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ORIGINAL ARTICLE

One Year Treatment with Omalizumab Is Effective and Well Tolerated in Japanese Patients with Moderate-to-Severe Persistent Asthma

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ABSTRACT

Background: We have previously demonstrated that addition of omalizumab to standard therapy improved asthma control by significantly improving lung function and reducing asthma exacerbations in Japanese patients with moderate-to-severe asthma. The aim of this study was to evaluate the effects of omalizumab on long-term disease control in Japanese patients with moderate-to-severe persistent asthma.

Methods: An open-label, 48-week study was conducted in 133 Japanese patients with moderate-to-severe persistent asthma. Omalizumab was administered subcutaneously every 2 or 4 weeks based on serum IgE level and body weight in each patient.

Results: Treatment with omalizumab significantly improved lung function. A subgroup of patients with inadequately controlled severe persistent asthma, despite high dose inhaled corticosteroids and other multiple controller therapies, which corresponds to the Japanese label (label population), showed greater improvements in morning PEF and FEV_1 than the whole study population (full Analysis Set). Serum free IgE levels decreased to below the target and were maintained during the treatment period in almost all patients. The majority of adverse events were mild-to-moderate in severity and there was no trend toward an increase in incidence of adverse events with increase in duration of omalizumab. In addition, the profile of adverse events in this study was similar to that in a 16-week, placebo-controlled study which the present authors had conducted previously in Japan. There were no anaphylactic reactions and no anti-omalizumab antibodies were detected.

Conclusions: Long-term treatment with omalizumab is effective and well tolerated in Japanese patients with moderate-to-severe persistent asthma.

KEY WORDS

asthma, efficacy, Japanese, omalizumab, safety evaluation

INTRODUCTION

Asthma is the cause of a significant health, economic and social burden, which increases with increasing asthma severity. Patients with inadequately controlled, severe asthma are at a particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life.[1-6] In recent years, several patient surveys have shown that many patients with asthma remain poorly controlled around the world, despite nationally promoted treatment standards and improved therapeutic agents.[7-9] In Japan, 2540 patients died from asthma in 2007[10] and the annual mortality rate is higher than in the United States or European countries.

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, selectively binds to the Cε3 domain of IgE that interacts with IgE receptors.[11] This antibody blocks the binding of IgE to high affinity receptors on the effecter cells, thereby preventing the

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IgE-mediated cellular responses.[12] In patients with moderate-to-severe allergic asthma, omalizumab significantly reduced the rate of exacerbations and emergency visits for asthma and improved asthma related quality of life.[13-20]

As we had previously demonstrated the noticeable clinical effects of omalizumab in a 16 week, randomized, double-blind, placebo-controlled study in Japanese patients with moderate-to-severe persistent asthma,[21] we conducted further investigation on the long-term efficacy and safety of omalizumab in Japanese patients.

The objective of this 1-year, open-label study was to evaluate the long-term efficacy and safety of omalizumab in Japanese patients with moderate-to-severe persistent asthma. In addition to the whole study population [full analysis set (FAS)], we also focused on a subgroup of patients with inadequately controlled severe persistent asthma, despite high dose inhaled corticosteroids (ICS) and other multiple controller therapies, which corresponds to the Japanese label (label population).

METHODS

PARTICIPANTS

Eligible patients were aged 20-75 years with moderate-to-severe allergic asthma according to the Japanese guidelines for diagnosis and management of asthma,[22] which is equivalent to the Global Initiative for Asthma (GINA) Guidelines 2002,[23] whose disease was poorly controlled. Poor control was defined as meeting one of the following criteria during the screening period: 1) asthma symptom score of $\geq$2.0 every 2-week period, 2) use of rescue medication on $\geq$one day every 2-week period, 3) diurnal variation in PEF of $\geq$20% on $\geq$one day every 2-week period, 4) FEV_1 or mean PEF of 40 to 80% of predicted normal value for the patient per week. All patients were receiving $\geq$400 μg/day inhaled beclomethasone dipropionate CFC (or equivalent) one month prior to the screening period. Further inclusion criteria included 5) a positive skin test or in vitro reactivity to a perennial aeroallergen or a serum total IgE level of more than the normal value (170 IU/mL), 6) a serum total IgE level of 30 to 700 IU/mL and body weight of 30 to 150 kg to allow optimal dosing of omalizumab.

