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High serum free IL-18 is associated with decreased omalizumab efficacy: findings from a 2-year omalizumab treatment study

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ABSTRACT

Objective: Omalizumab is more effective in severe allergic patients with eosinophilic asthma than those with non-eosinophilic asthma. IL-18, a unique cytokine involved in allergic but non-eosinophilic inflammation, might be associated with the latter condition. We aimed to clarify the roles of IL-18 related pathways in insufficient response to omalizumab treatment.

Methods: Patients with severe allergic asthma who completed 2-year omalizumab treatments at Kyoto University Hospital were included in this study (UMIN000002389). Associations between pretreatment levels of serum free IL-18 in addition to other mediators and asthma phenotypes including responses to omalizumab treatment were analyzed. Changes in serum free IL-18, periostin and total IgE levels during the treatment were also examined.

Results: Twenty-seven patients (19 females, average age of 55.7 years) were examined. Fifteen incomplete responders who experienced exacerbations in the second year, were significantly and more frequently obese and showed significantly earlier asthma onset, lower blood eosinophils and more exacerbations before omalizumab treatment than complete responders. Significantly more patients showed high baseline serum free IL-18 levels (≥ 141 pg/mL, a threshold for the highest tertile) among the incomplete responders than complete responders. Patients with high serum free IL-18 levels shared similar characteristics with incomplete responders, showing significant reductions in serum total IgE levels during omalizumab treatment. Finally, serum free IL-18 levels negatively correlated with serum periostin levels at baseline and in change ratios.

Conclusions: High baseline serum free IL-18 levels may predict reduced omalizumab efficacy in severe allergic patients with type-2 low asthma, regarding reduction of exacerbations.

Abbreviations: ANOVA: analysis of variance; IL-18 BP: IL-18 binding protein; YKL-40: chitinase 3-like 1

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Introduction

Omalizumab, a humanized anti-IgE monoclonal antibody, is effective in most patients with severe allergic asthma (1–3). Higher efficacy, represented by greater inhibition of exacerbations during a 48-week treatment period, is predicted in allergic asthma patients with high levels of fractional exhaled nitric oxide (FeNO), blood eosinophils and serum periostin, than in those with low levels of these markers (4). Meanwhile, successful discontinuation of omalizumab

after long-term treatment is associated with lower blood eosinophil count at discontinuation (5), indicating that patients with allergic but non-eosinophilic asthma may benefit from long-term omalizumab use to prevent worsened asthma control upon discontinuation. We previously reported that patients with incomplete response to omalizumab, defined by the presence of exacerbations during the first year of treatment, were characterized by early asthma onset and lower baseline levels of serum periostin and blood eosinophil counts,

despite being similarly atopic when compared with remaining complete responders (6). Nonetheless, incomplete responders showed significant reductions in serum free IgE levels to the same degree as complete responders and in number of exacerbations during the first 2 years of treatment. These findings support the suggestion that incomplete responders benefit to some extent from long-term use of omalizumab. These findings also suggest that insufficient responses may be associated with non-eosinophilic inflammatory pathobiology of severe asthma including the influence of interferon- γ (IFN- γ) (7,8), tumor necrosis factor- α (TNF- α) (9), interleukin (IL)-17 (10) and oxidative stress (11). However, insufficient omalizumab efficacy has not yet been explained through any specific inflammatory markers, instead being ascribed to comorbidities such as obesity and chronic rhinosinusitis (12,13).

IL-18 is another cytokine that may be involved in the pathobiology of severe asthma. Elevations in levels of serum IL-18 and related genetic polymorphisms are associated with asthma severity and poor control (14,15). IL-18 is considered a unique cytokine. It was originally discovered as an IFN- γ inducing factor (16), plays an important role in Th1 polarization (17) and may provide protection against viral and bacterial infection (18). Despite this role in Th1 polarization, IL-18 can also be involved in allergic inflammation (19,20) without inducing eosinophilic inflammation (21), suggesting that high IL-18 levels may reflect severe allergic asthma coupled with non-eosinophilic inflammation.

In this study, we aimed to determine if IL-18 related pathways associated with already known predictors of response to omalizumab treatment. Because IL-18 has two roles, one in Th1 polarization and another allergic inflammation, multiple other cytokines and chemokines in addition to serum levels of free IL-18 were measured prior to omalizumab treatment. Furthermore, to assess the potential of omalizumab as a disease modifier, changes in serum total IgE levels over the course of 2-year treatment with omalizumab were also examined.

