japan at present. This aqueous extracts were prepared from native pollens, and were demonstrated to contain 2.0 mg of protein per milliliter. Immunotherapy was begun outside of the pollen season (between May and July). Individual initial doses were determined by threshold skin tests. Doses were increased by 50% at weekly intervals until the highest tolerated dose or 0.5 mL of 1:100 wt/vol was reached. The maximum tolerated doses were 0.5 mL of 1:100 wt/vol in 56 of the 61 patients and 0.5 mL of 1:100 wt/vol in the remaining five patients. The maximum tolerated dose was attained within 4 to 8 months, and weekly injection was continued for the first few months after attainment of the maintenance dose. They then received injections of this dose on a biweekly basis for the next few months, and then monthly injections. Finally, the interval between injections was gradually increased up to 2 months.

Study Design

Pollination of Japanese cedars occurred in 1996 from the first week of February to the second week of April. This study design followed the principals outlined in the Declaration of the Helsinki.¹⁵ The 28 patients of the antihistamine-treated group were treated with antihistamine tablets (such as 120 mg/day of terfenadine) alone from the last week of January to the end of April. The 61 patients of the immunotherapy group continued to receive scheduled maintenance dose subcutaneous injections. The patients of the immunotherapy group were allowed to take rescue antihistamine tablets (such as emedastine difumarate) during the pollen season, if necessary.

Venous blood was collected twice from each patient, before the cedar pollen season of 1996 (between December, 1995 and January, 1996) and during the cedar pollen season of 1996 (first week of April, 1996). Venous

blood was also collected outside the pollen season from each of the nonatopic group. All the serum samples were separated and stored at -80°C , and were simultaneously used in the present determination of serum concentrations of cedar pollen-specific IgE, sIL-2R, and sICAM-1.

Determination of Serum Specific IgE, sIL-2R, and sICAM-1

Specific IgE antibodies, sIL-2R, and sICAM-1 in serum were determined at the same time. Specific IgE to Japanese cedar pollen was measured by the CAP system.¹⁶ Serum concentrations of sIL-2R were determined by the enzyme-linked immunosorbent assay (ELISA) (Cellfree, T cell science, Cambridge, MA), as previously described by Chilosi et al¹⁷ with some modification: methodology and justification of the method employed in this study have been described elsewhere.^{2,3} The minimum sensitivity of this assay was 40 U/mL of sIL-2R. The serum concentrations of sICAM-1 were examined with a sandwich ELISA. ELISA kit (R & D System, Minneapolis, MN) employing two antibodies to distinguish different epitopes of ICAM-1 molecules was used. The ELISA measurements were run in duplicate.

The seasonal increase rate in specific IgE, sIL-2R, and sICAM-1 was calculated using the following formula.

$$\text{SIR}(\%) = \frac{\text{VdPS} - \text{VbPS}}{\text{VbPS}} \times 100$$

where SIR = seasonal increase rate (%), VdPS = values during pollen season, and VbPS = values before pollen season.

Clinical Evaluation

Clinical evaluation for each patient was based upon our criteria using daily symptom diary cards during the first week of April in 1996. The details of the method employed in this study have been described elsewhere.^{2,3} In brief, all patients were asked to complete diary cards in the seven days before clinical assess-

ment. The daily symptom card includes the number of sneezing attacks, the number of nose blowings, and the degree of nasal obstruction. A careful survey of the diary card graded the three nasal symptoms (sneeze, rhinorrhea, and obstruction) on a scale of 0 to 3, depending on severity. The average daily scores of sum total of the three nasal symptom scores were used as total symptom scores (maximum: 9). According to their total symptom scores, the patients of the antihistamine-treated group were divided into the following two subgroups: good responders = total symptom scores were 0 to 2, and poor responders = total symptom scores were 3 to 9. The patients of the immunotherapy group were also divided into the following two subgroups based on their clinical response to immunotherapy: good responders = total symptom scores were 0 to 2 without rescue medication and poor responders = total symptom scores were 3 to 9 or need of rescue medication to control their nasal symptoms.

Statistical Analysis

For comparisons between groups, the Mann-Whitney U-test was used. For comparisons of paired values within a group, Wilcoxon's signed-rank test was used. Differences were considered significant when $P < .05$. Spearman's correlation coefficient (rs) was calcu-

lated to determine the degree of correlation between two different parameters, and significant correlation was accepted when $P < .05$ on Spearman's rank correlation analysis.

