Allergology International 64 (2015) 364–370

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original article

Omalizumab in Japanese children with severe allergic asthma uncontrolled with standard therapy

Hiroshi Odajima [a, *], Motohiro Ebisawa [b], Toshikazu Nagakura [c], Takao Fujisawa [d], Akira Akasawa [e], Komei Ito [f], Satoru Doi [g], Koichi Yamaguchi [h], Toshio Katsunuma [i], Kazuyuki Kurihara [j], Naomi Kondo [k], Kazuko Sugai [l], Mitsuhiko Nambu [m], Akira Hoshioka [n], Shigemi Yoshihara [o], Norio Sato [p], Noriko Seko [p], Sankei Nishima [a]

[a] Department of Pediatrics, Fukuoka National Hospital, Fukuoka, Japan
[b] Department of Allergy, Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan
[c] Yoga Allergy Clinic, Tokyo, Japan
[d] Institute for Clinical Research, Mie National Hospital, Mie, Japan
[e] Division of Allergy, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan
[f] Department of Allergy, Aichi Children's Health and Medical Center, Aichi, Japan
[g] Department of Pediatrics, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, Japan
[h] Department of Pediatrics, The Fraternity Memorial Hospital, Tokyo, Japan
[i] Department of Pediatrics, Jikei Daisan Hospital, Tokyo, Japan
[j] Department of Allergy, Kanagawa Children's Medical Center, Kanagawa, Japan
[k] Department of Pediatrics, Graduate School of Medicine, Gifu University, Gifu, Japan
[l] Department of Pediatrics, Fukuyama Medical Center, Hiroshima, Japan
[m] Department of Pediatrics, Tenri Hospital, Nara, Japan
[n] Department of Allergy and Rheumatology, Chiba Children's Hospital, Chiba, Japan
[o] Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan
[p] Clinical Development, Novartis Pharma K.K., Tokyo, Japan

ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form
7 April 2015
Accepted 1 May 2015
Available online 10 June 2015

Keywords:
Bronchial asthma
Children
Japanese
Omalizumab
Quality of life

Abbreviations:
AE, Adverse event; ELISA, Enzyme-linked immunosorbent assay; ER, Emergency room; $FEF_{25-75\%}$, Forced expiratory flow rate at 25%–75% of forced vital capacity; FEV_1, Forced expiratory volume in one second; FP, Fluticasone propionate; ICS, Inhaled corticosteroids; IgE, Immunoglobulin E; IV, Intravenous;

ABSTRACT

Background: Omalizumab has demonstrated clinical benefits in children with moderate to severe allergic asthma. However, no studies have been performed in Japanese asthmatic children. The aim of this study was to evaluate the efficacy including free IgE suppression and safety of omalizumab in Japanese children with severe allergic asthma. The primary objective was to examine whether omalizumab decreases serum free IgE levels to less than 25 ng/ml (target level of suppression).

Methods: Thirty-eight Japanese children (6–15 years) with uncontrolled severe allergic asthma despite inhaled corticosteroids (>200 μg/day fluticasone propionate or equivalent) and two or more controller therapies received add-on treatment with omalizumab in a 24-week, multicenter, uncontrolled, open-label study.

Results: The geometric mean serum free IgE level at 24 weeks was 15.6 ng/mL. Compared with baseline, total asthma symptom scores, daily activity scores and nocturnal sleep scores at 24 weeks were significantly improved. The rates of asthma exacerbation and hospitalization due to asthma were reduced by 69.2% and 78.2%, respectively ($p < 0.001$), versus baseline. Quality-of-life scores were also significantly improved ($p < 0.001$). In addition, 11 (28.9%) patients reduced the dose of any asthma controller medications. Thirty-six (94.7%) patients experienced at least one adverse event during the treatment period. All adverse events were mild or moderate in severity and no new safety concerns were detected. No patients discontinued the study.

Conclusions: In Japanese children with severe allergic asthma, omalizumab decreased free IgE levels to less than 25 ng/mL. Omalizumab improved asthma control and was well-tolerated, as well.

* Corresponding author. Department of Pediatrics, Fukuoka National Hospital, 4-39-1 Yakatabaru, Minami-Ku, Fukuoka 811-1394, Japan.
E-mail address: odaji@mfukuoka2.hosp.go.jp (H. Odajima).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.05.006

JPGL, Japanese pediatric guideline for the treatment and management of asthma;
LABA, Long-acting β_2-agonist;
LTRA, Leukotriene receptor antagonist;
PEF, Peak expiratory flow; QOL, Quality of life; SAE, Serious adverse event

Introduction

Asthma is one of the most common chronic diseases in childhood. In Japan, as well as in Western countries, the prevalence of pediatric asthma is increasing: between 1982 and 2002, it increased from 3.2% to 6.5%, representing a two-fold increase in just 20 years.[1] Asthma in children is often poorly controlled, usually as a result of undertreatment with controller medications; however, some children have poor asthma control even with the highest level of controller medications.[2,3]

Uncontrolled severe asthma results in a high risk of asthma exacerbations and impaired quality of life.[4] In particular, asthma exacerbations are associated with decline in lung function,[5] hospital admissions and emergency room (ER) visits,[6] and time lost from work and school.[7] They are frequently treated with systemic (oral or intravenous [IV]) corticosteroids, which, if used in multiple bursts over a period of years, can result in serious side effects such as a reduction in bone mineral accretion and an increased risk of osteopenia.[8]

The majority of children with asthma are atopic, and pediatric patients with severe asthma have higher mean immunoglobulin E (IgE) levels than those with moderate or mild asthma,[9] providing a particularly strong rationale for investigating anti-IgE therapy in this population.