Methods

Subjects

This study included adult patients with severe refractory asthma who were recruited from July 2009 to August 2011 and had completed 2 years of omalizumab treatment at Kyoto University Hospital. All the patients demonstrated positive results for at least one serum-specific IgE or intradermal test for common aeroallergens. Most patients were subjects of our previous

studies (3,6,22). The patients' characteristics were shown in the previous report in detail (3). Asthma diagnosis was based on the American Thoracic Society criteria (23). The study protocol (UMIN000002389) was approved by the Ethics Committee of Kyoto University and written informed consent was obtained from all participants.

Measurements

Omalizumab was subcutaneously administered to patients every 2–4 weeks according to Japanese prescribing information. Omalizumab efficacy was evaluated by incidence of asthma exacerbations requiring additional administration of systemic corticosteroids for at least 3 days. The number of asthma exacerbations was recorded in the year before omalizumab initiation and in the first and second year of treatment.

As described previously, blood granulocyte counts were determined at a baseline period of 4 weeks before the first administration of omalizumab. Serum free (24) and total IgE levels were determined at baseline, 16 weeks, 32 weeks and 2 years of treatment (6). Serum levels of periostin, IL-18 and IL-18 binding protein (BP) were also determined at baseline and 2 years of treatment. Serum levels of periostin were measured at Shino-test Corporation (Kanagawa, Japan) using enzyme-linked immunosorbent assays (ELISA). IL-18 and IL-18BP were measured using enzyme-linked immunosorbent assay kits from MBL (Nagoya, Japan) and R&D Systems (Minneapolis, MN, USA), respectively. Serum free IL-18 levels were calculated according to the law of mass action. The calculation was based on serum IL-18 and IL-18BP levels and used a dissociation constant of 0.4 nM, as the activity of IL-18 is considered to be affected by IL-18BP, of which affinity for IL-18 is higher than IL-18 receptor (25).

Serum levels of several relevant cytokines and chemokines were also measured at baseline using a BioPlex Pro Human Cytokine Panel, 27-Plex (BioRad Laboratories, Hercules, CA, USA) and LUMINEX 200 (Luminex Austin, TX, USA). Baseline levels of IL-1 β , IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17A, IL-17F, IL-18, IL-19, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100, IL-101, IL-102, IL-103, IL-104, IL-105, IL-106, IL-107, IL-108, IL-109, IL-110, IL-111, IL-112, IL-113, IL-114, IL-115, IL-116, IL-117, IL-118, IL-119, IL-120, IL-121, IL-122, IL-123, IL-124, IL-125, IL-126, IL-127, IL-128, IL-129, IL-130, IL-131, IL-132, IL-133, IL-134, IL-135, IL-136, IL-137, IL-138, 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a chemiluminescence analyzer (NOA 280; Sievers, Boulder, CO, USA) according to current ATS guidelines (26).

Statistical analyses

Statistical analyses were performed using JMP system version 12 (SAS Institute Japan, Tokyo, Japan). Wilcoxon rank sum test and Fisher's exact test were used to compare clinical indices between the two groups: patients who had exacerbations in the second year of treatment (incomplete responders) and the remaining patients (complete responders). Relationships between variables were assessed using Spearman's correlation coefficients.

The Wilcoxon signed rank test, adjusted for multiple comparisons using Bonferroni correction, was performed to compare the number of exacerbations and serum free IL-18 levels during the omalizumab treatment period. Changes in total IgE levels were examined via one-way repeated measures analysis of variance (ANOVA) tests, after log-transformation of total IgE levels to achieve normal distribution. Two-way repeated measures ANOVAs were performed to assess variations between stratified groups and at different time points. p values < 0.05 were considered statistically significant if not otherwise stated. All values are presented as mean $\pm$ standard error (SE).

Results

Association between serum free IL-18 and omalizumab efficacy

In total, 27 patients completed 2 years of treatment with omalizumab, 15 of whom experienced exacerbations in the second year of treatment (incomplete responders), while 12 experienced no exacerbations (complete responders) (Figure 1). Baseline characteristics for both groups are shown in Table 1. Serum free IL-18 levels tended to be higher in incomplete responders than in complete responders (Table 1).

