

Original Article

Real-world safety and effectiveness of omalizumab in Japanese patients with chronic spontaneous urticaria: A post-marketing surveillance study

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ABSTRACT

Background: The safety and efficacy of omalizumab in chronic spontaneous urticaria (CSU) patients has been established, but real-world long-term data remain scarce, especially in Japan.

Methods: 52-week, open-label, single-arm, observational study evaluated the safety and effectiveness of first-time omalizumab in Japanese CSU patients responding inadequately to conventional therapies.

Results: Overall, 235 of 280 patients completed the study. Most patients were aged ≥ 18 and < 65 years; adolescents (≥ 12 and ≤ 18 years) accounted for 9.6% of the total population. The mean $\pm$ standard deviation (SD) duration of CSU at baseline was 1.6 ± 3.1 years; 46.1% of patients had had CSU for < 6 months. At baseline, the mean $\pm$ SD of Urticaria Control Test (UCT) score, Weekly Urticaria Activity Score (UAS7), and Dermatology Life Quality Index (DLQI) were 5.1 ± 3.2 , 25.2 ± 11.9 , and 8.4 ± 5.9 , respectively. The mean $\pm$ SD duration of the observation period was 330.3 ± 86.2 days. Relapse was reported in 65 patients, 51, 9, and 5 of whom required retreatment with omalizumab 1, 2, and ≥ 3 times, respectively. The incidence of adverse events (AEs), serious AEs, and adverse drug reactions (ADRs) was reported in 11.8%, 1.4%, and 3.9% of patients, respectively. The most common AEs were urticaria (1.8%) and eczema (1.1%). No adolescents experienced ADRs. A cumulative of 92.8% of patients responded in the Physician's Global Impression of Change, with 81.3%, 75.0%, and 95.1% of patients achieving UCT ≥ 12 , UAS7 ≤ 6 , and DLQI ≤ 5 up to Week 52, respectively.

Conclusions: This study supports the safety and effectiveness of omalizumab in CSU patients who responded inadequately to conventional therapies in real-world clinical practice in Japan.

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Introduction

Chronic spontaneous urticaria (CSU) is a skin disorder characterized by the spontaneous development of wheals (hives), angioedema, or both, lasting for > 6 weeks.^{1,2} Globally, the point prevalence of chronic urticaria (CU) is 0.7%.³ The reported prevalence of CSU in Asia is 1.4%, but in Japan, the prevalence remains unknown.³ CSU with concurrent angioedema was reported in 11.0–20.0% of total CSU patients in Japan.^{4–6}

In a real-world web-based survey conducted in Japan, CU was well controlled in only 36.1% of patients. Patients with CU with a Urticaria Control Test (UCT) score of < 12 demonstrated an impaired quality of life (QoL), diminished work productivity, and activity impairment, with 64% reporting uncontrolled symptoms versus patients with a UCT score ≥ 12 .⁷

Omalizumab (Novartis, Basel), an anti-human IgE monoclonal antibody, was licensed in Japan in January 2009 for use in allergic asthma. It was licensed for use in CSU in March 2017 in patients who were not responding adequately to conventional therapy and in December 2019 it was licensed for seasonal allergic rhinitis.⁸ In February 2022, omalizumab was licensed for use in allergic asthma and CSU in more than 100 countries worldwide.

In Japan, the safety and efficacy of omalizumab in patients with CSU was demonstrated during the 12-week treatment period in the

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Abbreviations:

ADR	Adverse drug reaction
AE	Adverse events
ATE	Arterial thromboembolic event
CI	Confidence interval
CRF	Case report form
CSU	Chronic spontaneous urticaria
CU	Chronic urticaria
DLQI	Dermatology Life Quality Index
H1AH	H ₁ -antihistamines
H2AH	H ₂ -antihistamines

LTRA	Leukotriene receptor antagonist
OR	Odds ratio
PGIC	Physician's Global Impression of Change
PMS	Post-marketing surveillance
PRO	Patient-reported outcome
Q1, Q3	First quartile, third quartile
QoL	Quality of life
SAE	Serious adverse event
SD	Standard deviation
UAS7	Weekly Urticaria Activity Score
UCT	Urticaria Control Test

randomized, double-blind, placebo-controlled Phase III POLARIS (NCT02329223) study.⁶ Since there has been no clinical studies on the use of omalizumab after 12 weeks in Japanese subjects, the necessity of continued administration after Week 12 should be carefully determined with consideration of the patient's condition; however, in the real-world setting, treatment with omalizumab may be continued for longer than 12 weeks or patient may be retreated if symptoms recur after treatment discontinuation. Although the ultimate goal of treatment for CSU is to achieve complete control of the disease per guidelines,^{1,2} real-world clinical practice tends to focus on controlling symptoms and improving QoL to levels that are acceptable for patients. Clinical trials and real-world data on the long-term safety and effectiveness of omalizumab in patients with asthma are abundant.^{9–11} However, real-world long-term data on the safety and effectiveness of omalizumab in patients with CSU are scarce, especially for use in relapse after the cessation of treatment; therefore, there is a need to collect these data in a wider Japanese population, which may help to fully characterize the clinical utility of omalizumab and determine its impact on QoL in patients with CSU.

This post-marketing surveillance (PMS) study was conducted as an additional pharmacovigilance activity to collect clinical use data from patients with CSU receiving omalizumab for the first time and to investigate longer-term safety and effectiveness. In the POLARIS study, treatment efficacy was assessed by using prospective patient-reported outcomes (PRO) such as the Weekly Urticaria Activity Score (UAS7) and its component, the Weekly Itch Severity Score (ISS7). The UAS7 is a useful tool for the prospective measurement of disease activity in patients with CSU, whereas the UCT provides a retrospective measurement of disease activity, and the results of UCT correlate with those of UAS.¹² Moreover, UCT is an easy-to-use PRO.¹² In this study, we employed UCT, Dermatology Life Quality Index (DLQI), and Physician's Global Impression of Change (PGIC) in addition to UAS7 for more comprehensive assessment.

The primary objective of this study was to evaluate the longer-term safety (adverse drug reactions [ADRs], adverse events [AEs], and serious AEs [SAEs]) and the overall effectiveness of omalizumab (subcutaneous injection) in patients with CSU in the real-world clinical setting. Secondary objectives include evaluation of PGIC, UCT, UAS7, and DLQI of omalizumab in patients with CSU.

Methods*Study design*

This was an open-label, multicenter, uncontrolled, single-arm, special drug use, observational study with an observation period

of 52 weeks from the start of new treatment with omalizumab. Observation was to be continued and relevant information completed in case report forms (CRFs), even if omalizumab was discontinued. However, if, for reasons that rendered continuation of observation impossible (such as withdrawal of consent, observations no longer possible, patient death, and others), the study would be discontinued. Such cases were to be handled as withdrawal, and the reason had to be entered in the CRF.

This study was conducted in accordance with the Ministry of Health, Labour and Welfare Ministerial Ordinance on Good Post-Marketing Study Practice for drugs. Data were collected through CRFs recorded by attending physicians during routine medical practice visits. CRFs were collected from the start of omalizumab treatment to the end of the observation period or treatment discontinuation using a web-based electronic data capture system in a 2-volume format: Volume 1 contained data from the initiation of omalizumab treatment to Week 24 after initiation; Volume 2 contained data from the day after Volume 1 completion to Week 52 after treatment initiation.