Omalizumab is a humanized monoclonal anti-IgE antibody that binds IgE, rapidly suppressing free IgE concentrations; it prevents IgE from interacting with high-affinity IgE receptors on mast cells and basophils, thereby interrupting the allergic cascade.[10,11] Omalizumab is approved for the treatment of adults and adolescents (≥12 years) with moderate-to-severe (USA) or severe (EU) allergic (IgE-mediated) asthma,[12,13] and also for the treatment of adults with severe allergic asthma in Japan.[14] In the EU, the indication has recently been extended to include children (6–<12 years) with severe allergic asthma. In a randomized, double-blind, placebo-controlled study in children (6–<12 years) with moderate-to-severe allergic asthma, omalizumab significantly reduced asthma exacerbations compared with placebo.[15,16]

In the current study, the efficacy including free IgE suppression and safety of omalizumab in Japanese children aged 6–15 years with uncontrolled severe persistent allergic asthma were investigated for the first time, to confirm whether the outcome of treatment in a Japanese/Asian population is consistent with findings in previously studied populations.

Methods

Participants

Eligible patients were aged 6–15 years with a diagnosis of severe persistent allergic asthma according to the Japanese pediatric guideline for the treatment and management of asthma (JPGL) 2008.[17] All patients had uncontrolled asthma despite receiving inhaled corticosteroids (ICS) (>200 μg/day fluticasone propionate [FP] dry powder inhaler [or equivalent]) and two or more controller medications (leukotriene receptor antagonist [LTRA], long-acting β_2-agonist [LABA], theophylline, sodium cromoglycate, and oral corticosteroid), consistent with step 4 treatment (i.e. the most intensive treatment step) of the JPGL 2008. 'Uncontrolled' was defined as meeting one of the following criteria during the screening period: (1) asthma symptoms every day; (2) night-time symptoms in ≥2 out of the last 14 days; (3) limitation of daily activities in ≥2 out of the last 14 days.

In addition, patients had to have a history of two or more documented asthma exacerbations requiring treatment with a doubling of the maintenance ICS dose for at least 3 days and/or systemic (oral or IV) corticosteroids; one of these had to have occurred in the previous 12 months.

Patients were also required to have IgE sensitization to one of the perennial aeroallergens, demonstrate at least an increase of 12% in forced expiratory volume in one second (FEV_1) within 30 min of taking a short-acting β_2-agonist (SABA), and have serum total IgE levels of 30–1300 IU/mL and body weights of 20–150 kg to allow optimal dosing of omalizumab.

Patients were excluded if they had: (1) active lung disease, other than allergic asthma, that could potentially interfere with the outcome; (2) a history of food or drug-related severe anaphylactoid or anaphylactic reactions; (3) a positive skin test to omalizumab at screening; (4) platelet level ≤ 100,000/μL (100×10^9/L) at screening; or (5) a serious medical condition (e.g. cancer, hepatic failure, renal failure).

Study design

This was a multicenter, uncontrolled, open-label study, conducted at 17 centers in Japan, with a 2-week screening period, a 24-week treatment period (consisting of a 16-week fixed phase and an 8-week adjustable phase), and a follow-up investigation at 16 weeks after final dosing.

Omalizumab 75–375 mg was administered every 2 or 4 weeks by subcutaneous injection, with the dose being selected from a standard dosing table (Fig. 1)[15,18,19] according to baseline serum total IgE level and bodyweight.

The doses of ICS and other controller medications for asthma were kept constant for 4 weeks before the screening period, and were maintained during the screening period and the fixed phase of the treatment period (unless adjustment was required for an asthma exacerbation). During the first 4 weeks of the adjustable phase of the treatment period, doses could be adjusted downward according to the JPGL 2008 based on the investigator's judgment. During the remaining 4 weeks of the adjustable phase, the doses established during the first 4 weeks of the adjustable period were kept stable. Rescue medication use was permitted as required throughout the study.

Patients self-monitored and recorded their asthma symptoms, limitation of daily activities, sleep disturbances and rescue medication use in their diaries during the screening and treatment periods; they also measured and recorded their peak flow daily.

The study was conducted in accordance with good clinical practice, and the protocol was approved by each institution's ethics committee. Parents or legal guardians were informed of study procedures and medications, and provided written informed consent before their child's enrollment. The study was registered at http://clinicaltrials.gov with the identifier: NCT01155700.