RESULTS

Levels of and seasonal increase rates of specific IgE, sIL-2R, and sICAM-1 in serum are summarized in Tables 1–3.

Background of Subjects

There were no apparent differences in sexes between the 99 patients and the 27 nonatopic healthy volunteers. The age levels did not differ significantly between the 99 patients and the 27 nonatopic healthy volunteers ($P = .3963$). Neither the ages nor the duration of the disease differed significantly between the antihistamine-treated group and the immunotherapy group (age: $P = .6022$, duration of the disease: $P = .8151$).

Specific IgE, sIL-2R, and sICAM-1 Before the Pollen Season

Specific IgE to the cedar pollen was not detected in any individual of the nonatopic group. Serum levels of sIL-2R did not differ significantly among the three groups (the nonatopic group versus the antihistamine-treated group: $P = .3288$, the nonatopic group versus the immunotherapy group: $P = .3926$, and the antihistamine-treated group versus the immunotherapy

group: $P = .3819$). The levels of sICAM-1 in the antihistamine-treated group and in the immunotherapy group, however, were significantly higher than those in the nonatopic group (the nonatopic group versus the antihistamine-treated group: $P = .0015$ and the nonatopic group versus the immunotherapy group: $P = .0041$). Interestingly, none of specific IgE, sIL-2R, and sICAM-1 before the pollen season differed significantly between the antihistamine-treated group and the immunotherapy group (specific IgE: $P = .3819$, sIL-2R: $P = .3800$, sICAM-1: $P = .3885$).

Seasonal Changes in Specific IgE, sIL-2R, and sICAM-1

Seasonal increase in specific IgE during the pollen season was significant in the antihistamine-treated group ($P < .0001$), but not in the immunotherapy group ($P = .0675$). Neither the antihistamine-treated group nor the immunotherapy group demonstrated significant seasonal increase in sIL-2R (antihistamine-treated group: $P = .4123$, immunotherapy group: $P = .7505$). Significant increase in sICAM-1 levels were observed during the pollen season in both the antihistamine-treated group and the immunotherapy group (antihistamine-treated group: $P = .0020$, immunotherapy group: $P < .0001$).

Seasonally increased rates in both specific IgE and sICAM-1 were significantly smaller in the immunotherapy

Table 1. Specific IgE in 99 Patients with Allergic Rhinitis due to Japanese Cedar Pollen

	Before the Pollen Season, U/mL					During the Pollen Season, U/mL					Seasonal Increase Rate, %				
	Mean	SD	SE	Median	Range	Mean	SD	SE	Median	Range	Mean	SD	SE	Median	Range
Antihistamine-treated group (n = 28)	25.65	14.02	2.65	21.0	5.0–55.0	42.09	23.34	4.41	43.0	6.3–9.2	68.0	50.5	9.54	58.3	–23.5–180.0
Good responders (n = 12)	24.10	15.41	4.45	18.7	5.0–51.0	36.88	21.93	6.33	37.0	6.3–65.0	55.5	36.5	58.3	37.0	6.3–65.0
Poor responders (n = 16)	26.81	3.28	3.32	23.0	11.0–55.0	46.00	24.28	6.07	43.0	16.0–92.0	77.4	58.2	6.07	43.0	16.0–92.0
Immunotherapy group (n = 71)	29.49	29.14	3.46	17.0	0.8–100	30.61	28.32	3.36	37.0	0.9–140	11.7	28.2	3.36	37.0	0.9–140.0
Good responders (n = 37)	34.42	32.17	5.29	23.0	1.4–100	31.19	26.99	4.44	30.0	0.9–87.0	–3.7	13.9	4.44	30.0	0.9–87.0
Poor responders (n = 34)	24.13	24.80	4.25	21.0	0.8–100	29.99	30.10	5.16	20.0	1.2–140	28.5	30.4	5.16	20.0	1.2–140.0

Table 2. Soluble Interleukin-2 Receptor in Sera of 99 Patients with Allergic Rhinitis due to Japanese Cedar Pollen and 27 Healthy Controls