Study population

Patients with CSU who were not responding adequately to conventional therapies and who were receiving omalizumab for the first time for the indication of CSU, were included in the study. Patients aged < 12 years at the start of omalizumab treatment, patients with a history of hypersensitivity to any of the ingredients in omalizumab, or patients in an interventional study at the start of omalizumab treatment were excluded. All patients provided written consent to participate in this study. A detailed description of baseline demographic and clinical characteristics of patients is provided in [Table 1](#).

Outcomes and assessments

This analysis presents safety and effectiveness data from 280 patients with CSU who were enrolled in the study between May 2017 and August 2020.

Safety was assessed by the overall incidence of AEs, SAEs, ADRs, and priority investigation items. An ADR was judged as an AE for which a causal relationship with omalizumab was suspected by the investigator. Priority investigation items are the important identified risks or important potential risks in the risk management plan of omalizumab and defined in this study as anaphylaxis, malignant neoplasms, tendency to bleed, parasitic infection, hypereosinophilic syndrome, and arterial thromboembolic events (ATEs).

Table 1
Patient demographics and baseline characteristics (safety analysis set).

Factor	Safety analysis set		
	Total N = 280	With relapse n = 65	Without relapse n = 215
Sex			
Male	113 (40.4)	24 (36.9)	89 (41.4)
Female	167 (59.6)	41 (63.1)	126 (58.6)
Age at the start of treatment (years), mean (SD)	50.7 (20.7)	49.2 (21.7)	51.2 (20.4)
Age at the start of treatment			
≥ 12– < 18 years	27 (9.6)	4 (6.2)	23 (10.7)
≥ 18– < 65 years	162 (57.9)	40 (61.5)	122 (56.7)
≥ 65 years	91 (32.5)	21 (32.3)	70 (32.6)
Ethnicity			
Japanese	270 (96.4)	64 (98.5)	206 (95.8)
Others	10 (3.6)	1 (1.5)	9 (4.2)
BMI (kg/m²), mean (SD)	23.0 (3.5)	21.9 (2.7)	23.3 (3.7)
Complications			
Renal impairment	1 (0.4)	0 (0.0)	1 (0.5)
Hepatic function disorder	3 (1.1)	1 (1.5)	2 (0.9)
Medical history and complications			
Allergic conditions	12 (4.3)	4 (6.2)	8 (3.7)
Duration of disease[†] (years), mean (SD)	1.6 (3.1) (n = 230)	1.8 (3.2) (n = 53)	1.5 (3.0) (n = 177)
Duration of disease[†]			
< 6 months	129 (46.1)	30 (46.2)	99 (46.1)
6 months– < 1 year	30 (10.7)	5 (7.7)	25 (11.6)
1– < 3 years	32 (11.4)	6 (9.2)	26 (12.1)
3– < 5 years	15 (5.4)	5 (7.7)	10 (4.7)
≥ 5 years	24 (8.6)	7 (10.8)	17 (7.9)
Unknown/not specified	50 (17.9)	12 (18.5)	38 (17.7)
Presence of concomitant urticaria at the start of treatment	62 (22.1)	12 (18.5)	50 (23.3)
Allergic urticaria	16 (25.8)	3 (25.0)	13 (26.0)
Food-dependent exercise-induced anaphylaxis	2 (3.2)	1 (8.3)	1 (2.0)
Non-allergic urticaria	15 (24.2)	3 (25.0)	12 (24.0)
Aspirin-induced urticaria (urticaria due to intolerance)	2 (3.2)	0 (0.0)	2 (4.0)
Physical urticaria	22 (35.5)	5 (41.7)	17 (34.0)
Cholinergic urticaria	4 (6.5)	1 (8.3)	3 (6.0)
Contact urticaria	1 (1.6)	0 (0.0)	1 (2.0)
Angioedema	7 (11.3)	1 (8.3)	6 (12.0)
Prior medication[‡]	280 (100.0)	65 (100.0)	215 (100.0)
H1AH	279 (99.6)	65 (100.0)	214 (99.5)
One type (usual dose)	73 (26.2)	15 (23.1)	58 (27.1)
One type (≥ double)	106 (38.0)	26 (40.0)	80 (37.4)
At least 2 types of combination therapy	158 (56.6)	42 (64.6)	116 (54.2)
H2AH	129 (46.1)	29 (44.6)	100 (46.5)
LTRA	91 (32.5)	29 (44.6)	62 (28.8)
Steroids	107 (38.2)	25 (38.5)	82 (38.1)
Cyclosporine	17 (6.1)	3 (4.6)	14 (6.5)
Concomitant medication[‡]			
H1AH	265 (94.6)	NA	NA
H2AH	85 (30.4)	NA	NA
LTRA	69 (24.6)	NA	NA
Steroids	67 (23.9)	NA	NA
Tranexamic acid	30 (10.7)	NA	NA
UCT score, mean (SD)	5.1 (3.2) (n = 209)	4.5 (3.1) (n = 48)	5.3 (3.3) (n = 161)
UCT score category			
0–7	162 (57.9)	37 (56.9)	125 (58.1)
8–11	40 (14.3)	11 (16.9)	29 (13.5)
12–16	7 (2.5)	0 (0.0)	7 (3.3)
Unknown/unlisted	71 (25.4)	17 (26.2)	54 (25.1)
UAS7[§], mean (SD)	25.2 (11.9) (n = 92)	27.2 (11.9) (n = 22)	24.5 (12.0) (n = 70)
UAS7[§] category			
0	2 (0.7)	1 (1.5)	1 (0.5)
1–6	6 (2.1)	1 (1.5)	5 (2.3)
7–15	10 (3.6)	0 (0.0)	10 (4.7)
16–27	31 (11.1)	8 (12.3)	23 (10.7)
28–42	43 (15.4)	12 (18.5)	31 (14.4)
Unknown/unlisted	188 (67.1)	43 (66.2)	145 (67.4)
DLQI[¶], mean (SD)	8.4 (5.9) (n = 167)	9.0 (5.8) (n = 39)	8.2 (6.0) (n = 128)
DLQI[¶] category			
0–1	9 (3.5)	3 (4.9)	6 (3.1)
2–5	61 (23.8)	10 (16.4)	51 (26.2)
6–10	45 (17.6)	13 (21.3)	32 (16.4)

Table 1 (continued)

Factor	Safety analysis set		
	Total N = 280	With relapse n = 65	Without relapse n = 215
11–20	44 (17.2)	12 (19.7)	32 (16.4)
21–30	8 (3.1)	1 (1.6)	7 (3.6)
Unknown/unlisted	89 (34.8)	22 (36.1)	67 (34.4)

Data are presented as n (%) unless otherwise stated.

BMI, body mass index; DLQI, Dermatology Life Quality Index; H1AH, H1-antihistamines; H2AH, H2-antihistamine; LTRA, leukotriene receptor antagonist; N, total number of patients; n, number of patients; NA, not applicable; SD, standard deviation; UCT, Urticaria Control Test; UAS7, Weekly Urticaria Activity Score; y, year.