To delineate characteristics of patients with high serum free IL-18 levels, patients were divided into two groups according to baseline serum free IL-18 levels, with a cutoff of 141 pg/mL, the threshold of the highest tertile of all subjects. Patients with serum free IL-18 of ≥ 141 pg/mL were assigned to the 'high IL-18' group and the remaining patients to the 'low IL-18' group (Table 2). As expected, the high IL-18 group was characterized by younger average age at asthma onset, lower blood eosinophil counts, lower serum periostin

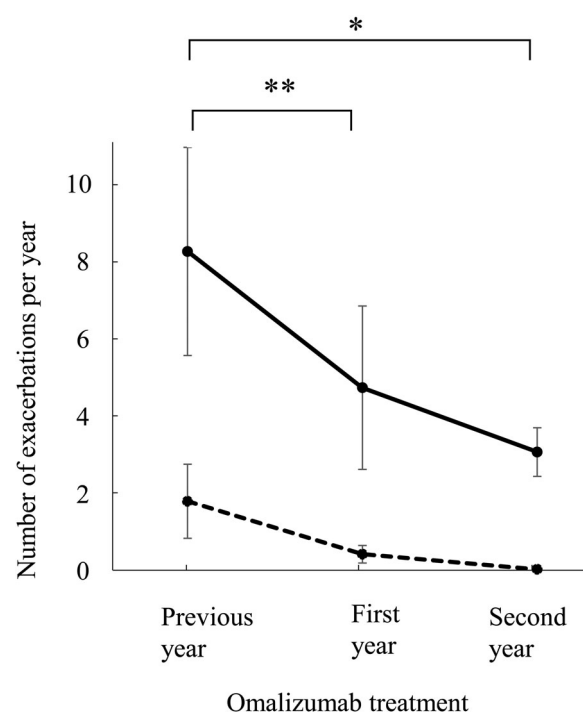


Figure 1. Number of asthma exacerbations per year. Solid line; patients with asthma exacerbations in the second year of omalizumab treatment (incomplete responders, $n = 15$). Dotted line; patients with no asthma exacerbations in the same period (complete responders, $n = 12$). Dots and bars indicate means and SEs, respectively. * $p = 0.01$ and ** $p = 0.003$ for incomplete responders.

and higher body mass index (BMI), demonstrating similar phenotypes to incomplete responders (Figure 2). In addition, baseline serum free IL-18 levels correlated positively with BMI ($\rho = 0.45$, $p = 0.02$) (Figure 3A) and negatively with baseline serum periostin ($\rho = -0.55$, $p = 0.003$) (Figure 3B). This negative correlation between serum free IL-18 and periostin levels remained even when analysis was confined to patients with BMI < 30 kg/m² ($\rho = -0.60$, $p = 0.007$) or < 25 kg/m² ($\rho = -0.63$, $p = 0.009$). Results from analysis of serum total IL-18 levels were similar to those of serum free IL-18 levels (data not shown).

Multiplex assay of cytokines and chemokines revealed that baseline serum levels of CCL4 and IL-17A were higher in incomplete responders than complete responders (Table 1). However, p values did not exceed the threshold for multiple comparisons. Furthermore, patients in the highest tertile for CCL4 or IL-17A shared no clinical features with incomplete responders, aside from an association between high serum IL-17A and younger age at asthma onset (data not shown). Serum levels of CCL4 and IL-17A correlated positively with one another ($\rho = 0.44$, $p = 0.02$) (Figure 4).

Table 1. Baseline characteristics according to responsiveness to omalizumab treatment.

	All patients (N = 27)	Complete responders (N = 12)	Incomplete responders (N = 15)	p value
Sex, male/female	8/19	4/8	4/11	0.71
Age, years	55.7 ± 16.5	63.3 ± 14.4	49.7 ± 16.0	0.04
Age at asthma onset, years	40.6 ± 17.9	50.9 ± 15.6	32.4 ± 15.5	0.006
BMI, kg/m ²	25.2 ± 5.9	22.8 ± 3.6	27.1 ± 6.7	0.06
BMI ≥ 30 / BMI < 30, kg/m ²	8/19	1/11	7/8	0.04
Number of exacerbations in the previous year	5.5 ± 8.8	1.8 ± 3.4	8.4 ± 10.6	0.002
Number of exacerbations in the first year	2.9 ± 6.5	0.42 ± 0.8	4.8 ± 8.4	0.007
Inhaled corticosteroid dose, µg/day ^a	1593 ± 658	1373 ± 319	1769 ± 805	0.19
Oral corticosteroid dose, mg/day ^b	3.3 ± 5.6	0.98 ± 1.8	5.2 ± 6.9	0.03
FEV ₁ (%predicted)	93.9 ± 25.0	102.2 ± 19.6	87.4 ± 27.5	0.31
Exhaled nitric oxide, ppb	44.9 ± 45.6	51.1 ± 55.9	39.6 ± 35.9	>0.99
Blood eosinophils, cells/µL	308 ± 393	426 ± 430	214 ± 347	0.03
Blood neutrophils, cells/µL	4260 ± 1954	4046 ± 1577	4433 ± 2251	0.98
Serum periostin, ng/mL	69.5 ± 26.7	71.4 ± 19.4	67.9 ± 31.9	0.27
Serum total IgE, IU/mL	159 ± 157	171 ± 163	150 ± 156	0.53
Serum free IgE, ng/mL	374 ± 485	300 ± 245	432 ± 618	0.73
Numbers of sensitisations	2.2 ± 1.7	1.8 ± 1.3	2.6 ± 1.9	0.21
Serum free IL-18, pg/mL	132.5 ± 64.5	109.4 ± 37.7	151.0 ± 76.2	0.09
Number of patients in high free IL-18 group ^c	9	1	8	0.02
Serum CCL4, pg/mL	47.4 ± 26.2	65.9 ± 29.3	97.2 ± 36.0	0.02*
Serum IL-17A, pg/mL	112.3 ± 41.1	94.2 ± 29.4	126.8 ± 44.2	0.02*