	Before the Pollen Season, U/mL					During the Pollen Season, U/mL					Seasonal increase Rate, %				
	Mean	SD	SE	Median	Range	Mean	SD	SE	Median	Range	Mean	SD	SE	Median	Range
Antihistamine-treated group (n = 28)	374.6	131.2	24.8	388	136–598	399.8	203.9	38.5	362	55–895	6.8	39.0	7.4	10.9	–65.0–82.3
Good responders (n = 12)	391.7	116.4	33.6	405	136–589	331.0	117.1	33.8	359	138–491	–11.1	31.0	8.9	–9.2	–62.5–26.4
Poor responders (n = 16)	361.8	143.6	35.9	375	157–598	451.4	241.1	60.3	378	55–895	20.3	39.9	10.0	28.0	–65.0–82.3
Immunotherapy group (n = 71)	371.6	200.9	23.8	301	105–879	357.4	232.5	27.6	280	96–1454	–0.8	31.5	3.7	3.7	–68.7–122.3
Good responders (n = 37)	397.1	209.9	34.5	325	111–832	339.5	206.1	33.9	278	96–832	–12.2	27.0	4.4	1.1	–68.7–22.8
Poor responders (n = 34)	343.9	189.8	32.6	295	105–879	377.0	260.0	44.6	326	136–1454	11.6	31.6	5.2	14.2	–64.0–122.3
Nonatopic group (n = 27)	353.6	88.8	17.1	336	196–552										

Table 3. Soluble Intercellular Adhesion Molecule-1 in Sera of 99 Patients with Allergic Rhinitis due to Japanese Cedar Pollen and 27 Healthy Controls

	Before the Pollen Season, U/mL					During the Pollen Season, U/mL					Seasonal Increase Rate, %				
	Mean	SD	SE	Median	Range	Mean	SD	SE	Median	Range	Mean	SD	SE	Median	Range
Antihistamine-treated group (n = 28)	315.6	139.7	26.4	324	100–623	385.3	189.5	35.8	389	103–825	22.7	36.9	7.0	20.5	–30.8–145.6
Good responders (n = 12)	322.4	169.1	48.8	310	100–623	352.6	234.8	67.8	239	103–825	4.6	25.7	7.4	4.1	–30.8–62.3
Poor responders (n = 16)	310.5	118.8	29.7	324	161–587	409.9	150.6	37.7	418	152–685	36.6	38.9	9.7	31.7	–25.6–145.6
Immunotherapy group (n = 71)	282.9	115.5	13.7	291	74–574	306.6	126.5	15.0	303	80–585	9.2	14.4	1.7	3.8	–12.0–58.8
Good responders (n = 37)	273.8	109.6	18.0	258	90–456	278.8	113.0	18.6	266	89–474	2.0	6.9	1.1	2.3	–12.0–23.4
Poor responders (n = 34)	292.7	122.5	21.0	296	74–574	336.8	134.9	23.1	321	80–585	17.0	16.4	2.8	14.4	–3.5–58.8
Nonatopic group (n = 27)	210.6	81.0	15.6	182	77–377										

group than in the antihistamine-treated group (specific IgE: $P < .0001$, sICAM-1: $P = .0293$). On the other hand, the seasonally increased rate in sIL-2R did not differ significantly between the antihistamine-treated group and the immunotherapy group ($P = .1985$).

Clinical Effect in the Antihistamine-Treated Group

The numbers of good responders and poor responders of the antihistamine-treated group were 12 and 16, respectively. None of specific IgE, sIL-2R, and sICAM-1 before the pollen season differed significantly between the good

responders and the poor responders (specific IgE: $P = .4566$, sIL-2R: $P = .7806$, sICAM-1: $P = .8892$). Specific IgE was significantly increased during the pollen season in both good responders ($P = .0022$) and poor responders ($P = .0008$, Fig 1). A significant seasonal increase in sIL-2R was observed in poor responders ($P = .0340$) but not in good responders ($P = .2094$, Fig 2). Similarly, seasonal increase in sICAM-1 was significant in poor responders ($P = .0038$) but not in good responders ($P = .3882$, Fig 3). Both the seasonally increased rates in

sIL-2R and sICAM-1 were significantly different between the good and poor responders (sIL-2R: $P = .0459$, sICAM-1: $P = .0107$), whereas the seasonally increased rate in specific IgE did not differ significantly between them ($P = .2185$).

