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Japanese Patients with Severe Asthma Identified as Responders to Omalizumab Treatment at 2 Years Based on the GETE Score Continued Treatment for an Extended Period

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Purpose: Omalizumab, the anti-IgE monoclonal antibody used to treat severe asthma, reduces asthma exacerbations, hospitalizations, and corticosteroid use. Although allergic asthma is a therapeutic target of omalizumab, omalizumab is not effective in all patients with severe allergic asthma and is not always available for long-term use. We retrospectively investigated factors related to long-term (≥2 years) use of omalizumab for severe asthma.

Patients and Methods: Of the 116 patients treated with omalizumab for severe asthma at our hospital between 2009 and 2017, 82 were included in this retrospective analysis. Thirty-four were excluded because of adverse events, financial difficulties, or hospital transfers. The number of asthma exacerbations, unscheduled visits, corticosteroid doses, asthma control test scores, pulmonary function test results, and fractional exhaled nitric oxide levels were evaluated.

Results: The median age of the study population was 58 years, with 66% female and 26% taking regular oral corticosteroids. After 2 years of treatment, 52 responders were identified using the global evaluation of treatment effectiveness (GETE) score. Improvements in asthma control test scores, airflow limitation, exacerbations, and oral corticosteroid use were observed in the responders. Multivariate analysis revealed that a peripheral blood eosinophil count of ≥200 or a perennial antigen-specific IgE antibody positivity of ≥2 predicted a response at the 2-year mark. However, Kaplan–Meier analysis demonstrated that neither high eosinophil counts nor perennial antigen-specific IgE positivity influenced the prolongation of treatment beyond 2 years, and responders at 2 years underwent omalizumab treatment for a significantly longer period than non-responders (HR = 9.89, $p < 0.001$), with GETE at 2 years being the only predictor of long-term omalizumab use.

Conclusion: In this retrospective study the GETE after 2 years of omalizumab therapy emerged as the most meaningful predictor of the long-term effectiveness of omalizumab treatment in patients with severe asthma, highlighting the benefits of prolonged therapy in certain populations. These findings may guide future therapeutic strategies for severe asthma.

Keywords: antigen-specific IgE antibody, GETE, predictive biomarker

Introduction

Asthma is a common chronic disease characterized by variable airflow limitation and bronchial hyperresponsiveness.[1–3] Asthma affects >300 million people worldwide and >8 million people in Japan. Of these, approximately 5% are intractable asthma cases, the symptoms of which cannot be controlled using existing treatments.

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Of the several asthma phenotypes/endotypes, immunoglobulin (Ig) E-mediated allergic asthma accounts for many of all asthma cases.[4,5] IgE is essential in the immune response against allergic asthma, and the development of omalizumab, a humanized anti-IgE monoclonal IgG1 antibody preventing its interaction with the high-affinity type 1 Fc-epsilon receptor (FcεRI), represented a paradigm shift in the management of severe allergic asthma.[4–7] Omalizumab was the first biological drug approved for the treatment of severe asthma in Australia (2002), the United States (2003), the European Union (2005), and Japan (2009). Its efficacy and safety have been established.[8–13] A Cochrane systematic review evaluating 25 randomized controlled trials assessing patients with severe allergic asthma demonstrated that omalizumab reduces asthma exacerbations, hospitalizations, and inhaled corticosteroid doses.[10,14–17] In Japan, omalizumab is available to the following patients with asthma: (i) patients with inadequate symptom control, even when treated with high doses of inhaled corticosteroids (ICS) adding multiple controller agents; (ii) patients who are positive for perennial inhaled antigen-specific IgE antibodies; and (iii) patients with body weight and serum IgE levels falling within the dose conversion table (IgE levels should be within the 30–1500 IU/mL serum IgE range).[18]

Allergic asthma is an observable clinical phenotype and a therapeutic target of omalizumab. However, because it is not effective in all patients with severe allergic asthma, it is essential but difficult to identify patients who are most likely to experience therapeutic benefits in clinical practice.[19] In daily clinical practice in real life, successful responses are achieved by adding omalizumab treatment in patients with severe allergic asthma, which is characterized by inadequate control, repeated exacerbation, and oral systemic steroid use.[20] The EXTRA study showed that high levels of peripheral blood eosinophils, fractional exhaled nitric oxide (FeNO), and serum periostin could be considered reliable indicators of type 2 asthmatic inflammation and could be independent biomarkers predicting a reduction in the rate of asthma exacerbation using omalizumab.[19–21] However, two real-world observational studies in asthma patients receiving omalizumab, the PROSPERO prospective study and the STELLAIR retrospective study, demonstrated that the therapeutic response to omalizumab was similar in patients with relatively high (≥300 cells/μL of blood) or low (<300 cells/μL of blood) pretreatment blood eosinophil counts.[20,22,23]

Although only a few reports have longer observation periods, the XPORT study and a long-term real-world study showed that continuation of omalizumab after long-term treatment (approximately 5 and 4 years, respectively) results in continued benefit through improved symptom control and reduced exacerbation risk.[11,24] However, biomarkers indicating continued long-term omalizumab treatment have not been identified. In this observational retrospective study, we present long-term effectiveness and safety data from 82 consecutive patients with poorly controlled severe asthma who received omalizumab, with the aim of investigating the factors related to long-term (≥2 years) use of omalizumab for severe asthma.

Materials and Methods

Study Population

This retrospective observational cohort study enrolled Japanese patients diagnosed with asthma who were prescribed omalizumab. Patients with severe asthma who were aged ≥20 years, whose asthma symptoms could not be controlled even with existing treatments, and who required omalizumab treatment as insurance medical treatment were recruited from our outpatient clinic at Juntendo University Hospital (Tokyo, Japan) between April 2009 and October 2017. Asthma was diagnosed based on a clinical history of episodic symptoms with airflow limitation and variations in pulmonary function, either by forced expiratory volume in 1 s or peak expiratory flow, in accordance with the Global Initiative for Asthma (GINA) guidelines.[25] Patients who (1) were diagnosed with interstitial pneumonia, infectious diseases, or cancer and (2) received other antibody preparations, were excluded. The Juntendo University Research Ethics Committee (Tokyo, Japan) reviewed and approved the present study, aligned with the Declaration of Helsinki, with opt-out consent instead of informed consent because patient files were retained retrospectively and stored anonymously (H21-0010). As an opt-out method, we disclosed the details of the present study to the public and informed patients of their right to refuse enrollment.