Baseline IgE (IU/mL)	Body weight (kg)									
	≥20～25	>25～30	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥30 ～ 100	75	75	75	150	150	150	150	150	300	300
>100 ～ 200	150	150	150	300	300	300	300	300	225	300
>200 ～ 300	150	150	225	300	300	225	225	225	300	375
>300 ～ 400	225	225	300	225	225	225	300	300		
>400 ～ 500	225	300	225	225	300	300	375	375		
>500 ～ 600	300	300	225	300	300	375				
>600 ～ 700	300	225	225	300	375					
>700 ～ 800	225	225	300	375						
>800 ～ 900	225	225	300	375						
>900 ～ 1000	225	300	375							
>1000 ～ 1100	225	300	375							
>1100 ～ 1200	300	300								
>1200 ～ 1300	300	375								

Do not dosed

Fig. 1. Omalizumab dosing table (mg/dose). The omalizumab dose was administered by subcutaneous injection every 4 weeks (white cells) or 2 weeks (gray-shaded cells).

Study assessments

The primary objective was to examine whether the geometric mean of the serum free IgE level at week 24 was ≤25 ng/mL. A reduction to this level of free IgE with omalizumab has previously been shown to be efficacious.[11] Free IgE levels were measured by enzyme-linked immunosorbent assay (ELISA) as previously described.[20,21]

Secondary or exploratory efficacy endpoints included change from baseline to week 24 in: 1) mean total asthma symptom score, which included morning, daytime and nocturnal asthma score (0 = no symptoms, 1 = wheezing or tightness in chest, 3 = mild asthma attack, 6 = moderate asthma attack, 9 = severe asthma attack) and cough score (0 = no or 1 = yes); 2) mean daily activity score (0 = not limited, 6 = slightly limited, 12 = almost limited, 18 = completely limited); and 3) mean nocturnal sleep score (0 = sleeping well, 3 = experiencing night symptoms, but able to sleep, 6 = awakening during the night sometimes, 9 = having difficulty sleeping). All of these were calculated according to the standard rating scale of the Japanese Society of Allergology.[22] In addition, we assessed asthma-specific quality of life (QOL) score, measured using the "QOL questionnaire for pediatric patients with bronchial asthma and their parents or caregivers-short form version 2008 (Gifu)",[23] which consists of a physical (sum of the components of asthma attack, instability of symptoms, exercise load) and an emotional (sum of the components of emotional burden and proper acceptance of asthma) domain, with each component consisting of 2 items each scored between 1 and 5 (1 = severe impairment; 5 = no impairment). We also measured mean rescue medication use and the use of asthma controller medications, as well as mean morning peak expiratory flow (PEF), FEV_1 and forced expiratory flow rate at 25%–75% of forced vital capacity ($FEF_{25-75\%}$). We also analyzed the change from baseline in the rates of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms that required doubling of the maintenance ICS dose for at least 3 days and/or systemic [oral or IV] corticosteroids), hospitalizations and ER visits due to asthma.

Safety assessments consisted of recording adverse events (AEs), serious adverse events (SAEs), vital signs and any clinically significant changes in laboratory values, including hematology and blood chemistry, during the 24-week treatment period. Anti-omalizumab antibodies (IgG) were measured by ELISA as previously described[21] at baseline and 16 weeks after the final dose.

Statistical analysis

For primary analysis, the geometric mean and 95% confidence interval (CI) of the serum free IgE level at week 24 were calculated, assuming that the serum IgE levels followed a log-normal distribution. Descriptive statistics were used to summarize secondary or exploratory efficacy endpoints. 95% CIs for the mean change from baseline were calculated at each post-baseline visit. The Wilcoxon signed-rank test for paired data was used for the rate of asthma exacerbations, hospitalizations, and ER visits for asthma, and for QOL to compare scores between baseline and post-treatment. Missing values were imputed using the last observation carried forward approach, as appropriate. Safety variables were summarized descriptively.

Results

Patient baseline characteristics

Of the 51 patients screened, 38 patients (6–15 years) were eligible for inclusion, were treated with omalizumab, and completed the study. No patients discontinued.

A summary of the demographic and baseline characteristics are shown in Table 1. The mean age and duration of asthma were 10.7 years and 8.4 years, respectively. 27 patients (71.1%) had allergic sensitization to at least 4 perennial allergens. Mean ICS dose (FP equivalent) was 469.7 μg/day—more than double the maximum approved dose (200 μg/day) for children in Japan—and most patients (97.4%) were using LTRA and LABA, respectively. Patients had experienced a mean of 3.1 asthma exacerbations, and 22 patients (57.9%) had been hospitalized at least once for an asthma-related event (mean number of hospitalizations: 1.4) in the year to study entry. At baseline, most patients (94.7%) had limitation of daily activities.

Efficacy

The geometric mean of serum free IgE levels, which was 778.7 ng/mL at baseline, markedly decreased to 15.6 ng/mL (95% CI, 13.8–17.5) at week 24, which is below the target level of 25 ng/mL.

Mean total asthma symptom score, daily activity score and nocturnal sleep score over time are shown in Fig. 2. Treatment with omalizumab led to statistically significant improvements in these scores at week 24 compared with baseline (Table 2). The number of patients whose scores were 0 (zero) was greatly increased at study completion compared with baseline: for total asthma symptom score, no patients at baseline and 11 patients (28.9%) at study completion; 2 patients (5.3%) and 24 patients (63.2%) for daily activity scores; and 9 patients (23.7%) and 26 patients (68.4%) for nocturnal sleep score.