Patients who had a history of the following were excluded from the study: 1) active lung disease other than allergic asthma, considered to interfere with the evaluation; 2) use of immunosuppressants within 3 months of the first visit; 3) a history of severe anaphylactoid or anaphylactic reactions; 4) positive reaction to omalizumab in the skin test at screening; 5) pregnant/nursing women; and 6) serious medical conditions (e.g., cancer, hepatic failure, and renal failure).

STUDY DESIGN

This open-label study was conducted at 24 medical centers in Japan and consisted of a 2-week screening period, a 48-week treatment period, and a 12-week follow-up period after final dosing.

Omalizumab (150 or 300 mg every 4 weeks or 225, 300, or 375 mg every 2 weeks) was administered to patients subcutaneously based on their serum total IgE level and body weight at baseline, which ensured a minimum dose of 0.016 mg/kg/IgE (IU/mL) every 4 weeks.[24]

The doses of ICS and other concomitant asthma medications were kept constant during the screening period and maintained during the treatment period as much as possible. Use of rescue medication was permitted as required throughout the study.

The study was conducted in accordance with the current good clinical practice, and the protocol was approved by each institutional ethics committee. Prior to the onset of the study, a written informed consent was obtained from all patients who were enrolled. The study was registered at http://clinicaltrials.gov with the identifier: NCT00219323.

EVALUATION OF EFFICACY

During the screening and treatment periods, morning PEF was measured by using a mini-Wright peak flow meter (ATS scale) and the best of three measurements was recorded daily in the patient diary. Symptoms of asthma, daily activity and nocturnal sleep limitations and use of asthma medications were also recorded in the diary and scores (asthma symptom score, daily activity score and sleep score) were calculated according to the standard rating scale of the Japanese Society of Allergology. Spirometry was performed at baseline and at 12, 24, 36 and 48 weeks of the treatment period.

SERUM FREE IgE LEVELS

Blood samples were collected for measurement of free IgE at baseline and at 16, 24 and 48 weeks of the treatment period. Free IgE were measured by ELISA as previously described.[25]

EVALUATION OF SAFETY

Adverse events were examined throughout the treatment period. Clinical laboratory tests were conducted at baseline and at 4, 12, 16, 24, 36 and 48 weeks of the treatment period. Anti-omalizumab antibodies (IgG subtype) were measured by using solid-phase ELISA at baseline and 12 weeks post final dosing.[26]

STATISTICAL ANALYSIS

Statistical analyses were performed using data from all patients who received at least 1 dose of omalizumab [full analysis set (FAS)]. Outcomes were also evaluated in a subgroup of patients with inadequately controlled asthma, defined as 1) FEV_1 or mean PEF of 40 to 80% of predicted normal value each week, 2) daily daytime asthma symptoms or 3) night-time

Table 1 Baseline demographic and clinical characteristics

	Full analysis set (*n* = 133)	Label population † (*n* = 37)
Age (years)		
Mean (SD)	47.7 (15.42)	54.5 (14.92)
Median (range)	47 (20-74)	53 (24-74)
Sex, *n* (%)		
Male	72 (54.1)	18 (48.6)
Female	61 (45.9)	19 (51.4)
Weight (kg), mean (SD)	61.2 (11.90)	57.2 (12.08)
Total serum IgE (IU/mL), median (range)	210 (31-680)	240 (31-680)
Duration of asthma (years), mean (SD)	13.7 (13.11)	18.3 (14.69)
Smoking history, *n* (%)		
Never smoked	68 (51.1)	19 (51.4)
Current smoker or ex-smoker	65 (48.9)	18 (48.6)
GINA (2002) asthma severity, *n* (%)		
Mild	5 (3.8)	0
Moderate	14 (10.5)	0
Severe	114 (85.7)	37 (100)
Profile of poor asthma control in the previous year		
Patients with ≥1 emergency room visits, *n* (%)	24 (18.0)	11 (29.7)
Patients with ≥1 hospitalization, *n* (%)	10 (7.5)	5 (13.5)
FEV_1 (% of predicted), mean (SD)	77.3 (20.47)	65.6 (19.09)
Morning PEF (L/min), mean (SD)	343.3 (114.17)	284.9 (102.49)
Equivalent BDP CFC dose (μg/day)		
Mean (SD)	1026 (568.3)	1487 (657.1)
Median (range)	800 (400-3600)	1600 (800-3600)
Concomitant medications, *n* (%)		
Long-acting β_2-agonists	54 (40.6)	29 (78.4)
Sustained-release theophyllines	79 (59.4)	30 (81.1)
Anti-leukotrienes	51 (38.3)	27 (73.0)
Oral corticosteroids	14 (10.5)	13 (35.1)

GINA, Global Initiative for Asthma; BDP, beclometasone dipropionate.

