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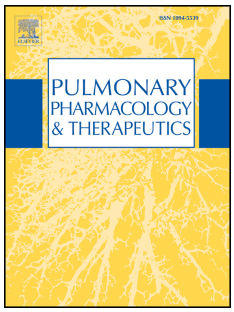

Real-life safety and efficacy of omalizumab in Japanese patients with severe allergic asthma who were subjected to dosing table revision or expansion: A post-marketing surveillance

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Credit Author Statement

All authors contributed to the conception and design of the study and were involved in the development and final approval of the manuscript.

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Writing - review & editing, Visualization, Supervision.

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Abstract

Background

Omalizumab is an anti-immunoglobulin E monoclonal antibody approved for patients with severe allergic asthma in Japan. With regard to omalizumab dosage in Japanese adults with severe allergic asthma in clinical practice settings, this post-marketing surveillance evaluated safety and efficacy of the dosing table revision (DTR) based on a dosing regimen of omalizumab administration every 4 weeks dosing regimen and dose table expansion (DTE) for patients with baseline IgE levels >700 IU/mL.

Methods

This 52-week, multicenter study, conducted from September 2013 to November 2018, evaluated omalizumab safety outcomes including adverse events (AEs), serious AEs (SAEs), adverse drug reactions (ADRs), efficacy outcomes including Global Evaluation of Treatment Effectiveness (GETE), change in oral corticosteroid dose, and asthma exacerbation-related events such as hospitalization, emergency room visits, and worsening of symptoms.

Results

Of the 405 patients registered in the study, safety was evaluated in 392 and efficacy in 390. The mean age of patients was 58.5 years and 58.7% were women. In total, 41.3% of the patients were subjected to DTE and 58.7% to DTR. In the safety dataset, 6.6% experienced an ADR, 32.9% experienced an AE, and 16.1% experienced an SAE. In the efficacy dataset, 63.3% of patients at Week 16 and 63.5% at Week 52 had an ‘effective’ or ‘good’ GETE score. Omalizumab was associated with a reduction in worsening of asthma symptoms requiring systemic corticosteroids and frequency of hospitalization. All outcomes were comparable among the DTE and DTR subgroups.

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Conclusion

The findings from this study support the safety and efficacy of omalizumab administered based on the revised and expanded dosing table in Japanese patients with severe allergic asthma.

Keywords

Omalizumab; post-marketing surveillance; effectiveness; safety; severe allergic asthma; adverse drug reaction

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Abbreviations

ADR, adverse drug reaction; AE, adverse event; CRF, case report form; DTE, dosing table expansion; DTR, dosing table revision; ER, emergency room; FEV_1, forced expiratory volume in 1 second; GETE, Global Evaluation of Treatment Effectiveness; GINA, Global Initiative for Asthma; GPSP, good post-marketing study practice; ICS, inhaled corticosteroid(s); IgE, immunoglobulin E; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid(s), PMDA, Pharmaceutical and Medical Devices Agency; PMS, post-marketing surveillance; PT, Preferred Term; RCT, randomized controlled trial; SABA, short-acting β_2 agonist; SAE, serious adverse event; SD, standard deviation; SOC, System Organ Class

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1. Introduction

Asthma is a chronic respiratory disease that is associated with a significant burden on patients [1]. A survey conducted in 2014 by the Japanese Ministry of Health, Labor, and Welfare reported that 1,177,000 patients visited hospitals due to asthma [2]. In addition to the disease burden, asthma has a significant economic impact in terms of healthcare resource utilization, with a recent study based on data from the Japan Medical Data Center reporting annual medical costs of US$4345 per patient with severe asthma [3].

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that was approved in Japan in 2009 as an add-on therapy in adults with severe allergic asthma and documented IgE sensitization to one or more perennial allergens [4, 5]. In 2013, the approval was extended to include pediatric patients aged ≥6 years [6, 7]. The efficacy and safety of omalizumab have been established through numerous global and Japanese randomized controlled trials (RCTs) and real-world studies that support its use as a treatment option in patients uncontrolled on standard-of-care therapy with inhaled corticosteroids (ICS) and long-acting β_2 agonists (LABAs) [6-10].

Omalizumab is administered to patients subcutaneously every 2 or 4 weeks with the dose adjusted based on the body weight of patients and the total serum IgE levels at baseline. A dosing table was developed to guide administration of omalizumab in patients to achieve neutralization of free serum IgE levels to <25 ng/mL in peripheral blood [11]. The dosing approved in 2009 was applicable to patients weighing >30 kg and ≤150 kg with baseline total serum IgE levels between 30 IU/mL and 700 IU/mL; the maximum approved dose was 375 mg every 2 weeks [5]. Although this range was comprehensive, real-world observations indicated that there were many patients with asthma who were ineligible for omalizumab due to their IgE levels (>700 IU/mL) and body weight (≥20–30 kg) being outside the 2009 posology,

supporting the need for dosing table expansion (DTE). This led to an update in the dosing table in Japan in 2013 to include patients weighing between 20 kg and 150 kg with baseline total serum IgE levels from 30 IU/mL to 1500 IU/mL; the maximum dose per administration increased from 375 mg to 600 mg every 2 weeks [7, 12].

The aim of dosing table revision (DTR) was to increase the time interval from every 2 weeks to every 4 weeks thereby increasing the dose per administration from 225 mg or 300 mg to 450 mg or 600 mg, respectively without affecting the safety and efficacy of omalizumab [13]. Patients subjected to DTR are highlighted in green in Figure 2. The application DTR in Japan was based on the findings from an extended clinical study in pediatric patients from Japan [6], pooled studies that included patients dosed with omalizumab ≥600 mg, global pharmacokinetic/pharmacodynamic and clinical studies that supported dosing change in the EU, and post-marketing studies [13]. However, these studies did not evaluate the efficacy of omalizumab based on the revised dosing table in Japanese adult patients with asthma. In addition, Japanese and EU patients with severe asthma have been reported to differ in terms of baseline characteristics such as age and body mass index [14, 15], which may have an impact on treatment. Hence, it is essential to evaluate whether the revised dosing table has similar safety and efficacy as in the Western asthma patients.

This post-marketing surveillance (PMS) study investigated the safety and efficacy of omalizumab in adult patients with severe allergic asthma who were treated in clinical practice settings based on DTE/DTR.