The mean (SD) number of puffs/tablets per week of asthma rescue medication was 6.6 (11.17) at baseline and 2.2 (4.82) at week 24, a significant reduction of 4.4 (95% CI: −6.9, −1.9) per week.

The rate of asthma exacerbations per patient-year over the 24-week treatment period was statistically significantly lower compared with baseline (0.92 vs 2.99; $p < 0.001$; relative reduction

Table 1
Baseline demographic and clinical characteristics.

	Omalizumab (n = 38)
Age (years), mean (SD)	10.7 (2.46)
Age distribution (years), n (%)	
6–9	14 (36.8)
10–15	24 (63.2)
Sex, n (%)	
Male	23 (60.5)
Female	15 (39.5)
Duration of asthma (years), mean (SD)	8.4 (3.05)
Total serum IgE (IU/mL), median (range)	335.5 (33.6–1050.0)
FEV_1 (% of predicted), mean (SD)	90.29 (19.336)
$FEF_{25-75\%}$ (% of predicted), mean (SD)	76.30 (27.227)
FEV_1 reversibility, mean (SD)	25.76 (24.228)
Number of asthma exacerbations† in the previous year, mean (SD)	3.1 (2.01)
Number of hospitalizations due to asthma in the previous year, mean (SD)	1.4 (1.69)
Number of ER visits‡ due to asthma in the previous year, mean (SD)	0.7 (1.09)
ICS dose at baseline (μg/day, fluticasone propionate equivalent)	
Mean (SD)	469.7 (199.84)
Median (range)	500 (250–1000)
Asthma long-term control medications at baseline, n (%)	
Leukotriene receptor antagonist	37 (97.4)
Long-acting β_2-agonist	37 (97.4)
Sustained-release theophylline	23 (60.5)
Sodium cromoglycate	3 (7.9)
Oral corticosteroid	0
Profile of inadequate asthma control at screening period, n (%)	
Asthma symptoms every day	12 (31.6)
Night-time symptoms ≥2 out of the previous 14 days	25 (65.8)
Limitation of daily activities ≥2 out of the previous 14 days	36 (94.7)

ER, emergency room; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; SD, standard deviation.
† Asthma exacerbations requiring a doubling of the maintenance ICS dose for at least 3 days and/or systemic (oral or IV) corticosteroids.
‡ If hospitalization and ER visit occurred on the same day, the event is counted as hospitalization.

69.2%; Fig. 3a). Significant improvement was also observed in a subgroup of patients treated with high-dose ICS (≥500 μg/day, FP equivalent) and two or more controller medications compared with baseline (n = 20, 0.54 vs 3.05; $p < 0.001$).

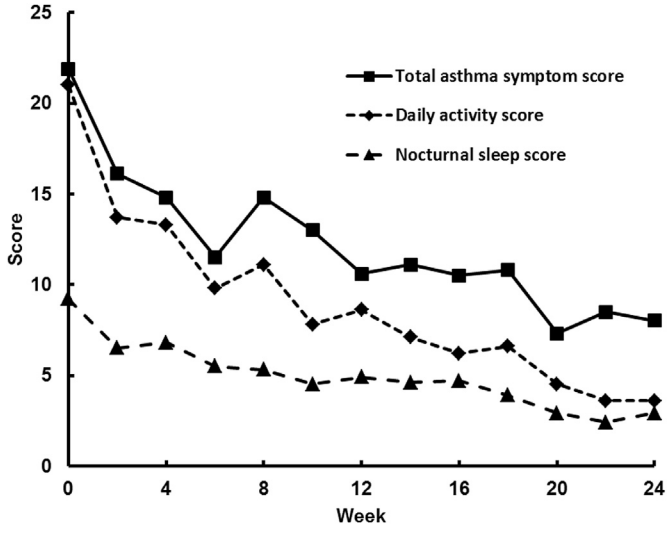

Fig. 2. Mean total asthma symptom score, daily activity score and nocturnal sleep score over 24 weeks. Scores were summarized in the value per week derived by two-weekly period.

Table 2
Change from baseline in total asthma symptom score, daily activity score and nocturnal sleep score at 24 weeks.

	Baseline n = 38	Week 24 n = 38
Total asthma symptom score†		
Mean (SD)	21.9 (20.27)	8.3 (11.48)
Change from baseline	−13.6 (19.23)	
95% CI	−20.0, −7.3	
Daily activity score†		
Mean (SD)	21.0 (17.87)	3.9 (7.98)
Change from baseline	−17.1 (17.90)	
95% CI	−23.0, −11.2	
Nocturnal sleep score†		
Mean (SD)	9.2 (9.82)	2.8 (6.39)
Change from baseline	−6.4 (11.29)	
95% CI	−10.1, −2.7	

The higher scores represent worsening of total asthma symptom, more impaired daily activity and nocturnal sleep, respectively.
† Scores were summarized in the value per week derived by last two weeks for the baseline and the 24-week treatment period.

The rate of hospitalizations for asthma per patient-year was 0.29 over the 24-week treatment period, compared with 1.33 at baseline, representing a reduction of 78.2% in patients receiving omalizumab ($p < 0.001$, Fig. 3b). ER visits due to asthma over the 24 weeks were reduced by 32.4% versus baseline, but the difference was not statistically significant ($p = 0.381$, Fig. 3c).

