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Real-world safety and efficacy of omalizumab in patients with severe allergic asthma: A long-term post-marketing study in Japan

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ABSTRACT

Background: Omalizumab (anti-IgE monoclonal antibody) is an approved add-on therapy for Japanese patients with severe allergic asthma. As directed by the Ministry of Health, Labor and Welfare Japan, a post-marketing surveillance (PMS) study on omalizumab was conducted between 2009 and 2017.

Methods: The PMS observed safety and efficacy of omalizumab in patients treated with open-label omalizumab for 52 weeks (with optional 2-year extension period). Primary safety outcomes included incidence and severity of adverse events (AEs) and adverse drug reactions (ADRs). Primary efficacy outcomes included physician-assessed global evaluation of treatment effectiveness (GETE). Asthma-exacerbation-related events including requirement for additional systemic steroid therapy, hospitalization, emergency room visits, unscheduled doctor visits, and absenteeism were also evaluated.

Results: Of 3893 patients registered, 3620 (age [mean ± SD] 59.3 ± 16.11 years) were evaluated for 52 weeks; 44.12% were aged ≥65 years and 64.45% were women. Overall, 32.24% reported AEs and 15.30% reported serious AEs. ADRs were seen in 292 (8.07%) patients. GETE results showed that the majority of patients experienced clinical improvements (58.29% at 16 weeks and 62.40% at 52 weeks). Nearly half of all patients (47.96%) were free from asthma exacerbations after therapy. Omalizumab also reduced all events related to asthma exacerbations. No specific ADRs were observed in the elderly population.

Conclusions: This post-marketing study confirmed the clinically meaningful benefits of omalizumab in a majority of patients from Japan, and showed safety and efficacy in a real-life clinical setting to be consistent with previous reports.

1. Introduction

Asthma is a chronic disease presenting a personal and societal burden for more than 350 million individuals worldwide, and the number of affected patients is expected to increase to 400 million by 2025 [1–3]. More than half of asthma patients (51–64%) are inadequately controlled on currently available treatments, signifying an urgent and unmet need that is further exemplified in those with severe asthma [4–6]. Nearly 3 million people in Japan have asthma (30% with moderate asthma and 7% with severe asthma) [7], and the national asthma prevalence among adults (> 20 years) is 9.1% [8].

Omalizumab is a validated and well established add-on therapy for inadequately controlled persistent allergic asthma despite GINA (Global Initiative for Asthma) Step 5 treatment [9,10]. It was introduced in Japan in 2009 for use in adult asthma (Japanese guidelines for adult asthma [JGL]) [11], and expanded in 2013 for use in pediatrics (≥6 years). Immunoglobulin E (IgE), the target molecule of omalizumab, is a potent and early stage mediator of airway inflammation that coordinates allergic pathogenesis through mast cells, basophils, and dendritic cells. IgE also plays an indirect role in the recruitment of eosinophils at the site of inflammation [12–14]. Allergy is the underlying cause of asthma in approximately 75–80% of cases in cohort

Abbreviations: ADRs, adverse drug reaction; AEs, adverse events; GETE, global evaluation of treatment effectiveness; GINA, Global Initiative for Asthma; HCRU, health care resource utilization; ICS, inhaled corticosteroid; IgE, Immunoglobulin E; IU, international units; JGL, Japanese guidelines for adult asthma; LABA, long-acting β_2-agonist; LTRA, leukotriene antagonist; OCS, oral corticosteroid; PMDA, Pharmaceutical and Medical Devices Agency; PMS, post marketing surveillance; Q, quartile; SABA, short-acting β_2-agonist; SAEs, serious adverse events; SD, standard deviation

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studies of severe asthma conducted in the EU and the US [15,16], and a recent study from Japan showed that 60% of Japanese patients with severe asthma had allergy [17,18]. The observed efficacy of omalizumab on asthma exacerbations, lung function, symptoms, quality of life, health care resource utilization (HCRU) and oral corticosteroid (OCS) sparing in clinical trials and real-world practice can be attributed to direct inhibition of IgE and disruption of the allergic cascade, attenuation of early and late-phase allergic responses, and restoration of antiviral mucosal immunity [12,19–30].

Despite the available treatment standards and improved therapies, 40% of Japanese patients with severe asthma remain poorly controlled [31–33]. Further, evaluations of long-term safety and effectiveness of omalizumab in Japanese clinical settings are limited. This prospective, non-interventional, post-marketing surveillance (PMS) study aims to describe the safety and efficacy of omalizumab in a real-world clinical practice environment for the first time following approval in Japan.

