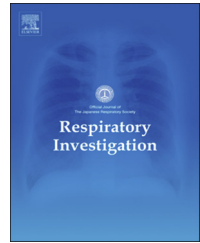




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Original article

Efficacy of long-term omalizumab therapy in patients with severe asthma



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ABSTRACT

Background: The efficacy of omalizumab, an anti-immunoglobulin E (IgE) antibody, has been studied in patients with severe bronchial asthma. We conducted a study to evaluate, on the basis of both objective and subjective measures, the efficacy of omalizumab as a long-term therapy in patients with severe and persistent asthma.

Methods: Omalizumab was administered subcutaneously every two or four weeks. The results of pulmonary function tests, Asthma Control Test (ACT) and Asthma Health Questionnaire (AHQ)-33 scores, the dosage of methylprednisolone during the 12-month treatment period, and the number of emergency visits prior to the start of treatment with omalizumab were compared in patients pre- and post-treatment with omalizumab.

Results: Fourteen patients were enrolled in the study between June 2010 and February 2012. Ten patients completed the study. With omalizumab treatment, there was no improvement in lung function; however, the number of emergency visits (19.3 before treatment vs. 1.2 after treatment, $p=0.020$) and the dosage of methylprednisolone (871.5 mg before treatment vs. 119.0 mg after treatment, $p=0.046$) decreased significantly. ACT and AHQ-33 scores at 16 weeks after treatment were significantly better than baseline scores. Four patients continued treatment with omalizumab for four years, and a reduction in their corticosteroid usage was noted.

Conclusions: Long-term omalizumab therapy in our patients was found to significantly reduce corticosteroid usage and the number of emergency visits. Long-term omalizumab therapy was effective and might have potential to reduce the frequency of asthma exacerbations.

The trial has not been registered because it is not an intervention study.

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1. Introduction

Bronchial asthma is a chronic inflammatory disorder of the airways. An estimated 300 million people worldwide are affected by bronchial asthma to some degree [1]. Although inhaled corticosteroids (ICSs) have been shown to decrease the risk of mortality, approximately 5% of asthma patients have severe asthma that is inadequately controlled by ICS and long-acting β_2 -agonist (LABA) therapies [2,3]. The long-term goals of asthma management are good symptom control, prevention of exacerbations, avoidance of fixed airway obstruction, and avoidance of adverse treatment effects. Patients with persistent symptoms or repeated exacerbations despite strict adherence to the Global Initiative for Asthma (GINA) guidelines for ICS therapy should be referred to a specialist with expertise in the management of severe asthma who can monitor step 4 treatment [4]. Anti-immunoglobulin E (anti-IgE) is suggested for patients who need step 5 treatment, especially those with allergic asthma [5]. IgE was discovered by Ishizaka et al., in 1966 and is known to play an important role in the inflammatory cascade triggered by allergen exposure in patients with atopic asthma [6]. After 36 years, the humanized monoclonal anti-IgE antibody omalizumab was approved in Australia for treatment of moderate to severe allergic IgE-mediated asthma. In Japan, omalizumab is now recommended for patients with severe persistent asthma that has been inadequately controlled at step 4 under the Japanese Asthma Prevention and Management Guideline 2009 [7].

Omalizumab has been reported to significantly reduce the frequencies of severe exacerbations and emergency medical visits and to improve both forced expiratory volume in 1 s (FEV_{1.0}) (% predicted) and mean morning peak expiratory flow (PEF) [8]. However, Holgate et al., reported that omalizumab improves asthma control in the first 16 weeks of treatment without significant improvement in FEV_{1.0} [9]. It

is possible that the efficacy of omalizumab for the prevention of asthma exacerbations is not reflected in the improvements in respiratory function.