Clinical Effect in the Immunotherapy Group

The numbers of good responders and poor responders to immunotherapy were 37 and 34, respectively. Specific IgE, sIL-2R, and sICAM-1 before the pollen season was not significantly different between the good

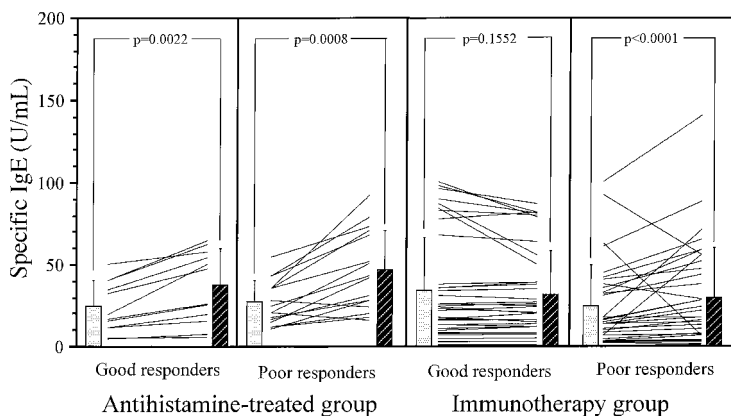


Figure 1. Seasonal changes in specific IgE. In the antihistamine-treated group, significant increases in specific IgE during the pollen season was observed in both good responders and poor responders. In the immunotherapy group, a significant increase in specific IgE during the pollen season was observed in poor responders but not in good responders. □ Before pollen season ▨ During pollen season

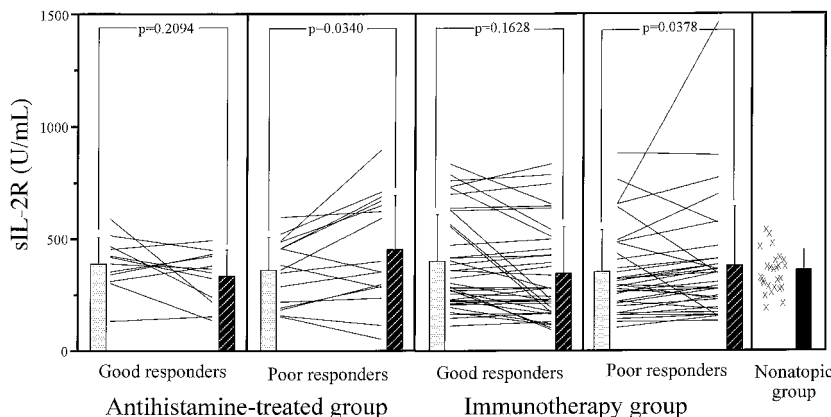


Figure 2. Seasonal changes in sIL-2R. Seasonal increase in sIL-2R was significant in poor responders of both the antihistamine-treated group and the immunotherapy group. In contrast, seasonal increase in sIL-2R was not significant in good responders, irrespective of treatment backgrounds. □ Before pollen season ▨ During pollen season

responders and the poor responders (specific IgE: $P = .1952$, sIL-2R: $P = .3336$, sICAM-1: $P = .6166$). Among the good responders, specific IgE, sIL-2R, and sICAM-1 were not significantly changed during the pollen season (specific IgE: $P = .1552$, Fig 1; sIL-2R: $P = .1628$, Fig 2; sICAM-1: $P = .1030$, Fig 3). In contrast, specific IgE, sIL-2R, and sICAM-1 were all significantly increased during the pollen season in the poor responders (specific IgE: $P = .0005$, Fig 1; sIL-2R: $P = .0378$, Fig 2; sICAM-1: $P < .0001$, Fig 3). Each rate of seasonal increase in spe-

cific IgE, sIL-2R, and sICAM-1 was significantly smaller in good responders than in poor responders (specific IgE: $P < .0001$, sIL-2R: $P = .0004$, sICAM-1: $P < .0001$).

Comparison Analysis of Good Responders

Serum levels of specific IgE, sIL-2R, and sICAM-1 before the pollen season did not differ significantly between the good responders of the antihistamine-treated group and the good responders of the immunotherapy group (specific IgE: $P = .7535$, sIL-2R: $P = .5076$, sICAM-1: $P =$

.5378). Seasonally increased rates between sIL-2R and sICAM-1 did not differ significantly (sIL-2R: $P = .6671$, sICAM-1: $P = .4639$). In contrast, the seasonally increased rate in specific IgE was significantly smaller in the good responders of the immunotherapy group than in the good responders of the antihistamine-treated group ($P < .0001$).

Comparison Analysis of Poor Responders

Specific IgE, sIL-2R, and sICAM-1 before the pollen season were not significantly different between the poor responders of the antihistamine-treated group and the poor responders of the immunotherapy group (specific IgE: $P = .1091$, sIL-2R: $P = .4415$, and sICAM-1: $P = .6623$). Seasonally increased rates in sIL-2R did not differ significantly between them ($P = .2614$), whereas both rates of seasonal increase in specific IgE and sICAM-1 were significantly smaller in the poor responders of the immunotherapy group than in the poor responders of the antihistamine-treated group (specific IgE: $P = .0013$, sICAM-1: $P = .0261$).