At week 24, omalizumab was associated with improvements compared with baseline across all individual components of QOL (Fig. 4a). Physical domain (Fig. 4b), emotional domain (Fig. 4c) and overall (Fig. 4d) scores reached almost the upper limit of the ranges, and showed statistically significant improvements versus baseline ($p < 0.001$).

Twenty-four weeks' treatment with omalizumab resulted in modest improvements in lung function. Mean (SD) morning PEF was 246.2 (72.22) L/min at baseline and 269.3 (95.59) L/min at week 24, representing a significant increase of 22.4 L/min ($p < 0.05$), but the change from baseline in mean (SD) % predicted morning PEF was not significant [82.0 (21.00) % vs 86.9 (33.15) %; difference of 5.17%]. Mean (SD) FEV_1 (% predicted) values and $FEF_{25-75\%}$ (% predicted) values were similar at baseline and at week 24 [90.3 (19.34) % and 89.7 (23.10) % for FEV_1 (% predicted); 76.3 (27.23) % and 75.8 (32.68) % for $FEF_{25-75\%}$ (% predicted)].

At week 24, 11 patients (28.9%) had reduced the dose of any asthma controller medication compared with the baseline (Table 3). No patterns were noted with respect to the specific classes of controller medications that were reduced.

Safety

Overall, 36 of 38 (94.7%) patients experienced at least one AE during the treatment period. All AEs were mild or moderate in severity. The most common AEs (≥20%) were nasopharyngitis, upper respiratory tract infection, asthma, and gastroenteritis (Table 4).

Six patients experienced SAEs (due to hospitalization) during the treatment period; asthma (asthma exacerbation) in five patients and urticaria in one patient. Relationship with omalizumab was not denied in two SAEs (asthma exacerbation and urticaria), which resolved completely with additional treatments.

No new safety concerns relating to AEs of particular clinical interest were evident. There were no cases of anaphylactic reactions, malignancies, serum sickness, Churg-Strauss syndrome, thrombocytopenia, or arterial thromboembolic events. No clinically relevant abnormalities in laboratory tests (including platelet

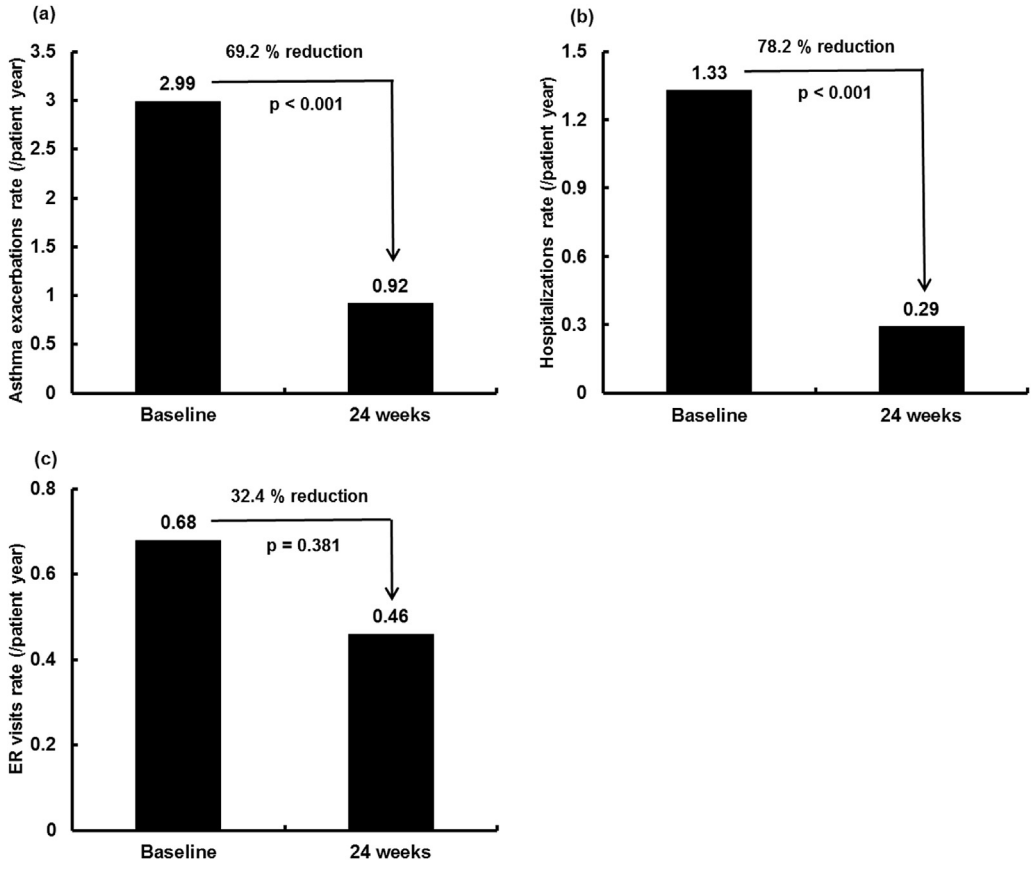

Fig. 3. Changes in rate (per patient-year) of asthma exacerbations (a), hospitalizations (b) and ER visits (c) due to asthma between baseline (previous 12 months before the start of the study plus the screening period) and 24 weeks of the treatment period. If hospitalization and ER visit occurred on the same day, the event was counted as a hospitalization. The rates at baseline were derived as the total number of events observed during previous 12 months before the study plus the study screening period divided by the total amount of time (in years) of the patients in this period. The rates at 24 weeks were derived as the total number of events observed during 24 weeks of treatment period divided by the total exposure (in years) of the patients in this period.