It is important to evaluate patients not only on the basis of their asthmatic symptoms, but also their social activities and emotions, which are not covered by standard questionnaires [10]. The Asthma Health Questionnaire (AHQ)-33 (Fig. 1) was developed and validated in Japan specifically to evaluate Japanese asthma patients' subjective health status, including both physiological and psychological symptoms [11]. We conducted a single-institution prospective study to evaluate the long-term efficacy of omalizumab in patients with severe and persistent asthma as assessed by pulmonary function test results, Asthma Control Test (ACT) and AHQ-33 scores, the dosage of methylprednisolone, and the number of emergency visits per year.

2. Patients and methods

2.1. Patients

Fourteen patients were enrolled in the study between June 2010 and February 2012. Enrollment criteria included the presence of severe and persistent asthma, defined according to the Japanese Asthma Prevention and Management Guideline 2009 [6] as treatment with high-dose ICS and one or more of the following additional medications: LABA, sustained-release theophylline, leukotriene receptor antagonist, or oral corticosteroid. In addition, patients must have shown reactivity to at least one perennial aeroallergen, have had a serum total IgE level of 30–1500 IU/mL, and have had a body weight of 30–150 kg. Patients must also have shown insufficient asthma control, which is defined as the presence of one or more of the following: asthma symptoms that interfere with

- I have a cough.
- I have phlegm.
- I wheeze.
- I have asthma attacks.
- I get headaches.
- I have shortness of breath.
- My chest or shoulders feel heavy.
- My chest feels tight.
- My asthma keeps me awake at night.
- Exercise brings on asthma symptoms.
- Fatigue brings on asthma symptoms.
- Having a cold triggers my asthma.
- Inhaling substances like tobacco smoke, dust, cold air, exhaust fumes, pollen or cosmetics brings on asthma symptoms.
- Consuming certain food, alcohol, or non-asthma medications (fever-reducing medications, analgesics, etc.) brings on asthma symptoms.
- Contact with pets brings on asthma symptoms.
- Changes in the weather or atmospheric pressure brings on asthma symptoms.
- I feel depressed because I have asthma.
- I feel upset because I have asthma.
- I feel anxious because I have asthma.
- I feel irritable because I have asthma.
- My asthma makes it difficult for me to concentrate.
- My asthma prevents me from feeling refreshed.
- I am worried about having asthma.
- I am worried about having to continue taking asthma medication.
- My asthma symptoms limit my ability to walk.
- My asthma symptoms limit my ability to run or go uphill.
- My asthma symptoms limit my household activities, such as housework.
- My asthma symptoms limit my social and professional activities.
- My coworkers, classmates and other people have difficulties understanding my asthma problems.
- I am reluctant to meet people who don't know I have asthma.

My asthmatic condition and its treatment are financially burdensome.

- I am worried that my asthma is a burden to my family.
- Considering the past 7 days, how is your overall of quality of life (QOL)? Please choose one of the following faces which is considered to express your QOL best.

RESPONSE ITEMS: 0. Not at all, 1. A bit, 2. Somewhat, 3. Quite a bit, 4. Very much

Fig. 1 – Asthma Health Questionnaire-33.

nighttime sleep on one or more days per week, asthma symptoms that restrict daily activities, or the need for rescue medication (short-acting inhaled β_2 -agonist) on one or more days per week.

The study protocol was approved by the Kawasaki Municipal Tama Hospital ethics committee (Approval date: Sept. 5, 2012; Approval no: 148).

2.2. Methods

Omalizumab was administered as add-on therapy by subcutaneous injection every two or four weeks, depending on the patient's baseline total IgE level and body weight upon enrolment into the study. The intended treatment period was 12 months. Efficacy of the omalizumab therapy was assessed by means of pulmonary function tests, ACT and AHQ-33 scores, the number of emergency visits during the 12-month period, and the methylprednisolone dosage at the end of the 12-month period.

Spirometry (FUDAC-77, Fukuda Denshi, Japan) was performed every four weeks, and ACT and AHQ-33 scores were obtained every four weeks. For each patient, the number of emergency visits during the 12-month period and the corticosteroid dosage at the end of the study period were compared with those before the start of omalizumab.