Incomplete or complete responders: patients with or without asthma exacerbations in the second year of omalizumab treatment, respectively. Data are presented as mean ± SD.

BMI, body mass index.

^aEquivalent to fluticasone propionate.

^bEquivalent to prednisolone, average of all patients; three complete responders and ten incomplete responders used oral corticosteroids daily.

^cPatients with serum free IL-18 ≥ 141 pg/mL (the highest tertile of free IL-18 levels).

*Unadjusted p values.

Table 2. Baseline characteristics according to serum free IL-18 levels.

	Serum free IL-18		p value
	Low group (N = 18)	High group (N = 9)	
Sex, male/female	6/12	2/7	0.68
Age, years	60.9 ± 13.8	45.4 ± 17.4	0.04
Age at asthma onset, years	46.2 ± 16.0	29.6 ± 17.0	0.03
BMI, kg/m ²	23.3 ± 4.3	29.0 ± 7.0	0.04
BMI ≥ 30 / BMI < 30, kg/m ²	3/15	5/4	0.07
Number of exacerbations in the previous year	3.4 ± 5.0	9.7 ± 12.9	0.04
Number of exacerbations in the first year	1.0 ± 1.8	6.6 ± 10.4	0.009
Number of exacerbations in the second year	1.2 ± 2.0	2.7 ± 3.0	0.07
Inhaled corticosteroid dose, µg/day ^a	1431 ± 148	1918 ± 209	0.42
Oral corticosteroid dose, mg/day ^b	2.0 ± 3.7	5.9 ± 7.8	0.09
FEV ₁ (%predicted)	94.5 ± 26.1	92.8 ± 24.4	>0.99
Exhaled nitric oxide, ppb	54.1 ± 52.0	24.3 ± 12.5	0.08
Blood neutrophils, cells/µL	3774 ± 1470	5235 ± 2493	0.17
Serum total IgE, IU/mL	167 ± 159	144 ± 159	0.50
Serum free IgE, ng/mL	322 ± 338	478 ± 711	0.80
Numbers of sensitisations	2.1 ± 1.6	2.6 ± 1.9	0.40
Serum free IL-18, pg/mL	98.9 ± 25.4	199.8 ± 67.4	<0.0001
Serum CCL4, pg/mL	73.7 ± 33.9	102.5 ± 34.5	0.06
Serum IL-17A, pg/mL	107.5 ± 40.4	122.1 ± 43.2	0.34

Values are presented as mean ± SD.

BMI, body mass index.

^aEquivalent to fluticasone propionate. High or low free IL-18 groups: Patients whose free IL-18 levels were ≥141 pg/mL (the highest tertile of free IL-18 levels) or <141 pg/mL.

^bEquivalent to prednisolone, average of all patients; seven patients in the low group and six patients in the high group used oral corticosteroids daily.

Changes in serum free IL-18 levels and negative relationship with changes in serum periostin

Among the 27 patients, serum free IL-18 levels were determined after 2 years of omalizumab treatment in 21 patients. Serum free IL-18 levels were significantly elevated compared with baseline levels (120.4 ± 8.8 pg/mL vs. 147.1 ± 6.7 pg/mL, $p = 0.003$). Serum free IL-18 levels

were significantly increased in the low IL-18 group ($n = 15$), however no significant change was observed in the high IL-18 group ($n = 6$) (Figure 5A). No significant changes were observed in serum periostin levels or BMI during treatment period, however changes in serum free IL-18 levels correlated negatively with changes in serum periostin levels ($\rho = -0.51$, $p = 0.02$) (Figure 5B).

