Allergology International xxx (xxxx) xxx

Contents lists available at ScienceDirect

Allergology International

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

Original Article

Real-life long-term safety and effectiveness of omalizumab in Japanese pediatric patients with severe allergic asthma: A post-marketing surveillance

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A R T I C L E I N F O

Article history:
Received 16 July 2020
Received in revised form
10 December 2020
Accepted 10 December 2020
Available online xxx

Keywords:
Allergic asthma
Omalizumab
Pediatric
Post-marketing surveillance
Safety

Abbreviations:

GETE	Global Evaluation of Treatment Effectiveness
JPAC	Japanese Pediatric Asthma Control Program score
PT	preferred term
SOC	system organ class

A B S T R A C T

Background: Omalizumab is approved as add-on therapy for pediatric asthma since 2013 in Japan, however, its data in clinical practice is limited. This post-marketing surveillance aimed to evaluate long-term safety and effectiveness of omalizumab in Japanese pediatric patients with severe allergic asthma in real-life setting.

Methods: This 104-week, multicenter surveillance was conducted from September 2013 to May 2019 by central registration method. Patients with severe allergic asthma aged ≥6 and < 15 years at initiation of treatment who were first-time omalizumab users were included. The primary endpoints included incidence of adverse drug reactions and physician's Global Evaluation of Treatment Effectiveness (GETE). The secondary endpoints included incidence of serious adverse events, adverse events and adverse drug reactions of special interest and asthma exacerbation-related events.

Results: Of the 128 patients enrolled, 127 completed the surveillance and were included for safety and effectiveness analysis. Thirteen patients experienced 20 adverse drug reactions with an incidence rate of 10.2%. The most frequent adverse drug reactions were pyrexia (2.4%) and urticaria (1.6%). In total, adverse events and serious adverse events occurred in 60 (47.2%) and 30 patients (23.6%) respectively. Two patients experienced anaphylactic reaction and 1 patient experienced type 1 hypersensitivity. 77.2% had an effective response to omalizumab according to GETE at final assessment, and frequency of all asthma exacerbation-related events decreased in post-treatment versus pre-treatment.

Conclusions: Long-term omalizumab treatment showed no new safety signals in pediatric patients with severe allergic asthma. The observed safety and effectiveness profile was consistent with previous studies.

Introduction

Asthma is a chronic respiratory disease affecting approximately 339 million individuals worldwide.[1] Over the past two decades, the prevalence of asthma has been reported to be 3.6%–19.6% in children (6–14 years of age) in Japan, with estimates differing based on the age group and region surveyed.[2–4] Approximately 50% of children with asthma in Japan are reported to be persistent and 20%–30% are moderate to severe asthma.[5] Furthermore, a web-based survey conducted in Japan demonstrated that 14.6% of pediatric patients with asthma aged 6–11 years had uncontrolled asthma,[6] highlighting unmet medical needs in Japanese children with asthma. According to the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2017, the ultimate treatment goal of pediatric asthma is complete remission or cure. However, the practical targets in daily life focus on controlling symptoms, normalizing respiratory functions, and improving quality of life.[4]

Omalizumab, an anti-human IgE monoclonal antibody, was approved in Japan in 2009 as an add-on long-term management therapy in adults with severe allergic asthma.[7,8] In 2013, omalizumab was also approved for pediatric patients with asthma aged ≥6 years based on a Phase III clinical trial enrolling 38 Japanese children with severe allergic asthma.[9,10] According to the JPGL 2017, omalizumab is recommended as one of the additional therapies for

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2021.01.001

Japanese children of 6 years or older in treatment step 4; inadequately controlled on high-dose inhaled corticosteroids (ICS) plus two or more controllers [Global Initiative for Asthma Step 5] with intended use before oral corticosteroids.[5,11]

There are numerous clinical trials and real-world studies that have assessed the efficacy and safety of omalizumab in adults with asthma who were uncontrolled despite treatment with standard-of-care of ICS and long-acting bronchodilators.[12–15] Only few studies have evaluated the safety and effectiveness of omalizumab in pediatric asthma in a real-life setting in the world.[16,17] Although there are some studies on pediatric patients in Japan that have evaluated the efficacy and safety of omalizumab in children 6 years or older with severe allergic asthma,[9,10,18] these were mostly randomized clinical trials and real life data of omalizumab on pediatric asthma patients are limited. Therefore, a real-world study to confirm the safety and effectiveness of omalizumab in routine medical practice was needed. This post-marketing surveillance was conducted to evaluate the long-term safety and effectiveness of omalizumab in Japanese children with severe allergic asthma in real-life clinical practice.