[†] Disease duration (y) = (date of the start of omalizumab - date of the first diagnosis of CSU+1)/365.

[‡] Medications that were used in >5% of patients are presented in this table.

[§] When the answers were recorded at least 4 days in 1 week, the scores obtained were converted to scores for 7 days. When the answers were not recorded for >3 days, the scores were considered as missing data.

[¶] As the DLQI is intended to be assessed in patients aged ≥ 17 y, patients of this age group (n = 256 patients) were included for assessment.

Effectiveness assessments in this study included PGIC, UCT, UAS7, and DLQI. PGIC is a comprehensive assessment of improvement of CSU from baseline in the order of “markedly improved,” “improved,” “no change,” “worsened,” or “not assessable.” The UCT is a questionnaire-based assessment of urticaria control consisting of 4 questions (scale 0–4), with the total score ranging from 0 (no control) to 16 (complete control). A score of ≥ 12 is considered “well controlled”; 8–11, “inadequately controlled”; and ≤ 7 , “uncontrolled.”¹² The UAS7 (range 0–42) is a weekly assessment of urticaria activity in the form of hives and itch score reported by patients in a diary, with higher values indicating more severe disease activity. A score of 0 is considered “complete control” 1–6, “well controlled”; 7–15, “mild activity”; 16–27, “moderate activity”; and 28–42, “severe activity” urticaria.¹³ Dermatology-specific QoL was assessed using DLQI, a questionnaire consisting of 10 questions (scale: 0–3, total: 0–30) used to measure the impact of skin disease on the QoL of a patient. A lower DLQI indicates lesser impact on a patient’s QoL. A score of 0–1 is considered as “no effect on life”; 2–5, “mild effect on life”; 6–10, “moderate effect on life”; 11–20, “significant effect on life”; and 21–30, “very significant effect on life.”¹⁴

Patients’ baseline factors were analyzed to examine the influence of baseline factors on the safety or effectiveness of omalizumab. These factors include sex; age at the start of treatment; body weight; disease duration of CSU; UCT, UAS7, and DLQI (all at the start of treatment); presence/absence of complications (renal impairment, hepatic function disorder); medical history and complications (allergic diseases); type of urticaria (angioedema); patients with any history of hypersensitivity; and prior and/or concomitant use of steroids at the start of treatment.

Registered patients are defined by registration information received by the patient registration center by Day 14 (Day 1 = start date of omalizumab treatment). The safety analysis set included patients with locked CRFs; it excluded those whose registration was not confirmed, who did not receive omalizumab, whose volume 1 of the CRF was not locked, who were not registered by Day 14 of omalizumab initiation, who did not have omalizumab initiation within the term specified in the contract with the site or whose contract expired during the period of volume 1, and/or who were ineligible due to inclusion/exclusion criteria violation.

The effectiveness analysis set included patients in the safety analysis set, but excluded those in whom PGIC had never been assessed.

Sample size

Sample size has been calculated in order to ensure statistical representativeness to describe the most relevant of the key

identified safety risks, which is anaphylaxis. As per POLARIS study, 2/73 patients (2.7%) had AEs indicative of anaphylaxis.⁶ Thus, assuming that the true incidence of anaphylaxis events in the study population would be ≥ 2.5 -times higher than the threshold incidence, 246 patients are required to detect a difference from the threshold incidence with a power of 90%. Assuming that approximately 8% of the patients would be excluded from the safety analysis population, the target sample size was set at 270 patients to ensure that 250 patients were enrolled for the safety analysis. To ensure that ≥ 25 adolescent patients (aged 12–18 years) were enrolled for the safety analysis, which was equivalent to at least 10% of the overall safety analysis population (250 patients), and by assuming that approximately 8% of the patients would be excluded from the safety analysis population, the target adolescent sample size was set at ≥ 27 patients of the overall 270 patients.

Results

Patient disposition and baseline characteristics

In total, 281 patients from 90 sites were registered and had their CRFs locked. Of them, 280 were included in the safety analysis set, excluding 1 ineligible patient who participated in another interventional study during the observation period (Fig. 1). One patient with unmeasured/unlisted primary efficacy variables was excluded, and 279 patients were included in the effectiveness analysis set. In total, 235 patients completed the predefined 52-week observation period, and 45 patients discontinued the study (Supplementary Fig. 1). Of these, reasons for treatment discontinuation were inability to continue observation due to change in address for 19 patients, withdrawal of consent for 5 patients, and ‘other’ for 21 patients, most of whom were lost to follow-up.

The demographic and disease characteristics of the safety analysis set at baseline are presented in Table 1. A total of 113 (40.4%) patients were male, 167 (59.6%) were female, with a mean $\pm$ SD age of 50.7 ± 20.7 years. More than half of the patients were aged ≥ 18 and < 65 years (57.9%). Adolescents aged ≥ 12 and ≤ 18 years accounted for 9.6% of the total patients.

Renal impairment, hepatic function disorder, and allergic conditions as part of their past medical history and complications were reported at baseline in 1 (0.4%), 3 (1.1%), and 12 (4.3%) patients, respectively. The mean $\pm$ SD duration of CSU at baseline was 1.6 ± 3.1 years; 129 (46.1%) patients had CSU for < 6 months. Sixty-two patients (22.1%) had other types of urticaria, which occurred as a complication alongside CSU. All patients received prior treatment for CSU. The most commonly used prior drug was histamine H1 antagonists (H1AH; 99.6%), followed by histamine H2 antagonists (H2AH; 46.1%) and steroids (38.2%). Throughout the study period,

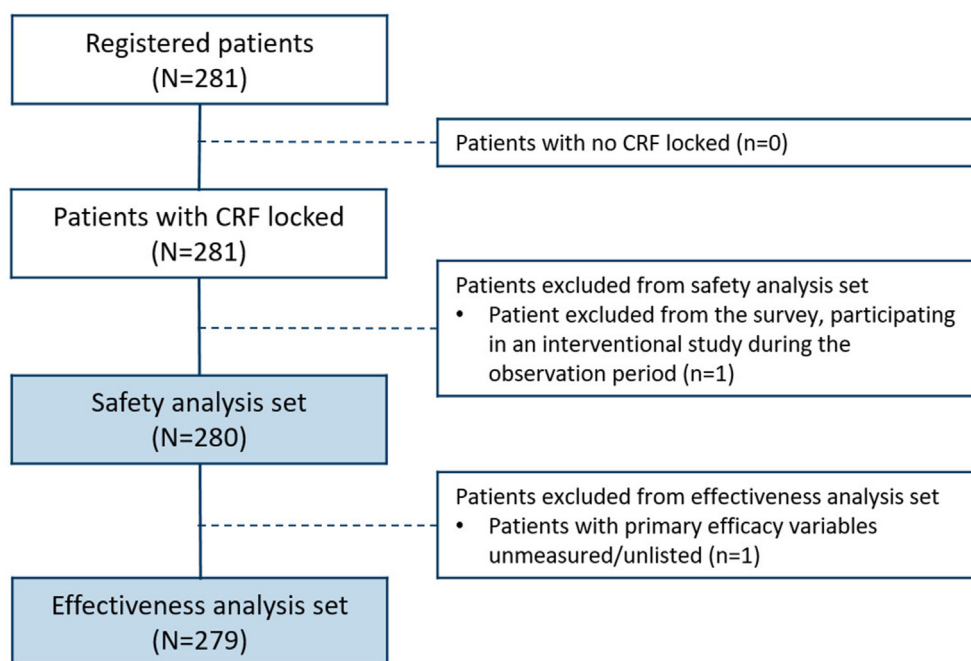


Fig. 1. Patient disposition. CRF, case record form; N, total number of patients; n, number of patients.

the most commonly used concomitant medications was H1AH (94.6%), followed by H2AH (30.4%), leukotriene receptor antagonists (LTRAs; 24.6%), oral steroids (23.9%), and tranexamic acid (10.7%). Concomitant use of oral steroids decreased from 22.1% at baseline to 15.2% by the end of the study period.