2. Material and methods

This 52-week, multicenter PMS was conducted from September 2013 to November 2018 in accordance with good post-marketing study practice (GPSP), and the data presented here are based on the study report submitted to the Japanese Pharmaceutical and Medical Devices Agency (PMDA) [16]; as such, informed consent was not mandated nor obtained. The surveillance was conducted in 203 sites with a central registration using an electronic data capture system (PostMaNet, Fujitsu FIP Corporation, Tokyo, Japan [17]). Patients were registered by the investigator, and patient details were recorded using case report forms (CRFs). The inclusion criteria for the surveillance were: adult patients (aged ≥15 years) with severe asthma, defined by poorly controlled refractory asthma symptoms despite conventional therapies, who had initiated omalizumab; patients who were first-time users of omalizumab; and patients who had initiated omalizumab as per the expanded dosing table.

2.1 Study endpoints

2.1.1 Safety

The primary endpoint for safety was incidence of adverse drug reactions (ADRs) during the 52-week study period. The secondary safety endpoints were incidence of ADRs by patient characteristics, incidence of adverse events (AEs), incidence of serious adverse events (SAEs), ADRs of special interest, and concomitant allergic diseases. AEs and ADRs of special interest included ‘anaphylaxis’, ‘malignant tumor’, ‘bleeding tendency’, ‘autoimmune disease’, ‘infection parasitic’, and ‘eosinophilic syndrome’.

2.1.2 Efficacy

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The primary efficacy endpoint was physician-reported Global Evaluation of Treatment Effectiveness (GETE) which was found to be the most meaningful measure of omalizumab response [18]. 'Excellent' or 'good' GETE scores were considered as effective, while 'moderate', 'poor', 'worsening', or 'not evaluable' scores were considered as not effective. The secondary efficacy endpoints included assessment of events related to asthma exacerbations. Asthma exacerbation events were assessed in terms of periods of event observation, worsening of asthma symptoms that required systemic steroids, hospitalization, emergency room (ER) visits, and absence from school/work due to asthma. Change in oral corticosteroid (OCS) dose and use were also evaluated.

2.2 Subgroup analysis

Safety and efficacy were also assessed in subgroups of patients categorized based on the following characteristics: gender, age (<65 years vs ≥65 years) at first omalizumab administration, patients with concomitant renal disorder, percent predicted forced expiratory volume in 1 second at baseline, short-acting β_2 agonist [SABA] and OCS use, patients with concomitant liver disorder, patients with concomitant allergic diseases (atopic dermatitis, allergic rhinitis, eosinophilic syndrome, and other allergic diseases), patients subjected to DTE/DTR, patients with baseline serum IgE levels >700 IU/mL versus those with serum IgE levels ≥30 IU/mL and ≤700 IU/mL, and patients receiving omalizumab <600 mg versus ≥600 mg (dose per administration) as per revised dosing table. Patients subject to DTE and DTR had different backgrounds; DTE patients could not be administered omalizumab prior to the expansion of dosing table, while DTR patients could only be administered omalizumab once every 2 weeks before the dose conversion table was revised. Thus, it was considered necessary to determine whether the safety and efficacy of omalizumab would differ between patients who were subject

to DTE, and those subject to DTR. Patients who were subject to either DTE or DTR were determined by their total serum IgE levels at baseline and body weight.

2.3 Statistical analysis

A target safety dataset with a sample size of 400 patients was estimated based on a 20% cutoff, extrapolated on the discontinuation/withdrawal rates from prior post-marketing surveillances. Summary statistics (mean, standard deviation [SD], maximum, minimum, median) were evaluated for all safety endpoints at baseline, Week 16, and Week 52. Frequencies of asthma exacerbations were assessed pre-treatment and post-treatment. Efficacy rate was defined based on proportion of patients with effective or not effective GETE scores in the overall population. GETE scores were evaluated at specific time periods (Weeks 8, 16, 26, 34, 42, and 52, or at discontinuation) and final assessment in the efficacy dataset. GETE scores were also evaluated in the long-term administration group comprising patients who continued omalizumab after the 16-week assessment. Change in OCS dose was evaluated at Weeks 16 and 52 in terms of: 'no dose reduction, or dose increase', percent reduction of '>0 to <50', '≥50 to <75', '≥75 to <90', or '≥75 to <90'. Patients with known dose of OCS at baseline and each assessment period were included in the efficacy analysis. Fisher's exact test was used for comparison between two groups with unpaired nominal data, and Mann–Whitney test was used for three or more groups with unpaired ordinal data (when the tabulation resulted in 2 × 2 contingency table, Fisher's exact test was used). The level of significance was 5% in two-tailed hypothesis tests. Data results that were 'unknown' or 'not reported' were not included in the tests. This study was designed to identify safety signals in patients treated with omalizumab. Due to its nature, the authors do not claim statistical significance between pre- and post-treatment for efficacy parameters such as exacerbation reduction and OCS sparing effect.

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3. Results

3.1 Study population

A total of 405 patients from 203 sites were registered for this surveillance; among these, 401 patients from 200 sites had fixed CRFs. Of the 401 patients included in the safety dataset, nine patients were excluded from the analysis: one patient was deemed ineligible for registration, eight patients were deemed to have dosage and administration outside the scope of the surveillance. Discontinuation/withdrawal occurred in 45.15% of patients (177/392). The reason for discontinuation/withdrawal were “Inadequate response” (13.0% [51/392]), “Onset of AE” (7.1% [28/392]), “Symptoms improved” (5.6% [22/392]), and “Other reasons” (12.8% [50/392]). Other reasons were patient’s convenience (19 patients) and cost (12 patients, too expensive to continue). In total, safety endpoints were evaluated in 392 patients (**Figure 1**)