Patient data were collected from the asthma hospital records of each patient before and during omalizumab treatment; the data included age at visit, age at diagnosis (onset of asthma), body mass index, asthma exacerbations, unscheduled visits, inhaled corticosteroid (ICS) dosage, comorbidities, asthma control test (ACT) scores, FeNO levels, pulmonary function test results, forced oscillation technique data, blood eosinophil counts, and serum IgE levels over time. The effectiveness of omalizumab was assessed using the physician-reported global evaluation of treatment effectiveness (GETE).[26,27] GETE scores rated as "excellent" or "good" were deemed effective, whereas "moderate", "poor", "worsening", or "not evaluable" scores were deemed ineffective

in this study. FeNO levels were measured according to the recommendations of the American Thoracic Society at a constant flow of 0.05 L/s against an expiratory resistance of 20 cm of water using an electrochemical hand-held NO analyzer (NIOX VERO®; Aerocrine AB, Solna, Sweden).

Determination of Serum IgE and Antigen-Specific IgE Antibody Levels

Serum total and antigen-specific IgE levels were determined using a fluorescence or chemiluminescence enzyme immunoassay system (SRL Inc., Tokyo, Japan). The antigen-specific IgE measured were grass pollen (Japanese cedar, Japanese cypress, alder, Japanese white birch, orchard grass, ragweed, mugwort, and timothy), house dust, dust mites, mold (Alternaria, aspergillus, candida, malassezia, Alternaria, penicillium, cladosporium, and mucor), animal dander (cat and dog), and insects (moth and cockroach). Antigen-specific IgE levels higher than class 2 were considered positive.

Statistical Analysis

The normality of the samples was examined using the D'Agostino–Pearson test. Differences in parameters between populations were analyzed for significance using Welch's *t* test and the Mann–Whitney *U*-test, as appropriate. Multiple groups were compared using Friedman's and Dunn's tests. Receiver operating characteristic (ROC) curve analyses were performed to discriminate between the long- and short-term omalizumab treatment groups. The continuation rate of treatment was estimated using the Kaplan–Meier survival curve. The continuation rates were compared using the Log rank test. Fisher's exact test was used to determine whether there was a difference in the classification of the number of specific IgE antibodies. Significance was set at $p \leq 0.05$. Statistical analyses were performed using GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA) and JMP Pro 17 (JMP Statistical Discovery, Cary, NC, USA). Fisher's exact test for m×n tables was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[28]

Results

Study Population

Of the 116 patients who were treated with omalizumab owing to difficulties in managing asthma symptoms with existing therapy, and who attended our hospital between 2009 and 2017, 82 who could be followed up were included in the study and retrospectively analyzed. Thirty-four patients were excluded because they were judged inappropriate for analysis, regardless of the therapeutic effect, including participants whose treatment was discontinued due to adverse events, for financial reasons, or because of transfer to another hospital. Adverse events following the first administration of omalizumab were observed in five patients, including one who had anaphylaxis.[29] The other four patients complained of fatigue, urticaria, weakness, or diarrhea. Fourteen patients (17.1%) discontinued treatment because of worsening conditions within 2 years, while 23 patients (28.0%) discontinued treatment because of worsening conditions after > 2 years of treatment. At the time of analysis, 17 patients (20.7%) were continuing omalizumab treatment. The remaining 28 patients (34.1%) were transferred to another hospital because of primary physician transfer or because they voluntarily discontinued their visits (Supplementary Table 1).

The baseline characteristics of the study population are presented in Table 1. The median (interquartile range) age of the patients was 58.0 (47.3–66.0) years (Table 1). Fifty-four (66%) patients were female, and 21 (26%) were receiving regular oral corticosteroid treatment (Table 1). When atopic factors were defined as having a personal or family history of atopic disease, 54 (66%) patients met these criteria, while 59 (72%) patients tested positive for one or more specific IgEs (Table 1). The median duration of asthma, daily dose of ICS, forced expiratory volume in 1 s/forced vital capacity, peripheral eosinophil counts, and serum total IgE levels were 17.0 (8.0–31.0) years, 1000 (800–1000) µg, 73.3 (60.1–83.8)%, 183.0 (68.0–577.0) cells/µL, and 132.0 (42.0–403.0) IU/ mL, respectively (Table 1). The numbers of asthma exacerbations and unscheduled hospital visits 1 year prior to omalizumab administration were 1 (0–5) and 0 (0–2), respectively (Table 1). Patients with missing information, including those transferred to our hospital from other medical facilities for omalizumab treatment, were considered to have missing data. The median duration and monthly dose of omalizumab treatment were 44.0 (32.0–68.3) months and 300 (150–450) mg, respectively (Table 1).