Correlational Analysis Among Seasonal Increase Rates

In the antihistamine-treated group, significant correlations were observed among the seasonally increased rates in specific IgE, sIL-2R, and sICAM-1 (specific IgE versus sIL-2R: $rs = 0.425$, $P = .0272$, specific IgE versus sICAM-1: $rs = 0.540$, $P = .0051$, sIL-2R versus sICAM-1: $rs = 0.432$, $P = .0247$). In the immunotherapy group, significant correlations were also observed among the seasonally increased rates in specific IgE, sIL-2R, and sICAM-1 (specific IgE versus sIL-2R: $rs = 0.446$, $P = .0002$, specific IgE versus sICAM-1: $rs = 0.509$, $P < .0001$, sIL-2R versus sICAM-1: $rs = .421$, $P = .0004$).

Analysis of the Duration of Immunotherapy

The duration (years) of immunotherapy did not differ significantly between good responders (mean: 5.6

years, SD: 3.9 years, SE: 0.6 years, median: 4 years, range: 1 to 15 years) and poor responders (mean: 4.7 years, SD: 4.2 years, SE: 0.7 years, median: 3 years, range: 1 to 15 years) to immunotherapy ($P = .1419$). Each rate, however, of the seasonal increase in specific IgE, sIL-2R, and sICAM-1 was inversely correlated with the duration of immunotherapy (IgE: $r_s = -0.397$, $P = .0006$; sIL-2R: $r_s = -0.232$, $P = .0426$, sICAM-1: $r_s = -0.346$, $P = .0017$).

DISCUSSION

There is increasing evidence that sIL-2R may reflect T cell activation *in vivo*¹ and that sICAM-1 may reflect the ongoing inflammatory response in the inflamed site.^{8–13} First, we studied serum levels of sIL-2R and sICAM-1 in patients with seasonal allergic rhinitis before the pollen season, as markers of T cell activation and ongoing inflammatory response. Since the serum levels of sIL-2R outside the pollen season did not differ significantly among the nonatopic group, the antihistamine-treated group and the immunotherapy group, T cell activation is not likely to occur outside the pollen season in patients with seasonal allergic rhinitis. In contrast, the serum levels of sICAM-1 outside of the pollen season in both the antihistamine-treated group and the immunotherapy group were significantly higher than those in the nonatopic group. This findings may suggest that endothelial cells are primed in patients with seasonal allergic rhinitis even outside the pollen season when the allergen does not naturally exist.

Japanese cedar pollinates heavily during early spring, and there is no significant interference by other pollens. Japanese cedar pollination therefore provides a very good *in vivo* model to study the effect of natural allergen provocation on the natural changes in immunologic and inflammatory variables. The second aim of this study was to determine seasonal changes in serum levels of specific IgE, sIL-2R, and sICAM-1 in response to natural exposure to the pollens. Our study design failed to examined their

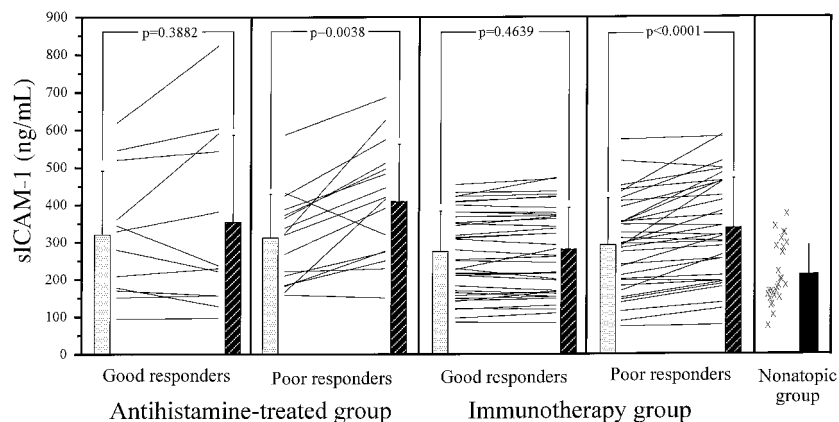


Figure 3. Seasonal changes in sICAM-1. Seasonal increase in sICAM-1 was significant in poor responders of both the antihistamine-treated group and the immunotherapy group. In contrast, seasonal increase in sICAM-1 was not significant in good responders, irrespective of treatment backgrounds. ■ Before pollen season ▨ During pollen season