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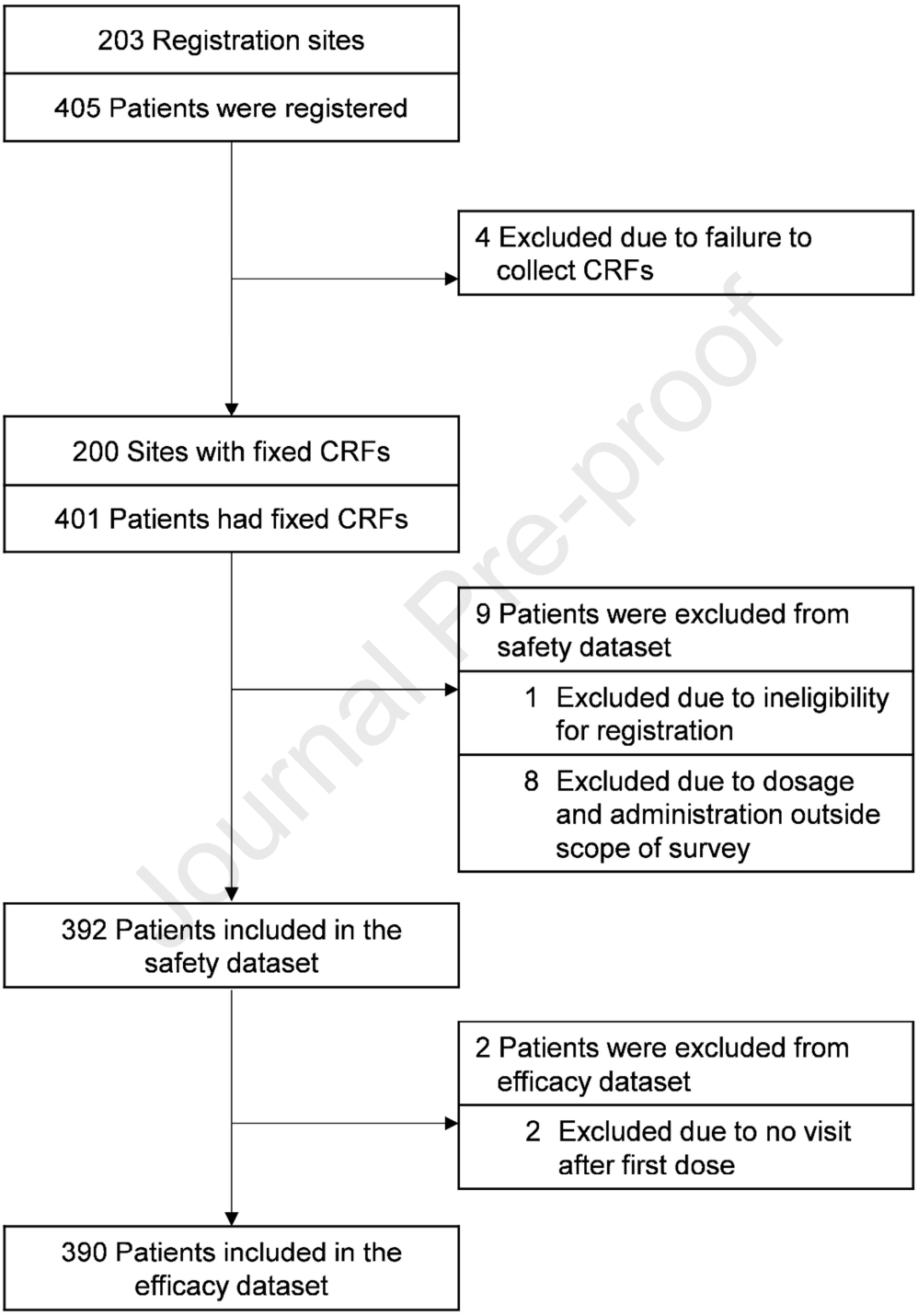
Figure 1. Patient disposition



CRF, case report form

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Demographics and baseline characteristics of patients in the safety set are presented in **Table 1**.

Table 1. Patient demographics and baseline characteristics (safety dataset)

Characteristic	**N = 392**
Age, years, mean ± SD	58.5 ± 16.7
<20	8 (2.0)
≥20 and <65	218 (55.6)
≥65	166 (42.4)
Gender	
Men	162 (41.3)
Women	230 (58.7)
Body weight, kg, mean ± SD	61.2 ± 14.9
Total serum IgE level, IU/mL, mean ± SD	599.3 ± 315.7
Duration of asthma, years, mean ± SD	18.4 ± 13.9
<5	28 (7.1)
≥5 and <10	42 (10.7)
≥10	132 (33.7)
Unknown/not reported	190 (48.5)
Smoking history	
Non-smokers	225 (57.4)
Smokers	133 (33.9)
Unknown/not reported	34 (8.7)
Positive antigen	
House dust (including mites)	243 (62.0)
Pollen	196 (50.0)
Fungi	155 (39.5)
Animals	87 (22.2)
Insects	76 (19.4)
Food	47 (12.0)
Other	18 (4.6)
Number of positive antigens	
0	9 (2.3)
1	89 (22.7)
2	98 (25.0)
≥3	143 (36.5)
Unknown/not tested	53 (13.5)
Total dosing period of omalizumab, days, mean ± SD	258.6 ± 127.7
<16 weeks	84 (21.4)
≥16 weeks and <52 weeks	180 (45.9)
≥52 weeks	128 (32.6)
$FEV_{1,}$ % predicted, mean ± SD	71.0 ± 24.6
Comorbidities	293 (74.7)
Atopic dermatitis	23 (5.9)
Allergic rhinitis	127 (32.4)
Other allergic diseases	4 (1.0)

