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Allergy International

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Letter to the Editor

Immunological changes over three years treatment with Japanese cedar SLIT drops in mono-sensitized and poly-sensitized individuals

Dear Editor,

Japanese cedar (JC) pollinosis is the most common seasonal allergy in Japan. It affects more than 40% of the Japanese population and has serious impacts on quality of life and productivity of affected individuals.¹ Treatment of JC pollen allergy has traditionally relied on pharmacotherapy like topical corticosteroids and antihistamines. Although these medications may offer temporary relief, they only address allergic symptoms and not the cause of the disease. In contrast to symptomatic allergy medications, SLIT is an immune modulatory treatment for adults and children that addresses the underlying immune mechanisms of the disease and may lead to persisting clinical effect.²

SLIT has been demonstrated to be clinically effective towards allergy and asthma caused by a number of different allergens,^{3,4} but due to the complexity of the disease no validated biomarkers for successful allergy immunotherapy (AIT) have yet been identified. In a recent position paper on AIT biomarkers, the relevance of *in-vivo* and *in-vitro* markers were discussed.⁵ Among the seven domains of biomarkers examined in the position paper, two serological markers of particular importance, IgE (total IgE; tIgE), allergen-specific IgE (sIgE) and allergen-specific IgG4 (sIgG4), were identified, with the recommendation that the sIgE/tIgE ratio should be examined in more detail as an AIT biomarker.⁵

Recently, a drop-based sublingual allergy immunotherapy (SLIT) product, Cedartolen®, was introduced in Japan as an alternative to symptomatic medication. A recent phase IV trial (JapicCTI-142585) examined the clinical efficacy, safety, and persistence of effect after 3 years of JC pollen SLIT drops (Cedartolen®) treatment.⁶ Clinical efficacy variables included ocular and nasal symptoms as well as patient recorded Quality of Life.⁶ Immunological parameters reported from the trial included sIgE, sIgG4 and sIgG4/sIgE ratios from the overall trial population as well as their respective correlations to adverse events.⁶

As an extension of the data reported in⁶, we now report novel data and additional analyses on the JCP SLIT-drop induced antibody responses (tIgE, JC sIgE, JC sIgE/tIgE ratio, JC sIgG4) from the same trial, but here with focus on the antibody responses in two subgroups of the trial population, mono and poly-sensitized patients, respectively. Treatment-induced antibody responses represent objective biomarkers and complement the clinical findings of the trial.

All subjects in the trial (n = 233) were recruited based on JC sensitization and allergic symptoms during the JC pollen season.⁶

The sensitization pattern was examined with a 7-allergen test-panel (Table 1). 48% of the subjects (112/233) were considered “mono-sensitized” to JC (Table 1). The immunological cross-reactivity between allergens from the two phylogenetically related tree species JC and Japanese cypress is substantial and determination of the primary sensitization may not be possible. Consequently, the “mono-sensitized” group comprised subjects whose IgE reacted either to JC alone (n = 21) or JC and Japanese cypress (n = 91) (Table 1). The remaining 52% of the subjects (121/233) were sensitized to additional allergens (“poly-sensitized”) (Table 1). In addition to JC/

Table 1
Patient background.

		All patients (N = 233)	Mono-sensitized (N = 21) [†] (N = 91) [‡]	Poly-sensitized (N = 121)
		n (%)	n (%)	n (%)
Sex	Male	107 (45.9)	45 (40.2)	62 (51.2)
	Female	126 (54.1)	67 (59.8)	59 (48.8)
Age (year)	12–19	20 (8.6)	12 (10.7)	8 (6.6)
	20–29	52 (22.3)	21 (18.8)	31 (25.6)
	30–39	54 (23.2)	26 (23.2)	28 (23.1)
	40–49	82 (35.3)	41 (36.6)	41 (33.9)
	50–64	25 (10.7)	12 (10.7)	13 (10.7)
	Mean (SD)	36.5 (11.6)	36.7 (11.9)	36.3 (11.4)
Number of sensitized allergens [§]	0	21 (9.0)	21 (18.8) [†]	0 (0.0)
	1, 2	138 (59.2)	91 (81.3) [‡]	47 (38.8)
	3, 4	58 (24.9)	0 (0.0)	58 (47.9)
	5, 6	16 (6.9)	0 (0.0)	16 (13.2)
	7	0 (0.0)	0 (0.0)	0 (0.0)
	Mean (SD)	2.1 (1.0)	2.1 (1.0)	2.1 (1.0)
JC sIgE (kU _A /L)	≥3.5 to <17.5	120 (51.5)	70 (62.5)	50 (41.3)
	≥17.5 to <50	73 (31.3)	31 (27.7)	42 (34.7)
	≥50 to <100	32 (13.7)	9 (8.0)	23 (19.0)
	≥100	8 (3.4)	2 (1.8)	6 (5.0)
Japanese cypress sIgE (kU _A /L) *	<0.7	31 (13.3)	21 (18.8) [†]	10 (8.3)
	≥0.7 to <3.5	108 (46.4)	57 (50.9) [‡]	51 (42.1)
	≥3.5	94 (40.3)	34 (30.4) [‡]	60 (49.6)
JC sIgE/tIgE ratio	Mean (SD)	0.23 (0.14)	0.28 (0.14)	0.19 (0.12)

SD, standard deviation; tIgE, total IgE; JC, Japanese cedar; sIgE, specific IgE.