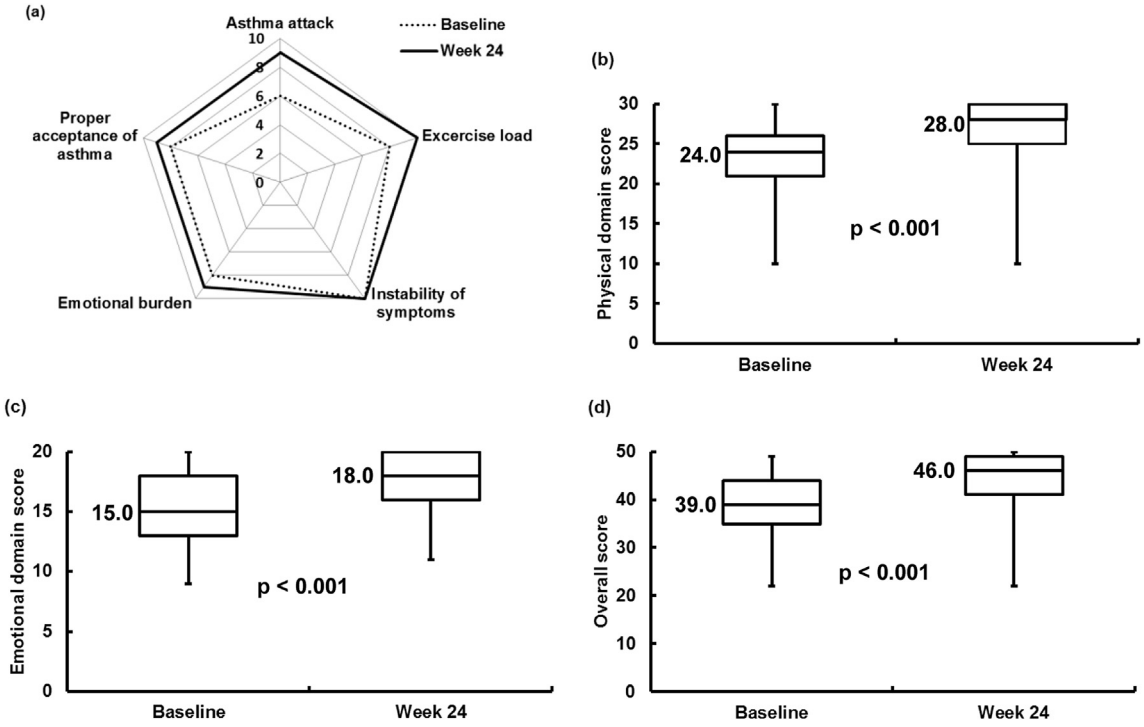

Fig. 4. Changes in QOL scores between baseline and at 24 weeks; (a) each component (median), (b) physical domain score, (c) emotional domain score, and (d) overall score. The boxes indicate the median, the 25th and 75th percentiles, while the extremes represent the minimum and maximum values.

Table 3
Summary of number of patients with dose reduction or discontinuation of asthma long-term controller medications.

	Omalizumab (n = 38)	
	Baseline n	Dose reduction or discontinuation[†] at week 24 n (%)[‡]
Any medication	–	11 (28.9)
Inhaled corticosteroid	38	4 (10.5)
Leukotriene receptor antagonist	37	2 (5.4)
Long-acting β_2-agonists	37	4 (10.8)
Sustained-release theophyllines	23	4 (17.4)
Sodium cromoglycate	3	1 (33.3)

[†] Discontinuation; Leukotriene receptor antagonist (2 patients), Long-acting β2-agonists (3 patients), Sustained-release theophyllines (4 patients), Sodium cromoglycate (1 patient).
[‡] The denominator of percentage for each asthma long-term medication is the number of patients who used each medication at baseline.

counts) were observed. No anti-omalizumab antibodies were detected.

Discussion

This is the first study investigating the efficacy including free IgE suppression and safety of omalizumab in Japanese pediatric patients with severe persistent allergic asthma uncontrolled with current standard therapy.

The primary objective was to examine whether omalizumab decreases serum free IgE levels to less than 25 ng/ml (target level of suppression). As a result, the geometric mean of serum free IgE levels at week 24 was <25 ng/mL, which indicates that the current dosing recommendations for omalizumab are appropriate for Japanese pediatric patients as well as for Japanese adult and Caucasian adult/pediatric patients.