2. Methods

2.1. Study design

This 52-week, open-label, multicenter observational study was conducted between March 2009 to January 2017 in accordance with good post-marketing study practice (GPSP) [34] as directed by the Pharmaceutical and Medical Devices Agency (PMDA) regulatory body of Japan, and as such, informed consent was not mandated nor obtained. The intent to cooperate in an all-patient survey was confirmed by a written document with medical institutions requesting a supply of omalizumab, and a contract for the survey was concluded with the head of the medical institution who agreed to participate in the survey. Japanese patients with severe allergic asthma were treated with omalizumab and followed up by physicians specializing in asthma care from multiple clinical centers (supplementary table 1). Patients with bronchial asthma who initiated the treatment with omalizumab due to poorly controlled refractory asthma symptoms despite standard therapy were included. The aim of the study was to conduct a comprehensive surveillance of asthmatic patients who were prescribed omalizumab, and excluded patients receiving omalizumab for on-label chronic spontaneous urticaria, for off-label uses other than asthma and any patients concomitantly receiving investigational (unapproved) therapies during the study period. Cases with incomplete documentation or poor data reliability were also excluded from the study. In patients remaining on omalizumab for ≥1 year, observation was extended for up to 2 years to follow incidence of malignancy events (supplementary figure 1).

Omalizumab dosing ranged from 75 mg to 600 mg subcutaneously every 2 or 4 weeks according to the dosing table, as appropriate to the patient's total serum IgE levels and body weight at baseline.

2.2. Study endpoints

The standard observation period per patient was 1 year. The primary safety outcomes included incidence of adverse events (AEs), serious AEs (SAEs) and adverse drug reactions (ADRs). AEs and ADRs were monitored throughout the study. Items of special interest (reported as ADRs of special interest) were categorized as anaphylaxis, eosinophilic syndromes, malignant tumor, autoimmune disease and bleeding tendency.

The primary efficacy outcomes included physician-reported global evaluation of treatment effectiveness (GETE) [35], events related to asthma exacerbations, and patient-reported asthma symptoms. Effective GETE was defined by “excellent” or “good” ratings, while ineffective GETE was defined by “moderate”, “poor”, or “worsening” ratings (supplementary table 2). If physicians did not observe any improvement in their patients by 16 weeks after the initiation of treatment, omalizumab was discontinued. All patients with baseline data completed the one-year observational period. Additionally, effective response to omalizumab took into consideration “moderate” GETE rating (slight improvement).

Annual asthma exacerbation frequencies before and after omalizumab treatment were calculated and analyzed for worsening of asthma symptoms requiring [1] hospitalization [2], emergency room visit [3], systemic steroid therapy [4], unscheduled doctor visit, and/or [5] absence from school/work (including housework).

Patient-reported asthma outcomes were collected every 4 weeks. Symptom severity was assessed 4 times a day (morning, daytime, evening, and at night), and activity of daily living (ADL) and quality of nighttime sleep was assessed once a day.

2.3. Statistical analyses

Target sample size assumed inclusion of all on-label omalizumab users following consultation with Japanese health authorities (PMDA). A study with 3000 patients would provide 95% power to detect at least one patient with onset of ADR with 0.1% of frequency. As an open label study, safety and efficacy outcomes were otherwise descriptive. For comparative tests among groups, Fisher's exact test was used between 2 groups with unpaired nominal data and the Mann–Whitney *U* test was used for 3 or more groups with unpaired ordinal data (exception: when the tabulation resulted in a 2 × 2 contingency table, Fisher's exact test was used). The Mantel–Haenszel test was used to examine confounding factors. The level of significance was 5% in 2-tailed hypothesis tests. Study results with a response of “Unknown or Not reported” were excluded from analysis.

3. Results

3.1. Study population

A total of 3893 patients registered for this study and 3673 (94.34%) patients from 1001 sites were with fixed case report forms (Fig. 1).

A total of 3620 patients were included in the safety set, of which 1497 (41.35%) patients discontinued or withdrew from the study. The most common reasons for discontinuation were insufficient efficacy of the drug (n = 471, 13.01%), improvement in symptoms (n = 247, 6.82%), onset of an AE (n = 288, 7.96%) and other reasons (n = 416, 11.49%) which included financial reasons (n = 152, 4.20%) and death (n = 16, 0.44%). Of the 3620 patients in the safety set, 27 patients (Fig. 1) were excluded and the remaining 3593 patients were included in the efficacy set.

Patient demographics and baseline characteristics are presented in Table 1. The age (mean ± SD) of patients was 59.3 ± 16.11 years. Special populations were categorized as pediatric (n = 7, 0.19%, if

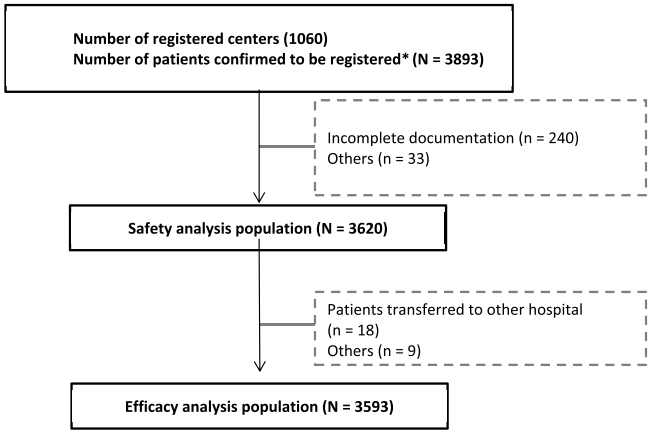

Fig. 1. Patient disposition.
*Patients transferred to another hospital are counted as 1 patient.