At baseline, the mean $\pm$ SD UCT score was 5.1 ± 3.2 ; more than half of the patients had a UCT score of ≤ 7 (57.9%), followed by UCT scores of 8–11 (14.3%) and 12–16 (2.5%). A total of 71 (25.4%) patients had no UCT assessment at baseline. At baseline, the mean $\pm$ SD UAS7 was 25.2 ± 11.9 , and UAS7 in 2 (0.7%) patients was 0, in 6 (2.1%) patients was ≥ 1 – ≤ 6 , in 10 (3.6%) patients was ≥ 7 – ≤ 15 , in 31 (11.1%) patients was ≥ 16 – ≤ 27 , in 43 (15.4%) patients was ≥ 28 – ≤ 42 , and most patients (67.1%) had no UAS7 data available. At baseline, the mean $\pm$ SD DLQI was 8.4 ± 5.9 . A total of 23.8%, 17.6%, 17.2%, and 3.1% of patients reported DLQI of 2–5, 6–10, 11–20, and 21–30, respectively (Table 1).

Administration and relapse status

The mean $\pm$ SD duration of the observation period was 330.3 ± 86.2 days. The patients received a total of 6.3 ± 3.8 doses of omalizumab throughout the observation period. The median (first to third quartiles [Q1–Q3]) administration interval in patients who had ≥ 2 doses of omalizumab (excluding the non-administration period until retreatment due to relapse) was 30.0 (28.5–34.0) days, which indicated that patients used omalizumab in accordance with the predefined range in the package insert (Table 2). A total of 113 (40.4%) patients received ≥ 4 consecutive doses of omalizumab as long-term treatment (Week 12 and thereafter) after the start of treatment.

Most patients received continuous administration in accordance with the package insert. There were 21 cases of doses less than 300 mg being administered due to sufficient efficacy. The most common reason for different administration interval was due to patient's convenience (including prolonged interval due to no visit by the patient) (Supplementary Table 1).

Presence/absence of relapse was assessed by physicians in all patients. A total of 65 (23.2%) patients relapsed throughout the observation period (Table 1), 24 (36.9%) of whom were male and 41 (63.1%) were female. The mean $\pm$ SD age at the start of treatment of

Table 2
Omalizumab administration during the study period (safety analysis set).

Factors	Safety analysis set N = 280
Observation period[†] (days), mean (SD)	330.3 (86.2)
Total omalizumab exposure[‡], n (%)	
< 12 weeks	97 (34.6)
≥ 12 –< 24 weeks	35 (12.5)
≥ 24 –< 52 weeks	140 (50.0)
Week 52	8 (2.9)
Total duration of omalizumab treatment[‡] (days), mean (SD)	195.6 (134.6)
Total number of omalizumab doses, mean (SD)	6.3 (3.8)
Minimum–maximum	1–14
Mean dosing interval (days/times)[§], median (Q1–Q3)	30.0 (28.5–34.0)
n = 261	
Total omalizumab dose (mg), mean (SD)	1864.0 (1126.5)
Omalizumab dose per administration[¶], n (%)	
< 300 mg	6 (2.1)
300 mg	274 (97.9)
> 300 mg	0 (0.0)

N, total number of patients; n, number of patients; Q, quartile; SD, standard deviation.

[†] Observation period = end date of the observation period – start date of the administration of omalizumab + 1.

[‡] Total duration of treatment with omalizumab = end date of treatment with omalizumab – start date of treatment with omalizumab + 1.

[§] Mean dosing interval (days/times) = total dosing interval/(total number of doses of omalizumab – number of cycles)/(number of cycles + 1 for retreatment due to relapse). One cycle is defined as the period from the first day of treatment at the time of retreatment due to initial or relapse to the day before the first day of treatment at the time of retreatment due to subsequent relapse. Patients who received at least 2 doses in any cycle were included.

[¶] Dose per administration of omalizumab (mg/dose) = total dose of omalizumab (mg)/total number of doses of omalizumab (times).

relapsed patients was 49.2 ± 21.7 years. No noteworthy trends were observed in terms of demographics based on relapse status.

In total, 215 patients experienced no relapse throughout the observation period. Of these, 99 had a period of time without relapse and had no treatment for at least 16 weeks, while 89 received omalizumab ≥ 4 consecutive times following the start of administration. Of the patients with relapse, 51, 9, and 5 patients required retreatment with omalizumab 1, 2, and ≥ 3 times, respectively. The duration until the retreatment was shorter after the second or subsequent relapse than that after the initial relapse. The mean duration of time from previous administration to retreatment after initial relapse and second or subsequent relapse was 98.0 ± 57.7 and 71.4 ± 21.6 days, respectively (Supplementary Fig. 2).

In patients who were initially well controlled (UCT score of ≥ 12) during omalizumab administration and who developed poor control (UCT score of < 12) after an interval of ≥ 6 weeks, the mean $\pm$ SD duration from the previous dose to the retreatment after the first and second relapse was 94.2 ± 46.7 and 65.0 ± 13.8 days, respectively (Supplementary Fig. 2).

Safety outcomes

AEs and SAEs were reported in 33 (11.8%) and 4 (1.4%) patients, respectively. The most common (in ≥ 2 patients) AEs were urticaria in 5 patients (1.8%); eczema in 3 patients (1.1%); and constipation, diarrhea, pruritus, malaise, and rib fracture in 2 patients (0.7%) each (Table 3). The breakdown of SAEs was bacterial prostatitis, urticaria, facial bone fractures, rib fracture, and subdural hematoma in 1 patient (0.4%) each.

The incidence of AEs (9/65 patients, 13.9%) and SAEs (1/65 patients, 1.5%) in patients with relapse was comparable to overall patients of AEs. The incidence of AEs was comparable (8/113 patients, 7.1%), while no SAE was reported in patients who received ≥ 4 consecutive omalizumab doses since the start of administration.