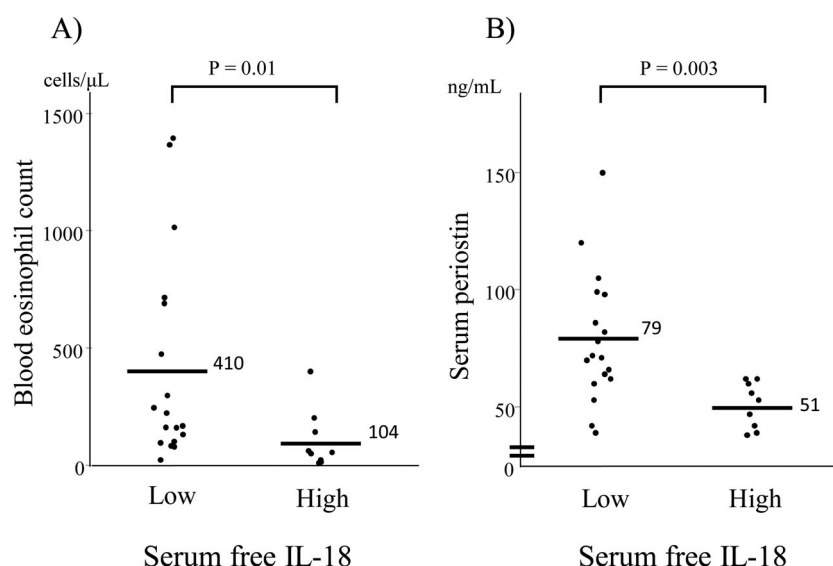


Figure 2. Comparisons of characteristics between high and low IL-18 groups; (A) blood eosinophils, (B) serum periostin. The high IL-18 group ($n=9$) included patients with serum free IL-18 levels in the highest tertile; the low IL-18 group ($n=18$) included all other patients. Numbers indicate mean values.

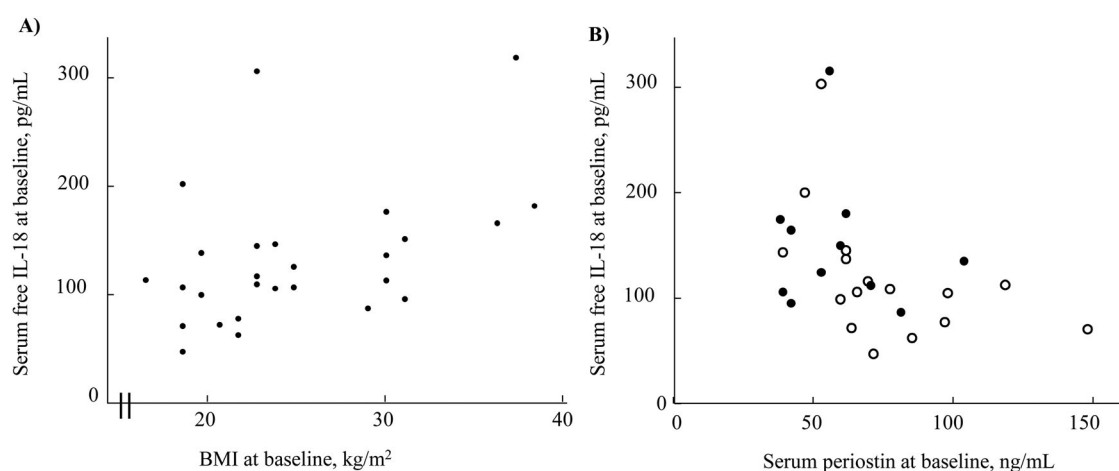


Figure 3. Associations between baseline serum free IL-18 and (A) BMI ($\rho = 0.45$, $p = 0.02$) and (B) baseline serum periostin (all patients, $\rho = -0.55$, $p = 0.003$; patients with BMI < 25 kg/m², $\rho = -0.63$, $p = 0.009$). Open circles; patients with BMI < 25 kg/m², closed circles; patients with BMI ≥ 25 kg/m². BMI, body mass index.

Changes in serum total IgE levels over 2-year omalizumab treatment period

Serum total IgE levels were determined in 22 patients throughout the 2-year treatment period. Following an initial increase at 16 weeks, possibly due to a prolonged half-life of the IgE-omalizumab complex, serum total IgE levels decreased over 2 years (Figure 6A). Similar reductions were also observed when analysis was confined to incomplete responders ($p = 0.003$), early-onset patients (< 40 years old) ($p = 0.002$), patients with low blood eosinophil counts (< 300 cells/ μ L) ($p < 0.0001$) (Figure 6B) and the high ($p = 0.003$) and low IL-18 groups ($p = 0.03$) (Figure 6C). Significant differences were observed in changes

between patients with high and low blood eosinophil counts ($p = 0.007$), and changes between the high and low IL-18 groups ($p = 0.006$).

