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Therapeutic Effect of Omalizumab in Severe Asthma: A Real-World Study in Korea

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Purpose: Omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody, has proved to be effective for the treatment of severe asthma. However, there is no direct evidence of effectiveness of omalizumab in Korean patients with severe asthma. We sought to evaluate the real-world effectiveness of omalizumab in Korean adult patients suffering from severe asthma and to identify predictors of favorable response. **Methods:** A retrospective analysis of electrical medical records was performed on severe allergic asthmatic patients with omalizumab treatment group (OT group) for more than 6 months between March 2008 and February 2016. Propensity score matching was applied to define the standardized treatment control group (STC group) treated without omalizumab. Asthma-related outcomes were compared between the 2 groups, and analyzed before and after omalizumab use in the OT group. Responders to treatment were defined as patients showing >50% reduction in asthma exacerbations and/or systemic steroid requirement during the outcome period. **Results:** One hundred twenty-four patients with severe asthma (62 in the OT group; 62 in the STC group) were enrolled in the study. Proportion of patients having the reduction of asthma exacerbation (53.2% vs 35.5%, P=0.015) and the rate of responders (67.7% vs 41.9%, P=0.007) were significantly higher in the OT group than in the STC group. Significant reductions were noted in asthma exacerbation (P=0.006), hospitalization (P=0.009), hospitalization days (P=0.006), systemic corticosteroid requirements (P=0.027), and sputum eosinophil count (P=0.031) in OT group compared with STC group. There were no significant differences in changes of forced expiratory volume in the 1 second (FEV1) levels between the 2 groups. No predictors of responders were found for omalizumab treatment. **Conclusions:** Omalizumab can reduce exacerbations/hospitalization/systemic steroid burst in Korean adult patients with severe asthma.

Key Words: Omalizumab; severe asthma; asthma exacerbation

INTRODUCTION

Severe asthma is defined as a clinical condition that requires treatment with high-dose inhaled corticosteroids (ICSs) plus second controller and/or systemic corticosteroids (SCSs) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[1] It has been shown to account for 5%-10% of the total asthma patients.[1] The frequency of hospitalization and emergency department visit is increased, and work productivity is decreased in patients with uncontrolled asthma.[2] Although severe asthmatics constitute a small proportion of patients with asthma, their per capita healthcare cost is substantial and increases relative to the severity of asthma.[3] Overall, severe asthma gives rise to a big burden in terms of patient health and social medical expenses.

Immunoglobulin E (IgE) plays a crucial role in developing and exacerbating asthma by binding to high-affinity receptors on mast cells and basophils and cross-linking in presence of an antigen in allergic asthma.[4] Omalizumab is a recombinant humanized monoclonal antibody against IgE.[5] It binds to free IgE and blocks interactions between IgE and inflammatory cells, subsequently reducing expressions of IgE receptors on inflammatory cells.[6] Patients with severe allergic asthma treated with omalizumab have been reported to show improvements in asthma symptoms, quality of life, exacerbation rate, and SCS use.[7,8] Recently, several reports suggest that omalizumab also

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has positive effects in patients with nonatopic asthma, with underlying mechanisms unrevealed.[9] Moreover, omalizumab could reduce asthma exacerbations in patients with aspirin-exacerbated respiratory disease (AERD), and seasonal asthma exacerbation associated with viral infections in childhood asthmatic patients.[10,11] However, the effect of omalizumab has not yet been determined in Korean patients with severe asthma. In addition, there is still a high unmet medical need to determine which patient may respond favorably to omalizumab treatment.

The real-world study draws attention because it can encompass a wide variety of patient characteristics, including adherence, comorbidities, smoking status and study eligibility, and can be complementary to results from randomized controlled trial (RCT).[12] The therapeutic effect of omalizumab in severe asthma is evidenced by many real-world studies;[13] however, most of the studies did not include a control group treated without omalizumab. The present study was conducted to assess the effect of omalizumab in Korean patients with severe asthma compared to control patients on standardized treatment without omalizumab, and to investigate predictors of favorable response to omalizumab in a real-world setting.

MATERIALS AND METHODS

Study design

This retrospective study was conducted at a single tertiary center, Ajou University Hospital in Suwon, Korea. Study subjects were divided into 2 groups: omalizumab treatment group (OT group) and standardized treatment control group (STC group) treated without omalizumab. All patients received the standard asthma management, medium to high-dose ICS with long-acting β_2-agonists and/or leukotriene receptor antagonists, for 6 months prior to the index date (baseline period). Omalizumab was administered subcutaneously every month in OT group, with a dose adjusted to body weight and baseline total IgE (range: 150 to 450 mg, mean: 233 mg), while the standard asthma management was maintained in STC group for 6 months after the index date (outcome period) (Fig. 1). Index date referred to the time of starting treatment with omalizumab. Data were collected for baseline and outcome periods between March 2008 and February 2016.

The skin prick test (SPT) was performed to confirm atopic status using the following allergens: house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), tree pollens (Alder, Birch, Hazel, Beech, Ash, and Oak), grass pollens (Orchard, Rye, Bermuda, Timothy, Kentucky, and Meadow), weed pollens (Ragweed, Mugwort, and Hop Japanese), molds (*Alternaria*, *Aspergillus*, *Cladosporium*, *Fusarium*, and *Candida*) and animal dander (Cat and Dog). A positive reaction was defined as a wheal of more than 3 mm in diameter or wheal size larger than a positive control (histamine) in SPT. If SPT was not feasible, specific IgE antibodies to clinically relevant allergens were measured, with a level greater than or equal to 0.35 kU/L considered a positive response. Specific IgE were measured using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden). Atopy was determined when SPT or allergen specific IgE were positive to at least one of the above-mentioned allergens, while nonatopic was deemed 'present' when those tests were all negative.