Table 1
Patients' demographics and baseline characteristics (safety set).

Characteristic	N = 3620
Age, mean ± SD, years*	59.3 ± 16.11
< 20 years, n (%)	33 (0.91)
20 to < 65 years, n (%)	1988 (54.92)
≥65 years, n (%)	1597 (44.12)
Unknown/unrecorded, n (%)	2 (0.06)
Women, n (%)	2333 (64.45)
Duration of asthma, years#	
Mean ± SD	18.90 ± 14.53
Median (Q1–Q3)	15.00 (7.75–28.00)
< 5 years, n (%)	363 (10.03)
≥5 years to < 10 years, n (%)	442 (12.21)
≥10 years, n (%)	1732 (47.85)
Smoking history, n (%)	
Yes	1098 (30.33)
IgE level, IU/mL¶	
Mean ± SD	367.55 ± 880.79
Median (Q1–Q3]	205.00 [87.00–421.50]
Positive antigen, n (%)	
Mites*	1694 (46.80)
House dust*	1619 (44.72)
Pollen	1495 (41.30)
Fungi	974 (26.91)
Animals	658 (18.18)
Total dosing period of omalizumab, days†	
Mean ± SD	252.5 ± 134.54
Median (Q1–Q3)	346.0 (113.0–365.0)
< 112 days (4 months), n (%)	847 (23.40)
≥112 days (4 months), n (%)	2755 (76.10)
Comorbidities, n (%)	2841 (78.48)
Allergic rhinitis	1261 (34.83)
Atopic dermatitis	256 (7.07)
Other allergic diseases	35 (0.97)
Pretreatment, n (%)	3500 (96.69)
LTRA	3057 (84.45)
ICS/LABA	2694 (74.42)
Extended-release theophylline	2367 (65.39)
OCS	1901 (52.51)
ICS	1336 (36.91)
Concomitant medications, n (%)	3590 (99.17)
LTRA	3152 (87.07)
ICS/LABA	2838 (78.40)
Extended-release theophylline	2429 (67.10)
OCS	1800 (49.72)
β_2-agonists (transdermal patch, oral, and long-acting inhalation)	1640 (45.30)
ICS	1324 (36.57)
SABA	667 (18.43)

*Commercially available allergen detection kits in Japan included both 'house dust' and 'mite', and both categories likely represented 'dust mite' allergen
n, number of patients; ICS, inhaled corticosteroid; Ig, immunoglobulin; IU, international units; LABA, long-acting β_2-agonist; LTRA, leukotriene antagonist; OCS, oral corticosteroids; Q, quartile; SABA, short-acting β_2-agonist; SD, standard deviation; *n = 3618, #n = 2537, ¶n = 3612, †n = 3602.

applying Japanese definitions [< 15 years]; n = 25, 0.69% if applying EU definitions [< 18 years]), elderly (n = 1597, 44.12% [≥65 years]), and pregnant (n = 7, 0.30%). Approximately two-thirds of patients were women (n = 2333, 64.45%). Most patients were out-patients (n = 3118, 86.13%). The duration (mean ± SD) of omalizumab treatment was 252.5 ± 134.54 days, and the first dose (mean ± SD) was 250.8 ± 79.40 mg. The majority of patients (n = 2289, 63.23%) were treated at 4-week intervals compared with patients treated at 2-week intervals (n = 1306, 36.08%), and dosing modifications due to change in weight were rare (n = 14, 0.39%). Concomitant medication patterns in the PMS showed that leukotriene antagonists (LTRAs) were the most co-prescribed medication (87.07%).

Table 2
Incidence of AEs, SAEs and ADRs by SOC (safety analysis set).