† A subgroup of patients with inadequately controlled severe persistent asthma despite high dose inhaled corticosteroids and multiple other controller therapies, which corresponds to the Japanese label.

awaking at least once a week who were receiving high-dose ICS plus additional controller medications out of long-acting β_2-agonist (LABA), theophylline, anti-leukotriene or oral corticosteroids, which corresponds to the Japanese label (label population).

The changes from baseline in morning PEF and FEV_1 in the FAS as well as in the label population were summarized using summary statistics every 2 weeks, and 1 sample t-test with respect to the change from baseline in morning PEF and FEV_1 was performed. Asthma symptom score, daily activity score and sleep score at each week in the FAS and the change from baseline were summarized using summary statistics every 2 weeks.

The safety and tolerability of the study drugs were summarized using appropriate descriptive methods.

RESULTS

PATIENTS

A total of 133 patients were enrolled in this study. Nine patients withdrew from the study; 5 due to administrative problems, 2 patients due to adverse events, 1 patient withdrew by consent and 1 patient died. No patients discontinued due to unsatisfactory therapeutic effects.

A summary of the demographic and baseline characteristics are shown in Table 1. Thirty seven patients were included in the label population. The majority of patients (85.7% in the FAS and 100% in the label population) had severe persistent asthma as defined by the GINA guidelines 2002.[23] Patients in the label population had less controlled asthma, compared with the FAS, despite receiving higher dose of ICS and more additional controller medications.