Discussion

To the best of our knowledge, this is the first study demonstrating an association between high serum free IL-18 levels and asthma exacerbation despite omalizumab treatment. Patients with high serum free IL-18 levels shared characteristics with incomplete responders; i.e. early asthma onset, high BMI and an allergic but non-eosinophilic endophenotype. Despite the definition of incomplete responders, these patients

showed significant reductions in total IgE levels over the course of 2 years of treatment with omalizumab, as did patients with high serum free IL-18. Finally, in patients with severe allergic asthma, serum free IL-18 levels were observed to be negatively correlated with serum periostin levels.

In this study, we identified high serum free IL-18 as a marker of incomplete responders, partially responding to omalizumab treatment but experiencing exacerbations in the second year of treatment. Incomplete responders or patients with high serum free IL-18 more frequently demonstrated asthma exacerbations before omalizumab treatment than their counterparts. These findings are consistent with previous findings of high serum IL-18 in patients with uncontrolled asthma (14,15) and asthma exacerbation

(27) and elevated IL-18 expression levels in lung tissue of patients with fatal asthma (28). Alongside the target cytokine (serum free IL-18), serum CCL4 and IL-17A levels were also higher at baseline in incomplete responders than in complete responders. However, patients in the highest CCL4 or IL-17A level tertiles shared no clinical features with incomplete responders, aside from an association between high serum IL-17A and younger age at asthma onset.

IL-18 was discovered as an IFN- γ inducing factor (16) and plays an important role in Th1 inflammation (17). IL-18 likely directly affects Th1 cells due to the expression of high levels of IL-18 receptors; conversely, it is less likely to affect Th2 cells, which express fewer IL-18 receptors (29,30). Nonetheless, IL-18 exerts an effect on basophils and induces IgE production in the presence of IL-4 (20). Mouse models of allergic asthma have demonstrated that IL-18 administration increases IgE production in an IL-4 dependent fashion (20). Elevation of serum IgE levels induced by IL-18 administration in mouse models is consistent with a positive correlation between serum IL-18 and IgE levels in patients with allergic diseases including asthma (31–34). Unlike increases in serum total IgE levels, the degree of eosinophilic inflammation induced by IL-18 administration varies according to timing (21). In ragweed sensitized mice, IL-18 administration alongside allergen exposure decreases eosinophil numbers in bronchoalveolar lavage by 89% compared with those exposed to allergen alone, with no effect on serum IgE levels. Thus, serum free IL-18 levels may be elevated in allergic conditions with no accompanying eosinophilia.

Obesity, a well-known risk factor for severe asthma, was among the characteristics of incomplete responders

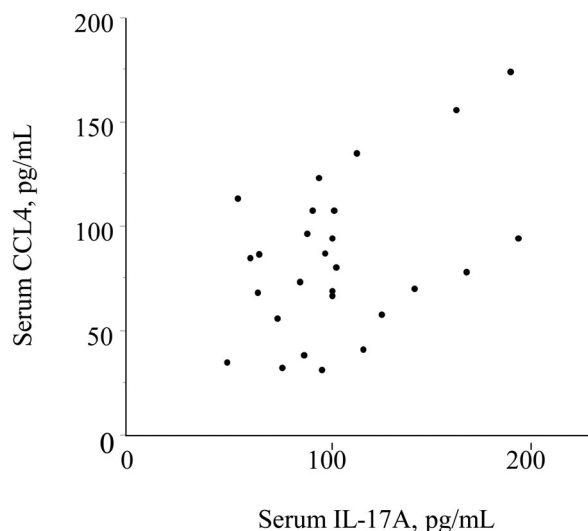


Figure 4. Association between baseline serum CCL4 and IL-17A levels ($\rho = 0.44$, $p = 0.02$).