	No of patients	% of patients	No of events	% of events
Adverse events*				
Total AEs	1167	32.24	1945	53.73
Total SAEs	554	15.30	743	20.52
SAEs related to omalizumab	36	0.99		
Most frequent ADRs by organ system				
Total ADRs	292	8.07	438	12.10
General disorders and administration site conditions	89	2.46	NR	NR
Skin and subcutaneous tissue disorders	83	2.29	NR	NR
Nervous system disorders	38	1.05	NR	NR
Respiratory, thoracic and mediastinal disorders	31	0.86	NR	NR
Musculoskeletal and connective tissue disorders	30	0.83	NR	NR
ADRs of special interest				
Total number of ADRs of special interest	23	0.64	NR	NR
Eosinophilic syndrome	14	0.39	NR	NR
Anaphylaxis	6	0.17	NR	NR
Autoimmune disease	5	0.14	NR	NR
Malignant tumor	1	0.03	NR	NR
Bleeding tendency	0	0.00	NR	NR

ADRs, adverse drug reactions; AEs, adverse events; NR, not reported; SAEs, serious adverse events, SOC, system organ class.
*Calculated by taking the number of patients in the study as the denominator and the number of patients with events (for SOC) or the number of episodes (for PT) as the numerator. Multiple episodes of the same event (PT) in the same patient were counted as 1 episode. AEs are shown in the following order: Internationally agreed order for SOCs (ascending) → incidence of PTs (descending) → PT codes (ascending).

3.2. Safety outcomes

3.2.1. Incidence of AEs

Overall, 1167 (32.24%) of 3620 patients experienced AEs (Table 2). The most frequently reported AEs by system organ class (SOC) were respiratory, thoracic and mediastinal disorders (n = 537, 14.83%) followed by infections and infestations (n = 426, 11.77%) and general disorders and administration site conditions disorder (n = 138, 3.81%). By preferred term (PT), the most common AEs reported were asthma (n = 425, 11.74%), nasopharyngitis (n = 193, 5.33%), pneumonia (n = 84, 2.32%), and bronchitis (n = 60, 1.66%). Four of 7 patients aged < 15 years and 8 of 25 patients aged < 18 years reported AEs; nasopharyngitis (n = 3 each) was the most common AE for both pediatric age categories.

3.2.2. Incidence of SAEs

In total, 554 (15.30%) patients reported SAEs in this study, of which 36 SAEs were related to omalizumab. The most common SAEs related to omalizumab were anaphylactic reaction (n = 4; 2 recovered and 2 improved), asthma (n = 3; 2 recovered and 1 improved), muscular weakness (n = 3; 2 recovered and 1 improved), hypersensitivity (n = 2; 1 recovered and 1 improved), and nausea (n = 2; both improved). By PT, the most commonly observed overall SAEs were asthma (n = 359, 9.92%), followed by pneumonia (n = 58, 1.60%), status asthmaticus (n = 12, 0.33%), cardiac failure (n = 11, 0.30%), bronchitis (n = 10, 0.28%), and influenza (n = 10, 0.28%).

3.2.3. Incidence of ADRs

In the 3620 patients in the safety analysis set, the incidence of ADRs was 8.07% (n = 292; Table 2), with no ADR by PT reported at an incidence > 1%. The common ADRs were malaise (n = 34, 0.94%), urticaria (n = 25, 0.69%), dizziness (n = 19, 0.52%), pyrexia, and rash

(n = 18, 0.50% each). Of the 3602 patients evaluated for the onset of ADRs, the highest incidence of ADRs (n = 149, 4.14%) occurred within the first 4 weeks of commencing therapy. The adjustment analysis by the Mantel-Haenszel test has revealed the following confounding factors that are thought to be related to the incidence of ADRs: age, gender, past medical history of anaphylactoid symptoms, previous medication (OCS and short-acting β_2-agonist [SABA]) and concomitant SABA. Incidence of ADRs was lower in patients ≥65 years (n = 105, 6.57%) compared with patients aged < 65 years (n = 187, 9.25%). The incidence of ADRs in women (n = 229, 9.82%) was higher than the incidence of ADRs in men (n = 63, 4.90%). The incidence of ADRs in patients with past anaphylactoid symptoms (n = 11, 22.45%) was higher than that in those without past anaphylactoid symptoms (n = 266, 7.87%). The incidence of ADRs in patients with previous medication of OCS (n = 175, 9.21%) was higher than that in those without previous OCS (n = 115, 6.76%). The incidence of ADRs in patients with previous medication of SABA (n = 71, 11.40%) was higher than that in those without previous SABA (n = 219, 7.35%). The incidence of ADRs in patients with concomitant medication of SABA (n = 72, 10.79%) was higher than that in those without concomitant SABA (n = 218, 7.43%). ADRs with ≥5 episodes found in women only were injection site reactions (n = 19, 0.52%), and anaphylactic reaction, wheezing, vomiting, and myalgia (reported as n = 5, 0.14% each). Of these, the serious ADRs were anaphylactic reaction (n = 4, 0.11%) and myalgia (n = 1, 0.03%), and the outcome of all serious ADRs was recovered or improved.

No ADRs were reported in 7 pediatric patients aged < 15 years. However, in patients between 15 and 18 years of age, ADRs were reported in 2 patients as non-serious episodes of headache, rash, and menstruation irregularity. No ADRs were reported in the 7 pregnant patients.