The following patient characteristics were evaluated: history of smoking, duration of asthma, and total serum IgE level upon enrollment. Study variables that were examined upon enrollment and every four weeks after the start of omalizumab treatment included lung function and ACT and AHQ-33 scores. Methylprednisolone dosage was assessed before the start of omalizumab and at the end of the study period, and the number of emergency visits was assessed for the year before the start of omalizumab and during the study period.

2.3. Statistical analysis

Differences in study variables over time were analyzed by Dunnett's multiple comparisons test. Correlations between ACT and AHQ-33 scores, between ACT scores and FEV1.0%, and between AHQ-33 scores and FEV1.0% were analyzed using Pearson's correlation coefficient. All statistical analyses were performed with Microsoft Excel for Mac 2011. A p value <0.05 was considered significant.

3. Results

3.1. Patient characteristics

Four of the 14 study patients failed to continue treatment for the entire 12-month period, so these patients were not included in the analysis. The characteristics of the remaining 10 patients upon enrollment are shown in Table 1. Patients' mean age was 58.2 ± 18.6 years, and the mean duration of asthma was 14.0 ± 11.0 years. One patient was an ex-smoker with a Brinkman Index of 120, and the other nine patients were never smokers. Patients' total serum IgE was 205.2 ± 163.7 IU/mL, and all patients showed in vitro reactivity to one or more perennial aeroallergens.

Table 1 – Patients' clinical characteristics upon enrollment ($n=10$).

Age (years)	58.2 ± 18.6 (21–81)
Sex (M/F)	6/4
Body weight	57.8 ± 21.7 (40–85)
Duration of asthma (years)	14.0 ± 11.0 (1–35)
Total serum IgE (IU/mL)	205.2 ± 163.7 (29–580)
Perennial allergen reactivity	
Single	$n=6$
Double	$n=4$
FVC (L)	2.5 ± 0.3 (1.12–4.42)
FEV1 (L)	1.8 ± 0.3 (0.65–3.20)
%FEV1 (G)	66.5 ± 5.0 (47.23–85.96)
PEF (L/min)	326.2 ± 52.7 (127.2–646.2)
V50 (L/sec)	1.9 ± 0.5 (0.32–3.72)
V25 (L/sec)	0.6 ± 0.2 (0.10–3.80)
ACT score	14.5 ± 2.1 (6–22)
AHQ-33 score	57.6 ± 9.6 (32–86)
Omalizumab	
Dosage (mg/month)	330.0 ± 161.6 (150–600)
Frequency	Every 2 weeks ($n=5$) Every 4 weeks ($n=5$)
OCS (mg/day)	5.9 ± 1.9 (0–20)

Values are shown as mean $\pm$ SD (range) unless otherwise indicated.

OCS, oral corticosteroid.

3.2. Efficacy of omalizumab

No significant improvement in measures of lung function was observed with omalizumab treatment (Figs. 2, 3). ACT and AHQ-33 scores at 12 weeks were significantly improved in comparison to baseline scores; however, there were no significant improvements after week 20 (Fig. 4). The methylprednisolone dosage and the number of emergency visits decreased significantly from those of the previous year (871.5 mg to 119.0 mg methylprednisolone, $p=0.046$, and from 9.3 to 1.2 visits, $p=0.020$) (Fig. 5). At 12 months, correlation was found between ACT and AHQ-33 scores, but not between ACT scores and FEV1.0%. A weak positive correlation was found between AHQ-33 scores and FEV1.0% at 12 months (Fig. 6).

Four patients continued the omalizumab treatment and were followed up for four years (Table 2). None of these four patients required an emergency visit or rescue medication during the first 1–2 years after the start of omalizumab therapy; however, three of the four patients required prednisolone during year three and/or year four (Table 3).

