Omalizumab reduces allergic rhinitis symptoms due to Japanese cedar pollen by improving eosinophilic inflammation

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Dear Editor:

Seasonal allergic rhinitis caused by Japanese cedar pollen (SAR-JCP) is a serious social problem in Japan, affecting 38.8% of the population [(1)]. Omalizumab, a recombinant humanised monoclonal anti-immunoglobulin (Ig)E antibody, reduces serum-free IgE levels by 84–99% [(2)]. The reduction of serum-free IgE levels induced by omalizumab ultimately downregulates FcεRI expression in basophils and mast cells [(3)]. Omalizumab significantly reduces nasal symptoms and improves the quality of life in patients with allergic rhinitis [(4,5)]; however, other than a decrease in free IgE, its biomarker activity is unclear. Allergic rhinitis reactions are more pronounced in nasal secretions and mucosa than in serum; however, no studies have examined the changes in proteins in nasal secretions after omalizumab administration. In this study, we aimed to elucidate the pathophysiology of the effect of omalizumab. This may serve as a basis for the identification of new biomarkers through the examination of proinflammatory proteins in nasal secretions, which may reflect the pathophysiology more accurately than peripheral blood.

In 12 patients with severe SAR-JCP (Table S1; supplementary material), eosinophil cationic protein (ECP) and cysteinyl leukotriene levels in nasal lavage fluid significantly decreased after treatment (Figure 1-A, B). Total IgE (0.87±1.21 ng/mL to 1.15±1.28 ng/mL, P=0.055) and histamine (13.07±21.50 ng/mL to 7.36±7.66 ng/mL, P=0.622) levels in nasal lavage fluid did not significantly differ before and after treatment. Symptoms improved significantly in these 12 patients (Figure S1; supplementary material).

In asthma, cytokines and other substances in the sputum reflect local conditions [(6)]. In nasal diseases, nasal lavage fluid is more likely to provide an accurate local assessment than peripheral blood. In this study, we showed that omalizumab treatment significantly reduced ECP and cysteinyl leukotriene levels in nasal secretions one month after treatment and improved subjective symptoms in patients. The improvement in eosinophilic inflammation and reduction in cysteinyl leukotriene levels may contribute to the improvement of clinical symptoms after one month of treatment. The decrease in cysteinyl leukotriene levels is likely owing to an improvement in eosinophilic inflammation, and these two results may be the result of a single event, an improvement in eosinophilic inflammation.

Free IgE in nasal secretions also decreases; however, because only total IgE was measured in this study, precise discussion of IgE was not possible. Regarding the failure to decrease histamine levels in nasal lavage fluid, Hanf et al. reported no difference in histamine levels in nasal lavage fluid after allergen loading in omalizumab-treated patients when compared with those in patients given placebo [(7)]. This can be attributed to the increase in histamine levels caused by molecules such as acetylcholine, substance P, and endotoxins, released by non-IgE-mediated responses [(8)]. Endotoxins (lipopolysaccharides) may induce sneezing symptoms (histamine release) in an IgE-independent manner, and this response also occurs in mast cell and basophil-depleted mice, suggesting the involvement of monocytes and macrophages [(8)]. Since pollen has an endotoxin attached to it, it is possible that histamine is released with non-IgE-mediated responses. IgE binding to mast cells/basophils releases histamine and leukotrienes, whereas stimulation with acetylcholine or substance P only increases histamine levels [(9)].