3.2.4. Incidence of anaphylaxis

Of 3620 patients, 8 (0.22%) experienced AEs of anaphylaxis, of which 6 (0.17%) were ADRs (anaphylactic reaction, n = 5; anaphylactoid reaction, n = 1) and the remaining 2 cases were not associated with omalizumab treatment. The mean number of days to onset of anaphylaxis from first administration in patients was 7.0 (range 1–30 days). Anaphylactic reaction occurred after the first dose of omalizumab in 4 out of 5 patients (1 case occurred after second administration). All patients recovered or improved within a mean duration of 5.4 days (range 1–17 days). The patient with anaphylactoid reaction recovered within 2 days.

3.2.5. Death

Death was reported as a reason for discontinuation/withdrawal from the study by 16 patients. During the observational period (not during the follow up), 62 patients with 75 AE episodes suffered from a fatal outcome. Of these 75 episodes, the association with omalizumab was not ruled out for two episodes (myocardial infarction and uterine cancer). The common causes of death included pneumonia (14 episodes) followed by asthma (8 episodes), acute cardiac failure (5 episodes), and sepsis, myocardial infarction and unknown reasons (3 episodes each).

3.3. Efficacy outcomes

Among the patients evaluated for GETE, omalizumab treatment was effective in 58.29% of patients at 16 weeks and in 62.40% at 52 weeks. When reporting improvement with omalizumab, and including 'moderate' GETE rating, the responder rates were 86.04% at 16 weeks and 89.38% at 52 weeks (Fig. 2).

Following omalizumab treatment, fewer events related to asthma exacerbation were seen across all categories, corresponding to reduced annualized asthma-related incidences (before vs. after treatment: mean ± SD) of: worsening of asthma symptoms requiring additional systemic steroid therapy (10.8 ± 55.24 vs. 4.7 ± 18.79), hospitalization (0.6 ± 3.12 vs. 0.4 ± 7.38), emergency room visits (2.0 ± 11.10 vs. 0.9 ± 8.65), unscheduled hospital visits (5.4 ± 26.23 vs. 2.0 ± 12.14), and absence from school/work (including housework; 4.3 ± 79.67 vs. 0.6 ± 9.38). The percentage of patients experiencing two or more annual asthma exacerbation requiring additional systemic steroid therapy was 63.35% before treatment and 42.02% after treatment, and thus was reduced by 21.33%. Also, nearly half of all patients were free from exacerbations following therapy (Fig. 3).

In patients receiving concomitant OCS, all events related to asthma exacerbation after treatment improved when compared to pre-treatment (supplementary figure 2). Omalizumab also reduced the mean OCS dose at 16 and 52 weeks when compared with baseline, both reductions statistically significant ($P < 0.0001$ at 16 and 52 weeks) (Fig. 4).

Difference between baseline and each time-point (16 or 52 weeks) was tested with one sample *t*-test; n, number of patients who continued omalizumab from baseline to each time-point (16 or 52 weeks); OCS, oral corticosteroids.

Patient-reported outcomes in 522 patients with asthma diaries showed reduced frequency of mild and moderate asthma attacks with treatment, though no obvious trend was noted for severe attacks. Omalizumab also improved ratings for activities of daily living and sleep quality, and reduced use of rescue medications. The symptom scores also indicated a reduction in wheezing and cough upon treatment with omalizumab (supplementary table 3).

The omalizumab dosing table has been adapted during the study period. The approved dosing conversion table for omalizumab was changed to 75–600 mg on August 20, 2013, when the majority of patients had been already enrolled in this surveillance. Out of the 3620 patients in the safety analysis set, there were 15 patients (0.41%) with a dose or dose-intervals change according to the new dosing conversion table. In these 15 patients, no ADRs were reported either before or after the change. There were also no patients whose physician's GETE worsened between the most recent evaluation before the change in dose or dose-intervals after the change.

4. Discussion

Over the last 15 years, approximately 400,000 patients with moderate-to-severe asthma have been treated with omalizumab [36]. Clinical trials and numerous observational studies illustrate omalizumab's therapeutic profile of clinical benefits, tolerability, and low risk for drug interactions [24,25,37–42].

The current study validates the safety and efficacy of omalizumab in a real-world clinical practice setting in Japan, and provides the first evidence for omalizumab-related outcomes in a large Japanese adult population with severe asthma. The incidence of ADRs reported in Japanese clinical studies prior to the approval of omalizumab was 47.2%, and in a real-life clinical setting, incidence of ADRs appears markedly lower. In this surveillance study, incidence of ADRs was significantly different for the following factors: age, gender, past medical history of anaphylactoid symptoms, previous medication (OCS and SABA) and concomitant SABA. A gender discrepancy in ADR was seen between women and men in this study, with incident ADRs in women and men of 9.82% and 4.90%, respectively. Gender differences in omalizumab safety were not apparent in patients treated for chronic urticaria (a disease more prevalent in women than men) [43–45] or patients treated during pregnancy [46]. ADR rates of 10% or lower associated with omalizumab use have been reported in prior observational studies [47], and are consistent with the findings in women in this study. The reasons why the incidences of ADRs were higher in women is unknown, but the ADRs that were commonly reported in women were previously described events and were listed as precautions on the package insert.