4. Discussion

There are treatment options to be considered when patients reach step 5 as outlined by the GINA guidelines. Add-on low-dose oral corticosteroid has been reported to be effective in patients with severe asthma [4], but significant adverse effects, such as osteoporosis and diabetes mellitus, often result. Bronchial thermoplasty performed via bronchoscopy, an interventional therapy for severe asthma that delivers thermal energy to the airway wall, has been investigated [12]. This procedure is thought to improve asthma-specific quality

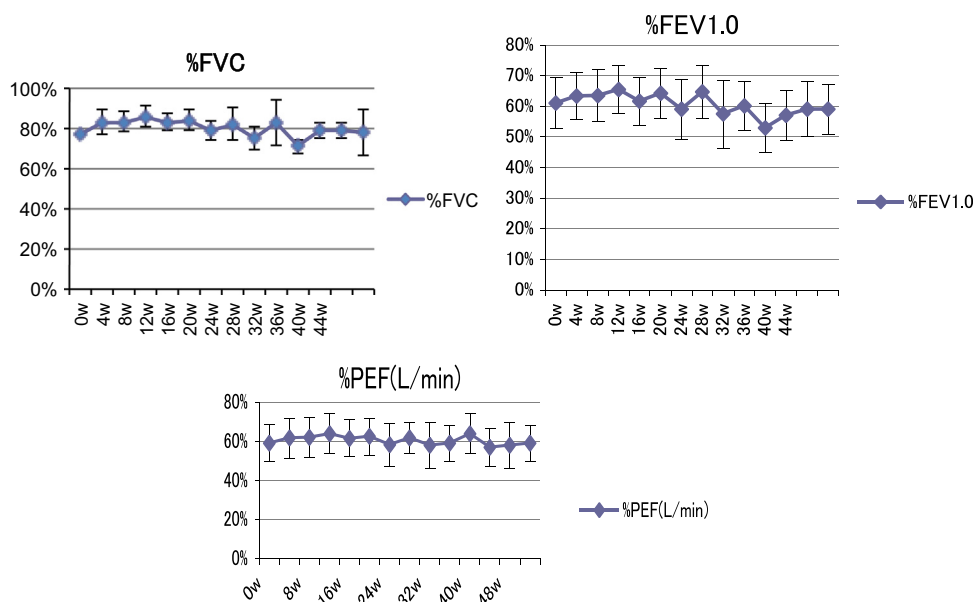


Fig. 2 – Measures of respiratory function obtained in the 10 study patients before the start of omalizumab and every four weeks thereafter. No improvements in lung function are seen.

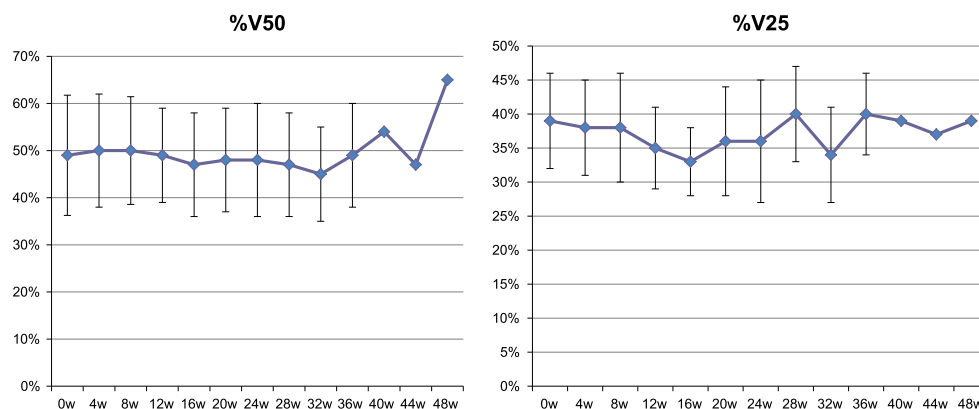


Fig. 3 – Asthma Control Test (ACT) and Asthma Health Questionnaire (AHQ)-33 scores obtained for the 10 study patients before the start of omalizumab and every four weeks thereafter. The higher the AHQ-33 scores, the worse the asthma symptoms. ACT and AHQ-33 scores at 16 weeks were significantly improved in comparison to scores at week 0 (baseline scores).

of life by reducing severe exacerbations, but the evidence is limited. Another recommended treatment for step 5 patients is anti-IgE therapy. However, patients' responses to this therapy vary greatly, so it is difficult to select the optimal treatment course for each patient.