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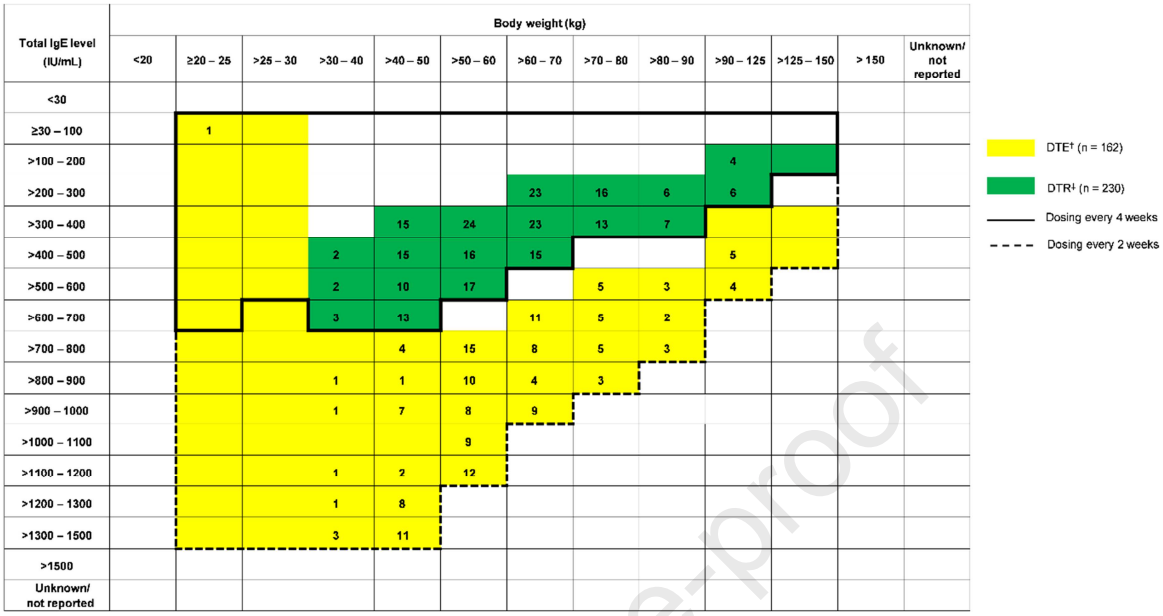
Previous treatment	
OCS	192 (49.0)
SABA	105 (26.8)
Concomitant medications	
ICS + LTRA	9 (2.3)
ICS + LABA	23 (5.9)
ICS + LABA + LTRA	78 (19.9)
ICS + LABA + LAMA	7 (1.8)
ICS + LABA + extended-release theophylline	12 (3.1)
ICS + LABA + two or more other drugs[†]	219 (55.9)
Others	23 (5.9)
OCS	115 (29.3)
SABA	50 (12.8)

Data are n (%) unless stated otherwise
[†]SABAs administered for treating asthma attack and OCS was not included
FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2 agonist; SD, standard deviation

The mean age of patients in the safety dataset at baseline was 58.5 years, with 42.4% aged ≥65 years. In total, 41.3% were men and 58.7% were women. A majority of patients tested positive to an antigen, with sensitivity to house dust (including mites) being the most common. The most common comorbid condition was allergic rhinitis, prevalent in almost one-third of patients. The mean duration of omalizumab treatment was 258.6 days with nearly one-third of patients receiving 600 mg omalizumab at the first dose (n = 148). More than half of patients were on a 4-week dosing interval at first dose (n = 231). The dose interval or dose was adjusted due to changes in body weight in 1.8% of patients. Majority of patients were treated with ICS/LABA as a concomitant medication. Nearly 50% of patients had a prior treatment with OCS, while 29.3% were concomitant users at baseline. The patient characteristics in the efficacy dataset were comparable to the safety dataset.

Overall, 41.3% (n = 162) were subjected to DTE and 58.7% (n = 230) to DTR (**Figure 2**). The mean body weight (± SD) at baseline for dose determination was 61.2 (± 14.9) kg, with a mean total serum IgE level (± SD) at baseline of 599.3 (± 315.7) IU/mL.

Figure 2. Patient disposition as per the dose conversion table (safety dataset)



The cells represent the number of patients in each category. †Patients subjected to DTE; ‡Patients subjected to DTR

DTE, dosing table expansion; DTR, dosing table revision; IgE, immunoglobulin E

3.2 Safety outcomes

3.2.1 Incidence of ADRs

Of 392 patients, 6.6% experienced ADRs (n = 26; **Table 2**). The most common ADRs by System Organ Class (SOC) [19] were general disorders and administration site conditions (2.6%); and skin and subcutaneous tissue disorders (1.3%). The most common ADRs by Preferred Term (PT) were urticaria, asthma, arthralgia, injection site erythema, and pyrexia. The incidence of ADRs was highest within 4 weeks after start of omalizumab treatment (3.6%, n = 14).

3.2.2 Incidence of AEs

In total, 32.9% (n = 129) of patients experienced AEs (**Table 2**). The most common AEs by SOC [19] were respiratory, thoracic, and mediastinal disorders (17.4%); infections and infestations

(13.0%); and general disorders and administration site conditions (6.4%). The most common AEs by PT—occurring in >1% of patients—were asthma, nasopharyngitis, bronchitis, pneumonia, aggravated concomitant disease, and pyrexia.

3.2.3 Incidence of SAEs

Overall, 16.1% of patients (n = 63) experienced an SAE (**Table 2**). The most common SAEs by SOC were respiratory, thoracic, and mediastinal disorders (11.5%); and infections and infestations (3.6%). The most common SAEs by PT were asthma, pneumonia, pyrexia, eosinophilic granulomatosis with polyangiitis, cardiac failure, hemoptysis, status asthmaticus, and aggravated concomitant disease.

Table 2. Incidence of AEs, SAEs, and ADRs (safety dataset)

	Number of patients (%)	**Number of events**
Patients with ADRs	26 (6.6)	34
Patients with any AEs	129 (32.9)	230
Patients with SAEs	63 (16.1)	89

	Number of patients (%)
Most frequent ADRs[†]	
Urticaria	3 (0.8)
Asthma	2 (0.5)
Arthralgia	2 (0.5)
Injection site erythema	2 (0.5)
Pyrexia	2 (0.5)
Most frequent AEs[†]	
Asthma	55 (14.0)
Nasopharyngitis	14 (3.6)
Pneumonia	11 (2.8)
Aggravated concomitant disease	8 (2.0)
Pyrexia	6 (1.5)
Bronchitis	6 (1.5)
Influenza	4 (1.0)
Pharyngitis	4 (1.0)
Sinusitis	3 (0.8)
Headache	3 (0.8)