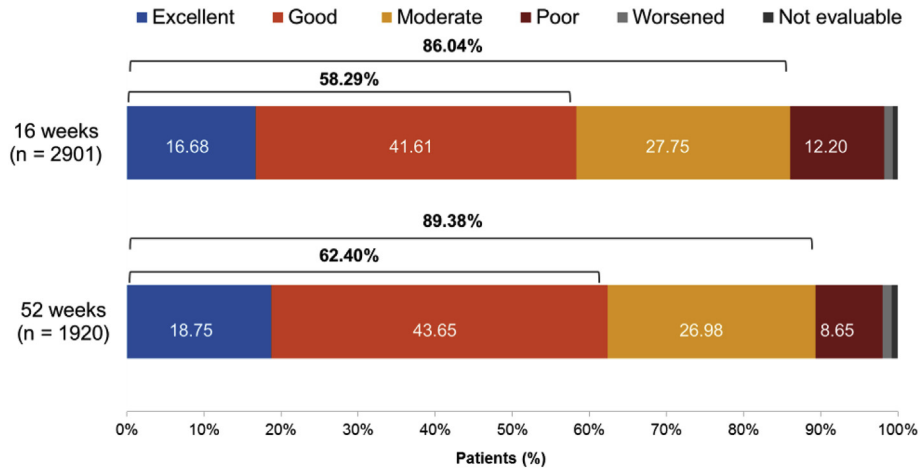

Fig. 2. Proportion of patients with GETE evaluations at 16 and 52 weeks.
n, number of patients; GETE, Global Evaluation of Treatment Effectiveness.