Omalizumab is a treatment option for patients who show reactivity to one or more perennial aeroallergens, but it is difficult to predict which patients will respond to omalizumab treatment. Bousquet et al., investigated whether patients' response to omalizumab can be predicted. Patients who benefited most from this therapeutic option were those receiving high-dose beclomethasone dipropionate, had a history of frequent emergency asthma treatments, or had poor lung function [13]. To identify candidates for omalizumab among patients with severe asthma, Hanania et al., investigated the following three biomarkers of Th2-driven inflammation: fractional exhaled nitric oxide, peripheral

blood eosinophil count, and serum periostin levels. With omalizumab treatment, reductions in exacerbations were highest in the patients in whom these biomarkers were most markedly elevated, indicating that such patients may receive the greatest benefit from omalizumab therapy [14].

Four of our 10 study patients continued omalizumab therapy and were followed-up for four years. These four patients benefited from the omalizumab and have continued therapy even beyond four years. If patients who will most benefit from omalizumab can be identified before the therapy is started, patients who will not benefit from omalizumab treatment can be spared out-of-pocket expenses.

To evaluate the efficacy of omalizumab, we studied patients with severe bronchial asthma by measuring respiratory function, ACT and AHQ-33 scores, the methylprednisolone dosage at the end of the treatment period, and the number of emergency visits during the 12 months of

treatment. Although we observed no significant improvement in lung function, subjective improvements, shown by the AHQ-33 and ACT scores, were seen during the first 12 weeks of treatment. Bousquet et al., reported a patient response of 61% at four weeks and 87% at 12 weeks, with patient response defined by at least one of the following: reduction in symptom scores, reduction in rescue medications, improved lung function, or improved quality of life [13]. Hanania et al., reported, from a placebo-controlled trial, that omalizumab improved mean Asthma Quality of Life Questionnaire scores during their 48-week study period. In their study, 35.4% patients used high dose ICS and LABA without other asthma controllers, and only 17.1% used OCS [14]. In our study patients, although there were significant improve-

ments in subjective symptoms for the first 12 weeks, after week 20, there seemed to be no further improvement in subjective symptoms. However, during the study period, the number of ER visits and the dosage of methylprednisolone were decreased. Thus, this plateau in subjective symptoms may be because patients were more highly motivated to control their asthma symptoms during the first 12 weeks and/or because a placebo effect had worn off.

Humbert et al., reported the benefits of omalizumab observed in a double-blind study [8], and Ohta et al., reported the efficacy of omalizumab in an Asian population [15]. These two studies provided evidence that omalizumab improved morning PEF and FEV1.0. However, Holgate et al., reported on the efficacy of omalizumab in significantly reducing the usage of rescue medication and improving subjective symptoms [9]. In our study, no significant improvement in respiratory function was observed. It is possible that this lack of improvement was due to a longer history of asthma in our patients, which could have resulted in remodeling of the airway wall. Breathing function was assessed during follow-up visits, which were pre-scheduled at regular four-week intervals. Thus, the results of respiratory function tests would not necessarily correspond to the measures of asthma control and cannot be relied on as an indication of the asthma control.

In the present study, we utilized two questionnaires, ACT and AHQ-33. The ACT is a self-administered test that asks five simple questions pertaining to asthma control. Arioka and colleagues developed the AHQ as a disease-specific questionnaire adapted to Japanese life and culture [11]. The AHQ aids investigators in understanding patients' emotions, social activities, and economic circumstances in addition to their asthmatic symptoms. We found that using the ACT and AHQ questionnaires together was informative in evaluating the efficacy of omalizumab in patients with severe asthma.