Methods

Surveillance description

This 104-week, multicenter surveillance was conducted from September 2013 to May 2019 in accordance with good post-marketing study practice,[19] by a central registration method using Electronic Data Capture system (PostMaNet, Fujitsu FIP Corporation, Tokyo),[20] with a protocol agreed upon in consultation with the Japanese Pharmaceutical and Medical Devices Agency, and as such, informed consent was not mandate nor obtained. Personal data was not obtained either. This surveillance was conducted in 66 sites including 19 prefectural/municipal hospitals (28.8%) and 14 medical practitioners/clinics (21.2%), and patients were registered by investigators between the start date of omalizumab treatment (Day 1) and Day 14. Patient details were recorded using case report forms after each observation treatment observation period (Week 16, Week 52, and Week 104) by investigator. Case report forms were checked by the post-marketing surveillance data management department in Novartis then asked investigators to correct the case report forms by query form as needed. Omalizumab dosing ranged from 75 mg to 600 mg and was administered subcutaneously every 2 or 4 weeks, according to the dosing table, based on the patient's total serum IgE levels and body weight at baseline.[21]

Pediatric patients aged $\geq$6 and < 15 years at the initiation of treatment who were first-time omalizumab users with severe allergic asthma and were poorly controlled despite conventional therapies were included in this study. Patients who discontinued omalizumab were observed for 26 weeks after treatment discontinuation with a maximum observation period of 104 weeks per patient. All the results were validated by double programming; two or more analysis researchers programed independently, compared these results and confirmed that results were matched.

Endpoints

Safety

The primary endpoint for safety included incidence of adverse drug reactions and infection. An adverse event was defined as any unfavorable or unintended sign (including an abnormal laboratory finding) symptom, or disease temporally associated with the use of omalizumab, related or non-related to omalizumab. Adverse drug reactions were defined as adverse events where causal relationship with omalizumab could not be ruled out (except for 'not related').

The secondary endpoints for safety included incidence of serious adverse events and concomitant allergic diseases. Adverse events and adverse drug reactions of special interests were 'anaphylaxis', 'malignant tumor', 'bleeding tendency', 'autoimmune disease', 'infection parasitic', and 'eosinophilic syndrome'.

The safety of omalizumab by patient characteristics was also evaluated.

Effectiveness

The primary endpoint for effectiveness was physician's Global Evaluation of Treatment Effectiveness (GETE) score. Based on asthma symptom information, a comparison between the start of treatment and each assessment point or discontinuation in terms of patients' status was defined as excellent: asthma is completely controlled, good: asthma has markedly improved, moderate: asthma has improved, but only slightly, unchanged: no significant change, worsening: asthma symptoms are generally worsened and not evaluable: unable to evaluate. Furthermore, 'excellent' or 'good' GETE were defined as effective, while 'moderate', 'unchanged', 'worsening' or 'not evaluable' were considered as not effective. The asthma exacerbation-related events were classified into four categories: 'worsening of asthma symptoms requiring additional systemic steroid therapy', 'hospitalization due to asthma', emergency room visit due to asthma', and 'absence from school due to asthma'

The secondary endpoints for effectiveness included asthma exacerbation-related events and Japanese Pediatric Asthma Control Program (JPAC) score.[22] In JPAC, five items recorded on case report forms (severity of stridor, number of dyspnea attacks, frequency of nighttime awakening, asthma symptoms during exercise, and β_2-agonist use) were rated on a 0 to 3-point scale (out of 15). The sum of the JPAC score was classified into 3 categories; Score 15: asthma being completely controlled; Score 12-14: asthma being adequately controlled; Score $\leq$11: asthma being poorly controlled. High JPAC scores mean good asthma control. The data at the last time point were used for the final evaluation of physician's GETE score and JPAC score.

The effectiveness of omalizumab by patient characteristics was also evaluated.

Statistical analysis

As per a previous clinical study in pediatric patients, assuming an incidence rate of adverse drug reactions of 26.3%, a total of 107 patients was required to provide $\geq$95% power to detect at least 20 patients with adverse drug reactions. The percentage of discontinuation/withdrawal was assumed to be $\leq$ 10%. A target sample size of 120 was determined to ensure availability of at least 107 patients in the safety analysis set. The GETE data were tabulated at each assessment point (at Week 8, 16, 26, 34, 42, 52, 60, 68, 78, 86, 94,104, or Week 26 after discontinuation) and at the final assessment in the effectiveness analysis set. Effectiveness ratio was defined as the percentage of patients with 'effective' or 'not effective' GETE to the overall population.

For comparison among groups, Mann–Whitney test was used for comparison of 3 or more groups with unpaired ordinal data (when the tabulation resulted in 2 $\times$ 2 contingency table, Fisher's exact test was used) and Fisher's exact test was used for comparison of 2 groups. The level of significance was 5% in 2-tailed hypothesis tests. Data results that were categorized as 'unknown', 'not reported', or 'not tested' were not included in the analysis.