Table 1 Baseline Characteristics of the Study Population

n = 82	Number (%), or Median (Interquartile Range)		Number (%), or Median (Interquartile Range)
Male / Female	28 (34.1%) / 54 (65.9%)	Hospitalizations (/year)	0.0 (0.0–0.0)
Age (years)	58.0 (47.3–66.0)	ACT scores, n = 51	18.0 (12.5–22.0)
Age at asthma onset (years)	40.0 (20.0–52.0)	FeNO (ppb), n = 59	44.9 (26.6–64.8)
Duration of asthma (years)	17.0 (8.0–31.0)	FVC (L), n = 72	2.8 (2.4–3.3)
BMI (kg/m^2)	23.2 (20.2–25.8)	PEFR (L/s), n = 72	6.4 (4.8–7.6)
Smoking history		FEV_1 (L), n = 72	2.1 (1.5–2.5)
never-smoker	46 (56.1%)	$\%FEV_1$ (predicted, %), n = 72	87.1 (64.6–97.8)
ex-smoker	33 (40.2%)	$FEV_1\%$ (%), n = 72	73.3 (60.1–83.8)
current-smoker	3 (3.7%)	Peripheral eosinophils (cells/μL), n = 81	183.0 (68.0–577.0)
Family history	13 (15.9%)	Total IgE (IU/ mL), n = 81	132.0 (42.0–403.0)
Atopic factor	54 (65.9%)	Number of sensitized specific IgE	2.0 (0.0–3.0)
NERD	11 (13.4%)	Number of perennial antigen-specific IgE	1.0 (0.0–2.0)
Atopic dermatitis	13 (15.9%)	Number of seasonal antigen-specific IgE	0.0 (0.0–1.0)
Allergic rhinitis	38 (46.3%)	One or more positive specific IgE	59 (72.0%)
Chronic sinusitis	14 (17.1%)	One or more positive seasonal antigen-specific IgE	26 (31.7%)
Urticaria	5 (6.1%)	One or more positive perennial antigen-specific IgE	46 (56.1%)
COPD	9 (11.0%)	Number of sensitized aeroallergens subgroups §	1.0 (0.3–2.0)
Daily dose of ICS (FP equivalent dose, μg)	1000 (800–1000)	Sensitization to grass pollen, n = 81	27 (32.9%)
OCS maintenance therapy	21 (25.6%)	Sensitization to house dust	24 (29.3%)
Monthly dose of omalizumab (mg)	300.0 (150.0–450.0)	Sensitization to dust mites, n = 81	26 (31.7%)
Duration of omalizumab treatment (month)	44.0 (32.0–68.3)	Sensitization to mold	19 (23.2%)
Asthma exacerbations (/year)	1.0 (0.0–5.0)	Sensitization to animal dander	9 (11.0%)
Unscheduled visits (/year)	0.0 (0.0–2.0)	Sensitization to insect	12 (14.6%)

Notes: § Aeroallergen subgroups consist of six: grass pollen, house dust, dust mites, mold, animal dander, insect.

Abbreviations: ACT, asthma control test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; $FEV_1\%$, FEV_1 second/forced vital capacity; FP, fluticasone propionate; FVC, forced vital capacity; GETE, global evaluation of treatment effectiveness; ICS, inhaled corticosteroid; IgE, immunoglobulin E; NERD, nonsteroidal antiinflammatory drug-exacerbated respiratory disease; OCS, oral corticosteroids; PEFR, peak expiratory flow rate.

Responders to Omalizumab Treatment

We retrospectively classified patients with asthma using their GETE scores. Patients who fell into the "excellent" or "good" GETE score categories were considered responders, whereas those outside these categories were classified as non-responders. After one year of omalizumab treatment, 61 (74%) patients were identified as responders. After two years, 52 (63%) patients, including 10 from the initial non-responders, were identified as responders. Responders had a significantly longer duration of omalizumab treatment than non-responders (Table 2). Additionally, responders showed a significantly higher prevalence of IgE positivity for one or more perennial antigens, particularly house dust and mites,

Table 2 Responder Group Analysis of Omalizumab Treatment

	Responders (n = 52)	Non-Responders (n = 30)	*p* value
Sex (M/F)	15 (28.8%)/37 (71.2%)	11 (36.7%)/19 (63.3%)	0.472
Age (years)	58.0 (49.9–66.3)	57.5 (43.5–66.0)	0.532
Age at asthma onset (years)	42.0 (23.0–52.5)	36.0 (20.0–50.0)	0.571
Duration of asthma (years)	18.0 (9.0–27.0)	16.0 (8.0–33.8)	0.928
Duration of omalizumab treatment (months)	58.0 (40.0–83.8)	29.0 (7.3–42.0)	<0.001*
BMI (kg/m^2)	23.1 (20.1–25.6)	23.3 (20.3–25.9)	0.865
Smoking history (never/ex/current)			0.300†
never-smoker	32 (61.5%)	14 (46.7%)	
ex-smoker	19 (36.5%)	14 (46.7%)	
current-smoker	1 (1.9%)	2 (6.7%)	

(*Continued*)

Table 2 (Continued).

	Responders (n = 52)	Non-Responders (n = 30)	*p* value
Family history	7 (13.5%)	6 (20.0%)	0.534
Atopic factor	33 (63.5%)	21 (70.0%)	0.633
NERD	4 (7.7%)	7 (23.3%)	0.088
Atopic dermatitis	7 (13.5%)	6 (20.0%)	0.534
Allergic rhinitis	21 (40.4%)	17 (56.7%)	0.175
Chronic sinusitis	12 (23.1%)	2 (6.7%)	0.072
Urticaria	3 (5.8%)	2 (6.7%)	1.000
COPD	9 (17.3%)	4 (13.3%)	0.718
Daily dose of ICS (FP equivalent dose, μg)	1000 (1000–1050)	1000 (800–1000)	0.073
Daily dose of OCS (PSL equivalent dose, mg)	0 (0.0–0.3)	0 (0.0–1.9)	0.313
Asthma exacerbations (/year)	1.0 (0.0–5.0)	2.0 (0.0–5.0)	0.516
Unscheduled visits (/year)	0.0 (0.0–2.0)	0.0 (0.0–3.0)	0.487
Hospitalizations (/year)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.917
ACT scores, n = 51	18.0 (14.5–22.0)	18.5 (10.8–22.5)	0.594
GETE			0.001*‡
Excellent	8 (15.4%)	0 (0.0%)	
Good	44 (84.6%)	0 (0.0%)	
Moderate	0 (0.0%)	8 (26.7%)	
Poor	0 (0.0%)	8 (26.7%)	
Worsening	0 (0.0%)	14 (46.7%)	
FeNO (ppb), n = 59	47.3 (30.5–72.9)	32.0 (18.4–61.0)	0.080
FVC (L), n = 72	2.8 (2.3–3.3)	2.8 (2.5–3.5)	0.497
PEFR (L/s), n = 72	6.6 (5.0–8.4)	5.7 (4.8–7.1)	0.258
FEV_1 (L), n = 72	2.1 (1.5–2.5)	2.1 (1.5–2.4)	0.887
%FEV_1 (predicted, %), n = 72	87.3 (65.1–98.3)	86.9 (65.1–97.3)	0.992
FEV_1% (%), n = 72	75.1 (61.1–83.8)	65.1 (55.9–82.5)	0.468
Peripheral eosinophils (cells/μL), n = 81	221.0 (68.0–236.8)	118.5 (59.3–99.5)	0.068
Total IgE (IU/ mL), n = 81	253.0 (51.0–507.5)	95.5 (40.5–245.8)	0.063
Number of antigen-specific IgE	2.0 (1.0–3.0)	1.0 (0.0–1.8)	0.014*
Number of seasonal antigen-specific IgE	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.601
Number of perennial antigen-specific IgE	2.0 (0.0–2.0)	0.0 (0.0–1.0)	0.004*
One or more positive specific IgE	41 (78.8%)	18 (60.0%)	0.079
One or more positive seasonal antigen-specific IgE	15 (28.8%)	11 (36.7%)	0.623
One or more positive perennial antigen-specific IgE	34 (65.4%)	10 (33.3%)	0.006*
Number of sensitized aeroallergens subgroups §	2.0 (1.0–2.3)	1.0 (0.0–1.0)	0.006*
Sensitization to Grass pollen	16 (30.8%)	11 (36.7%)	0.631
Sensitization to House dust	21 (40.4%)	3 (10.0%)	0.005*
Sensitization to Dust mites	22 (42.3%)	3 (10.0%)	0.003*
Sensitization to Mold	12 (23.1%)	7 (23.3%)	1.000
Sensitization to Animal dander	8 (15.4%)	1 (3.3%)	0.145
Sensitization to Insect	9 (17.3%)	3 (10.0%)	0.521