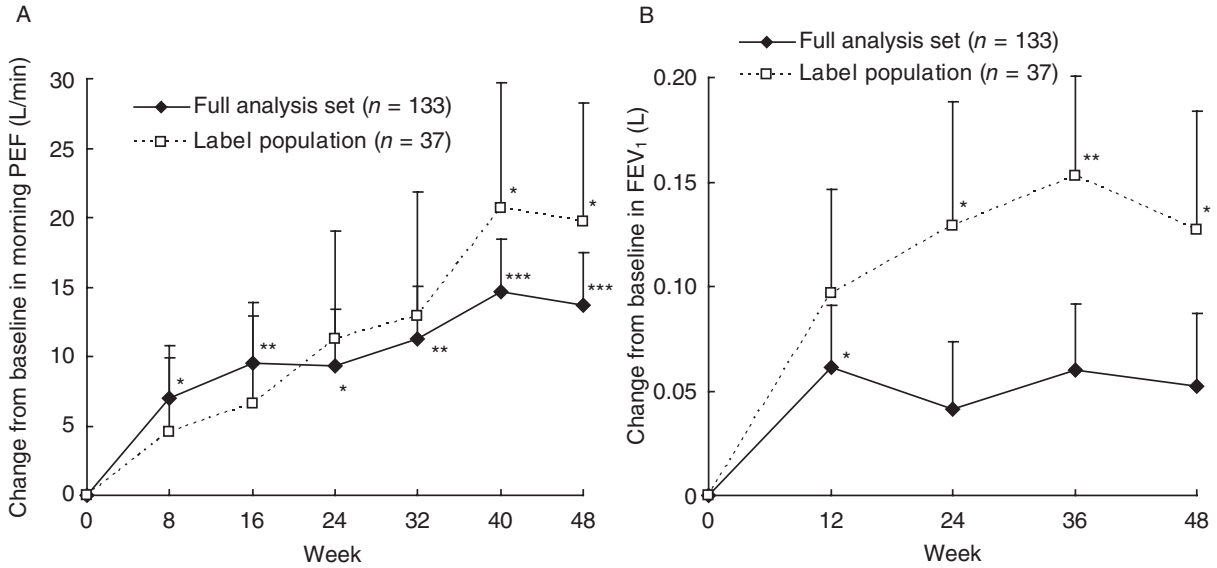

Fig. 1 Changes over time from baseline in mean morning PEF (**A**) and FEV_1 (**B**). Data are means + SE. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with the baseline (one sample t-test). At baseline, mean (SD) PEF was 343.3 L/min (114.18) in the full analysis set (FAS) and 285.0 L/min (102.55) in the label population (A subgroup of patients with inadequately controlled severe persistent asthma despite high dose inhaled corticosteroids and multiple other controller therapies, which corresponds to the Japanese label). Mean (SD) baseline FEV_1 was 2.32 L (0.915) and 1.76 L (0.680), respectively.

LUNG FUNCTION (MORNING PEF AND FEV_1)

Changes over time from baseline in mean morning PEF and FEV_1 are shown in Figure 1A, B. Treatment with omalizumab resulted in significant increases from baseline in mean morning PEF. At week 48 (study completion), the mean change from baseline in morning PEF was 13.7 L/min ($P < 0.001$) in the FAS and 19.7 L/min ($P = 0.028$) in the label population.

Significant improvements were also seen in the changes from baseline in FEV_1. The mean change from baseline in FEV_1 was 0.127 L ($P = 0.031$) in the label population at the time of study completion.

Morning PEF and FEV_1 further improved in the label population compared with the FAS (Fig. 1A, B).

ASTHMA SYMPTOM SCORE, DAILY ACTIVITY SCORE AND SLEEP SCORE

Treatment with omalizumab led to improvements in asthma symptom scores. Daily activity scores and sleep scores at the time of study completion slightly improved (lower) compared with baseline (Table 2).

SERUM FREE IgE LEVELS

Serum free IgE levels decreased markedly, compared to the baseline levels, to below the target (50 ng/mL) at 16, 24, and 48 weeks of the treatment period in almost all patients [127 of 128 (99.2%), 125 of 126 (99.2 %) and 128 of 131 (97.7%), respectively].

SAFETY

Overall, 131 of 133 (98.5 %) patients experienced at least one adverse event. The majority of adverse events were mild-to-moderate in severity and only 3 patients experienced severe adverse events.

The most common adverse events were nasopharyngitis (63.2%), injection site reactions (35.3%), upper respiratory tract inflammation (21.1%) and headache (18.8%) (Table 3). Injection site reactions were the most frequently reported drug-related adverse events occurring in a total of 38 (28.6 %) patients. All of the injection site reactions were of a mild degree and resolved without any additional treatment.

There was generally no trend toward an increase in incidence of adverse events with an increase in duration of omalizumab (Table 4).

Six patients experienced serious adverse events; these included 1 death due to an asthmatic attack. No serious adverse events were considered to be drug-related.

Two patients discontinued treatment prematurely because of adverse events (urticaria and iron deficiency anaemia/hiatus hernia), which were of a severe degree. Urticaria, which developed 10 days after the first dose, was suspected to be drug-related and resolved completely with additional treatments.

There were no anaphylactic reactions, and neither evidence of immune complex disease, nor clinically important abnormalities in vital signs and laboratory tests were found. No anti-omalizumab antibodies were detected.

Table 2 Change from baseline in asthma symptom score, daily activity score and sleep score in the full analysis set (FAS)

	Asthma symptom score (*n* = 132)	Daily activity score (*n* = 133)	Sleep score (*n* = 132)
Baseline			
Mean (SD)	15.5 (17.42)	18.9 (26.74)	10.2 (13.23)
Median (range)	11.0 (0.0-119.8)	0.0 (0.0-112.0)	3.2 (0.0-56.0)
Change from baseline			
8 weeks	*n* = 132	*n* = 132	*n* = 132
Mean (SD)	-1.5 (15.97)	0.4 (18.24)	-0.2 (10.82)
Median (range)	-1.1 (-43.5-112.8)	0.0 (-56.0-64.0)	0.0 (-28.3-32.0)
16 weeks	*n* = 130	*n* = 130	*n* = 130
Mean (SD)	-4.8 (14.44)	-2.1 (19.80)	-1.6 (11.64)
Median (range)	-2.9 (-87.3-32.7)	0.0 (-96.0-59.4)	0.0 (-32.0-30.0)
32 weeks	*n* = 125	*n* = 125	*n* = 125
Mean (SD)	-6.7 (17.01)	-3.4 (21.39)	-2.0 (10.57)
Median (range)	-3.5 (-110.3-33.5)	0.0 (-78.0-120.0)	0.0 (-32.0-36.0)
48 weeks	*n* = 123	*n* = 123	*n* = 123
Mean (SD)	-6.2 (12.73)	-3.3 (16.89)	-2.3 (10.25)
Median (range)	-4.0 (-65.8-26.0)	0.0 (-56.0-56.0)	0.0 (-32.0-28.0)