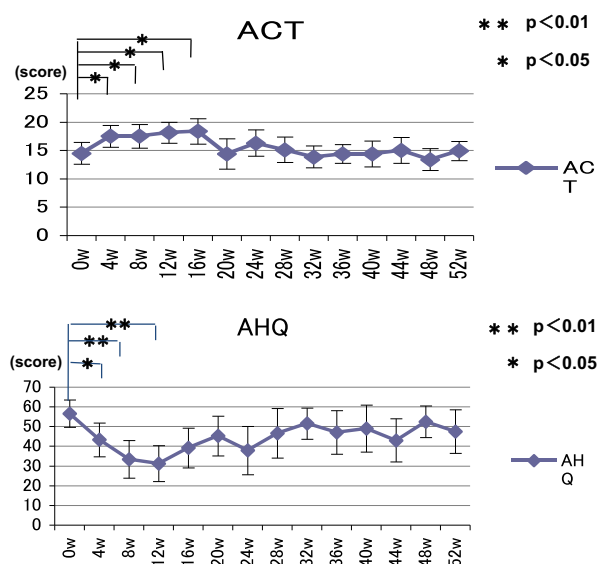


Fig. 4 – Bar graphs showing patients' methylprednisolone (m-PSL) dosage and the number of emergency visits before the start of omalizumab therapy and 12 months after the start of therapy. Omalizumab significantly reduced the methylprednisolone usage and the number of emergency visits.

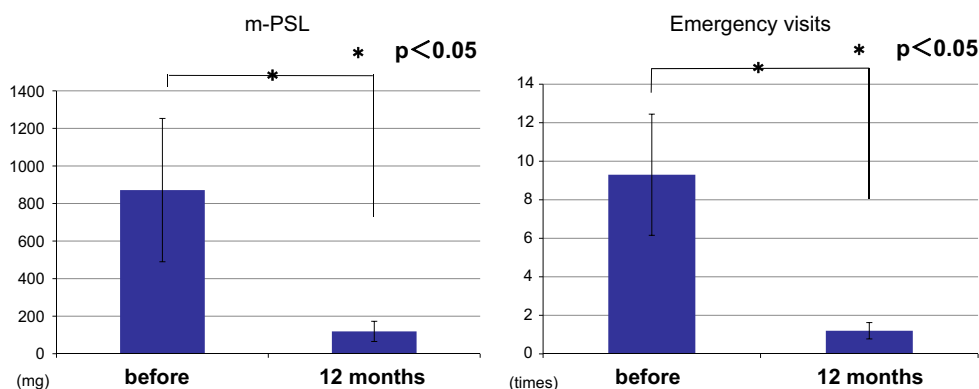


Fig. 5 – Scatter plots showing the correlation between Asthma Control Test (ACT) and Asthma Health Questionnaire (AHQ)-33 scores, ACT scores and forced expiratory volume in 1 s (FEV1.0%), and AHQ-33 scores and FEV1.0%.

5. Conclusion

Omalizumab administration for 12 months was shown to significantly reduce both the number of emergency visits and the methylprednisolone dosage in our patients with severe