Notes: Data are shown as the median (interquartile range), or number (%).*$p < 0.05$. †Compared never smoker, ex-smoker, and current smoker. ‡Compared Excellent, Good, Moderate, Poor, Worsening. § Aeroallergen subgroups consist of six: Grass pollen: House dust: Dust mites: Mold: Animal dander: Insect.

Abbreviations: ACT, asthma control test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FEV_1%, FEV_1 second/forced vital capacity; FP, fluticasone propionate; FVC, forced vital capacity; GETE, global evaluation of treatment effectiveness; ICS, inhaled corticosteroid; IgE, immunoglobulin E; NERD, nonsteroidal antiinflammatory drug-exacerbated respiratory disease; OCS, oral corticosteroids; PEFR, peak expiratory flow rate; PSL, prednisolone.

than non-responders (Table 2). Responders with a 2-year GETE score showed improvements in the ACT score, number of exacerbations, number of unscheduled visits, daily dose of regular OCS use, and airflow limitation at 2 years, whereas no differences were observed in non-responders other than a reduction in the number of unscheduled visits (Table 3). In responders, regular OCS treatment was significantly reduced at 1 and 2 years, with discontinuation achieved in some

Table 3 Changes in Parameters from Baseline at 2 Years After Omalizumab Treatment

Responder (n = 52)	Baseline	2 Year After	*p* value
ACT, n = 16	18.0 (14.5–22.0)	22.2 (20.8–25.0)	0.002*
FVC (L), n = 33	2.8 (2.3–3.3)	3.0 (2.3–3.8)	<0.001*
PEFR (L/s), n = 33	6.6 (5.0–8.4)	6.3 (5.3–7.9)	0.017*
FEV_1 (L), n = 33	2.1 (1.5–2.5)	2.1 (1.7–2.8)	<0.001*
$\%FEV_1$ (predicted, %), n = 33	87.3 (65.1–98.3)	89.0 (73.0–99.5)	<0.001*
$FEV_1\%$ (%), n = 33	75.1 (61.1–83.8)	74.3 (61.6–83.1)	0.359
Peripheral eosinophils (cells/μL), n = 21	221.0 (78.0–602.5)	290.0 (90.0–523.0)	0.812
Total IgE (IU/ mL), n = 14	253.0 (51.0–507.5)	293.5 (176.8–561.5)	0.952
Daily dose of OCS (PSL equivalent dose, mg)	0.0 (0.0–0.3)	0.0 (0.0–0.0)	<0.001*
Asthma exacerbations (/year)	1.0 (0.0–5.0)	0.0 (0.0–0.5)	<0.001*
Unscheduled visits (/year)	0.0 (0.0–2.0)	0.0 (0.0–0.0)	<0.001*
Hospitalizations (/year)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.125
Non-responder (n = 30)	**Baseline**	**2 year after**	***p* value**
ACT, n = 11	19.0 (11.0–24.0)	23.0 (17.0–24.0)	0.381
FVC (L), n = 20	2.8 (2.5–3.6)	2.8 (2.4–3.2)	0.553
PEFR (L/s), n = 20	6.0 (4.8–7.3)	5.7 (4.8–7.1)	0.697
FEV_1 (L), n = 20	2.1 (1.5–2.5)	1.9 (1.4–2.5)	0.813
$\%FEV_1$ (predicted, %), n = 20	87.1 (66.1–97.8)	84.9 (70.1–98.6)	0.970
$FEV_1\%$ (%), n = 20	66.0 (56.1–81.8)	71.1 (57.1–83.6)	0.836
Peripheral eosinophils (cells/μL), n = 15	118.5 (68.0–249.8)	120.0 (67.5–175.5)	0.762
Total IgE (IU/ mL), n = 12	71.0 (39.0–310.5)	96.0 (72.3–186.5)	0.367
Daily dose of OCS (PSL equivalent dose, mg)	0.0 (0.0–1.9)	0.0 (0.0–0.0)	0.501
Asthma exacerbations (/year)	2.0 (0.0–5.0)	1.0 (0.0–3.0)	0.333
Unscheduled visits (/year)	0.0 (0.0–3.0)	0.0 (0.0–0.0)	0.049*
Hospitalizations (/year)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	>0.999

Notes: Data are presented as the median (interquartile range). *$p < 0.05$.