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Results

Study population

A total of 128 patients from 66 sites were enrolled, of which 127 patients had fixed case report forms; one patient was excluded due to 'failure to collect case report forms'. All 127 patients were included in the safety and effectiveness analysis set (Fig. 1).

Demographics and baseline characteristics of patients in the safety set are presented in Table 1 and Table 2. The mean age of patients at baseline was 9.9 years with majority being in the age group of ≥6 to <12 years. 55.1% were males and 44.9% were females. The mean weight ±SD was 34.6 ± 11.6 kg and mean total IgE level ±SD was 568.7 ± 395.9 IU/mL at baseline. Patient distribution as per the dose determination table is shown in Supplementary Figure 1. The median (min−max) duration of omalizumab treatment was 715 (1−750) days, with approximately 40% patients receiving treatment for 78−104 weeks. All patients except one were positive to an antigen, with sensitivity to house dust (including mites) being the most common. Majority of the patients presented comorbidities, of which allergic rhinitis was the most prevalent (76.4%). Majority of the patients received 2 or more concomitant medications for asthma, and approximately half of them were on a combination therapy with ICS, LABA and leukotriene receptor antagonist.

Table 1
Demographics, clinical characteristics and patient composition at the baseline (safety dataset).

Characteristic	N = 127
Age, years, mean ± SD	9.9 ± 2.5
<6	0
≥6 and < 12	93 (73.2)
≥12 and < 15	34 (27.8)
Gender	
Male	70 (55.1)
Female	57 (44.8)
Animals	63 (49.6)
Foods	22 (17.3)
Fungi	15 (11.8)
Insects	7 (5.5)
Other	0
Number of positive antigens	
1	26 (20.5)
2	43 (33.9)
≥3	57 (44.9)
Unknown/not tested	1 (0.8)
Concomitant medications	123 (96.1)
Inhaled corticosteroids + Leukotriene receptor antagonist	11 (8.7)
Inhaled corticosteroids + Long-acting β_2 agonist	7 (5.5)
Inhaled corticosteroids + Long-acting β_2 agonist + Leukotriene receptor antagonist	68 (53.5)
Inhaled corticosteroid + Long-acting β_2 agonist + extended-release theophylline	1 (0.8)
Inhaled corticosteroid + Long-acting β_2 agonist + two or more other controllers[‡]	34 (26.8)

Data presented as n (%), unless specified.
[‡] Short acting β_2 agonist (rescue) and oral corticosteroid burst use are not included.

Safety outcomes

Incidence of adverse drug reactions

Of the total 127 patients in the safety analysis set, 13 patients experienced 20 adverse drug reactions with an incidence rate of 10.2% (Table 3). The most frequent adverse drug reactions by system organ class (SOC) were 'general disorders and administration site conditions' (3.9%), 'immune system disorders', 'nervous system disorders' 'respiratory, thoracic and mediastinal disorders' and 'skin and subcutaneous tissue disorders' (1.6% each). Other adverse drug reactions were 'cardiac disorders', 'vascular disorders' and 'gastrointestinal disorders' (0.8% each, data not shown). The most frequent adverse drug reactions by preferred team (PT) were pyrexia (2.4%) and urticaria (1.6%). The incidence of adverse drug reactions was highest within 4 weeks after initiation of omalizumab treatment (7.9%).

Incidence of adverse events

Of 127 patients, 60 patients experienced 109 adverse events with an incidence rate of 47.2% (Table 3). The most frequent adverse events (≥5%) by SOC were 'respiratory, thoracic and mediastinal