In total, 11 (3.9%) patients reported ADRs. The most commonly (in ≥ 2 patients) reported ADRs were diarrhea and malaise in 2 patients (0.71%) each. No serious ADRs were observed in the safety analysis set. The incidence of ADRs was 6.2% (4/65 patients) and 1.8% (2/113 patients) in patients with relapse and patients who received ≥ 4 consecutive omalizumab doses since the start of administration, respectively. The incidence of ADRs tended to be lower in patients who recorded lower UCT scores at the start of treatment (UCT score of 12–16, 28.6% of patients; 8–11, 2.5% of patients; 0–7, 3.1% of patients). The adjusted odds ratio (OR) with 95% confidence interval (CI) was 0.05 (< 0.01 , 0.72) for “UCT score of 8–11” and 0.08 (0.01, 0.59) for “UCT score of ≤ 7 ,” assuming “UCT score of ≥ 12 ” as the reference. However, caution must be exercised when interpreting results as there were only 7 patients with “UCT score of 12–16”. Patients with any history of hypersensitivity tended to have a higher incidence of ADRs than patients without (15.4% vs 2.9%; adjusted OR [95% CI]: 6.40 [1.24, 32.98]), assuming patients “without” hypersensitivity as the reference (Supplementary Fig. 3). No ADRs were reported in the 27 adolescent patients as well as in patients with special background characteristics (patients with renal impairment or hepatic function disorder complications). There were no pregnant women in the study. In elderly patients (aged ≥ 65 years), ADRs including somnolence, pruritus, rash, and rheumatoid arthritis were observed in 1 patient each.

Most of the reported ADRs occurred at an early stage after initiating omalizumab; no delayed ADRs were observed. The incidence of ADRs was 2.1% (≤ 4 weeks), 0.4% (4–8 weeks), 0.7% (8–12 weeks), 0 (12–24 weeks), and 0.8% (> 24 weeks).

The incidence of AEs leading to discontinuation was 1.4% (4/280 patients), with 4 patients experiencing a total of 5 events: 1 event each of anaphylactic reaction, stress, presyncope, dyspnea, and

psoriatic arthropathy. Of these events, the ADR leading to discontinuation was 1 event of psoriatic arthropathy in 1 patient.

The occurrence of AEs and ADRs in the priority investigation items is shown in Table 4. AEs regarding anaphylaxis were seen in 2 (0.7%) patients, and ATEs (subdural hematoma) were seen in 1 (0.4%) patient; no ADRs were observed.

For the AEs defined as anaphylaxis in the priority investigation items of this study, 1 patient (a 14-year-old male) reported dyspnea and urticaria the day after the second administration of omalizumab; the other patient (a 39-year-old female) reported an anaphylactic reaction on the day of the second administration of omalizumab. The administration of omalizumab was discontinued in both instances, and neither event was serious; both patients

Table 3
Incidence of AEs (safety analysis set).

System Organ Class Preferred Term	Safety analysis set Incidence of AEs, n (%) N = 280
Total	33 (11.8)
Infections and infestations	5 (1.8)
Appendicitis	1 (0.4)
Nail dermatophytosis	1 (0.4)
Folliculitis	1 (0.4)
Nasopharyngitis	1 (0.4)
Bacterial prostatitis	1 (0.4)
Immune system disorders	1 (0.4)
Anaphylactic reaction	1 (0.4)
Psychiatric disorders	1 (0.4)
Stress	1 (0.4)
Nervous system disorders	4 (1.4)
Headache	1 (0.4)
Loss of consciousness	1 (0.4)
Migraine	1 (0.4)
Presyncope	1 (0.4)
Somnolence	1 (0.4)
Eye disorders	1 (0.4)
Eyelid edema	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	2 (0.7)
Dyspnea	1 (0.4)
Oropharyngeal pain	1 (0.4)
Gastrointestinal disorders	6 (2.1)
Constipation	2 (0.7)
Diarrhea	2 (0.7)
Abdominal pain	1 (0.4)
Lip swelling	1 (0.4)
Hepatobiliary disorders	1 (0.4)
Liver disorder	1 (0.4)
Skin and subcutaneous tissue disorders	12 (4.3)
Urticaria	5 (1.8)
Eczema	3 (1.1)
Pruritus	2 (0.7)
Acne	1 (0.4)
Dermatitis contact	1 (0.4)
Drug eruption	1 (0.4)
Rash	1 (0.4)
Musculoskeletal and connective tissue disorders	3 (1.1)
Arthralgia	1 (0.4)
Psoriatic arthropathy	1 (0.4)
Rheumatoid arthritis	1 (0.4)
General disorders and administration site conditions	5 (1.8)
Malaise	2 (0.7)
Asthenia	1 (0.4)
Condition aggravated	1 (0.4)
Injection site reaction	1 (0.4)
Injury, poisoning, and procedural complications	4 (1.4)
Rib fracture	2 (0.7)
Facial bone fracture	1 (0.4)
Fall	1 (0.4)
Subdural hematoma	1 (0.4)
Exposure through breast milk	1 (0.4)

Multiple episodes of an event in the same patient are counted only once.
AE, adverse event; N, total number of patients; n, number of patients.

Table 4
Incidence of priority investigation items (safety analysis set).

Priority investigation items	Incidence of AEs, n (%) N = 280	
Preferred Term	AEs	ADRs
Total	3 (1.1)	0 (0.0)
Anaphylaxis	2 (0.7)	0 (0.0)
Malignant neoplasm	0 (0.0)	0 (0.0)
Bleeding tendency	0 (0.0)	0 (0.0)
Parasitic infection	0 (0.0)	0 (0.0)
Hypereosinophilic syndrome	0 (0.0)	0 (0.0)
ATEs	1 (0.4)	0 (0.0)
Subdural hematoma	1 (0.4)	0 (0.0)

Multiple episodes of an event (PT) in the same patient are counted only once.
ADR, adverse drug reaction; AE, adverse event; ATE, arterial thromboembolic event;
N, total number of patients; n, number of patients.

recovered on the day of onset. A causal relationship with omalizumab was excluded by the investigator and deemed to be caused by the primary disease. For AEs defined as ATEs in the priority investigation items of this study, an 84-year-old male reported the event on Day 17 after the fourth administration of omalizumab when subdural hematoma was observed. The event was serious, and the patient recovered. A causal relationship with omalizumab was not suspected.

No AEs or ADRs considered priority investigation items were observed among patients who received omalizumab ≥ 4 consecutive times since the start of administration.

Effectiveness outcomes

The proportion of responders (rated “markedly improved” or “improved”) in the PGIC was 82.3% at Week 4 and maintained at

> 80% throughout the observation period (Fig. 2). The cumulative proportion of responders in the PGIC was 91.2% up to Week 12 and increased slightly to 92.0% and 92.8% up to Weeks 24 and 52, respectively (Table 5). The median time (Q1–Q3) to first-time response after initiating omalizumab treatment was 29.0 (29.0–32.0) days, with mean $\pm$ SD doses of 1.1 ± 0.4 .

The proportion of responders assessed as “markedly improved” or “improved” was lower among patients who were retreated with omalizumab after relapse compared to the overall population and it became progressively lower as the number of relapses increased (Table 5).