Pruritus	3 (0.8)
Urticaria	3 (0.8)
Arthralgia	3 (0.8)
Otitis media	2 (0.5)
Respiratory tract infection	2 (0.5)
Eosinophilic granulomatosis with polyangiitis	2 (0.5)
Cardiac failure	2 (0.5)
Chronic obstructive pulmonary disease	2 (0.5)
Dyspnea	2 (0.5)
Hemoptysis	2 (0.5)
Allergic rhinitis	2 (0.5)
Status asthmaticus	2 (0.5)
Wheezing	2 (0.5)
Upper respiratory tract inflammation	2 (0.5)
Chronic eosinophilic rhinosinusitis	2 (0.5)
Abdominal pain	2 (0.5)
Vomiting	2 (0.5)
Chest pain	2 (0.5)
Injection site erythema	2 (0.5)
Injection site pain	2 (0.5)
Edema peripheral	2 (0.5)
Most frequent SAEs[†]	
Asthma	38 (9.7)
Pneumonia	7 (1.8)
Pyrexia	3 (0.8)
Eosinophilic granulomatosis with polyangiitis	2 (0.5)
Cardiac failure	2 (0.5)
Hemoptysis	2 (0.5)
Status asthmaticus	2 (0.5)
Aggravated concomitant disease	2 (0.5)

[†]Data represent AEs, SAEs, and ADRs by Preferred Term occurring in more than one patient. Percentage was calculated per applicable patient in each item/category
ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event

3.2.4 Fatality

Of 392 patients in the safety dataset, four died. One was aged <65 years and the AE leading to death was asthma. Two were aged between 65 years and 74 years, with AEs leading to death being ‘gastrointestinal hemorrhage with aggravated concomitant disease’ or ‘gastrointestinal

hemorrhage and anemia with aggravated concomitant disease' in one patient, and 'acute cardiac failure' in the other patient. The fourth patient was aged ≥75 years, with the AEs leading to mortality being asthma, cardiac failure, and respiratory failure. None of the fatalities was deemed to be related to omalizumab.

3.3 Efficacy outcomes

3.3.1 Physicians' GETE

Among the 390 patients in the efficacy dataset assessed using GETE, omalizumab treatment was found to be effective across all time periods. Omalizumab was effective in 63.3% of patients (n = 209) at Week 16 and 63.5% (n = 134) at Week 52, with an overall effectiveness at final assessment of 50.0% (n = 195) throughout the study (**Figure 3**). Among the 308 patients in the long-term administration group, omalizumab was effective in 53.2% of patients at final assessment.

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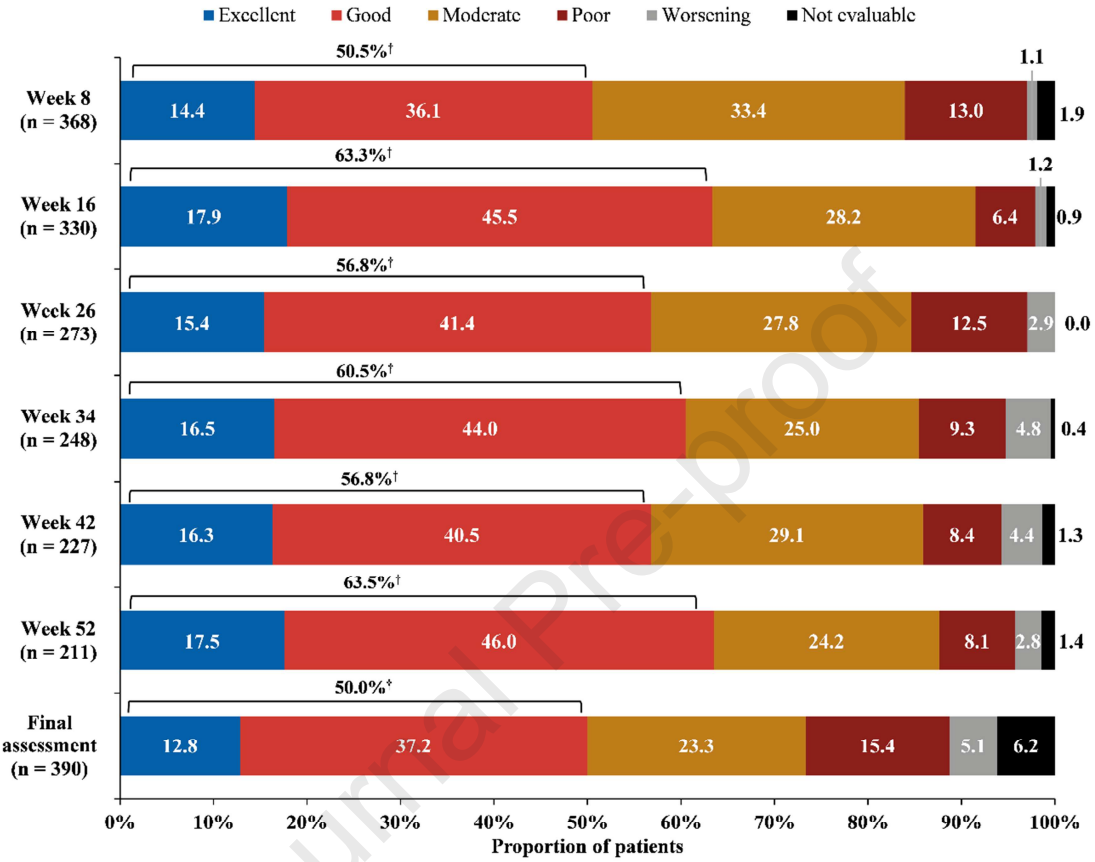
Figure 3. Physicians' GETE evaluation in patients with omalizumab (efficacy dataset)



Data represent proportion of patients with treatment effectiveness assessed as per physicians' GETE

†Proportion of patients with excellent and good GETE

GETE, Global Evaluation of Treatment Effectiveness

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3.3.2 Asthma exacerbation

The proportion of patients with asthma exacerbation related events, including worsening of asthma symptoms requiring systemic steroids, hospitalization, emergency room visits and absence from school/work, was lower post-omalizumab treatment compared with pre-treatment (**Figure 4**). The annual ratio of asthma exacerbation related events was also decreased post-treatment vs pre-treatment; worsening of asthma symptoms requiring systemic corticosteroids (pre-treatment vs post-treatment, mean ± SD, 4.1 ± 8.1 times/year vs 2.3 ± 5.6 times/year), hospitalization (0.4 ± 1.0 times/year vs 0.2 ± 1.2 times/year), visits to the ER (0.9 ± 2.8 times/year vs 0.4 ± 1.5 times/year), and absence from school/work (including housework; 1.9 ± 9.4 times/year vs 0.5 ± 2.0 times/year). Similar reductions in frequency of exacerbation-related events were observed in patients in the long-term administration group.