[†] These patients were sensitized to only Japanese cedar (n = 21).

[‡] These patients were sensitized to both Japanese cedar and Japanese cypress (n = 91).

[§] The value (≥0.7 kU_A/L, class 2) was indicated as sensitized allergens. *Dermaphagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, Japanese cypress, orchard grass, Japanese alder were measured.

* Japanese cypress specific IgE value was measured by old cypress ImmunoCAP. The value in Table 1 was converted to value in new cypress ImmunoCAP by correction factor (x1.891, calculated by Torii's in house data).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2021.11.008>

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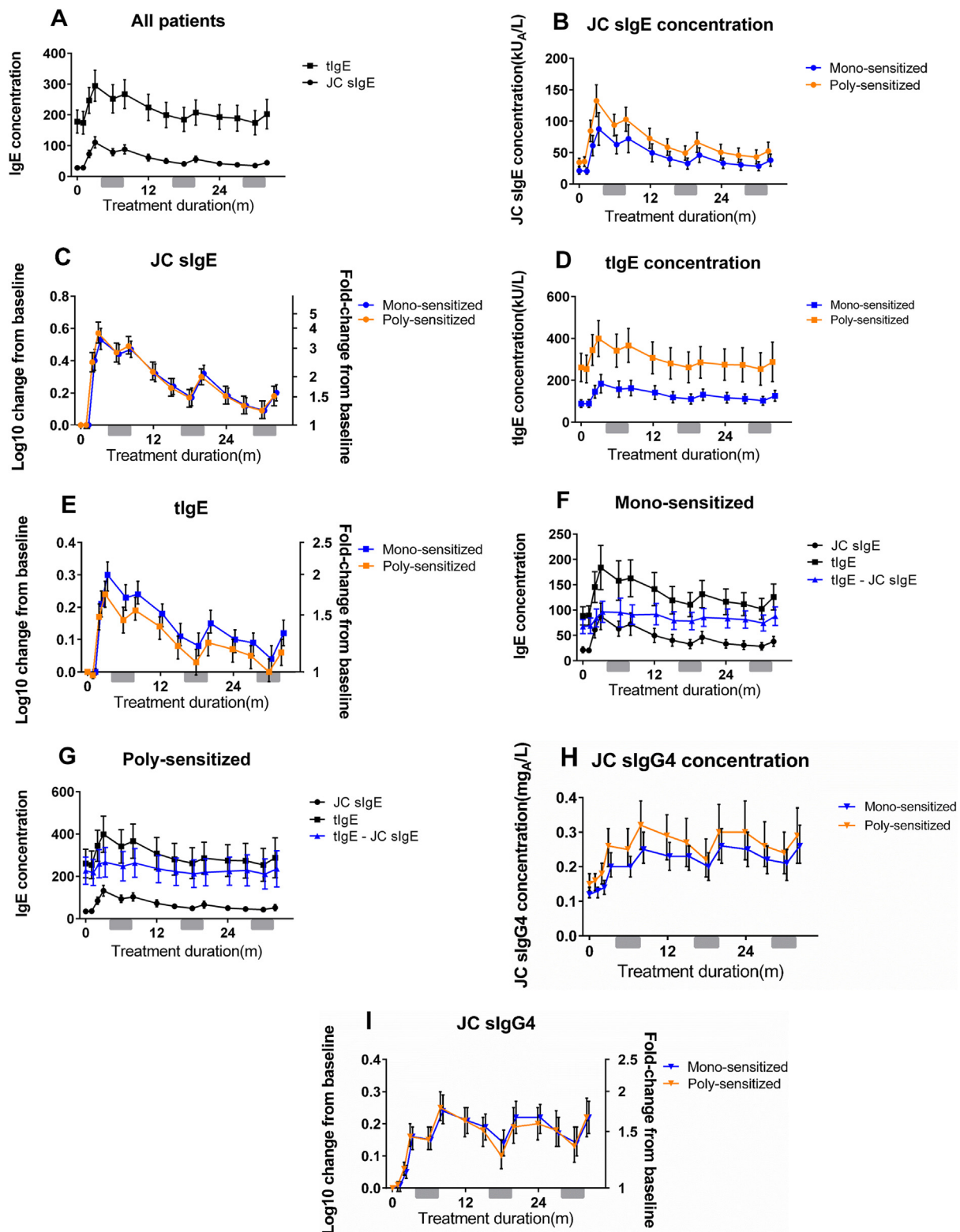