The reduced ECP and cysteinyl leukotriene levels suggests that

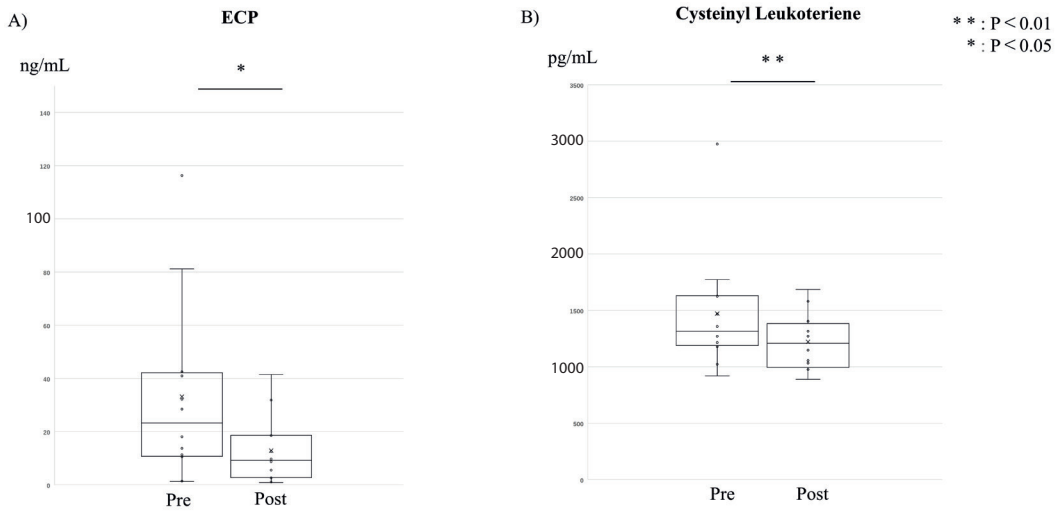

Figure 1. ECP and cysteinyl leukotriene levels in nasal secretions one month (single dose) after treatment with omalizumab. ECP: eosinophil cationic protein ; Pre: before omalizmnab administration ; Post: one month after omalizumab administration. Mann-\Vhitney U test was used to compare the values before and one month after treatment. Statistical significance was set at P<0.05. **: P<0.01; *: P<0.05.

the long-term therapeutic effect of omalizumab on SAR-JCP symptoms may be mainly due to the reduction in chemical mediators.

In conclusion, the therapeutic effect of omalizumab on SAR-JCP symptoms may be attributed to improvement in eosinophilic inflammation. Based on our results, ECP and cysteinyl leukotriene concentrations in nasal lavage fluid may be potential biomarkers of the effect of omalizumab on SAR-JCP.

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None.

Authorship contribution

KH, IS, YW, and TS designed the study and wrote the manuscript. KH, NO, AO, YO, MT, YI, and HK contributed to data collection. KH, AM, and KM performed the statistical analysis and interpretation of the results. All involved authors have commented on and reviewed the paper.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

None.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Materials and methods

Study design

In this prospective observational study, we analysed patients with seasonal allergic rhinitis caused by Japanese cedar pollen (SAR-JCP) who received omalizumab. This study was conducted between February 2020 and May 2020 and approved by the Ethics Committee on Research Involving Human Subjects, Showa University School of Medicine (approval number: 3192). This study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants before commencing the study.

Participants underwent blood sampling (eosinophils and total IgE), evaluation of symptoms (sneezing, rhinorrhoea, nasal congestion, nasal itching, and ocular itching) on a 5-point scale (0: none, 1: mild, 2: moderate, 3: severe, 4: very severe), evaluation of allergic rhinitis-related quality of life using the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) [1], and nasal lavage solution collection before and one month after omalizumab administration.

Nasal lavage and biomarker analysis

Nasal lavage fluid was collected by placing the participant in a backward-bent head position, injecting 5 mL of saline into each bilateral nasal cavity, shifting the head position to the left or right several times, and then bending forward to expel the solution through the nostrils and oral cavity, which was then mixed with the nasal discharge collected immediately thereafter by blowing the nose with a saran wrap. The nasal lavage fluid was centrifuged at 3,000 rpm, and the supernatant was collected and stored at -80°C. The collected nasal lavage fluid was assayed for eosinophil cationic protein (ECP), IgE, histamine, and cysteinyl leukotriene using ELISA kits. The Human EOSINOPHIL CATIONIC PROTEIN ELISA KIT (AVISCERA BIOSCIENCE) was used for ECP detection (quantitative range, 0.156–10 ng/mL). Dilution studies were performed using 25-fold dilutions. A Human IgE ELISA KIT (Bethyl Laboratories, Inc.) was used to detect IgE (quantitative range, 0.69–500 ng/mL). Dilution studies were performed, and the assay was performed at 1× dilution. Histamine levels were measured using the Histamine Research ELISA kit (Immu Smol). Dilution studies were performed and the samples were assayed at 1× dilution (quantitative range, 0.5–50 ng/mL). For cysteinyl leukotrienes, a cysteinyl leukotriene ELISA kit (Cayman) was used. Dilution studies were performed and assayed at 2-fold dilutions (quantitative range, 8.6–2,500 pg/mL).

Participants

SAR-JCP was diagnosed based on the history of cedar pollen-induced clinical symptoms for at least two consecutive years; the serum-specific IgE antibody against cedar pollen was class ≥3 [≥3.5 UA/mL or ≥13.5 lumicount (kU/L)]. We enrolled patients who fulfilled the following inclusion criteria: (i) age, >12 years; (ii) serum total IgE levels, 30–1500 IU/mL; (iii) baseline body weight, 30–150 kg; and (iv) those whose severe symptoms persisted even after treatment with histamine H1 receptor antagonists (various types), nasal corticosteroids (fluticasone propionate 110 µg/day), and ophthalmic antihistamines (epinastine hydrochloride ophthalmic solution 0.05% four times/day). We included patients who had all of the following symptoms: sneezing, itchy nose, runny nose, and stuffy nose, with at least one or more of these symptoms having a score of ≥3 (e.g. a patient with scores of sneezing: 1, rhinorrhoea: 1, nasal congestion: 3, nasal itching: 1 would be included because the symptom nasal congestion has a score of 3). Patients taking oral steroids were excluded. Twelve participants received omalizumab after the peak period of pollen dispersal and were evaluated four weeks after treatment. All the 12 participants completed the protocol (Table1). The peak period of cedar and cypress pollen dispersal was defined as the starting day when 30 grains/cm^2 were counted [2].