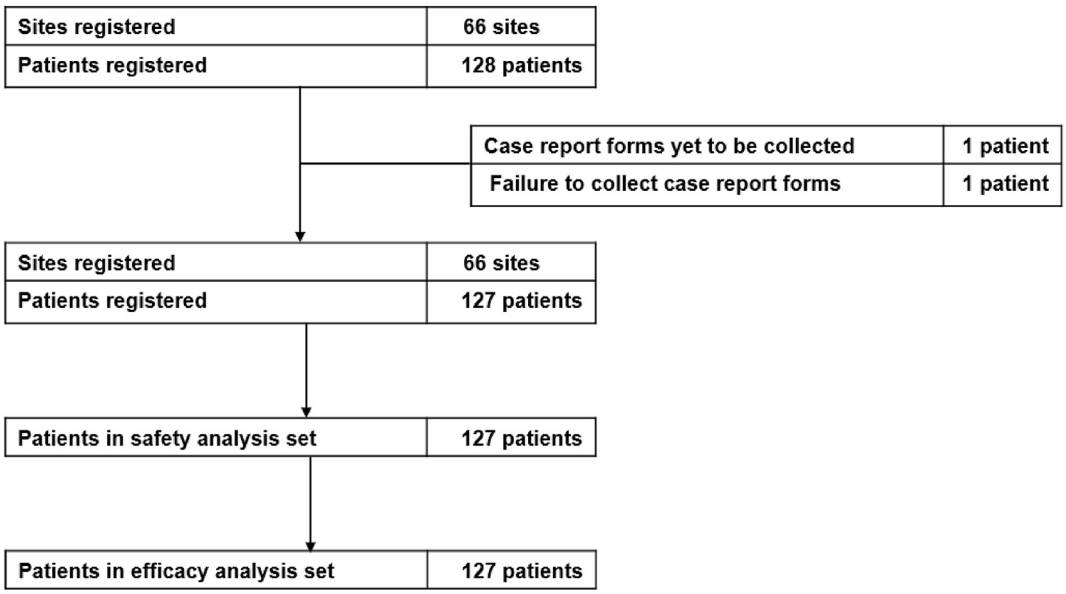

Fig. 1. Patient disposition.

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Table 2
Status of omalizumab administration (safety dataset).

Variable	N = 127
Total dosing period of omalizumab, days, mean ± standard deviation	561.3 ± 240.6
<16 weeks	13 (10.2)
≥16 weeks and <52 weeks	17 (13.4)
≥52 weeks and <78 weeks	11 (8.7)
≥78 weeks and <104 weeks	51 (40.2)
≥104 weeks	35 (27.6)
Dose intervals (at initial dose)	
2 Weeks	38 (29.9)
4 Weeks	89 (70.1)

Data presented as n (%), unless specified.

Table 3
Safety overview (safety dataset).

	Number of patients n (%) N = 127
Patients with adverse drug reactions	13 (10.2)
Patients with any adverse events	60 (47.2)
Patients with serious adverse events	30 (23.6)
	Number of patients n (%)
Most frequent adverse drug reactions by SOC †	
General disorders and administration site conditions	5 (3.9)
Immune system disorders	2 (1.6)
Nervous system disorders	2 (1.6)
Respiratory, thoracic and mediastinal disorders	2 (1.6)
Skin and subcutaneous tissue disorders	2 (1.6)
Most frequent adverse drug reactions by PT †	
Pyrexia	3 (2.4)
Urticaria	2 (1.6)
Most frequent adverse events† by PT	
Asthma	33 (26.0)
Nasopharyngitis	6 (4.7)
Pyrexia	6 (4.7)
Upper respiratory tract inflammation	4 (3.1)
Pneumonia	3 (2.4)
Most frequent serious adverse events† by PT	
Asthma	27 (21.3)
Influenza	3 (2.4)
Adverse events of special interests	
Adverse event: Anaphylaxis	3 (2.4)
Adverse drug reaction: Anaphylaxis	2 (1.6)
Most frequent adverse drug reactions of special interests by PT	
Anaphylactic reaction	1 (0.8)
Type 1 hypersensitivity	1 (0.8)

Number of events: adverse drug reactions, 20; adverse events, 109; serious adverse events, 39.
PT, preferred term; SOC, system organ class.
† Data represent adverse events, serious adverse events and adverse drug reactions occurring in more than 2 patients. Percentage was calculated per applicable patient in each item/category.

disorders' (31.5%), 'infections and infestations' (18.1%), and 'general disorders and administration site conditions' (7.9%, data not shown). The most frequent adverse events by PT, with an incidence rate of ≥2% included asthma, nasopharyngitis, pyrexia, upper respiratory tract inflammation bronchitis, gastroenteritis and pneumonia.

Incidence of serious adverse events

Thirty patients experienced 39 serious adverse events with an incidence rate of 23.6%. The most frequent serious adverse events by SOC were 'respiratory, thoracic and mediastinal disorders' (22.1%), and 'infections and infestations' (5.5%, data not shown).The most frequent serious adverse events by PT, occurring in ≥2% of patients were asthma, influenza (Table 3).

Incidence of adverse events and adverse drug reactions of special interest

Of 127 patients; one patient experienced anaphylactic reaction as an adverse event of special interest. Of these adverse events, adverse drug reactions of special interests were anaphylactic reaction and type 1 hypersensitivity each in 1 patient (Table 4). However, all of these patients continued treatment with omalizumab without discontinuation or dropout. Furthermore, no malignant tumor, bleeding tendency, autoimmune disease, infection parasitic, and eosinophilic syndrome were reported throughout the study.