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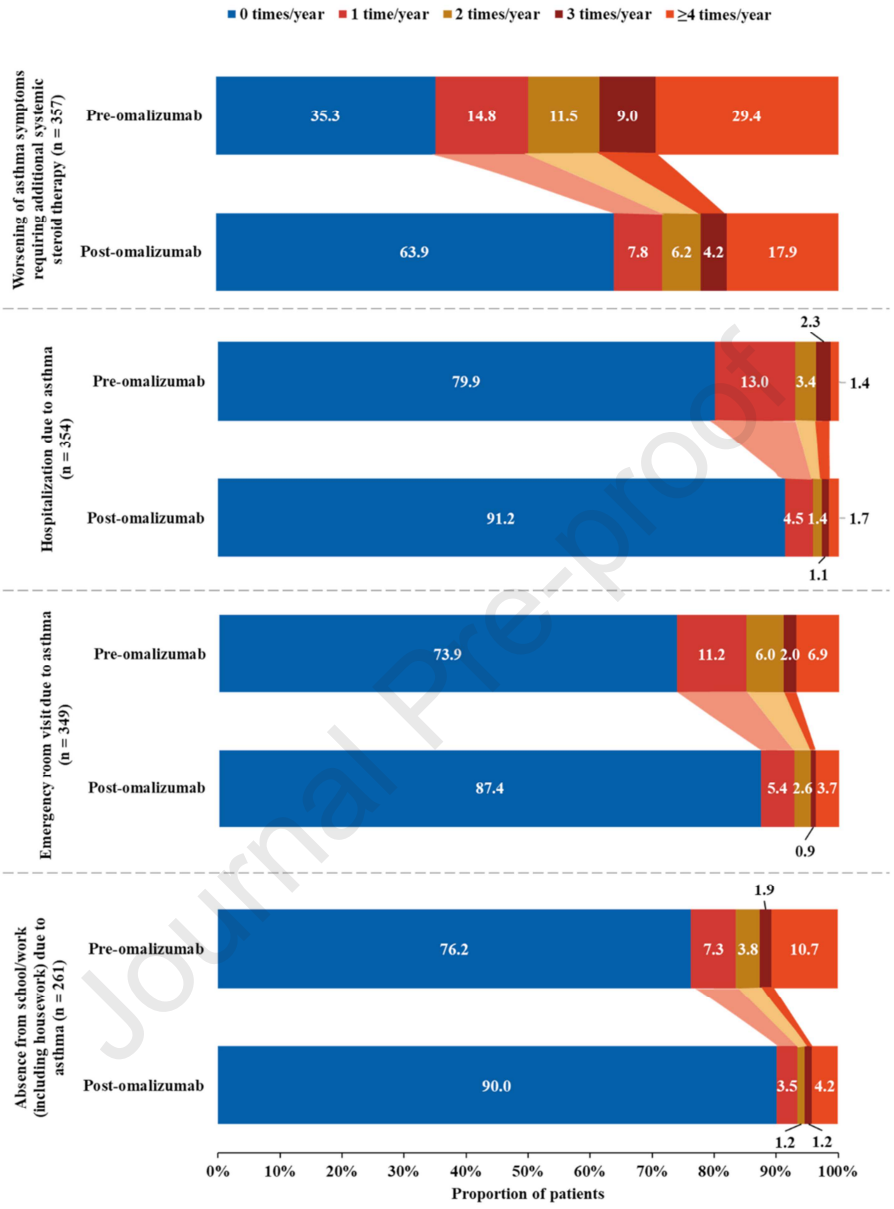
Figure 4. Effect of omalizumab on asthma exacerbation-related events



Data represent proportion of patients with asthma exacerbation-related events

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3.3.3 Change in OCS dose

Of the 392 patients in the safety dataset, 92 were receiving OCS at baseline. Treatment with omalizumab was associated with an overall reduction in OCS dose of 10.4% at Week 16 (mean ± SD, −1.1 ± 4.1 mg/day, n = 92) and 50.3% at Week 52 (−7.3 ± 8.4 mg/day, n = 60) compared with baseline (**Additional file 1: Table S1, Figure S1a**). At Week 52, more than 80% of patients had ≥50% OCS dose reduction and 13.3% (n = 8) had ≥90% reduction (**Additional file 1: Figure S1b**).

3.3.4 Safety and efficacy outcomes by subgroup

Among patients subjected to DTE (n = 162), incidence of ADRs was low (4.9%), with the most common ADR by PT being arthralgia (**Table 3**). Of the 230 patients subjected to DTR, only 7.8% experienced ADRs, with the most common ADRs by PT being asthma, urticaria, and injection site erythema (**Table 3**).

Of the 126 patients with baseline total serum IgE levels >700 IU/mL and ≤1500 IU/mL, 4.8% reported ADRs, with the most common ADR by PT being arthralgia. Among the 266 patients with baseline total serum IgE levels between 30 IU/mL and 700 IU/mL, 7.5% reported ADRs. The most common ADRs were asthma, urticaria, injection site erythema, and pyrexia (**Table 3**).

Among the 148 patients receiving omalizumab ≥600 mg, 7.4% reported ADRs, with urticaria being the most common ADR by PT (n = 3; 2.0%). In patients receiving omalizumab <600 mg (n = 244), 6.2% experienced ADRs, with arthralgia, injection site erythema, and pyrexia being the most common ADRs by PT (n = 2; 0.8% each).

The incidence of ADRs in patients aged ≥65 years (n = 166) was comparable to patients aged <65 years (n = 226; 6.6% vs 6.6%, respectively), with arthralgia, eosinophilic granulomatosis

with polyangiitis, hyperglycemia, tinnitus, dyspnea, pruritus, pain in extremity, chills, injection site irritation, peripheral edema, inflammation, and weight increase occurring specifically in the elderly patients (≥65 years; all ≤1.2%). The proportion of patients with ADRs was comparable in the subgroups based on other baseline characteristics such as comorbidities (**Additional file 1: Figure S2**).

Efficacy rates were comparable between patients with baseline total serum IgE levels >700 IU/mL and those with serum IgE levels between 30 IU/mL and 700 IU/mL (*P* = 0.8283). There were no differences in efficacy of omalizumab between patients subjected to DTE and DTR (*P* = 0.6808; **Table 3**).