DISCUSSION

This is the first study investigating the long-term efficacy and safety of omalizumab in Japanese patients with moderate-to-severe persistent asthma.

Treatment with omalizumab provided significantly improved lung function, which was maintained during 48 weeks of the treatment period. Improvements in morning PEF and FEV_1 from baseline in the label population were greater than in the FAS, though patients in the label population had lower lung function at baseline, despite receiving higher-dose ICS and more controller medications, including LABA and oral corticosteroids, than the FAS. These results could strongly support the potential role of omalizumab in management of patients with inadequately controlled asthma despite standard medications.

In addition to lung function, asthma symptom scores also improved. Modest improvements in daily activity score and sleep score may be because daily activity or nocturnal sleep limitations were not mandatory requirements in the inclusion criteria and about half of the patients had baseline values of zero in daily activity scores [50.4% (67 patients)] and in sleep scores [45.5% (60 patients)], respectively. These patients might have influenced the power to detect the changes and in fact, greater improvements in change from baseline were seen in subgroups of patients with any scores at baseline (mean [SD] and median [range]: -10.0 [20.65] and -8.0 [-56.0-39.4] for daily activity scores, -6.6 [10.91] and -6.0 [-32.0-24.0] for sleep scores, at study completion).

Though this was an open-label, uncontrolled study and there are limitations in interpretations of the results, this study suggests that there is no evidence of loss of efficacy with long-term omalizumab treatment.

As consistent with the efficacy results, serum free IgE levels decreased markedly to below 50 ng/mL at 16, 24, and 48 weeks of the treatment period in almost all patients.

One year treatment with omalizumab was generally well tolerated. The majority of adverse events were of a mild-to-moderate degree and there was no trend toward an increase in incidence of adverse events with an increase in duration of omalizumab.

In addition, the profile of adverse events in this study was similar to that in the omalizumab group in the 16-week, placebo-controlled study[21] which the present authors had conducted previously in Japan. Despite the longer treatment period in this study compared with the previous study, the percentage of patients experiencing $\geq$1 adverse events and $\geq$1 drug-related adverse events in this study was comparable with that in the previous study [adverse events, 98.5% for this study and 90.1% (136 of 151) for the previous study; drug-related adverse events, 45.9% and 48.3% (73 of 151), respectively]. In both studies, the most common adverse events were nasopharyngitis, injection site reactions, upper respiratory tract inflammation and headache. The most frequently reported drug-related adverse events were also injection site reactions [28.6% for this study and 33.1% (50 of 151) for the previous study].

There were no cases of anaphylaxis and no cases of significant immune complex-mediated disorders. No anti-omalizumab antibodies were detected.

Therefore, there is no evidence that new or more serious adverse events occur with long-term omalizumab treatment.

Results of several large randomized studies[13-21] have established omalizumab as an effective and well tolerated agent for use as add-on therapy in patients

Table 3 Number (%) of patients with most frequently reported adverse events (≥5%) and drug-related adverse events (≥3%)

