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Letter to the Editor

Long-term course of serum total and free IgE levels in severe asthma patients treated with omalizumab

Dear Editor,

Omalizumab, a human immunoglobulin G1 antibody to immunoglobulin E (IgE), is an antibody drug indicated for the treatment of asthma. It can improve symptoms in patients with intractable atopic asthma and reduce the risk of exacerbation and is one of the few drugs that improve the quality of life of patients. As omalizumab improves airway inflammation and causes IgE level depression, there is a possibility that IgE production levels will be reduced after long-term omalizumab administration. The reduction in IgE production in such patients would be advantageous for the management of atopic asthma. However, not enough research has been conducted on the long-term effects of omalizumab administration on IgE production.

In general, serum total IgE levels are believed to reflect IgE production levels in the body. However, the traditional methods of measuring IgE levels, such as the ImmunoCAP method for measurement of total serum IgE (Thermo Fisher Scientific, Waltham, MA, USA), cannot distinguish between omalizumab-binding IgE and free IgE. Hence, these methods cannot evaluate IgE production levels in omalizumab-administered patients. On the other hand, it is conceivable that serum free IgE levels are associated with IgE production levels in omalizumab-administered patients.

Using a mathematical model, Lowe *et al.* simulated changes in total blood IgE after several years of continued treatment with omalizumab, based on data on total blood IgE from 10 clinical trials, and predicted that total blood IgE levels would gradually decline with the long-term use of omalizumab. They further predicted that this long-term decline in IgE level would be more marked as the duration of omalizumab treatment extended.¹ However, this was merely a prediction based on a mathematical model. At present, several methods are available for measuring free IgE after omalizumab administration.^{2,3}

No reports have actually directly measured changes in serum free IgE levels as an indicator of IgE production during long-term omalizumab treatment.

As we previously reported, the method that we established involves measuring IgE by Enzyme-Linked Immunosorbent Assay (ELISA) using antibodies refined from human FcεRI recombinant proteins.⁴ In our previous report, we showed the term course of serum free IgE levels at baseline and at 4 weeks in four cases.⁴ In the short term, two cases of them did not reach the target concentration of free IgE (below 25 ng/ml). Here we presented data from 8 patients in whom we measured fluctuations in total serum IgE and

free IgE levels over 24 months after omalizumab administration at the Nihon University Itabashi Hospital. In this report, three cases (case No. 1, 3, 4) in our previous report⁴ are included. Patient characteristics are shown in Table 1. All patients were evaluated for therapeutic effects on the 16th week of administration of omalizumab and were observed to have improved clinical symptoms. Thus, we determined an appropriate response to omalizumab and continued with the treatment. We obtained written consent from all patients to have the measurements taken, and these measurements were taken with the approval of the ethics committee of the institution (RK-120413-09).

The target value of serum free IgE levels during omalizumab treatment is reported to be <25 ng/ml.⁵ As shown in Figure 1A, the trough value of serum free IgE gradually decreased after administration of omalizumab, and at around 52 weeks, it reached the target value of <25 ng/ml in all patients. Figure 1B shows the changes over time in serum total IgE levels before and after administration of omalizumab. Total serum IgE temporarily increased after administration of omalizumab and generally tended to decrease overall. However, it did not decrease in some cases, and the trend was thus not as remarkable as that of free IgE.

Lowe *et al.* presented a mathematical model based on the data of total serum IgE levels reported in 10 clinical trials conducted to date to determine changes in serum IgE levels after several years of continuous omalizumab therapy.⁶ This model has predicted the possibility that total serum IgE levels gradually decrease with the

Table 1
Patient characteristics.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	44	63	60	59	37	70	50	57
Sex	F	F	M	M	M	M	F	M
Age of onset (years)	35	38	35	38	5	54	10	49
Smoking (1 packyear)	10.0	0.0	34.0	20.0	2.4	0.0	0.0	30.0
	Quit	Never	Quit	Current	Quit	Never	Never	Quit
Allergic rhinitis	+	–	+	+	+	+	–	–
BMI (Kg/cm ²)	27.9	19.2	22.2	32.0	24.9	21.9	32.8	24.3
FEV _{1.0} /FVC (%)	84.2	68.0	30.6	61.1	79.0	43.5	62.9	57.0
FEV _{1.0} (% predicted)	99.6	88.8	44.1	63.8	83.7	51.5	71.2	75.5
Total IgE (ng/ml)	1020.0	134.4	568.8	381.6	192.0	1795.2	1039.2	115.2
Free IgE (ng/ml)	616.0	113.0	583.0	326.0	154.0	1150.0	1110.0	75.0
Blood eosinophil (no.)	291.5	78.0	572.7	210.0	216.3	560.0	616.2	69.6
ACT	15	20	15	13	20	11	22	25