Table 3. Safety and efficacy analysis by baseline total serum IgE level and DTE/DTR

	Total number of patients, N	**Number of patients with ADR (%)**	***P* value**[†]
3a. Safety dataset			
Total IgE levels, IU/mL			
≥30 and ≤700	266	20 (7.5)	0.3874
>700 and ≤1500	126	6 (4.8)	
Patients subjected to update in dosing table			
DTE	162	8 (4.9)	0.3064
DTR	230	18 (7.8)	
		Number of patients (%)	
Most frequent ADRs in patients with serum IgE levels ≥30 IU/mL and ≤700 IU/mL[‡]			
Asthma		2 (0.8)	
Urticaria		2 (0.8)	
Injection site erythema		2 (0.8)	
Pyrexia		2 (0.8)	
Most frequent ADRs in patients with serum IgE levels >700 IU/mL and ≤1500 IU/mL[‡]			
Arthralgia		2 (1.6)	

Most frequent ADRs in patients with DTE[‡]	
Arthralgia	2 (1.2)
Most frequent ADRs in patients with DTR[‡]	
Asthma	2 (0.9)
Urticaria	2 (0.9)
Injection site erythema	2 (0.9)

	Total number of patients, N	Omalizumab effectiveness,[#] n (%)	*P* value[†]
3b. Efficacy dataset			
Total serum IgE levels, IU/mL			
≥30 and ≤700	265	134 (50.6)	0.8283
>700 and ≤1500	125	61 (48.8)	
Patients subject to update in dosing table			
DTE	161	78 (48.4)	0.6808
DTR	229	117 (51.1)	

Percentage was calculated per applicable patient in each item/category
[†]*P* values estimated based on Fisher's exact test
[‡]Data represent ADRs occurring in more than one patient
[#]Assessed based on 'excellent' and 'good' GETE scores
ADR, adverse drug reaction; DTE, dosing table expansion; DTR, dosing table revision; IgE, immunoglobulin E

Analysis of omalizumab efficacy rate by patient characteristics indicated that patients without prior treatment with OCS showed a greater response to omalizumab compared with those with prior OCS treatment (*P* = 0.0084; **Additional file 1: Figure S3**). Efficacy analysis ('excellent'/'good' GETE score) by comorbidity showed that omalizumab was highly effective in all patients regardless of the comorbidity, with the efficacy being marginally more significant in asthmatic patients with comorbid allergic rhinitis compared with those without allergic rhinitis (**Additional file 1: Figure S3)**.

Omalizumab showed comparable efficacy in patients evaluated based on the other baseline characteristics and comorbid conditions (**Additional file 1: Figure S3**).

4. Discussion

Omalizumab has been successfully adopted into clinical practice with an estimated exposure of more than 500,000 patient-years in adults reported in 2016 [20]. Numerous observational studies and clinical trials have shown the safety and efficacy of omalizumab in patients with asthma [21, 22].

To the best of our knowledge, this is the first study investigating the safety and efficacy of omalizumab in patients with asthma who were subjected to DTE/DTR in a real-life setting. The findings from this PMS study support the safety and efficacy of omalizumab in Japanese patients with severe allergic asthma who were subjected to the revised dosing table. Approximately 40% of patients in the study received omalizumab based on DTE and 60% based on DTR.

Omalizumab was well tolerated with no clinically relevant ADRs reported in the safety dataset and was effective in reducing OCS dose and incidence of asthma-related exacerbation events, and improving asthma symptoms. These results were observed both in the overall safety and efficacy datasets and in the subgroups assessed based on patient characteristics.

Overall, no new safety signals were reported in patients administered omalizumab based on the revised dosing table. The AEs, SAEs, and ADRs in patients subject to DTE/DTR were comparable to reports from the numerous real-life studies and clinical trials [7, 23]. Only two patients in the study had ADRs of special interest; one reported anaphylaxis and the other reported eosinophilic granulomatosis with polyangiitis. Furthermore, ADRs in subgroups based on baseline characteristics such as age, body weight, duration of disease, and serum IgE level did not differ markedly from the overall safety dataset. The incidence of ADRs was relatively higher in women compared with men (8.7% vs 3.7%, respectively); although the reasons for this difference are not yet known, reports suggest that ADRs are generally high in female patients

and may be due to differences in manifestation of disease and variation in the distribution and clearance of drugs [24, 25]. Nevertheless, the proportion of ADRs among genders was comparable to reports from a previous real-world study in Japanese patients with severe asthma [7], well within the overall ADR incidence reported in other PMS studies [7, 26], and was as per the events described previously and listed as precautions in the package insert [5]. These data suggest that omalizumab can be administered based on the revised dosing without any need for a change in the safety labeling. The safety profile observed in this study is similar to the known safety profile listed in the product label [5].

In terms of efficacy, patients administered omalizumab based on the revised dosing table had a treatment benefit that was comparable to other PMS and real-world studies and RCTs. Omalizumab was effective ('excellent' and 'good' GETE) at 16 weeks in more than 60% of patients subjected to the revised dosing table, with similar proportions also reported in other studies [7, 22]. Omalizumab was associated with a marked reduction in the frequency of events related to asthma exacerbations, including hospitalization and ER visit, and absenteeism, compared with the pre-treatment period. These findings support the efficacy of omalizumab in maintaining asthma control and reducing the disease burden in patients with severe asthma. After treatment with omalizumab, there was a nearly 40% reduction in the proportion of patients who experienced worsening symptoms (requiring systemic corticosteroids) ≥4 times/year compared with pre-treatment (post-treatment: n = 64 vs pre-treatment: n = 105). These reductions were also sustained in the long-term administration group and support the efficacy of omalizumab demonstrated in other PMS [7] and real-world studies and RCTs [22, 27].

The Global Initiative for Asthma (GINA) 2020 guidelines recommend the use of omalizumab as an add-on therapy in patients who remain inadequately controlled with Step 5 treatment of high-

dose ICS/LABA and other controllers [1, 28, 29]. The 2017 Japanese guidelines recommend the use of omalizumab as an add-on therapy in Step 4 patients with severe persistent asthma who remain symptomatic despite treatment with high-dose ICS and two or more controller agents [2]. In the present study, approximately half of the patients were receiving ICS plus LABA with two or more controllers such as leukotriene receptor antagonists and theophylline prior to initiating omalizumab. The use of multiple controller therapies reflects that these patients were uncontrolled to a large extent, and indicates their burden of asthma, highlighting the need for initiating omalizumab as an add-on therapy in these patients.