Abbreviations: ACT, asthma control test; FEV_1, forced expiratory volume in 1 second; $FEV_1\%$, FEV_1 second/forced vital capacity; FVC, forced vital capacity; IgE, immunoglobulin E; OCS, oral corticosteroids; PEFR, peak expiratory flow rate; PSL, prednisolone.

cases (Figure 1A). Univariate analysis was conducted to assess the factors predicting a response after 2 years of omalizumab treatment. The findings indicated that the number of peripheral blood eosinophils and antigen-specific IgE antibodies, especially perennial antigen-specific IgE antibodies, were independently correlated with a response (Table 4). ROC curve analysis was used to determine the optimal cutoff values for responders and non-responders. An eosinophil count of 196 (sensitivity, 59%; specificity, 73%; AUC, 0.62; $p = 0.07$) and positive perennial antigen-specific IgE antibody count of 1.5 (sensitivity, 52%; specificity, 87%; AUC, 0.68; $p < 0.01$) were considered the best cut-off points for predicting responders for omalizumab treatment using the Youden index (Figure 1B and C). Based on the ROC analyses for eosinophil count and specific IgE, cutoffs of > 200 and > 2 were adopted. In the univariate analysis, patients with 200 or more eosinophils and two or more antigen-specific IgEs were significantly associated with a response (Table 4). Furthermore, antigen-specific IgE-positive patients were significantly associated with perennial rather than seasonal antigens, particularly house dust and mites (Table 4). In multivariate logistic regression analysis, peripheral blood eosinophil counts > 200 (OR = 3.36, $p = 0.03$) and having ≥ 2 positive perennial antigen-specific IgEs (OR = 6.86, $p = 0.02$) at the onset of omalizumab treatment were independently associated with a response to omalizumab treatment (Table 5).

Responders at 2 Years Based on the GETE Score That Influenced the Duration of Long-Term Omalizumab Treatment

The time to discontinuation of omalizumab treatment was analyzed using the Kaplan–Meier method based on the results of the multivariate analysis. Patients were divided into two groups: those with a peripheral blood eosinophil count of ≥

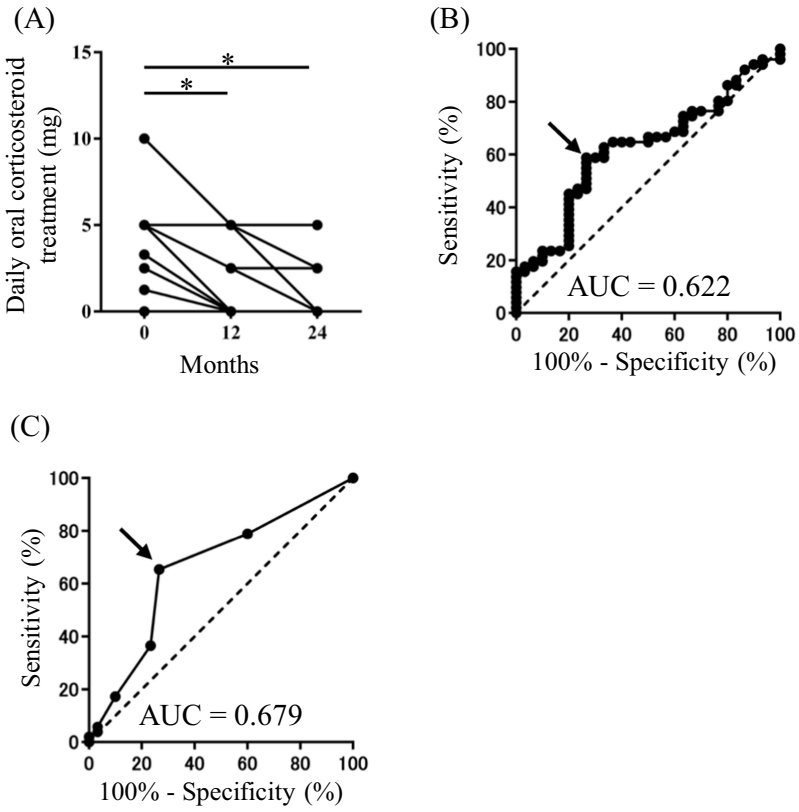

Figure 1 Use of OCS over time in responders and ROC curve to predict responders to omalizumab treatment. (**A**) The median reduction in the dose of OCS in the responders, determined by the GETE score after 2 years of omalizumab treatment. The bars indicate the median values. *$p < 0.05$. (**B** and **C**) The cut-off values for the number of eosinophils of 196 (sensitivity, 59%; specificity, 73%; AUC, 0.622; p = 0.07) (**B**) and positive perennial antigen-specific IgE antibodies of 1.5 (sensitivity, 87%; specificity, 70%; AUC, 0.822; p < 0.001) (**C**) to differentiate between responders and non-responders are indicated with arrows.

200, and those with < 200 eosinophils before omalizumab treatment. Similarly, patients were categorized according to antigen-specific IgE levels: those with ≥ 2 positive IgEs for perennial-specific antigens and those with ≤ 1. Analyses spanning up to 2 years revealed that patients with peripheral blood eosinophils ≥ 200 (HR = 2.94, $p = 0.045$) and those with ≥ 2 positive perennial specific antigens (HR = 5.56, $p = 0.002$) showed significant continuation of treatment (Figure 2A and D). However, beyond the 2-year mark, this significant difference disappeared (Figure 2B and E). When assessing long-term use that extended beyond 2 years, the analysis included patients who were transferred to hospitals

Table 4 Univariable Analysis with or and Associated 95% CIs for Responders of Omalizumab Treatment

Variables	Univariate Analysis		
	OR	95% CI	*p* value
Sex, female	1.43	0.54–3.72	0.47
Age (years)	1.01	0.98–1.04	0.58
Duration of asthma (years)	1.00	0.96–1.03	0.77
BMI (kg/m^2)	1.00	0.91–1.10	0.93
Smoking history, never:ex	1.68	0.66–4.33	0.27
NERD	0.27	0.07 −1.00	0.06
Atopic dermatitis	0.62	0.19–2.13	0.44
Allergic rhinitis	0.52	0.21–1.28	0.16
Chronic sinusitis	4.20	1.04–28.35	0.07

(*Continued*)

Table 4 (Continued).