Associated with free IgE reduction, treatment with omalizumab led to significant improvements in asthma control. Compared with baseline, total asthma symptom scores, daily activity scores and nocturnal sleep scores were markedly improved. The frequencies of asthma exacerbations and hospitalizations due to asthma were reduced by 69.2% and 78.2%, respectively. QOL scores were also significantly improved, almost to the upper limits of the range. In addition, approximately 30% of patients were able to reduce the dose of any asthma controller medications. These consistent improvements including QOL were not observed in the previous randomized controlled trial,[15] but this could be explained by the differences in the QOL questionnaire used in the studies. The questionnaire[23] used in this study assesses the QOL of both children with asthma and their parents or caregivers, while the pediatric asthma quality of life questionnaire[24] used in the previous randomized controlled trial focuses only on pediatric patients. Because the parents (or caregivers) are deeply involved in daily lives and therapies of their children and poorly controlled asthma of their children impair both QOLs,[25,26] this study could more comprehensively evaluate the QOLs affected by pediatric asthma. Although there is a limitation due to the nature of this study (uncontrolled, non-randomized), our results support the role of omalizumab in the management of Japanese children with severe allergic asthma.

Regarding lung function at baseline, FEV_1 (% predicted) value was normal (90.3%), while $FEF_{25-75\%}$ (% predicted) was diminished (76.3%); this is consistent with the expected characteristics of severe persistent asthma.[27] Overall, omalizumab was associated with little change in lung function between baseline and week 24 (PEF, FEV_1 and $FEF_{25-75\%}$), which was also observed in previous studies.[18,28] One possible reason might be because omalizumab does not have a direct bronchodilator effect, it may not be effective enough to improve lung function in severe asthma patients who were already treated with LABA in association with high dose ICS. In children and adolescents with severe asthma, a progressive decline in lung function is observed over time,[3,29] and asthma exacerbations are thought to be associated with excess lung function decline.[5] Therefore, the longer-term effects of omalizumab on lung function should be investigated further.

Twenty-four-week treatment with omalizumab was generally well tolerated. No patients discontinued the study. All adverse events were mild or moderate in severity and particular AEs of concern for pediatric patients were not observed. Six patients experienced SAEs, all of which resolved completely with additional treatments. The safety profile of omalizumab in the study was comparable to that observed in the previous study,[15,16] and no new safety concerns were identified.

Several randomized studies have established omalizumab as an effective and well-tolerated agent for use as add-on therapy in pediatric patients with moderate to severe persistent allergic asthma,[15,16,18] but the impact of long-term treatment with omalizumab on the natural course of asthma is a key unanswered question. There is some evidence that omalizumab might have a disease-modifying effect. Nopp et al. reported that most of the adult asthmatic patients who stopped omalizumab after approximately 6 years had improved or unchanged disease 3 years after stopping.[30] In contrast, withdrawal of omalizumab after less than a year of treatment resulted in a return to the pre-treatment clinical state within months.[31] Lowe et al. have suggested that IgE production in patients with allergic asthma might be reduced during long-term treatment with omalizumab.[32] Long-term effect of omalizumab has never been investigated yet in children. Because pediatric severe asthma often persists into adult life, sometimes in a troublesome way,[33] any disease-modifying effect of omalizumab would be of interest.

In conclusion, the results of this study indicate that omalizumab is effective on symptoms, exacerbations and QOL, and is well tolerated as an add-on therapy in Japanese pediatric patients with uncontrolled severe persistent allergic asthma.

Table 4
Incidence of adverse events.

	Omalizumab (n = 38) n (%)
Patients with any adverse event	36 (94.7)
Discontinued due to adverse event	0
Patient with serious adverse events	6 (15.8)
Asthma (asthma exacerbation)	5 (13.2)
Urticaria	1 (2.6)
Most frequent adverse events[†]	
Nasopharyngitis	10 (26.3)
Upper respiratory tract infection	10 (26.3)
Asthma	8 (21.1)
Gastroenteritis	8 (21.1)
Bronchitis	5 (13.2)
Headache	5 (13.2)
Abdominal pain	4 (10.5)
Stomatitis	4 (10.5)
Urticaria	4 (10.5)
Arthralgia	3 (7.9)
Constipation	3 (7.9)
Contusion	3 (7.9)
Influenza	3 (7.9)
Injection site pain	3 (7.9)
Pyrexia	3 (7.9)
Patients with any drug-related adverse events	10 (26.3)
Most frequent drug-related adverse events[†]	
Headache	4 (10.5)
Injection site pain	3 (7.9)

[†] Occurring in three or more patients.

Acknowledgments

This clinical phase III study was sponsored by Novartis Pharma.

Conflict of interest

SN served as medical consultant funded by Novartis Pharma. NSa and NSe are employees of Novartis Pharma.

Authors' contributions

HO contributed to implementation of the study, interpretation of the data, and drafting the manuscript. ME, TN, TF, AA, KI, SD, KY, TK, KK, NK, KS, MN, AH, and SY contributed to implementation of the study, interpretation of the data and reviewing the manuscript. NSa contributed to the study design, implementation of the study, interpretation of the data, and drafting the manuscript. NSe contributed to analysis of the data and drafting the manuscript. SN gave advice on the study design, implementation of the study, interpretation of the data, and drafting the manuscript. All authors read and approved final manuscript.