Omalizumab treatment improved UCT score, UAS7, and DLQI throughout the observation period. The cumulative proportions of patients achieving UCT ≥ 12 were 118 (67.4%), 136 (76.0%), and 148 (81.3%) up to Weeks 12, 24, and 52, respectively. Cumulatively, 85 (46.7%) patients achieved 16 points in UCT assessment up to Week 52 (Fig. 3a). The median time (Q1–Q3) to the first UCT ≥ 12 and a UCT score of 16 after initiating omalizumab treatment was 34.5 (29.0–85.0) and 57.0 (32.0–92.0) days, with mean $\pm$ SD doses of 1.9 ± 1.6 and 2.4 ± 2.1 , respectively.

The cumulative proportion of patients achieving UAS7 ≤ 6 and UAS7 = 0 was 57 (68.7%) and 45 (54.2%) patients up to Week 12, 61 (73.5%) and 49 (59.0%) patients up to Week 24, and 63 (75.0%) and 52 (61.9%) patients up to Week 52, respectively (Fig. 3b). The median time (Q1–Q3) to the first UAS7 ≤ 6 after initiating omalizumab treatment was 29.0 (29.0–57.0) days, with a mean $\pm$ SD dose of 1.7 ± 1.3 . The median time (Q1–Q3) to the first UAS7 = 0 after initiating omalizumab treatment was 47.5 (29.0–85.0) days, with a mean $\pm$ SD dose of 2.1 ± 1.6 . The cumulative proportion of patients achieving DLQI ≤ 5 was 90.4% up to Week 12, 92.8% up to Week 24, and 95.1% up to Week 52 (Fig. 3c). Cumulatively, 95 (70.4%), 104 (75.4%), and 114 (80.3%) patients achieved DLQI ≤ 1 up to Weeks 12, 24, and 52, respectively. The median time (Q1–Q3) to the first DLQI

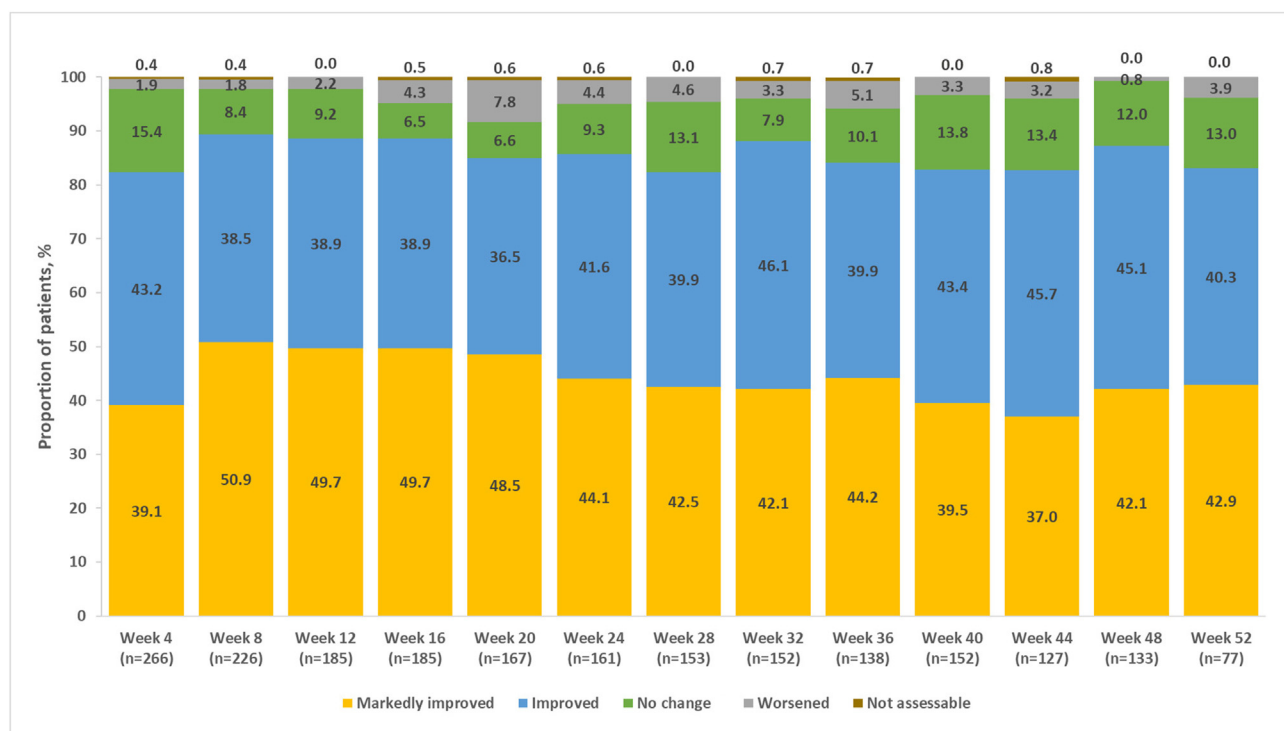


Fig. 2. Physician's Global Impression of Change in the overall population throughout the observation period (effectiveness analysis set). The physician assessed the changes in CSU from treatment initiation at each visit, on a scale of 1–5: “Markedly improved” (indicating 5), “Improved” (indicating 4), “No change” (indicating 3), “Worsened” (indicating 2), and “Not assessable” (indicating 1).

CSU, chronic spontaneous urticaria; n, number of patients.

Table 5
Cumulative Physician's Global Impression of Change (effectiveness analysis set).

Timeframe	Markedly improved	Improved	No change	Worsened	Not assessable	Response rate [†] (95% CI)
Overall						
Up to Week 12 (N = 274)	150 (54.7)	100 (36.5)	22 (8.0)	2 (0.7)	0 (0.0)	250 (91.2) (87.3, 94.3)
Up to Week 24 (N = 276)	177 (64.1)	77 (27.9)	20 (7.3)	2 (0.7)	0 (0.0)	254 (92.0) (88.2, 94.9)
Up to Week 52 (N = 279)	185 (66.3)	74 (26.5)	19 (6.8)	1 (0.4)	0 (0.0)	259 (92.8) (89.2, 95.6)
Relapsed patients						
From the start of treatment until the first relapse (N = 65)	51 (78.5)	14 (21.5)	0 (0.0)	0 (0.0)	0 (0.0)	65 (100.0) (94.5, 100.0)
From the time of retreatment after the first relapse until the second relapse (N = 65)	33 (50.8)	29 (44.6)	1 (1.5)	2 (3.1)	0 (0.0)	62 (95.4) (87.1, 99.0)
From the time of retreatment after the second relapse to the third relapse (N = 14)	7 (50.0)	4 (28.6)	1 (7.1)	2 (14.3)	0 (0.0)	11 (78.6) (49.2, 95.3)

Cumulative response was defined as the best assessment result obtained from the day after the treatment with omalizumab to each assessment time-point.

CI, confidence interval; N, total number of patients.

[†] Response rate was defined as “markedly improved” + “improved.” The denominator was the total number of patients with the best response (including undeterminable cases).

≤ 5 and DLQI ≤ 1 after initiating omalizumab treatment was 29.0 (29.0–57.00) and 35.0 (29.0–85.0) days, with mean $\pm$ SD doses of 1.5 ± 1.4 and 1.9 ± 1.6 , respectively.