Variables	Univariate Analysis		
	OR	95% CI	*p* value
COPD	0.61	0.17–3.00	0.61
FeNO (ppb), n = 59	1.01	1.00–1.02	0.14
Peripheral eosinophils (cells/μL), n = 81	1.00	1.00–1.00	0.05*
Peripheral eosinophils 200 or more (cells/μL), n = 81	3.75	1.45–10.45	<0.01*
Total IgE (IU/ mL), n = 81	1.00	1.00–1.00	0.36
Number of antigen-specific IgE	1.43	1.03–1.97	0.03*
Number of seasonal antigen-specific IgE	0.97	0.60–1.59	0.90
Number of perennial antigen-specific IgE	1.61	1.12–2.49	0.02*
One or more positive specific IgE	2.48	0.93–6.79	0.07
One or more positive seasonal antigen-specific IgE	0.72	0.28–1.89	0.80
One or more positive perennial antigen-specific IgE	3.78	1.49–10.09	<0.01*
Two or more positive specific IgE	5.19	1.99–14.68	<0.01*
Two or more positive seasonal antigen-specific IgE	1.18	0.34–4.78	0.80
Two or more positive perennial antigen-specific IgE	7.02	2.33–26.34	<0.01*
Both seasonal and perennial antigen-specific IgE	1.64	0.43–7.96	0.49
Number of sensitized aeroallergens subgroups §	1.82	1.20–2.96	<0.01*
Sensitization to Grass pollen	0.77	0.30–2.01	0.58
Sensitization to House dust	6.10	1.84–27.84	<0.01*
Sensitization to Dust mites	6.36	1.92–29.03	0.02*
Sensitization to Mold	0.99	0.35–2.97	0.98
Sensitization to Animal dander	5.27	0.90–100.45	0.13
Sensitization to Insect	1.88	0.51–9.05	0.37

Notes: *$p < 0.05$. § Aeroallergen subgroups consist of six: Grass pollen: House dust: Dust mites: Mold: Animal dander: Insect.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; NERD, nonsteroidal antiinflammatory drug-exacerbated respiratory disease.

Table 5 Multivariable Analysis with or and Associated 95% CIs for Responders of Omalizumab Treatment

Variables	Multivariate Analysis		
	OR	95% CI	*p* value
Peripheral eosinophils 200 or more (cells/μL)	3.36	1.18–10.37	0.03*
One or more positive perennial antigen-specific IgE	0.90	0.22–3.55	0.88
Two or more positive perennial antigen-specific IgE	6.86	1.46–36.92	0.02*

Note: *$p < 0.05$.
Abbreviations: CI, confidence interval; IgE, immunoglobulin E; OR, odds ratio.

(26 patients) and those who discontinued hospital visits (two patients). Nonetheless, even after the exclusion of these patients from the analysis, no noticeable differences were observed (Figure 2C and F).

Finally, patients were categorized into responders and non-responders based on their GETE scores at the 1- and 2-year marks, followed by an analysis of the duration until the discontinuation of omalizumab treatment using the Kaplan–Meier method. No differences in continued use were observed between responders and non-responders based on the 1-year GETE score within the initial 2 years of treatment or for long-term use beyond 2 years (Figure 3A and B). All patients who responded based on the 2-year GETE score continued omalizumab treatment for the full 2 years (Figure 3D). Furthermore, responders based on the 2-year GETE score exhibited a substantial increase in continued long-

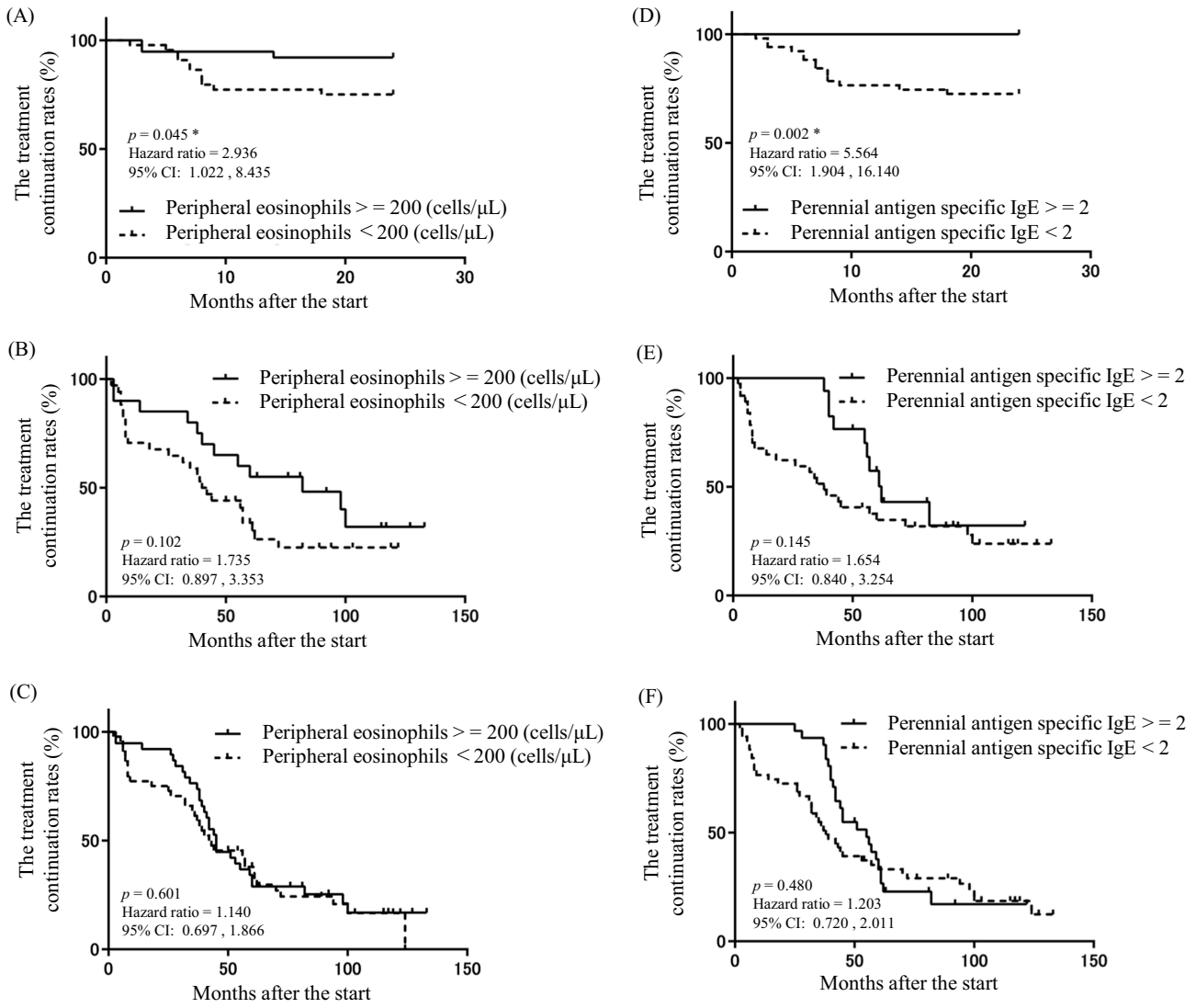

Figure 2 Kaplan–Meier estimates of cumulative rates of time to discontinuation of omalizumab treatment. The patients were divided into two groups: those with peripheral blood eosinophils of ≥200 and those with <200 before omalizumab treatment (**A**–**C**); or those with ≥2 positive IgE for perennial specific antigens and those with ≤1 (**D**–**F**). Kaplan–Meier analysis for the period leading up to 2 years (**A** and **D**), beyond the 2-year mark (**B** and **E**), and beyond the 2-year mark excluding patients who transferred and discontinued hospital visits (**C** and **F**), respectively.