Effectiveness outcomes

Physician's GETE

Of the total 127 patients in the effectiveness analysis set, 91 (73.4%) patients and 67 (85.9%) patients at Week 16 and at Week 104, respectively, were reported to be 'effective' as defined by GETE (Fig. 2). Of all, 98 (77.2%) patients were 'effective' ('excellent', 53 [41.7%] and 'good', 45 [35.4%]) and 29 (23.8%) patients were 'not effective', at the final assessment by GETE (Fig. 2). Among the 118 patients in the long-term treatment group, 92 patients (78.0%) were 'effective' and 26 (22.0%) patients were 'not effective' at the final assessment. Patients who discontinued omalizumab during the 104-week treatment period were followed for up to a maximum of 26 week, however, efficacy assessment such as GETE was not measured, because the primary objective of this surveillance was safety. Therefore, we are not sure if the efficacy of omalizumab persisted after discontinuation.

Asthma exacerbation-related events

Fewer asthma exacerbation-related events were observed in post-treatment with omalizumab compared to pre-treatment. The proportion of patients without asthma exacerbation-related events were higher for post-treatment with omalizumab compared with pre-treatment (pre-treatment vs post-treatment: worsening of asthma symptoms requiring systemic steroid, 25.2% vs 74.0%; frequency of hospitalization, 54.0% vs 85.0%; visits to the emergency room, 43.6% vs 78.2%; absence from school, 36.4% vs 78.2%; Fig. 3). Similarly, long-term omalizumab treatment also showed reduction in frequency of exacerbation-related events in the long-term administration patient group.

Table 4
Adverse events and adverse drug reaction of special interest (safety dataset).

AE of special interest (by Preferred Terms)	Age (at initial dose), gender	dose/dose interval	the days from first dose to onset	outcome
Anaphylactic reaction	10-year-old girl	300mg/4 week	99 day	Resolved on the onset day
Anaphylactic reaction	13 years old boy	525mg/2 week	732 day	Resolved on the day following the date of onset
Type I hypersensitivity	10 years old girl	525mg/2 week	The day of first dose	Resolved on the day of onset

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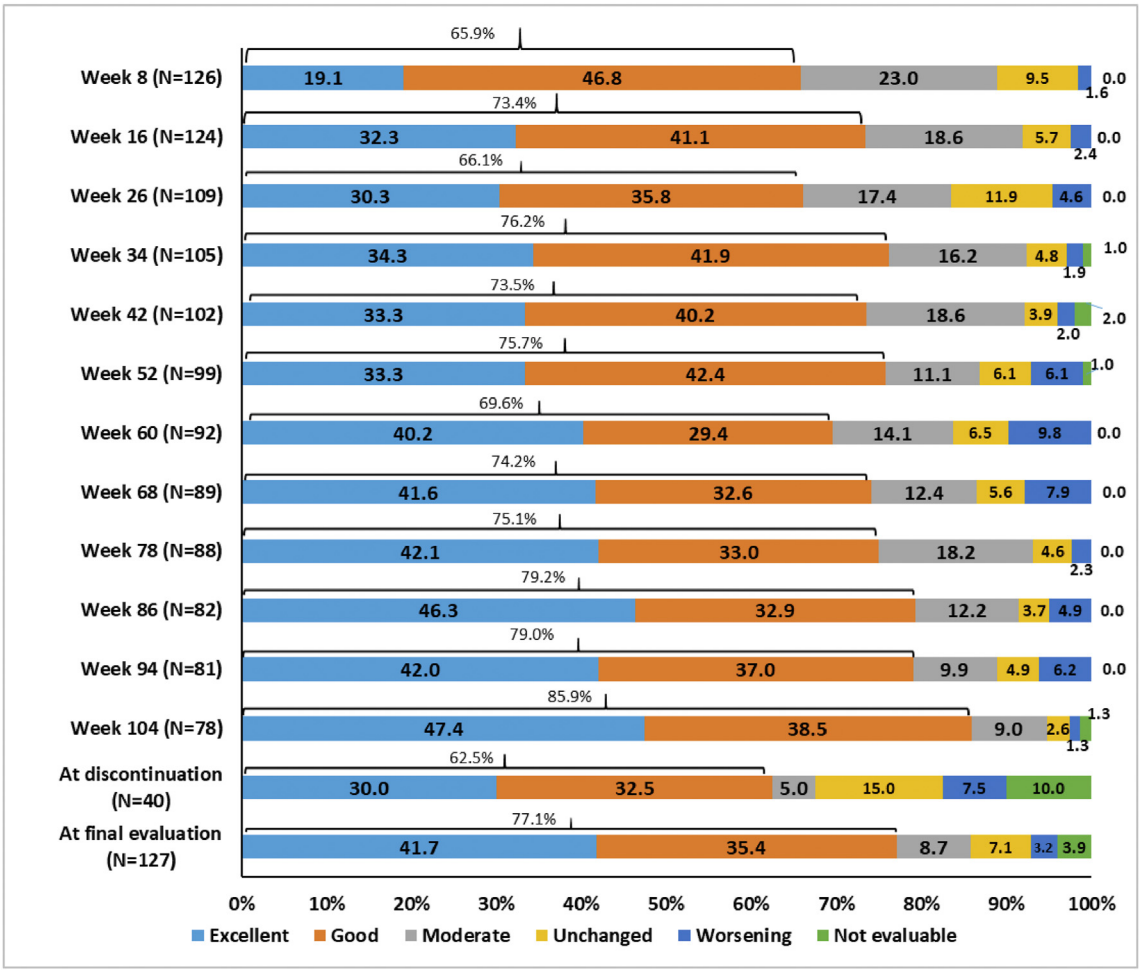