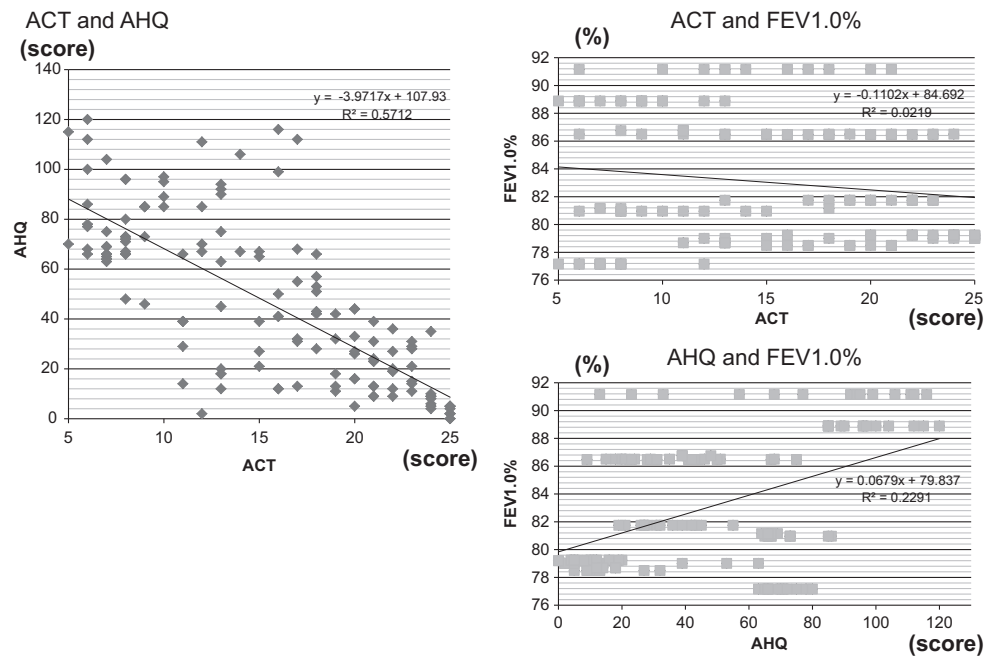


Fig. 6 – Weak positive correlation was found between Asthma Health Questionnaire (AHQ)-33 scores and forced expiratory volume in 1 s (FEV1.0%) at 12 months.

Table 2 – Characteristics^a of the 4 patients who continued omalizumab treatment.

	41-year-old man	66-year-old woman	42-year-old woman	79-year-old man
BMI	27.1	22.0	30.0	22.5
Duration of asthma (years)	5	26	4	2
Total serum IgE (IU/mL)	39	190	160	190
FVC (L)	4.42	1.81	2.49	1.99
FEV1 (L)	3.20	1.02	2.12	0.88
%FEV1 (G)	72.34	56.27	85.22	44.04
PEF	9.65	3.92	6.74	2.16
V50 (L/sec)	2.97	0.32	3.80	0.38
V25 (L/sec)	0.75	0.26	0.95	0.17
ACT	16	22	18	17
AHQ-33	41	36	51	32
Reactivity to perennial aeroallergens (no.)	2	1	4	1
Blood eosinophil count (μl)	49	1137	2480	334

BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; %FEV1, percentage of predicted FEV1; PEF, peak expiratory flow; V50, maximal airflow rate at 50% vital capacity; V25, maximal airflow rate at 25% vital capacity; ACT, Asthma Control Test; AHQ-33, Asthma Health Questionnaire-33.

^a Determined upon enrollment.

Table 3 – Key measures of clinical status of the 4 patients who remained on omalizumab, years 0–4.

	Year 0	Year 1	Year 2	Year 3	Year 4
41-year-old man					
PSL (mg)	1200	1120	0	0	0
m-PSL (mg)	3240	0	0	0	0
No. emergency visits	30	0	0	0	0
No. hospitalizations	0	0	0	0	0
66-year-old woman					
PSL (mg)	275	0	0	20	35
m-PSL (mg)	1040	40	0	0	0
No. emergency visits	12	1	0	0	0
No. hospitalizations	1	0	0	0	0
42-year-old woman					
PSL (mg)	380	120	0	15	28
m-PSL (mg)	120	120	0	1120	0
No. emergency visits	3	0	0	5	0
No. hospitalizations	0	0	0	0	0
79-year-old man					
PSL (mg)	60	0	0	0	0
m-PSL (mg)	250	125	0	250	0
No. emergency visits	2	1	0	0	0
No. hospitalizations	0	0	0	0	0

PSL, prednisolone; m-PSL, methylprednisolone.

Conflict of interest

The authors have no conflict of interest.

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asthma. We also obtained data suggesting that long-term omalizumab therapy is effective and that it might reduce the frequency of asthma exacerbations.

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