Fig. 1. A: JC sIgE and tIgE concentration in all patients. B: JC sIgE concentration in mono-sensitized patients and poly-sensitized patients. C: change from baseline level of JC sIgE in mono-sensitized patients and poly-sensitized patients. D: tIgE concentration in mono-sensitized patients and poly-sensitized patients. E: change from baseline level of tIgE in mono-sensitized patients and poly-sensitized patients. F: JC sIgE, tIgE and difference between tIgE and JC sIgE in mono-sensitized patients. G: JC sIgE, tIgE and difference between tIgE and JC sIgE in poly-sensitized patients. H: JC sIgG4 concentration in mono-sensitized patients and poly-sensitized patients. I: change from baseline level of JC sIgG4 in mono-sensitized patients and poly-sensitized patients. D, E, H: Mean and 95%CI were calculated using the log10 transformed data. Right y-axis indicated fold-change from baseline. F, G: Mean of (tIgE - JC sIgE) was calculated by averaged difference between tIgE and JC sIgE individual patients. Serum samples were collected at 0, 0.5, 1, 3, 6, 8, 12, 15, 18, 20, 24, 27, 30, and 33 months after SLIT. Number of patients in all patients was 188–233 at each points. Number of patients in mono-sensitized patients was 99–112 at each points. Number of patients in poly-sensitized patients was 89–121 at each points. Data was expressed as mean $\pm$ 95% confidence intervals. Black line: all patients, blue line: mono-sensitized patients, orange line: poly-sensitized patients, circle: JC sIgE, square: tIgE, upward triangle: tIgE minus JC sIgE, downward triangle: JC sIgG4, gray box on x-axis: Japanese cedar pollen season. JC sIgE; kU/L, tIgE; kU/L, sIgG4; mg/L, m, months; tIgE, total IgE; JC, Japanese cedar; sIgE, specific IgE.

Japanese cypress, poly-sensitized individuals were positive for IgE to one or more of the following allergens: House dust mite (*Dermaphagoides pteronyssinus* and *Dermatophagoides farinae*), cat, dog, orchard grass and Japanese alder. Examining the IgE responses in mono and poly-sensitized individuals separately is relevant due to the single-allergen species content of most SLIT products. In fact, IgE towards other allergens than JC contributes to the tIgE concentration and influences the sIgE/tIgE ratio which has been suggested to correlate with the outcome of AIT.^{5,7}

The typical expression pattern of sIgE during pollen AIT, particularly SLIT, is a transient increase in sIgE during the first weeks of treatment followed by subsequent increases through the successive pollen seasons.⁸ This pattern is also evident in the current trial. Although the baseline level of tIgE was higher compared to sIgE, similar fluctuations of sIgE and tIgE occurred during SLIT (Fig. 1A). When mono and poly-sensitized subjects were examined separately, the initial increase in sIgE seemed to be higher in the poly-sensitized group compared to the mono-sensitized group (Fig. 1B) but when measured relative to baseline, no difference between mono and poly-sensitized subjects could be detected (Fig. 1C).

Moreover, the tIgE expression patterns in the mono and poly-sensitized groups were similar (Fig. 1D). The higher baseline value of tIgE in the poly-sensitized group was expected as the presence of IgE to other allergens than JC contributed to the level of tIgE.

Compared to baseline, the relative change in tIgE during the course of treatment was lower in the poly-sensitized group compared to the mono-sensitized group, most likely as a result of the higher tIgE baseline, but the overall tIgE fluctuation pattern during the course of the trial was similar in the two groups (Fig. 1E).

The finding of similar overall expression patterns of tIgE in the mono- and poly-sensitized groups differing only with regard to baseline was interesting as it indicated that the only, or at least predominant, reason for the observed treatment-induced fluctuations in tIgE expression was changes in JC sIgE. This is illustrated in Figs. 1F and G where the concentrations of sIgE were subtracted from the concentrations of tIgE at each time-point resulting in flattening of the curves and marked reductions in season-induced fluctuations.

An often-used biomarker of AIT is the expression of sIgG₄ induced by SLIT.⁵ As seen in Figure 1H, the concentration of JC sIgG₄ increased during the first weeks after treatment initiation followed by transient increases during the successive pollen seasons, consistent with previous reports.⁸ Although the levels of JC sIgG₄ appeared higher in poly-sensitized compared to mono-sensitized subjects, there were no differences between the two groups. When changes in the JC sIgG₄ expression levels were compared to the baseline-levels to baseline, the fold-changes from baseline of sIgG₄ were nearly identical in the two groups (Fig. 1I), supporting similar immunological responses to AIT in mono and poly-sensitized individuals.