Fig. 2. Physicians' GETE evaluation in patients with omalizumab (effectiveness dataset). GETE, global evaluation of treatment effectiveness.

JPAC scores

Of the 127 patients, the JPAC scores were obtained from 58 patients at both baseline and final assessment. High JPAC scores indicated good asthma control. The percentages of patients who were "completely controlled" (score 15) and "adequately controlled" (score 12–14) increased from baseline to final assessment, 8.6%–48.3% and 12.1%–24.1%, respectively. The ratio of patients who were "poorly controlled" (score ≤11) decreased from 79.3% at baseline to 27.6% at final assessment (Supplementary Fig. 2).

Safety and effectiveness analysis by patient characteristics

Analysis of the incidence rate of adverse drug reactions by patients' demographics and clinical characteristics demonstrated no statistically significant difference for the incidence rate of adverse drug reactions (Supplementary Table 1). Similarly, effectiveness analysis by patients' demographics and clinical characteristics did not show any statistically significant difference for the effectiveness rate assessed by GETE (Supplementary Table 2).

Discussion

This post-marketing surveillance evaluated the safety and effectiveness of long-term omalizumab treatment in pediatric patients with severe allergic asthma under routine medical practice. Overall, the demographics and baseline characteristics of the patients enrolled in this surveillance were comparable to the randomized controlled trials and other real-life studies. Similar proportions of male and female were included in this surveillance, however previous studies reported inclusion of slightly higher proportion of males.[10,23] The baseline IgE levels were slightly high in the present surveillance with a mean IgE level of 568.7 IU/mL compared to the other studies (ranging from 335 IU/mL to 476 IU/mL).[10,23] The mean duration of asthma was comparable to that of randomized controlled trials in Japan and the US, and the French real-life studies.[10,16,17,23] Similar to the previously reported real-life study in France,[17] the majority of patients in this surveillance had comorbidities with allergic rhinitis being the most common. The baseline demographics and clinical characteristics of the patients included in this surveillance would present a further understanding of the clinical profile of patients eligible for omalizumab.

Regarding the safety, this surveillance showed that omalizumab was well tolerated in pediatric patients with 10.2% (13/127) patients experiencing adverse drug reactions, of which only 2 patients discontinued omalizumab treatment by Week 16. Overall, the safety profile was similar to the previous studies[23–25] with no new safety signals observed during the 104-week treatment period. The incidence of adverse drug reactions (10.2%) in the present surveillance was lower to the findings from a 24-week open label Japanese study evaluating safety and efficacy of omalizumab in pediatric patients (26.3%).[10] The most frequent adverse drug reactions in this surveillance were pyrexia and urticaria whereas the most common adverse drug reactions in the 24-week clinical study were headache, injection site pain, injection site