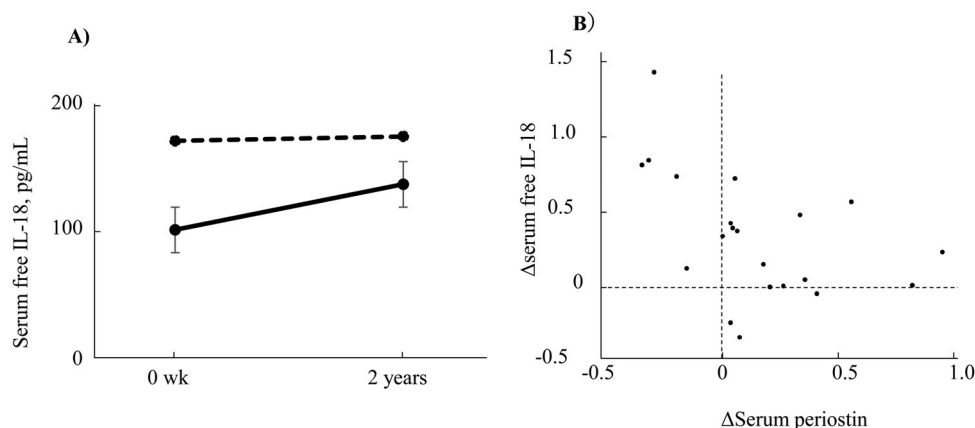


Figure 5. (A) Changes in serum free IL-18 levels during the 2-year omalizumab treatment period. Solid line represents low IL-18 group ($n = 15$, $p < 0.0001$); dotted line represents high IL-18 group ($n = 6$, $p = 0.9$). Dots and bars indicate means and SEs, respectively. (B) Association between changes in serum free IL-18 levels and serum periostin levels ($\rho = -0.51$, $p = 0.02$). Δ = (value after 2 years of treatment – baseline value)/baseline value.

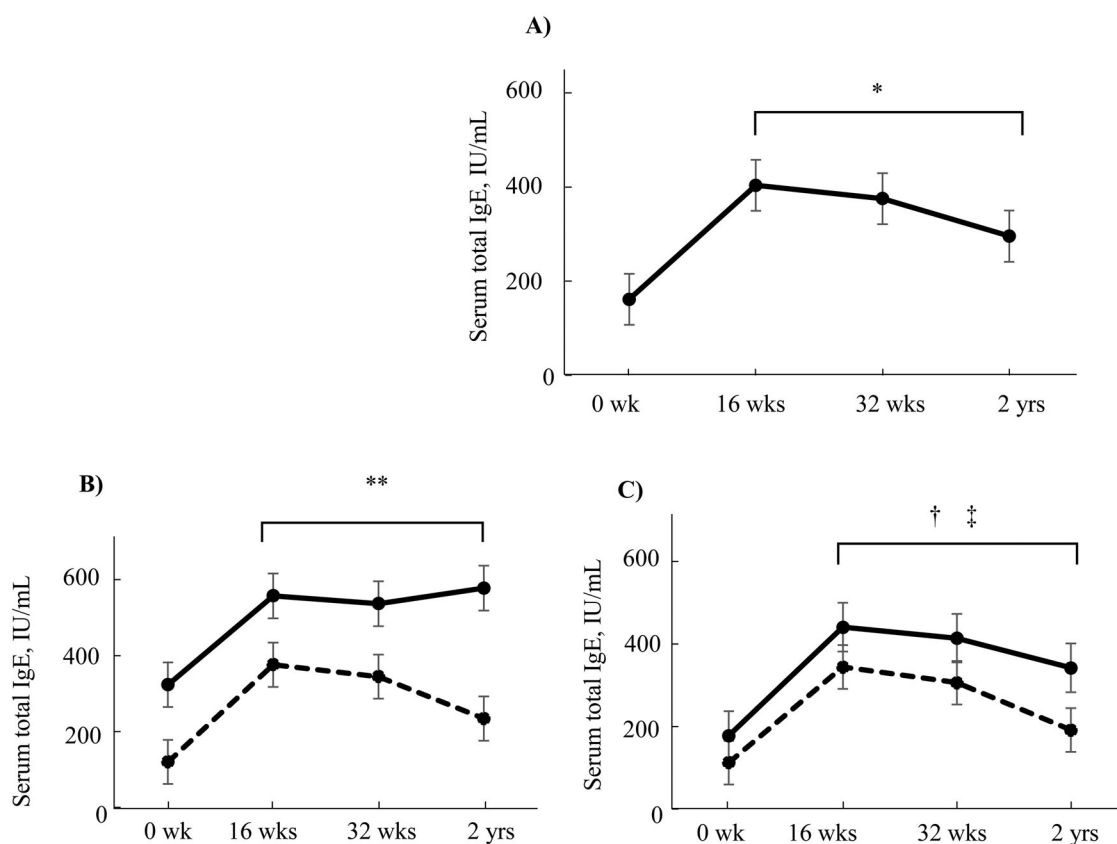


Figure 6. Changes in serum total IgE levels during the 2-year omalizumab treatment period; (A) in unstratified patients ($n=22$, $*p=0.0005$), (B) in patients with high and low blood eosinophil counts (solid line, ≥ 300 cells/ μL , $n=4$; dotted line, <300 cells/ μL , $n=18$, $**p<0.0001$ for low blood eosinophil group), and (C) in the high and low IL-18 groups (dotted line, the high IL-18 group, $n=6$, $\dagger p=0.003$; solid line, the low IL-18 group, $n=16$, $\ddagger p=0.03$). Dots and bars indicate means and SEs, respectively.