term use beyond 2 years of treatment (HR = 9.89, $p < 0.001$) (Figure 3E). Furthermore, the differences between responders and non-responders based on GETE scores at 1 and 2 years persisted even after the exclusion of patients who were transferred or discontinued treatment (Figure 3C and F).

Discussion

Criteria for identifying patients who are likely to respond to omalizumab based on pretreatment characteristics are currently lacking.[30] Total and specific IgE levels have not consistently shown a predictive value for omalizumab responses in previous reports.[31] A pooled analysis of five studies identified the physician's global evaluation of treatment effectiveness (GETE) after 4 months of omalizumab therapy as the most meaningful measure of response. The GETE combines various evaluation aspects including patient interviews, review of medical notes, spirometry, symptom diaries, use of rescue medications, and peak expiratory flow (PEF).[30] In this study, patients with peripheral blood eosinophil counts of ≥ 200 before omalizumab treatment or with ≥ 2 positive IgEs for perennial-specific antigens were significantly more likely to remain on omalizumab treatment for 2 years than those who did not. However, this difference was not

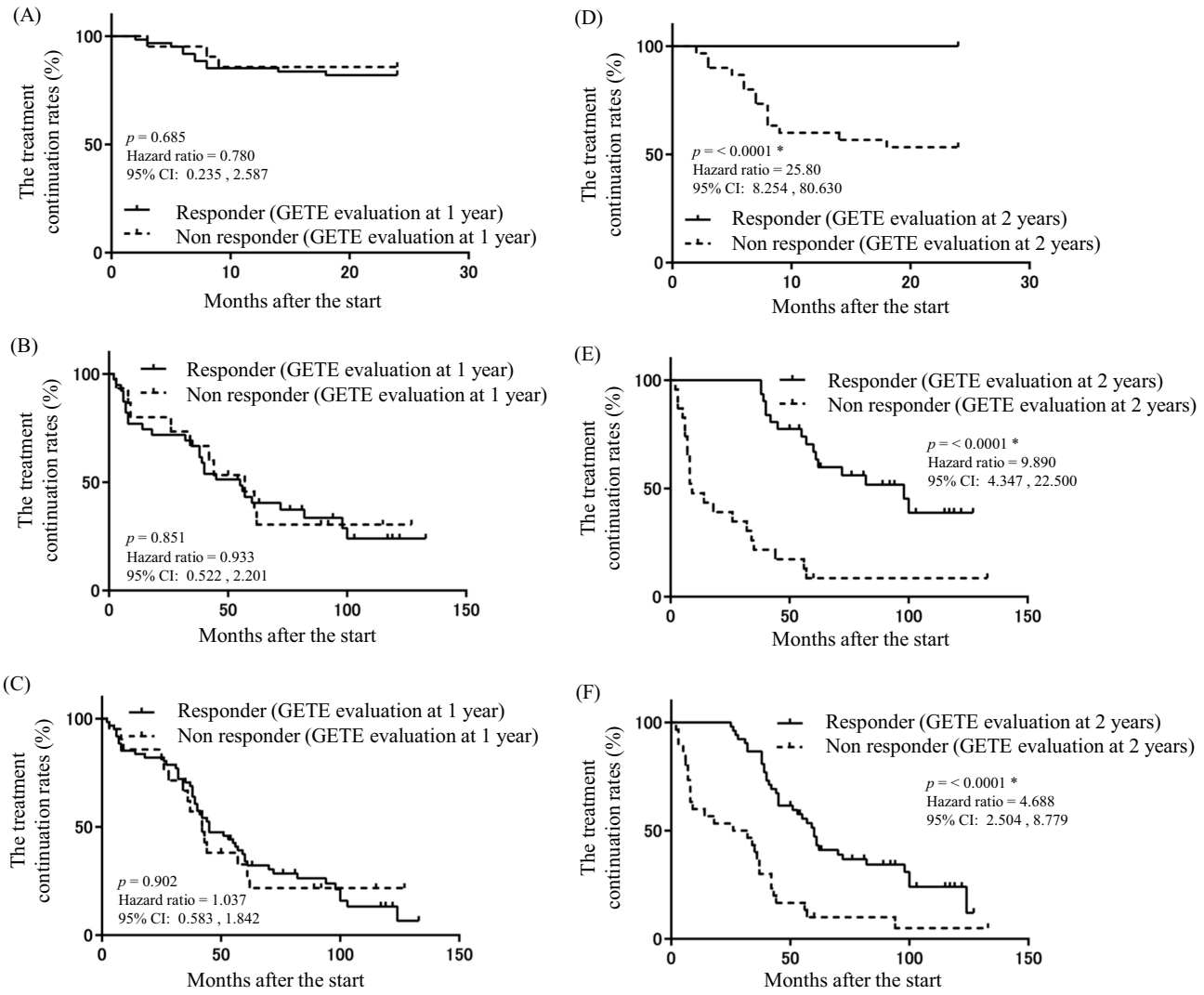

Figure 3 Kaplan–Meier estimates of cumulative rates of time to discontinuation of omalizumab treatment. The patients were divided into responders and non-responders based on their GETE scores at 1 (**A**–**C**) and 2 years (**D**–**F**). Kaplan–Meier analysis for the period leading up to 2 years (**A** and **D**), beyond the 2-year mark (**B** and **E**), and beyond the 2-year mark excluding patients who transferred and discontinued hospital visits (**C** and **F**), respectively.