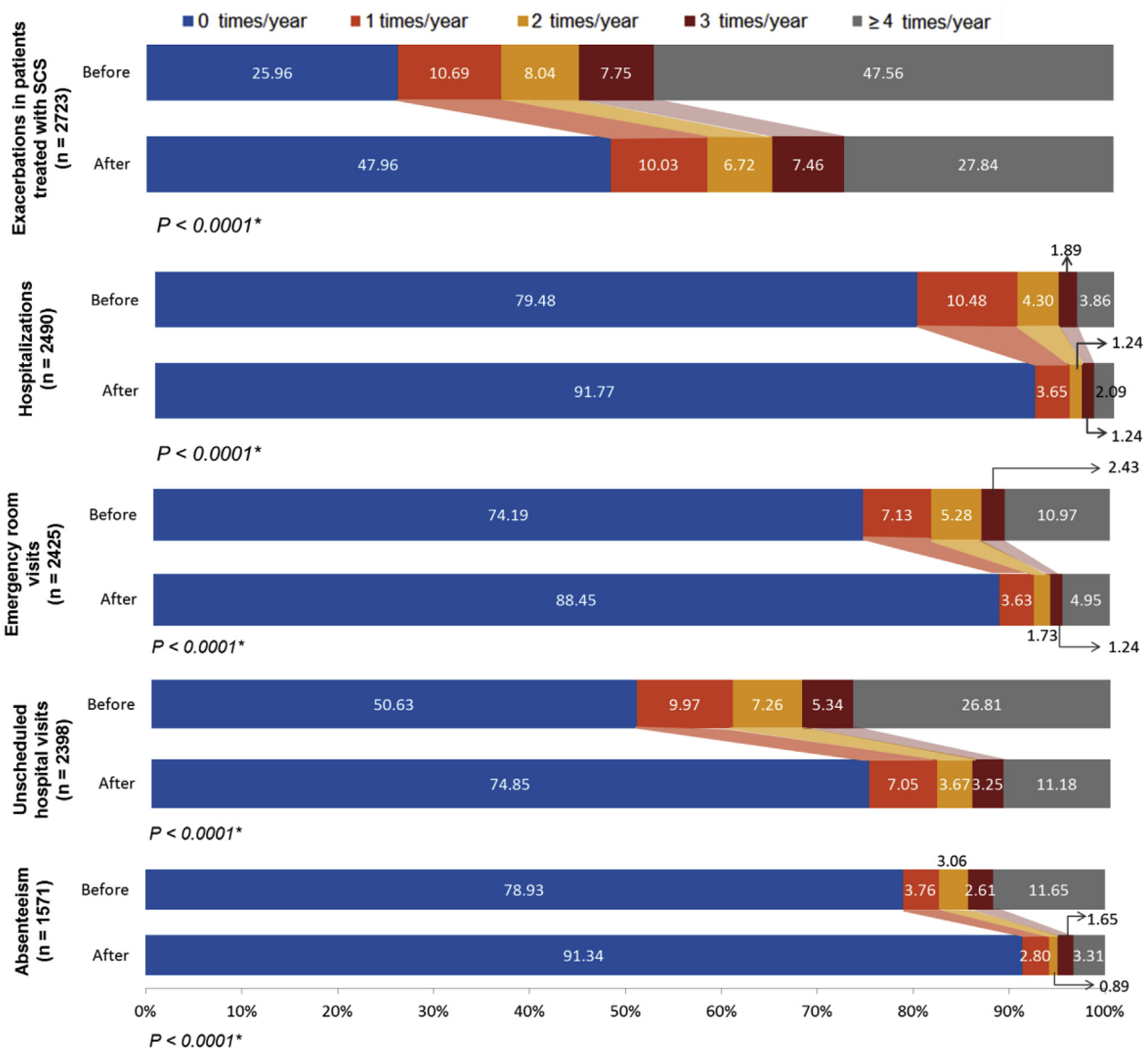

Fig. 3. Exacerbations and related events in patients across all events at baseline.
n, number of patients; SCS, systemic corticosteroid; *Difference between before and after treatment was tested using Wilcoxon signed-rank test.

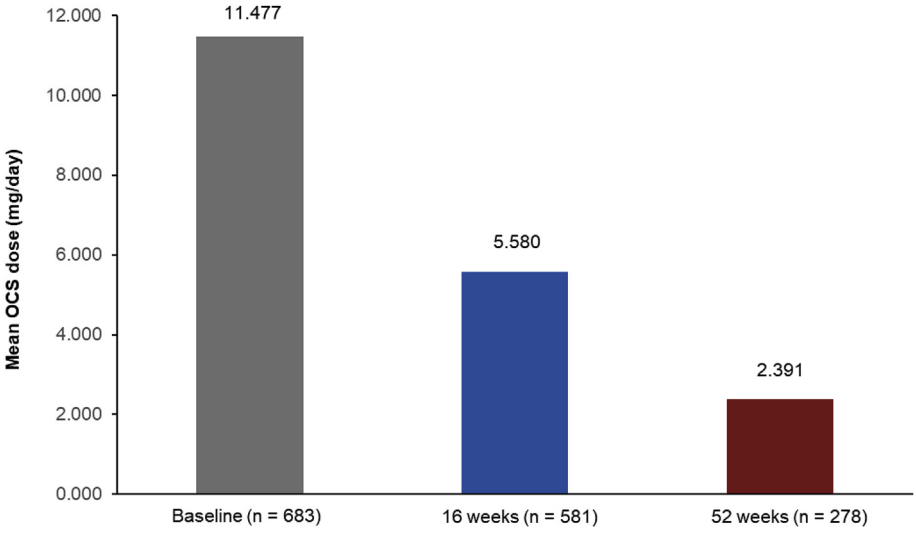

Fig. 4. Mean change in OCS dose from baseline in patients receiving omalizumab treatment.

In general, favorable safety trends were observed across the entire PMS study population. In this study, ADRs of special interest occurred in a minority of patients (0.64%) and were classified as eosinophilic syndromes (0.39%), anaphylaxis (0.17%), autoimmune disease (0.14%), malignant tumor (0.03%), and bleeding tendency (0%). The incidence of eosinophilic events was the highest with 13 cases of blood eosinophilia, 2 cases of eosinophilic granulomatosis with polyangiitis, and 1 case of eosinophilic pneumonia. Observed rates of anaphylactic or anaphylactoid reaction were similar to previous estimates of around 0.2% [48]. All of the patients reporting anaphylaxis in this study improved. A single case of malignancy (uterine cancer) occurred during the study period. Increased malignancy potential was not associated with omalizumab therapy when assessed prospectively comparing cohorts of omalizumab (n = 5007) and non-omalizumab users (n = 2829) in the US [42]. In summary, no noteworthy or newly reportable safety signals by study items of special interest, by patient characteristics, by concomitant medication use, or by ADRs in special populations (in particular, no ADRs specific to patients ≥65 years old) were observed in this study.

Robust reductions in exacerbations were observed following omalizumab therapy. Omalizumab's largest treatment effect was seen in those patients with the poorest asthma control (the difference in the group of patients with ≥4 exacerbations before and after omalizumab therapy was 47.56% and 27.84%, respectively). Moreover, nearly half (47.96%) of the treated patients were free from annual exacerbations following therapy. Similarly, hospitalizations, emergency room visits, and unplanned medical care were significantly reduced.

Of demographic interest, the study population was enriched for older (≥65 years) patients with asthma (1597 patients, 44.12%), a distinguishing feature when compared with previous patient cohorts receiving omalizumab in most trials [20,30,40,49], registries [41,50,51], or real-world studies [32,37,38,52]. In the context of available data, enrolled patients were older (by mean age) in the current study (59.3 years) when compared with the eXpeRience registry (45.0 years) and the severe asthma adult cohort of SARP III (49.7 years) [41,53]. Clinical efficacy in patients older than 50 years was previously shown in a subgroup of 174 German patients receiving omalizumab (mean age was not reported) [54]. This prospective investigation in a large elderly cohort of severe asthma patients affirms the beneficial profile of omalizumab despite advancing age.