System organ class	Preferred term	Full analysis set (n = 133) n (%)
Adverse events (≥5%)		
Total adverse events		131 (98.5)
Gastrointestinal disorders	Enterocolitis	8 (6.0)
	Diarrhoea	7 (5.3)
	Gastritis	7 (5.3)
	Toothache	7 (5.3)
General disorders	Injection site reactions	47 (35.3)
and administration site conditions	Injection site erythema	20 (15.0)
	Injection site swelling	15 (11.3)
	Injection site pain	12 (9.0)
	Injection site haemorrhage	10 (7.5)
	Injection site pruritus	10 (7.5)
	Oedema peripheral	7 (5.3)
Infections and infestations	Nasopharyngitis	84 (63.2)
	Acute bronchitis	16 (12.0)
	Influenza	11 (8.3)
	Pharyngitis	8 (6.0)
	Dental caries	8 (6.0)
	Gastroenteritis	7 (5.3)
Investigations	C-reactive protein increased	15 (11.3)
	White blood cell count increased	13 (9.8)
	Glucose urine present	8 (6.0)
	Alanine aminotransferase increased	7 (5.3)
Musculoskeletal and connective tissue disorders	Back pain	12 (9.0)
Nervous system disorders	Headache	25 (18.8)
Respiratory, thoracic	Upper respiratory tract inflammation	28 (21.1)
and mediastinal disorders	Pharyngolaryngeal pain	7 (5.3)
Skin and subcutaneous tissue disorders	Pruritus	8 (6.0)
	Eczema	7 (5.3)
Drug-related adverse events (≥3%)		
Total drug-related adverse events		61 (45.9)
General disorders	Injection site erythema	19 (14.3)
and administration site conditions	Injection site swelling	13 (9.8)
	Injection site pruritus	9 (6.8)
	Injection site pain	8 (6.0)
	Injection site haemorrhage	5 (3.8)
	Injection site induration	5 (3.8)
	Injection site warmth	4 (3.0)
Investigations	Immunology test abnormal	5 (3.8)

with severe persistent allergic asthma inadequately controlled with high-dose ICS plus a LABA (European Union labeling) or those with moderate to severe disease inadequately controlled with ICS (United States labeling). Omalizumab has recently (January 2009) been approved in Japan as an add-on therapy for patients whose symptoms are inadequately controlled despite standard medications (high-dose ICS plus additional controller medications), which is similar to the indication in the European Union. In addition, international asthma management treatment guidelines (by GINA[23] and the National Heart, Lung, and Blood Institute[27]) acknowledge the importance of omalizumab as a treatment option in these difficult-to-treat patient populations. Further investigations will likely reveal additional roles of IgE or mast cells in the pathophysiology of severe asthma (e.g., remodeling of the airway wall), as well as the therapeutic potential of omalizumab.

In conclusion, the results of this study indicate that

Table 4 Adverse events in every 12 weeks (≥5%) in the full analysis set (FAS)

Period (weeks)	0-12 (n = 133)	13-24 (n = 131)	25-36 (n = 129)	37-48 (n = 125)	Over all (n = 133)
System organ class	n (%)	n (%)	n (%)	n (%)	n (%)
Total adverse events	106 (79.7)	104 (79.4)	89 (69.0)	86 (68.8)	131 (98.5)
Eye disorders	2 (1.5)	2 (1.5)	6 (4.7)	2 (1.6)	9 (6.8)
Gastrointestinal disorders	21 (15.8)	15 (11.5)	15 (11.6)	15 (12.0)	42 (31.6)
General disorders and administration site conditions	34 (25.6)	25 (19.1)	21 (16.3)	12 (9.6)	57 (42.9)
Infections and infestations	54 (40.6)	59 (45.0)	42 (32.6)	42 (33.6)	102 (76.7)
Injury, poisoning and procedural complications	1 (0.8)	3 (2.3)	4 (3.1)	2 (1.6)	9 (6.8)
Investigations	6 (4.5)	14 (10.7)	21 (16.3)	28 (22.4)	49 (36.8)
Musculoskeletal and connective tissue disorders	10 (7.5)	9 (6.9)	12 (9.3)	8 (6.4)	34 (25.6)
Nervous system disorders	18 (13.5)	10 (7.6)	10 (7.8)	4 (3.2)	32 (24.1)
Respiratory, thoracic and mediastinal disorders	20 (15.0)	26 (19.8)	18 (14.0)	13 (10.4)	45 (33.8)
Skin and subcutaneous tissue disorders	15 (11.3)	8 (6.1)	8 (6.2)	10 (8.0)	31 (23.3)
Vascular disorders	2 (1.5)	1 (0.8)	3 (2.3)	1 (0.8)	7 (5.3)

omalizumab is effective and well-tolerated in the long-term control of Japanese patients with moderate-to-severe persistent asthma.

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