References

1. Nishima S, Chisaka H, Fujiwara T, Furusho K, Hayashi S, Hiraba K, et al. Surveys on the prevalence of pediatric bronchial asthma in Japan: a comparison between the 1982, 1992, and 2002 surveys conducted in the same region using the same methodology. *Allergol Int* 2009;**58**:37–53.
2. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;**114**:40–7.
3. Chipps BE, Szefler SJ, Simons FE, Haselkorn T, Mink DR, Deniz Y, et al. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2007;**119**:1156–63.
4. Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the expert panel report 3 guidelines, increases risk for future severe asthma exacerbations in the epidemiology and natural history of Asthma: outcomes and treatment regimens (TENOR) study. *J Allergy Clin Immunol* 2009;**124**:895–902. e1–4.
5. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007;**30**:452–6.
6. Chipps BE, Zeiger RS, Dorenbaum A, Borish L, Wenzel SE, Miller DP, et al. Assessment of asthma control and asthma exacerbations in the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) observational cohort. *Curr Respir Care Rep* 2012;**1**:259–69.
7. Diette GB, Markson L, Skinner EA, Nguyen TT, Algatt-Bergstrom P, Wu AW. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. *Arch Pediatr Adolesc Med* 2000;**154**:923–8.
8. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood asthma management program (CAMP) study. *Pediatrics* 2008;**122**:e53–61.
9. Borish L, Chipps B, Deniz Y, Gujrathi S, Zheng B, Dolan CM, et al. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2005;**95**:247–53.
10. Presta LG, Lahr SJ, Shields RL, Porter JP, Gorman CM, Fendly BM, et al. Humanization of an antibody directed against IgE. *J Immunol* 1993;**151**:2623–32.
11. Hochhaus G, Brookman L, Fox H, Johnson C, Matthews J, Ren S, et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin* 2003;**19**:491–8.
12. Xolair (omalizumab) full prescribing information, July 2010. Available at: http://www.xolair.com/allergic-asthma/prescribing-information.html [accessed 03.04.15].
13. Xolair (omalizumab) product information (summary of product characteristics-annex I), October 2010. Available at: http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000606/human_med_001162.jsp&mid=WC0b01ac058001d124 [accessed 03.04.15].
14. [Xolair (omalizumab) prescribing information, August 2013]. Available at: http://product.novartis.co.jp/xol/document/ (in Japanese). [accessed 03.04.15].
15. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;**124**:1210–6.
16. Kulus M, Hébert J, Garcia E, Fowler Taylor A, Fernandez Vidaurre C, Blogg M. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin* 2010;**26**:1285–93.
17. Kondo N, Nishimuta T, Nishima S, Morikawa A, Aihara Y, Akasaka T, et al. Japanese pediatric guidelines for the treatment and management of bronchial asthma 2008. *Pediatr Int* 2010;**52**:319–26.
18. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;**364**:1005–15.
19. Sorkness CA, Wildfire JJ, Calatroni A, Mitchell HE, Busse WW, O'Connor GT, et al. Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. *J Allergy Clin Immunol Pract* 2013;**1**:163–71.
20. Ädelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;**106**:253–9.
21. Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;**100**:110–21.
22. Miyamoto T, Shida T, Tomioka T, Makino S, Kabe J, Nakajima S, et al. [Report of the expert committee for reviewing the criteria for severity of bronchial asthma]. *Arerugi* [*Jpn J Allergol*] 1994;**43**:71–80 (in Japanese).
23. Kondo N, Hirayama K, Matsui E, Teramoto T, Kaneko H, Fukao T, et al. [QOL questionnaire for pediatric patients with bronchial asthma and their parents or caregivers. Preparation and evaluation of the short form version 2008 (Gifu)]. *Arerugi* [*Jpn J Allergol*] 2008;**57**:1022–33 (in Japanese).
24. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res* 1996;**5**:35–46.
25. Stelmach I, Podlecka D, Smejda K, Majak P, Jerzyńska J, Stelmach R, et al. Pediatric asthma caregiver's quality of life questionnaire is a useful tool for monitoring asthma in children. *Qual Life Res* 2012;**21**:1639–42.
26. Dean BB, Calimlim BC, Sacco P, Aguilar D, Maykut R, Tinkelman D. Uncontrolled asthma: assessing quality of life and productivity of children and their caregivers using a cross-sectional internet-based survey. *Health Qual Life Outcomes* 2010;**8**:96.
27. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske Jr RF, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;**170**:426–32.
28. Deschildre A, Marguet C, Salleron J, Pin I, Rittié JL, Derelle J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J* 2013;**42**:1224–33.
29. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;**349**:1414–22.
30. Nopp A, Johansson SG, Adédoyin J, Ankerst J, Palmqvist M, Oman H. After 6 years with Xolair; a 3-year withdrawal follow-up. *Allergy* 2010;**65**:56–60.
31. Slavin RG, Ferioli C, Tannenbaum SJ, Martin C, Blogg M, Lowe PJ. Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations. *J Allergy Clin Immunol* 2009;**123**:107–13. e3.
32. Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. *Br J Clin Pharmacol* 2011;**72**:306–20.
33. Phelan PD, Robertson CF, Olinsky A. The Melbourne asthma study: 1964-1999. *J Allergy Clin Immunol* 2002;**109**:189–94.