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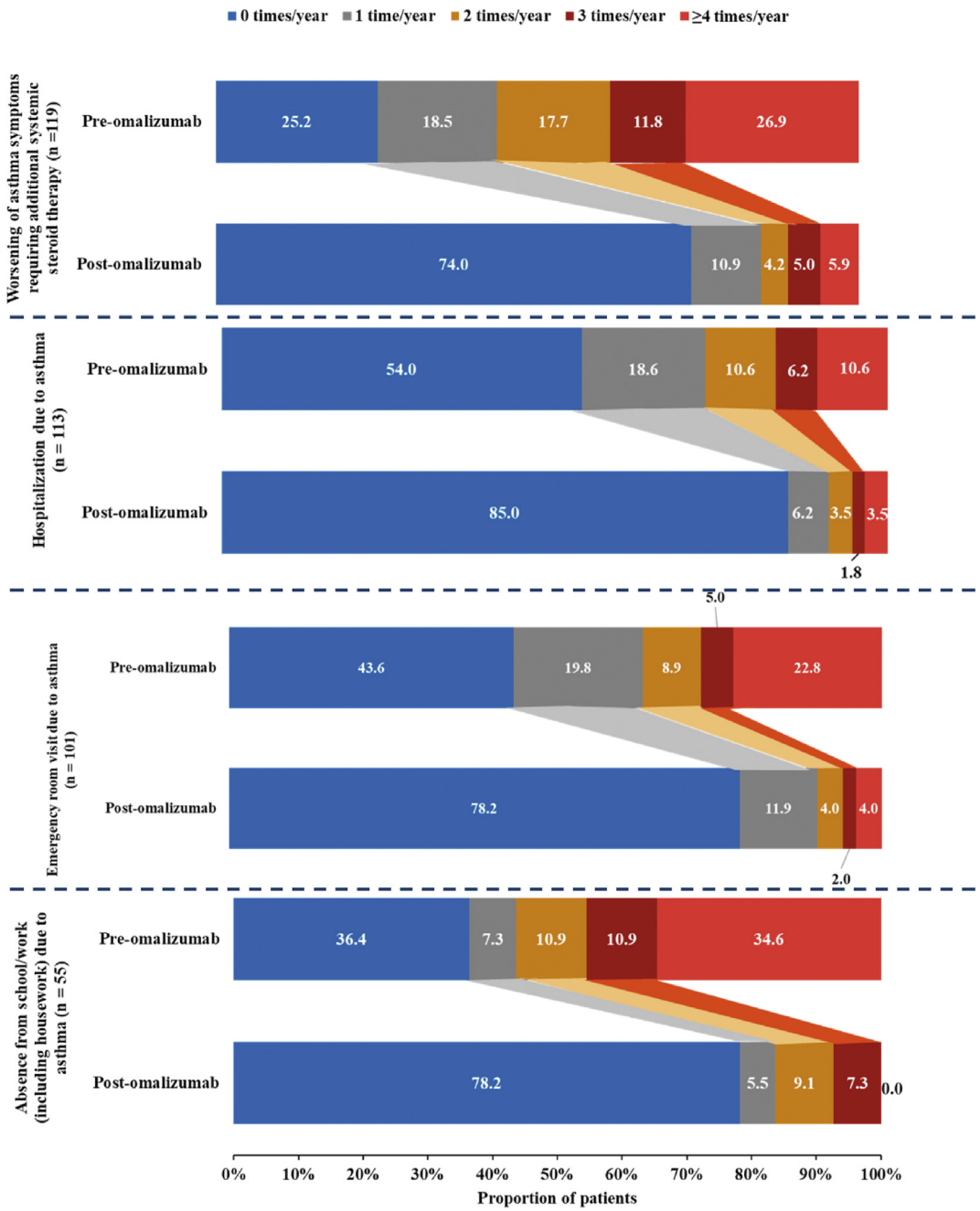

Fig. 3. Effectiveness of omalizumab on asthma exacerbation-related events.

erythema, injection site swelling, and urticaria.[10] It should be noted that each of the adverse drug reactions in both studies occurred in a small number of patients and hence a trend cannot be determined.

Data from the 24-week clinical study reported an incidence rate of adverse events of 94.7%.[10] The extension of the same study showed that 100% of patients reported at least one adverse events during the ≥104-week treatment period.[9] Lanier *et al.*, in a global 52-week randomized controlled trial enrolling children aged 6–12 years, reported that most patients (90.3%) experienced at least one adverse events and the overall incidence of adverse events was similar between the omalizumab and placebo groups.[23] The incidence rate of adverse events in the present surveillance (47.2%) was lower than the randomized controlled trial,[23] probably due to the difference between randomized controlled trials and post-marketing surveillance. The safety profile of omalizumab in the present study were in line with other real life studies evaluating omalizumab in children.[26,27] Anaphylaxis defined as adverse events of special interests was observed in 3 patients with 2 experiencing anaphylactic reaction and 1 experiencing type 1 hypersensitivity. Of these adverse events, adverse drug reactions of special interests were anaphylactic reaction and type 1 hypersensitivity each in 1 patient. 1 anaphylactic patient was 'non-serious' and related with omalizumab, and the other patient is 'serious' and relationship with omalizumab was 'not related'. The one patient with type 1 hypersensitivity was 'non-serious' and related with omalizumab. These patients continued treatment with omalizumab throughout the surveillance. Anaphylaxis is described as one of the important

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precaution in omalizumab product description[21] and is a concern for physicians in routine practice. Other pre-defined adverse events and adverse drug reactions of special interest including malignant tumor, bleeding tendency, autoimmune disease, infection parasitic, and eosinophilic syndrome, were not reported in this surveillance. Furthermore, the status of the concomitant allergic disease after omalizumab treatment either improved or remain unchanged, except in 2 of 97 patients with allergic rhinitis and 1 of 11 patients with other allergic diseases, confirming that omalizumab treatment did not have any adverse effects on the underlying concomitant allergic diseases.