Although patients without prior OCS use showed a better response to omalizumab versus those with prior OCS use in this study, which may be due to prior OCS users having more uncontrolled asthma, a majority of the treated patients had ≥50% reduction in OCS dose. These findings add to the evidence from other studies that support the OCS-sparing effect of omalizumab [7, 29-33]. The GINA guidelines recommend the administration of OCS only in patients who remain uncontrolled despite treatment with biologics [1]. These recommendations have also been proposed by the Japanese asthma guidelines [2]. Long-term use of OCS has been associated with many side effects such as osteoporosis and hypertension, indicating the need for prudent use of OCS [34, 35]. The reduction in the OCS dose post-administration of omalizumab in this study is consistent with our previous PMS study report [7].

The findings from the overall population were also largely replicated in patient subgroups assessed based on baseline characteristics, except for the difference in efficacy in patients with and without prior OCS use, as discussed earlier. Omalizumab was equally effective among patients in the DTE and DTR subgroups, and those with IgE greater than and less than 700 IU/mL subgroups. Of note, omalizumab was effective in nearly 60% of patients with comorbid

allergic rhinitis. Allergic rhinitis occurs as a comorbidity in nearly 80% of patients with asthma and increases the risk of asthma-related hospitalization and ER visits [37, 38]. The effectiveness of omalizumab in asthmatics with allergic rhinitis observed in our study supports its potential use in patients with this comorbidity.

The study has a few potential limitations. As a PMS study, the surveillance was dependent on the participating medical institutions for collection of CRFs from patients; some of the CRFs could not be obtained due to a non-collection by the participating institution. The data collected from the different institutions may have slight variations due to the difference in the instruments and institutional environment among the participating medical centers. As a non-interventional observational study, no comparators were included and no statistical assessments were conducted to compare the degree of effectiveness post-treatment with baseline. Another potential limitation could be an underestimation of the proportion of comorbid allergic rhinitis (safety dataset, 32.4%), which is much lower than other studies in the Japanese population (~ >60%) [39, 40]. Despite these limitations, the findings from the study support the safety and effectiveness of omalizumab in patients receiving treatment based on the revised dosing table. Early initiation of omalizumab prior to OCS may have a beneficial effect in patients. Omalizumab tends to be efficacious in patients with severe allergic asthma and comorbid allergic rhinitis. Many patients in routine clinical practice tend to have high serum IgE levels >700 IU/mL especially those with allergic comorbidities such as food allergy, atopic dermatitis or fungal sensitization. The revision in the posology of omalizumab has expanded the spectrum of patients who would benefit from omalizumab, and is supported by the efficacy and safety findings from this PMS study. Further, the expanded dosing table would aid clinicians with improved management of asthma symptoms and ensure better disease control in patients with allergen-sensitized high serum IgE levels.

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5. Conclusions

In conclusion, the data from this real-world study suggest that omalizumab is effective and well tolerated with no new safety signals in severe asthmatic adults from Japan who received treatment based on the revised/expanded dosing table. The treatment effectiveness was observed regardless of the baseline characteristics such as age, serum IgE level, and comorbidity. These findings support the administration of omalizumab based on the revised dosing table in patients with severe asthma in routine medical practice.

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6. Data availability

Novartis is committed to sharing access to patient-level data and supporting documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the study in line with applicable laws and regulations.

CRediT authorship contribution statement

Koichiro Asano: Investigation, Writing - review & editing, Visualization, Supervision. Kazuya Sumi: Conceptualization, Resources, Writing - review & editing. Hajime Yoshisue: Conceptualization, Resources, Writing - review & editing. Noriko Nakamura: Conceptualization, Resources, Methodology, Writing - review & editing, Visualization. Makoto Nagasaki: Conceptualization, Resources, Methodology, Writing - review & editing, Visualization, Supervision. Takayoshi Sasajima: Conceptualization, Resources, Methodology, Formal analysis, Writing - review & editing, Visualization. Hisako Matsumoto:
Writing - review & editing, Visualization, Supervision.

Authors' contributions

All authors contributed to the conception and design of the study and were involved in the development and final approval of the manuscript.

Ethics approval and consent to participate

The study was conducted as per the guidelines in the Declaration of Helsinki and Good Clinical Practice guidelines. The data presented here are based on the study report submitted to the

Japanese Pharmaceutical and Medical Devices Agency (PMDA); as such, informed consent was not mandated nor obtained.

Declaration of competing interests

Koichiro Asano (KA) received consultancy fees from Teijin Pharma Ltd; expert testimony fees from Novartis Pharma and Sanofi; and lecture fees from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharma, MSD, and Novartis Pharma, outside the submitted work. Hisako Matsumoto (HM) received lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharma, Sanofi, and Novartis Pharma; and received research grants from Novartis Pharma outside this work. Kazuya Sumi (KS), Hajime Yoshisue (HY), Noriko Nakamura (NN), Makoto Nagasaki (MN), and Takayoshi Sasajima (TS) are employees of Novartis Pharma K.K.

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Highlights

- This post-marketing surveillance evaluated safety and efficacy of the revised dosing table (DTR) and expanded dosing table (DTE) with regard to omalizumab dosage in Japanese adults with severe allergic asthma in clinical practice settings
- This 52-week, multicenter study evaluated omalizumab safety outcomes including adverse events (AEs), serious AEs (SAEs), adverse drug reactions (ADRs), efficacy outcomes including Global Evaluation of Treatment Effectiveness (GETE), change in oral corticosteroid dose, and asthma exacerbation-related events such as hospitalization, emergency room visits, and worsening of symptoms
- Omalizumab was associated with a reduction in worsening of asthma symptoms requiring systemic corticosteroids and frequency of hospitalization. All outcomes were comparable among the DTE and DTR subgroups.
- The findings from this study support the safety and efficacy of omalizumab administered based on the revised and expanded dosing table in Japanese patients with severe allergic asthma

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