The GINA and Japanese Asthma Guidelines (2017) recommend using LTRAs and theophylline as alternate or add-on therapy, and the reported rates of use reflect typical clinical practices in Japan [10]. Regarding potential for AEs, toxicity, and drug interactions, the safety profile of omalizumab is favorable to theophylline. The current data presents an interesting exploration regarding the burden of multi-medication regimens in Japan (frequently incorporating theophylline) and highlights the struggle to achieve and maintain asthma control when maximizing the available options within the current treatment paradigm.

In severe asthma, patients treated with OCS as concomitant medication are presumed to be patients who have difficulty in achieving asthma symptom control. Theoretically, it would be more difficult to gain a therapeutic effect in these patients; however, in patients receiving OCS, improvements were reported in all events related to asthma exacerbation after treatment with omalizumab compared to pre-treatment. OCS are a frequent concomitant medication and prospective studies show OCS use in patients who are prescribed omalizumab to be between 30% and 50% [39,41,42,55,56]. Likewise, half of the Japanese patients in this study reported OCS use. Phase III asthma registration studies in Japan attempted to exclude OCS users, and evidence for OCS-sparing effects needed to be generated independently. Results of the current study align with previous findings that omalizumab had numerous therapeutic benefits in severe asthma patients irrespective of OCS use, and additionally, omalizumab use also reduced OCS exposure [41,57–59]. Although Japanese asthma guidelines recommend omalizumab before considering OCS [11], the rate of OCS use remains high in Japan. Whether prevalence of OCS use reflects refractory disease or reluctance to use omalizumab due to practical factors such as cost, formulary availability, patient or physician preference, or other variables, was not assessed in this study. The clinical benefits related to omalizumab are well characterized here, and this evidence may encourage additional opportunities to reduce OCS exposure in Japanese patients with severe asthma, considering the side effects associated with long-term OCS use.

While outside the scope of our study, clinical (real-world) evidence supporting the efficacy of omalizumab as a treatment strategy for non-allergic asthma, asthma and chronic obstructive pulmonary disease (COPD) overlap, and other non-IgE-mediated diseases is also growing [60–66], as is the mechanistic understanding for potential airway remodeling effects [67–73]. In the future, omalizumab therapy may be more broadly applicable.

The study was conducted according to the local regulatory requirements under GPSP. Study limitations include the open-label design without a control group, and variable data capture outside of a monitored trial environment as noted by partial adherence with asthma symptom diaries. Symptom reporting, available for 522 patients, showed improving trends similar to prior reports in Japanese patients

with poorly controlled moderate-to-severe asthma following omalizumab therapy [24,25].

This study has a couple of other limitations. Majority of patients were aged 20–65 years and many had a smoking history; this may predispose this population to other respiratory conditions such as COPD, which might influence treatment response. However, the diagnosis of COPD was not clearly recorded in the survey data. Additionally, we assessed the symptoms through diaries provided to patients, and did not use symptoms questionnaires such as ACQ, ACT or AQLQ; instead patient-reported outcomes were captured by patient symptom diaries, thus the assessment relied on patient reporting, although not all patients completed these assessments.

Despite certain study limitations in our study, the results successfully demonstrate real-world practices and outcomes associated with omalizumab use in Japan.

5. Conclusion

This 52-week prospective, post-marketing study with an optional 2-year extension arm showed that the real-world safety and efficacy outcomes following long-term omalizumab therapy in Japanese patients with severe allergic asthma were consistent with previous reports. Almost half of the study population was over 65 years of age, demonstrating clinical efficacy of omalizumab for severe asthma irrespective of advancing age.

Author contributions

All authors contributed to the conception and design of the study, facilitated the writing and reviewed the manuscript. All authors contributed to the development of the manuscript and approved the final version.

Conflicts of interest

Prof Mitsuru Adachi reports non-financial support from Novartis, during the conduct of the study; personal fees from Boehringer Ingelheim, Kyowa Hakko Kirin and Kyorin Pharmaceutical. Prof Terumasa Miyamoto has no conflict of interest. Prof Ken Ohta reports non-financial support from Novartis, during the conduct of the study; grants from Ministry of Health, Labour and Welfare, grants and personal fees from Environmental Restoration and Conservation Agency, grants and personal fees from MSD, personal fees from Kyorin, AstraZeneca, Astellas and Boehringer Ingelheim, outside the submitted work. Masanari Kozawa, Hajime Yoshisue, Ki Lee Milligan, Makoto Nagasaki, and Takayoshi Sasajima are employees of Novartis Pharma K.K.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2018.06.021.

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