in this study. This is consistent with findings that insufficient response to omalizumab is often observed in patients with comorbidities, including obesity, chronic rhinosinusitis, nasal polyps and gastroesophageal reflux disease (12,13). Previous studies have reported that serum IL-18 levels are elevated in obese patients (35,36), possibly in an inflammasome-dependent manner (37), and a positive correlation was observed in our study between serum free IL-18 levels and BMI. Moreover, negative correlations were observed between levels of serum free IL-18 and periostin, one of the representative type 2 inflammatory markers (38), both at baseline and in ratios of change. Considering that serum periostin levels correlate negatively with BMI (39–42), obesity may be a confounding factor of this relationship between free IL-18 and periostin. However, this relationship was observed even when analysis was confined to leaner patients. No such relationship was observed between serum periostin and serum YKL-40, another marker of obesity in literature (43), which was also measured in this study ($\rho = 0.43$, $p = 0.03$ for YKL-40 and BMI; $\rho = -0.14$, $p = 0.5$ for YKL-40 and

periostin). Thus, serum free IL-18 may reflect non-type 2 inflammation, which is not limited to obesity.

Omalizumab reduces Fc ϵ receptor I expression and antigen presentation by plasmacytoid dendritic cells (44,45). Theoretically, this induces reduced IgE production after long-term omalizumab treatment; mathematical models also predict this reduction of IgE production after long-term treatment (46,47). Consistent with these predictions, in our study, serum total IgE levels declined over the 2-year omalizumab treatment period. Notably, the decline in serum total IgE levels was evident in patients with low blood eosinophil counts (<300 cells/ μL), but not in those with high blood eosinophil counts. This is in keeping with the association reported between successful discontinuation after long-term omalizumab treatment and lower blood eosinophil counts upon discontinuation (5). Patients with low blood eosinophil counts or high serum free IL-18 levels may thus benefit from omalizumab treatment in terms of reductions in IgE levels.

There were a few limitations to this study. Firstly, the sample size was small, particularly for stratification according to blood eosinophil count or clinical

indices. However, longitudinal evaluation may compensate for these weaknesses. Secondly, this study enrolled patients with severe allergic asthma who completed a 2-year period of omalizumab treatment. Therefore, the negative correlation observed between serum free IL-18 and periostin should be examined in subjects not-limited to severe allergic asthma in order to generalize this association. Lastly, sputum IL-18 levels and triggers of exacerbations were not analyzed in this study. Recent studies have highlighted a protective role for IL-18 against viral and bacterial airway infection (48,49), demonstrating that IL-18 levels in sputum and bronchial fluid are decreased in severe asthma (50). Therefore, our present findings of serum IL-18 may not be suitable for extrapolation to local IL-18 levels. Nonetheless, the effects of systemic inflammation on pathobiology of severe asthma are non-negligible (50,51), and thus the present findings are worth reporting.

Conclusions

High serum free IL-18 levels prior to treatment may predict limited omalizumab efficacy in terms of reduction of exacerbations but may predict reduction of serum total IgE levels following long-term treatment. The present study suggests that high serum free IL-18 may be involved in discrepancies between allergic but non-eosinophilic or low-periostin conditions. Mechanisms underlying the negative correlation between serum free IL-18 and periostin in severe allergic asthma patients should be further clarified.

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Disclosure statement

H. M. reports receipt of lecture fees from Novartis, AstraZeneca, GlaxoSmithKline, Astellas Pharma, Boehringer Ingelheim, KYORIN Pharmaceutical Co., outside the submitted work. Y.G. reports receipt of honoraria from Novartis, AstraZeneca, GlaxoSmithKline, Astellas Pharma, Boehringer Ingelheim, outside the submitted work. K. I. reports grants from Japan Science and Technology Agency (JST), grants from the Japan Society for the promotion of Science, during the conduct of the study, grants from Shino-Test Corporation, advisor fees from Chugai Pharmaceutical Co. Ltd, advisor fees

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Notes on contributors

C. M. involved in performance of free IL-18 level measurements; analyses and interpretation of data; drafting the manuscript. H. M. contributed to conception of the study; involved in patient recruitment, diagnosis and management; performed data acquisition and interpretation; and wrote and revised the manuscript. T. T. involved in patient management; performed data acquisition and blood tests. Y. G., R. I. and S. H. involved in the performance of free serum IgE level measurements. K. I., J. O. and S. O. involved in the performance of serum periostin level measurements. M. S. and K. O. involved in the performance of blood tests. I. I. and T. O. involved in patient diagnosis and management. T. N. and Y. I. involved in the performance of data acquisition. A. N. contributed to conception of the study and involved in patient recruitment, patient diagnosis and management. T. H. supervised the study.

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