Dosage and administration of omalizumab

Omalizumab was administered subcutaneously every 4 weeks based on serum total IgE levels and baseline body weight. The dose was the same as that used for patients with asthma. The study examined biomarkers before and one month after administration of a single dose of omalizumab.

Outcome measures

Statistical analysis

All statistical analyses were performed using JMP Pro 16.2 (SAS Institute Inc. Cary, NC, USA). Mann–Whitney U test was used to examine the proteins in nasal secretions and peripheral blood before and after treatment, because the populations are identical and outliers may exist. Statistical significance was set at $P<0.05$.

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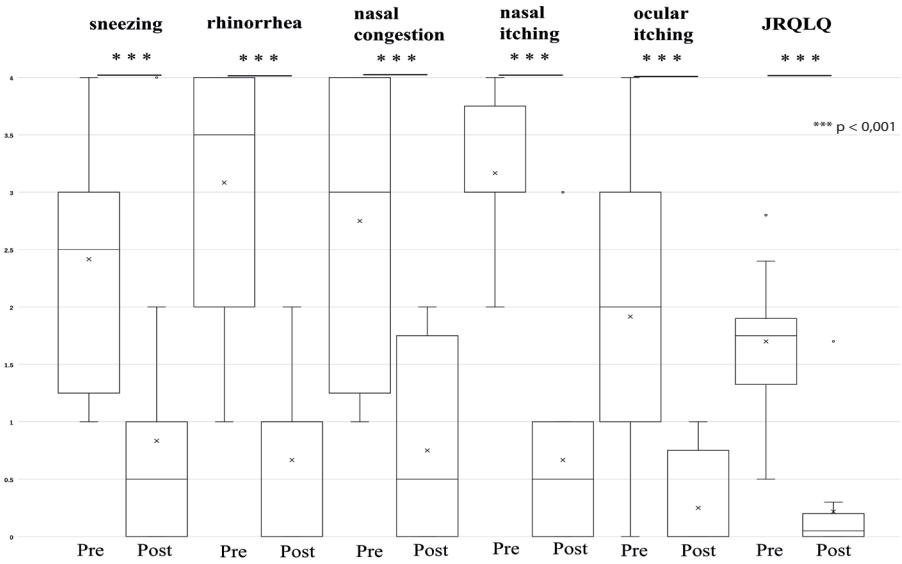

Figure S1. Improvement in patients' symptoms and quality of life scores before and one month after omalizumab administration. Sneezing, rhinorrhoes, nasal congestion, nasal itching, ocular itching and JRQLQ, all improved significantly after 1 month of treatment. Mann-Whitney U test was used to examine. Statistical significance was set at P<0.05. ***: P < 0.001. Pre; before omalizumab administration; Post; one month after omalizumab administration.

Table S1. Patient characteristics.

Case	Sex	Age	Omalizumab dosage (mg)	Specific IgE levels of Japanese cedar (Ua/mL)	Specific IgE levels of Japanese cypress (Ua/mL)	Specific IgE levels of Mite (Ua/mL)
1	M	24	300	4.51 (class3)	0.51 (class1)	2.49 (class2)
2	F	38	150	15.8 (class3)	4.56 (class3)	N/A
3	M	28	300	9.76 (class3)	2.58 (class2)	3.29 (class2)
4	F	28	300	10.1 (class3)	2.34 (class2)	0.47 (class1)
5	F	28	150	11.7 (class3)	1.16 (class2)	N/A
6	F	42	300	18.5 (class4)	9.15 (class3)	6.5 (class3)
7	M	30	300	4.2 (class3)	N/A	N/A
8	M	29	600	42.5 (class4)	26.3 (class3)	27.2 (class3)
9	F	26	300	7.8 (class3)	0.42 (class1)	N/A
10	F	28	300	31.7 (class4)	10.1 (class3)	12.3 (class3)
11	M	29	450	44.9 (class4)	1.63 (class2)	17.6 (class4)
12	M	39	300	45.5 (class4)	6.36 (class3)	7.06 (class3)

Case	Total IgE levels in peripheral blood before omalizumab administration (IU/mL)	Total IgE levels in peripheral blood after 1 month of administration omalizumab (IU/mL)
1	96	541
2	62	369
3	89	642
4	79	443
5	57	275
6	216	986
7	44	209
8	679	3657
9	124	618
10	172	815
11	315	1305
12	167	1163