The sIgE/tIgE ratio at baseline has been proposed to correlate with the outcome of AIT in mono-sensitized subjects.^{7,9} However, no consensus about cut-off values for correlation exist (e.g. $\geq 6\%$ sIgE/tIgE⁹ and $\geq 16.2\%$ sIgE/tIgE⁷ have been proposed), and other trials failed to corroborate the predictive value of the sIgE/tIgE ratio.⁵ As demonstrated here, the poly-sensitized group of subjects showed increased baseline tIgE and a different sIgE/tIgE ratio compared to the mono-sensitized group (Table 1), but the clinical scores (expressed as the total nasal symptom and medication score, TNSMS) in the first season of the trial were similar in the full cohort (TNSMS = 5.47 ± 3.38)⁶ and the mono-sensitized (TNSMS = 5.66 ± 3.86) and poly-sensitized (TNSMS = 5.28 ± 2.84)

groups (mean $\pm$ SD). Similar clinical effects in mono- and poly-sensitized individuals have previously demonstrated in other SLIT trials.¹⁰ Taken together, additional data are needed to establish the relevance of the sIgE/tIgE ratio as a biomarker for successful AIT. A limitation of this study was that the design of the clinical trial did not support identification of individual responders and non-responders which prevented the demonstration of a correlation between the immunological biomarker response and clinical effect. To firmly establish tIgE and sIgE as surrogate biomarkers of clinical effect, larger clinical trials that include individual patient baseline data are needed.

The data presented here suggested that the changes in tIgE expression during JC SLIT were predominantly if not entirely driven by changes in JC sIgE, regardless of mono or poly-sensitization status. Furthermore, the observed changes in tIgE were similar to changes in sIgE over time as a result of treatment and followed a pattern typical for SLIT, indicating that the fluctuations of tIgE in the initial months of treatment could be useful as a biomarker of SLIT-treatment.

Acknowledgements

We thank Mrs. Y. Tanaka and M. Kudo for valuable technical work. We appreciate Dr. K. Lund for useful suggestions in this work. This work was funded by Torii Pharmaceutical Co., Ltd.

Conflict of interest

SK and KOD are employees of Torii Pharmaceutical. KO is advisor to Torii Pharmaceutical. KO has received honoraria and payment for writing or reviewing the manuscript from Torii Pharmaceutical. TM and KO have received research funding from Torii Pharmaceutical. KM has no conflict of interest.

Tomokazu Matsuoka^a, Satoko Kobayashi^b, Katsuyo Ohashi-Doi^{b,*}, Keisuke Masuyama^c, Kimihiko Okubo^d

^a Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medicine, Yamanashi University, Yamanashi, Japan

^b Torii Pharmaceutical Co., Ltd., Tokyo, Japan

^c Department of Otorhinolaryngology, Suwa Central Hospital, Nagano, Japan

^d Department of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

* Corresponding author. Torii Pharmaceutical Co., Ltd., 3-4-1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8439, Japan.

E-mail address: katsuyo.doi@torii.co.jp (K. Ohashi-Doi).

References

1. Matsubara A, Sakashita M, Gotoh M, Kawashima K, Matsuoka T, Kondo S, et al. [Epidemiological survey of allergic rhinitis in Japan 2019]. *J Otolaryngol Jpn* 2020;123:485–90 (in Japanese).
2. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717–25.
3. Blanco C, Bazire R, Argiz L, Hernández-Peña J. Sublingual allergen immunotherapy for respiratory allergy: a systematic review. *Drugs Context* 2018;7:212552.
4. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma. A randomized clinical trial. *JAMA* 2016;315:1715–25.
5. Shamji MH, Kappen JH, Akdis M, E. Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy* 2017;72:1156–73.
6. Nomura Y, Okubo K, Nakamura T, Sawaki S, Kitagou H, Idei N, et al. Long-term treatment of Japanese cedar pollinosis with Japanese cedar pollen SLIT drops and persistence of treatment effect: a postmarketing clinical trial. *Allergol Int* 2021;70:96–104.

7. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. *J Allergy Clin Immunol* 2009;**123**:1103–10.
8. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 2014;**133**:621–31.
9. Li Q, Li M, Yue W, Zhou J, Li R, Lin J, et al. Predictive factors for clinical response to allergy immunotherapy in children with asthma and rhinitis. *Int Arch Allergy Immunol* 2014;**164**:210–7.
10. Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized Subjects. *Allergy* 2013;**68**:252–5.

Received 24 February 2021

Received in revised form 8 November 2021

Accepted 10 November 2021

Available online xxx