observed for long-term use (beyond 2 years). Responders at 2 years based on GETE scores were found to continue omalizumab treatment for significantly longer than the non-responder group. Although the effectiveness of omalizumab treatment is typically evaluated first at 4 months,[30] there was no difference in continued use between the responder and non-responder groups in terms of the GETE score at 1 year. This study is the first to show that evaluation at 2 years is associated with subsequent long-term use. Furthermore, previous studies have suggested that both perennial antigen-specific IgE-positive and-negative patients respond positively to omalizumab treatment. Although these findings were observed after 1 year of treatment, the results at the 2-year mark in our study imply a potentially greater efficacy in perennial antigen-specific IgE-positive cases. However, the results of this study also suggest that it is impossible to predict the effectiveness beyond a treatment period of 2 years or more in antigen-specific IgE-positive cases. Since the GETE used in this study is subjective to the physician, this may be a natural result because the physician decided on long-term use, but the GETE score after 1 year of treatment did not reflect the continuation of long-term treatment. This underscores the need for ongoing evaluation using the GETE score beyond the second year, as evident from the GETE after 2 years, reflecting long-term use. Our findings indicate a potential decline in the effectiveness of omalizumab treatment over time, emphasizing the importance of regular evaluation. Furthermore, the results of this study suggest that omalizumab treatment is more likely to be effective in patients with perennial antigen-specific IgE positivity, particularly

for house dust and mites, or high eosinophil counts, which is consistent with previous reports.[7,21,32,33] However, there are discrepancies in reports indicating the effectiveness in seasonal antigen-specific IgE-positive patients.[34,35]

On the other hand, the reasons for omalizumab's failure to regulate asthma symptom control remain unclear, despite its continued use as a treatment option. As the first biologic available for severe asthma, omalizumab was initially used when clinicians had no alternative therapies, leading to its prolonged use. Over time, the option to switch to alternative biologics has become available, particularly for patients with insufficient symptom control. Several real-world studies have demonstrated the benefits of switching from omalizumab to other biologics. It is plausible that omalizumab may be insufficient for controlling eosinophils, especially in patients with high eosinophilic involvement.[36–44] Additionally, while omalizumab is associated with a lower incidence of anti-drug antibodies compared to other biologics used in asthma treatment, the possibility remains that prolonged use could lead to the formation of such antibodies, potentially diminishing its therapeutic efficacy.[45] Further research is required to investigate the underlying mechanisms behind the diminished therapeutic response to omalizumab observed in this study.

Free or circulating IgE binds to two IgE receptors (FcεRI and CD23/FcεRII, termed high- and low-affinity receptors, respectively). FcεRI expresses on the surface of basophils and mast cells. Omalizumab targets IgE, inhibits IgE binding to FcεRI, reduces circulating free IgE levels, decreases FcεRI expression in dendritic cells (DCs), mast cells, basophils, and eosinophils, and prevents their interaction.[46–50] Multiple systematic reviews evaluating patients with allergic asthma treated with omalizumab have mentioned that omalizumab reduces asthma exacerbations, hospitalizations, and inhaled corticosteroid doses.[10,14–16,47,51] Importantly, the biomarkers initially used in early omalizumab trials, serum IgE levels, and the presence of antigen-specific IgE were not shown to be effective in predicting clinical response; however, a previous study suggested that type 2 biomarkers, including peripheral blood eosinophils, the amount of exhaled FeNO, and serum periostin levels, are more effective.[19–21] Conversely, it has been suggested that type 2 biomarkers do not necessarily predict efficacy, there have even been reports of significantly higher baseline eosinophil counts in omalizumab non-super responders, and biomarkers for predicting the efficacy of omalizumab in severe asthma remain controversial.[20,22,23,52,53]

Omalizumab treatment is thought to decrease FcεRI on mast cells, basophils, and DCs; stabilize mast cells; suppress mediator release; decrease eosinophils in bronchial tissue; increase circulating regulatory T cells; reduce antiviral immunity; and reduce epithelial cytokines, including interleukin (IL)-33, IL-25, thymic stromal lymphopoietin, and IL-13.[46–50,54–56] Although few reports are available to support clinicians in the long-term use of omalizumab, these immune changes can support the long-term efficacy of omalizumab.

Finally, the limitations of this study are that it was performed at a single center among a small number of patients, that it was a retrospective observational cohort study, that some patients lacked data (only a quarter of the patients had baseline and 2-year data, including ACT scores), and that we were unable follow-up some patients owing to transfers to other hospitals. Another significant limitation is that the response to omalizumab treatment was assessed using the GETE score, a subjective evaluation by physicians, and the only asthma-related quality-of-life measure employed was the ACT questionnaire. Furthermore, antigen-specific IgE measurements to determine allergen sensitivity were based exclusively on serological testing, without the inclusion of skin prick tests. Although the efficacy of omalizumab in patients with severe asthma has been reported using type 2 biomarkers such as eosinophils, FeNO, and periostin, this study found no association between type 2 biomarkers and long-term omalizumab treatment. Long-term treatment involves multiple complex factors, suggesting that this discrepancy arises because the biomarkers predicting long-term treatment outcomes differ from those for suppressing asthma exacerbations or discontinuing omalizumab treatment. Furthermore, in this study, 68 of 82 patients (83%) were long-term omalizumab users for more than 2 years, and the effects of suppression of asthma exacerbations and reduction in OCS dose were observed in responders. However, it is important to highlight that even after excluding the 28 patients who were transferred or discontinued hospital visits, only 17 out of the remaining 54 (31%) patients continued omalizumab treatment for more than two years at our hospital. There were a few reports of adverse events and anaphylaxis in one (0.86%) of the 116 patients who received omalizumab. These findings are consistent with those of previous reports and confirm the efficacy and safety of omalizumab in the real world of Japan.

Conclusion

We have provided the first report that the physician's GETE evaluation after 2 years of treatment is the most reliable method of identifying patients who will respond to omalizumab treatment in the long term. Further studies are necessary to determine whether the findings of this study are beneficial in patients with asthma.

Abbreviations

ACT, asthma control test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FEV_1%, FEV_1 second/forced vital capacity; FP, fluticasone propionate; FVC, forced vital capacity; GETE, global evaluation of treatment effectiveness; ICS, inhaled corticosteroid; IgE, immunoglobulin E; NERD, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; OCS, oral corticosteroids; PEFR, peak expiratory flow rate; ROC, receiver operating characteristic.

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