The proportion of responders was analyzed based on the patient factors (Supplementary Fig. 4, 5). Responders of adolescent patients were not statistically different from adult patients in the PGIC and the UCT assessment (Supplementary Fig. 4, 5). Patients weighing < 60 kg (97.7%) were more likely to achieve “markedly improved” or “improved” in the PGIC assessment than those weighing 60–80 kg (87.5%) (Supplementary Fig. 4); although fewer patients were evaluated, the improvement was not significantly different in the UCT assessment (Supplementary Fig. 5). Patients with a CSU duration of 1–3 years (66.7%) were less likely to have their best scores of UCT ≥ 12 than those with a CSU duration of < 6 months (87.1%) (Supplementary Fig. 5); however, the differences were not statistically significant in the PGIC assessment (Supplementary Fig. 4).

Discussion

The current study demonstrated the long-term safety and effectiveness of omalizumab in a real-world setting. This is the first report on omalizumab-related outcomes in a real-world large Japanese population with CSU. The incidence of ADRs in the safety analysis set was 3.9% (11 patients). The most common ADRs included diarrhea and malaise, reported in 2 patients each. Priority investigation AEs were observed in 3 patients in the safety analysis set (anaphylaxis in 2 patients, ATEs in 1 patient). No AEs related to malignant neoplasms were observed in this study, with the limitation, in this regard, of its duration of observation up to 1 year only. The AEs corresponding to anaphylaxis were dyspnea, urticaria, and anaphylactic reaction, whereas the ATE was subdural hematoma. The causal relationship between all events and the drug was not suspected; the outcome of the events was reported as “recovered” or “recovering.”

No ADRs were observed in patients with special background features (renal impairment or hepatic function disorder complications). There were no pregnant women in the study. In elderly patients, ADRs included somnolence, pruritus, rash, and rheumatoid arthritis, which were observed in 1 patient each. The results of this study showed no new safety concerns regarding long-term treatment with omalizumab.

Urticaria symptoms may fluctuate considerably from day to day. Assessing disease activity at the time of presentation to the physician is rarely representative of actual disease status.¹² Apart from the physician assessment at the point of visit, PRO measurement tools, such as UCT and UAS7, can be helpful to understand the symptom status. Omalizumab treatment improved PGIC, UCT score, UAS7, and DLQI throughout the observation period. The proportion of responders in PGIC was maintained at over 80% throughout the long-term observation period. In the overall population in this study, the longer the observation period, the higher the cumulative effectiveness. Additionally, 67.4% of patients achieved a cumulative UCT ≥ 12 up to Week 12, which is in agreement with the previous data from the SUNRISE study where 74.6% of patients achieved UCT ≥ 12 at Week 12 with omalizumab treatment.¹⁵ Overall, 68.7% versus 67.7% of patients achieved a UAS7 ≤ 6 in this study versus the SUNRISE study.¹⁵ The current study results were in line with those of an earlier report stating that UCT is a reliable tool for measuring disease control,¹⁵ consistent with findings from a previous study from Thailand.¹⁶ The proportion of patients achieving complete control in the UCT assessment (UCT = 16) was lower than that in the UAS7 assessment (UAS7 = 0). It is worth noting that the UCT aided in assessing QoL elements in addition to hives and itching; hence, achieving complete control in UCT could be considered a more appropriate indication of patient satisfaction on treatment outcome.

The cumulative proportion of patients achieving a UAS7 ≤ 6 up to Week 12 was 68.7% in this study versus 57.5% in POLARIS.⁶ The incidence of AEs in the safety analysis set was 11.8% versus 54.8% in POLARIS⁶; the incidence of SAEs in the safety analysis set was 1.4% versus 4.1% in POLARIS.⁶ There were generally fewer AEs/SAEs in this real-world study than in clinical trials, although it was difficult to compare them directly because of differences in study design itself. It is of note that the demographic features were different between this study and POLARIS. In POLARIS, 54.8% of patients were female (vs 59.6% in the current study), who were aged 44.6 years (vs 50.7 years in the current study) and weighed 65.3 kg (vs 59.9 kg in the current study).⁶ Unlike the stricter inclusion/exclusion criteria applied to POLARIS, this PMS study included 22.1% of patients with concomitant other type of urticaria with the same magnitude of effectiveness. When compared with the overall population, including those from adult patients, nothing notable was observed in the proportion of responders in adolescent