seasonal changes in untreated patients because of ethical reasons. In the poor responders to antihistamines as well as immunotherapy, each level of specific IgE, sIL-2R, and sICAM-1 was significantly increased during the pollen season than before the season. Our findings may suggest seasonal enhancement of specific IgE response, T cell activation, and ongoing inflammatory responses following natural allergen exposure. The possibility cannot be excluded, however, that other nonspecific stimuli or inflammatory conditions such as viral respiratory tract infections might occur during the pollen season and influence sIL-2R and sICAM-1 levels.^{5–7,18}

Immunotherapy has been reported to blunt the usual rise in specific IgE that occurs during the pollen season.^{3,19,20} In the present study, specific IgE levels were significantly increased during the pollen season not only in poor responders but also in good responders to antihistamines. In addition, the seasonally increased rates in specific IgE did not differ significantly between them. On the other hand, specific IgE levels did not fluctuate significantly during the pollen season in the good responders to immunotherapy. The seasonally increased rates in specific IgE were significantly smaller in good responders than in poor responders to immunotherapy. These findings there-

fore suggest that immunotherapy inhibited the seasonal increase in specific IgE response and the magnitude of the inhibition affected its clinical effect.

It is also of clinical interest to note whether seasonal increase in sIL-2R or sICAM-1 can also be modulated by successful treatment. A significant seasonal increase in sIL-2R was observed in those with poor response to antihistamines, but not in those with good response to antihistamines. In addition, the seasonally increased rates in sIL-2R were significantly smaller in those with good response than in those with poor response to antihistamines. Our findings therefore suggest that successful treatment using antihistamines can inhibit the seasonal increase in sIL-2R and that the degree of inhibition of seasonal T cell activation can affect the clinical effect.

Similarly, sIL-2R levels were not significantly increased during the pollen season in those with good response to immunotherapy, and the seasonally increased rates in sIL-2R were significantly smaller in those with good response than in those with poor response to immunotherapy. It is therefore likely that immunotherapy can inhibit seasonal T cell activation, and that the magnitude of inhibition is probably involved in its clinical effect. In addition, seasonally increased rates

in sIL-2R did not differ significantly between the good responders to antihistamines and the good responders to immunotherapy. Seasonal changes in sIL-2R may therefore, serve as objective evidence for successful clinical outcome in the treatment of seasonal allergic rhinitis, irrespective of whether the patients were treated with antihistamines or immunotherapy, which is consistent with our previous study.³

Serum levels of sICAM-1 have been studied extensively in patients with allergic diseases, but therapeutic effects on sICAM-1 levels remain unclear. In the present study, sICAM-1 levels were significantly increased during the pollen season in poor responders to antihistamines, but not in good responders to antihistamines, and the seasonally increased rates in sICAM-1 were significantly smaller in good responders than in poor responders to antihistamines. Similarly, sICAM-1 levels were not significantly increased during the pollen season in good responders to immunotherapy, and the seasonal increase rate in sICAM-1 was significantly smaller in the good responders than in the poor responders to immunotherapy. It is therefore likely that successful treatment with antihistamines and immunotherapy can inhibit the seasonal activation of ongoing inflammatory response, and that the degree of inhibition by antihistamines and immunotherapy plays a role in mediating their clinical effects.

Following an acute asthmatic episode, serum levels of sICAM-1 were reported to remain elevated for at least 28 days, even with aggressive pharmacotherapy using bronchodilators and systemic corticosteroids.¹¹ In patients with seasonal allergic rhinitis due to Japanese cedar pollen, serum levels of sICAM-1 were reported to remain high after the season, when levels of other parameters such as symptoms and blood eosinophil counts had roughly returned to initial preseasonal levels.¹² Taking together these lines of evidence and

the present findings, it is therefore likely that serum levels of sICAM-1 are at most under limited steroid control, but that antihistamines and immunotherapy can reduce or prevent the seasonal increase in sICAM-1 during the pollen season.

In conclusion, seasonal changes in sICAM-1 and sIL-2R are probably objective markers to monitor the clinical effect of antihistamines and immunotherapy on seasonal allergic rhinitis. In addition, seasonal changes in specific IgE, unlike as sIL-2R and sICAM-1, are likely a particular index exhibiting the clinical effect of immunotherapy.

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