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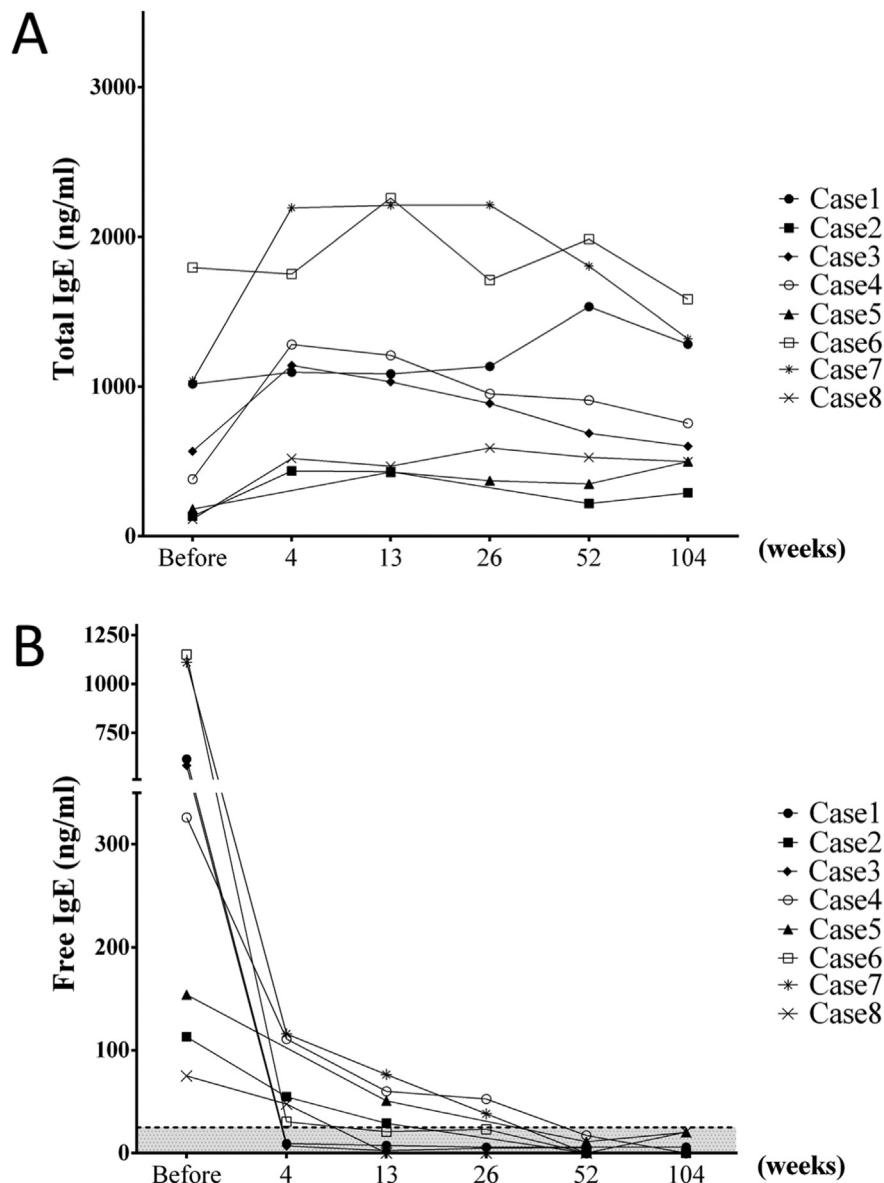


Fig. 1. Serum free IgE and total IgE variation over time: from before to after administration of omalizumab. **(A)** Variation in total IgE over time: from before to after administration of omalizumab. **(B)** Variation in serum free IgE over time: from before to after administration of omalizumab. The gray area indicates the concentration <25 ng/ml.

long-term use of omalizumab.⁶ However, as shown in Figure 1, it is difficult to estimate serum free IgE levels from serum total IgE levels during omalizumab therapy.

After omalizumab administration, the apparent total serum IgE levels increase as shown in Figure 1. This is because while the half-life of human serum IgE is 2.4 days, the binding of the IgG1 antibody omalizumab to IgE extends the half-life to 20 days.¹ Due to this reason, compared with total IgE levels, serum free IgE levels might be more directly associated with IgE production in omalizumab-administered patients. Our cases indicate that long-term administration of omalizumab reduces free IgE levels. This suggests that long-term administration of omalizumab may reduce IgE production in severe atopic asthma patients.

Although the mechanism of decrease in IgE production as a response to continued omalizumab therapy is unknown, several mechanisms can be proposed. First, IgE production is regulated by Th2 cytokines and CD40.⁷ Omalizumab therapy can decrease

the production of Th2 cytokines as a result of its treatment effects. The lowered expression of high-affinity IgE receptors expressed on dendritic cells may also be related to reduction in IgE synthesis.⁶ Furthermore, CD23/FcεRII is known to play a very important role in IgE homeostasis⁸; the decreased expression of one type of low-affinity IgE receptor, CD23/FcεRII, may also trigger reduction in IgE synthesis. Binding of omalizumab to IgE has been reported to inhibit binding between CD23/FcεRII and IgE.⁹

Lowered IgE production and improved atopy status may be one of the advantages of omalizumab treatment. For example, reduction in IgE levels might ameliorate airway responsiveness against allergens. In addition, although the high cost of omalizumab is one drawback of this therapy, lowered IgE production may enable a reduction in omalizumab dose.

In conclusion, our cases indicate that the measurement of serum free IgE could provide useful information regarding omalizumab therapy, including the current IgE production levels.

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Conflict of interest

YG and SH received lecture fees from AstraZeneca, Kyorin Pharmaceutical, Novartis Pharma, Nippon Boehringer Ingelheim. The rest of the authors have no conflict of interest.

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