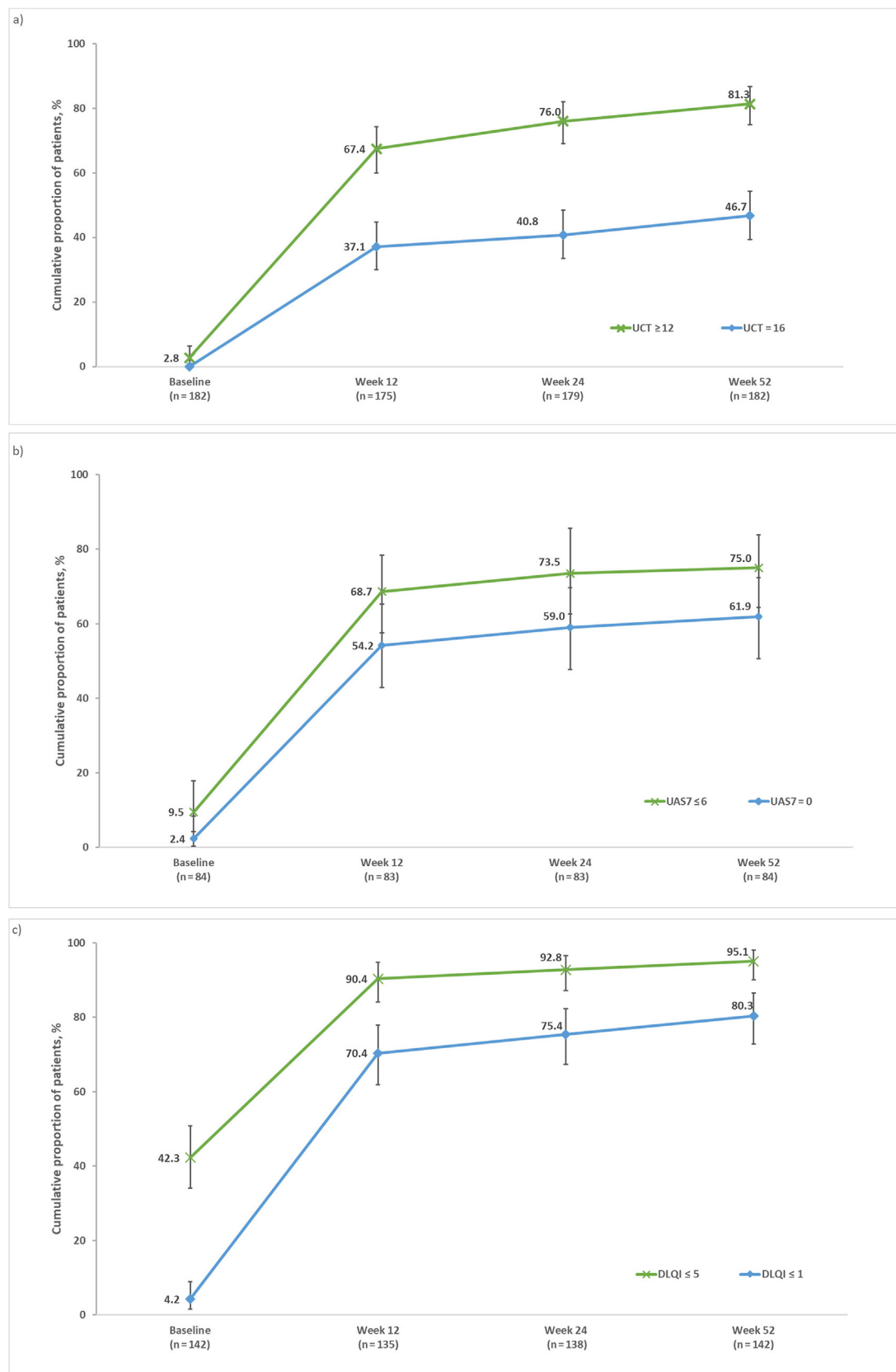


Fig. 3. Cumulative response in the PRO of patients with CSU over the observation period. **a)** UCT; **b)** UAS7; **c)** DLQI (effectiveness analysis set). Mean and 95% CI values are presented. UCT score of ≥ 12 : Well controlled and UCT score of 16: complete control in the UCT questionnaire; UAS7 of ≤ 6 : Improved and UAS7 of 0: No symptom in the UAS7 questionnaire; DLQI of ≤ 5 : Mild effect on life and DLQI of 0: No effect on life in the DLQI questionnaire. CI, confidence interval; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; N, total number of patients; PRO, patient-reported outcome; UAS7, Weekly Urticaria Activity score; UCT, Urticaria Control Test.

patients (aged 12–18 years). The median UAS7 at the start of treatment was 33.5 in POLARIS versus 25.0 in the current study.⁶ However, unlike POLARIS, patients in this real-world study did not require discontinuation of prior treatments, which might reduce the symptoms to some extent. In fact, a significant number of patients in this PMS study had been previously treated with LTRAs, cyclosporine, or steroids. Therefore, this PMS study showed a safety and effectiveness profile of omalizumab which is consistent with what has been shown in the POLARIS randomized clinical trial, even in patients with various background features.

In the current study, a lower proportion (23.2% [65/280]) of patients have relapsed over the observation period than those previously reported (48.7%–66.6%).^{17–19} This result should be interpreted with caution because the definitions of relapse and treatment regimen as well as disease duration are different among studies. Several studies reported that the shorter the disease duration, the lower the relapse rate.^{18,19} The overall shorter disease duration in this study may have contributed to the lower relapse rate. The proportion of responders in PGIC following up to the first, the second, and the third relapse in this real-world study was 100.0%, 95.4%, and 78.6%, respectively, which was lower than that in patients with comparable symptoms controlled in the Phase III OPTIMA study.¹⁷ Unlike in clinical trials, selection bias can be introduced because it reflects patients' willingness to retreatment. Although data are not available, another possibility is that the retreatment period after relapse was short. A study from Italy suggested that clinical response increased in repeat of 6-month retreatment cycles.²⁰ In addition, faster and higher rates of relapse have been reported in groups with high baseline IgE levels and in very early responders to omalizumab.^{19,21} Clinical features including baseline IgE, disease duration CSU, and periods of treatment with omalizumab are issues to be investigated in future studies, in relation to relapse and poor retreatment response.

In PGIC analysis, patients who weighed < 60 kg were more likely to score better compared to patients ≥ 60–< 80 kg, while all patients ≥ 80 kg also responded to treatment although odd ratio was not estimable. Moreover, since no other significant differences were identified in other efficacy measures, body weight may not play a role in affecting omalizumab's effectiveness.

In clinical practice, medical cost is often taken into account. Generally, the high cost of biologics imposes an economic burden on the patient and society. With over 60% of patients with CSU remaining symptomatic, despite treatment with H1AH, this will impose a substantial financial burden not only on patients, but also on healthcare systems.²² Several studies previously reported the cost-effectiveness of omalizumab in patients with CSU.^{23–25} In this study, more than half the patients received omalizumab for more than 24 weeks. Cumulatively, 61.9% of patients achieved a UAS7 = 0, and 46.7% of patients achieved a UCT score of 16 up to Week 52, showing complete urticaria control, and 80.3% of patients achieved DLQI ≤ 1 up to Week 52 showing no impact on their QoL. It is considered that a considerable number of patients will benefit from omalizumab when aiming for complete urticaria control.

The limitation of this study is inherent to PMS studies. Data collection for this study depended on the participating medical institutions based on the CRFs collected from patients; in clinical practice, some CRFs could not be obtained owing to a delay or non-collection by the participating institutions, due to the incompleteness of data. It was not possible to determine the impact of confounding factors such as drugs taken or administration intervals of omalizumab. This study used the multiple logistic regression model to adjust for the confounders; however, as this was an observational study with no control group, it was difficult to demonstrate whether the obtained results indicate the impact of exposure to omalizumab by itself. Several studies have mentioned that high

total IgE levels may predict the response of omalizumab. However, we did not collect IgE level in this study as it is not required to prescribe omalizumab for patients with CSU.^{21,26,27}

The present results show that treatment effectiveness and the risk of relapse are not associated with disease duration in Japanese clinical practice. However, the number of patients in this study was limited and nearly half the patients had a disease duration of < 6 months. Therefore, a correlation between longer disease duration and treatment resistance has not been proven. Despite these limitations, results from this study reflected the real-world effectiveness of omalizumab.

The current study supports the safety and effectiveness of omalizumab in patients with CSU who were not responding adequately to conventional therapies in real-world clinical practice in Japan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2022.09.003>.

Conflict of interest

MH received research grant from Eisai, GlaxoSmithKline, Kaken Pharmaceutical, Kyowa Kirin, Mitsubishi Tanabe, Novartis, Sanofi, and Taiho Pharmaceutical, honorarium from Kaken Pharmaceutical, Kyorin Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe, MSD, Novartis, Sanofi, Taiho Pharmaceutical, Teikoku Seiyaku, and Uriach. AF received lecture and/or consultation fees from Taiho Pharmaceutical, Novartis, Mitsubishi Tanabe, Kaken Pharmaceutical, Sanofi, and Kyowa Hakko Kirin and received funds for sponsored/joint research from Novartis and Taiho Pharmaceutical. AI received advisory board honoraria, consulting fees or speaker honoraria from AbbVie, Eli Lilly Japan, Maruho, Novartis, Sanofi, Leo Pharma, and Torii Pharmaceutical and received research grants from AbbVie, Eli Lilly Japan, Pfizer, Novartis, Otsuka Pharmaceutical, Amgen, Sanofi, and Japan Tobacco. TS, NN, MK, TS, and JK are employed by Novartis.

Authors' contributions

MH, AF, and AI contributed to data acquisition, TS, NN, MK, and TS contributed to planning, implementation, data collection, and data analysis of the surveillance. JK facilitated the writing of the manuscript. All authors contributed to the interpretation of the data and the development of the manuscript and approved the final version.

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