As for the effectiveness, long-term omalizumab treatment was effective in improving asthma control and reducing asthma exacerbation-related events in children with severe allergic asthma. According to GETE, omalizumab was 'effective' in approximately 80% patients at the final assessment in this surveillance. Similar results were observed in the long-term treatment group with approximately 78% of patients being 'effective' at the final assessment. These results are similar to the randomized controlled trial conducted in the United States,[23] although our surveillance cannot be directly compared with the randomized controlled trial. In an open-labelled, extension study of the 24-week core study, Odajima *et al.* reported 76.3% patients achieving completely- or well-controlled asthma at the final assessment by JPAC compared with 23.7% at the start of the extension study, although the patient number and the evaluation period were different[9] from our surveillance. Similar results were also reported in a real-world study enrolling pediatric patients in France.[16] In this surveillance, treatment with omalizumab was associated with reduction in the asthma exacerbation-related events. A similar observation has been reported from a 1-year real-life study on children with uncontrolled severe allergic asthma in Italy, demonstrating a significant reduction in the number of asthma exacerbations during treatment with omalizumab compared with the previous year (1.0 vs 7.2 after 6 months [$p < 0.001$] and 0.8 after 12 months] $p < 0.001$], respectively).[27]

There are several reports implicating a disease modifying effect of omalizumab after long-term treatment,[28–31] represented by one showing that substantial proportion of asthma patients were controlled for 3 years since discontinuation after 6-year treatment with omalizumab.[29]

Treatment with omalizumab also improved asthma control as assessed by JPAC. At final assessment, the proportion of patients who were 'completely controlled' increased from 8.6% at baseline to 48.3% post-treatment and those who were 'adequately controlled' increased from 12.1% at baseline to 24.1% post-treatment. These findings confirm the effectiveness of long-term treatment with omalizumab in children with severe allergic asthma under a routine medical practice.

Regarding the long-term outcomes of omalizumab, it has been recently shown that there was no decrease in effectiveness over the 3 years during the prospective real-life observational study in Germany; the effectiveness of omalizumab, assessed by asthma symptoms, quality of life, GETE and exacerbations, was sustained throughout the three years, with no observed tachyphylaxis.[32]

In the present surveillance, the effectiveness of omalizumab was also sustained during the long-term treatment under a real-life condition. The effectiveness of omalizumab tended to increase along with the duration of treatment continuation (e.g., 85.9% was effective at week 104; Fig. 2), probably because the patients with effective response continued treatment with omalizumab (e.g., 62.5% was effective at discontinuation; Fig. 2).

The potential limitations of present surveillance includes the non-interventional observational study design without any comparator arms, and therefore, the safety and effectiveness assessments are based on a comparison with baseline. The surveillance depended on the participating medical institutions for collection of case report forms from patients; some case report forms could not be obtained due to a delay or non-collection by the participating institutions and others included the completion without re-reviewing. Because this surveillance was conducted under a routine medical practice, the differences in concomitant medications, omalizumab dose intervals, laboratory test methods, and other parameters may have influenced the outcomes. Despite these limitations, the findings from this surveillance would support safety, tolerability and effectiveness of long-term treatment with omalizumab in children with severe allergic asthma in a real-life clinical setting in Japan. These findings may assist physicians in guiding therapies for pediatric patients with uncontrolled asthma.

The findings from this post-marketing surveillance suggest no new safety signals with long-term omalizumab treatment in children with severe allergic asthma. Effectiveness of omalizumab in terms of GETE, improvement in asthma control and reduction in asthma exacerbation-related events was also demonstrated. The safety and effectiveness profile observed in this surveillance suggested that omalzumab is an established medicine for pediatric patients with severe allergic asthma in a real-life setting.

Acknowledgements

This study was funded by Novartis Pharma K.K. Tokyo, Japan.

The authors thank Hiral Joshi, Jisha John and Archana Jayaraman of Novartis, Hyderabad, India for providing medical writing support/editorial support, which was funded by Novartis, in accordance with Good Publication Practice guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2021.01.001.

Conflict of interest

The authors are employees of Novartis Pharma K.K., Tokyo, Japan

Authors' contributions

NN, MN and TS contributed to planning, implementation, data collection and data analysis of the surveillance. All the authors contributed to interpretation of the results, drafting and revising the manuscript, and agree to be accountable for all aspects of the work.

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Please cite this article as: Nakamura N et al., Real-life long-term safety and effectiveness of omalizumab in Japanese pediatric patients with severe allergic asthma: A post-marketing surveillance, Allergology International, https://doi.org/10.1016/j.alit.2021.01.001