Airway reversibility was considered to be positive if forced expiratory volume in 1 second (FEV1) increases by more than 12% and 200 mL from pre-bronchodilator use. Hyperresponsiveness was positive when PC20 is less than 25 mg/mL of methacholine. Airway reversibility and hyperresponsiveness test which were performed at the initial visit were adopted. Chronic SCS use was defined as treating with SCS for ≥50% of the baseline period to prevent exacerbation. A history of emer-

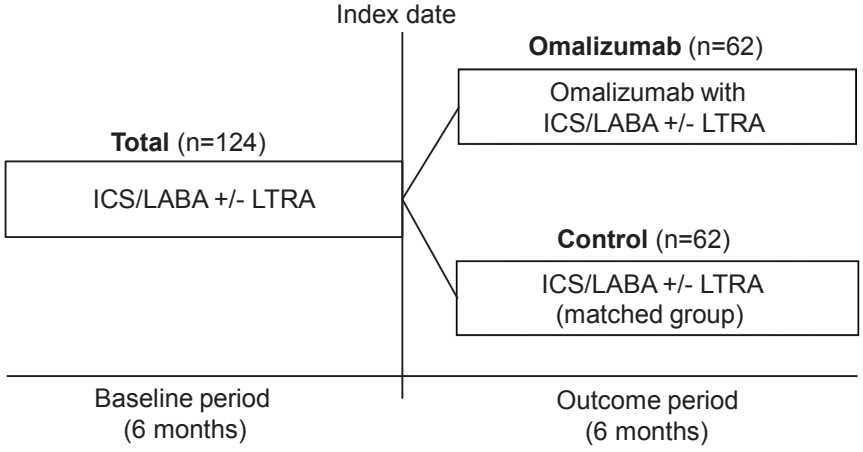

Fig. 1. Study design. All patients had the standard asthma management during the baseline period of 6 months. Omalizumab was administered subcutaneously every month in the omalizumab treated group, while only the standard asthma management was maintained in the control group. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

gency department visit was based on medical recording whether patients had visited emergency department with complaining asthma exacerbation symptoms within a previous year before the index date.

AERD was diagnosed when patients had a typical history of asthma exacerbation after ingestion of aspirin/nonsteroidal anti-inflammatory drugs or positive response during the lysine-aspirin bronchial provocation test (more than 20% reduction in FEV1).

Study population

All study patients, aged ≥18 years, were diagnosed as having severe uncontrolled asthma with at least one of following criteria during the baseline period despite having been treated with medium to high-dose ICS with long-acting β_2-agonists and/or leukotriene receptor antagonists: 1) documented asthma exacerbation, 2) asthma-related emergency department visit and/or hospitalization, 3) poor symptom control defined as a score <20 on the Asthma Control Test, and 4) worsening symptoms on tapering of ICS or SCS, and 5) FEV1 <80% of predicted. Immunodeficient patients and those who were receiving intravenous immunoglobulin were excluded from the study. Patients with clinical features of asthma and chronic obstructive pulmonary disease (COPD), referred to as "Asthma-COPD overlap", were excluded by decision of physicians. This study was approved by the Ethical Review Board of Ajou University (AJIRB-MED-MDB-16-276).

Study outcomes

The primary outcome was the proportion of patients having the reduction of asthma exacerbation. The secondary outcomes were the proportion of responders, and changes in clinical and laboratory parameters including number of asthma exacerbation, hospitalization, hospitalization days, SCS requirement, FEV1% predicted during the outcome period in the OT and STC groups. Investigation of predictive markers, among demographic and laboratory results, for favorable responders to omalizumab treatment was also attempted. In addition, effect of omalizumab was analyzed according to the atopic status, treatment season, and comorbid AERD. Seasonal effect was evaluated in terms of the season classified into 4 groups according to the index date: spring (March to May), summer (June to August), fall (September to November), and winter (December to February).

Asthma exacerbation was defined as at least 1 intravenous systemic steroid treatment and/or bursts of SCS use at prednisolone equivalent dose ≥45 mg for 3 consecutive days for relieving asthma symptoms. A responder was defined as >50% reduction in exacerbations or SCS requirement between the baseline and outcome periods.[14,15]

Adverse events associated with omalizumab treatment were monitored every visit depending on patients' report and/or an objective investigation by physicians. Patients were recommended to remain at hospital at least 1 hour after the administration of omalizumab to find immediate systemic reactions.

Statistical analysis

Propensity score matching was used to select the STC group among severe asthmatic patients in order to reduce a selection bias, which was performed using logistic regression that includes following variables: age, gender, and duration of asthma, step of asthma treatment based on the Global Initiative for Asthma guideline, season of the study period, blood eosinophil level, and total IgE. During this approach, missing values were replaced using the multivariate imputation by chained equations with random forest imputations, which was performed using R (version 3.3.2; R project for Statistical Computing, Vienna, Austria; http://www.r-project.org).

Clinical characteristics were examined by the *t* test and Fisher's exact test. If continuous variables were not assumed to be normally distributed, the Mann-Whitney *U* test was applied. Binary logistic regression estimated odds ratios (ORs) to determine responses in terms of the season. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of the study population

Among the total 124 selected patients, 62 received omalizumab plus standard asthma management and 62 were treated with standard asthma management except for omalizumab.

The percentages of atopic patients were 71.0 in the OT group and 72.6 in the STC group. The most commonly sensitized allergens were house dust mites in both groups, with an identical proportion of 58.1%. However, the level of specific IgE to *D. farinae* was significantly higher in the STC group than in the OT group (20.9±26.0 vs 8.0±17.7 kU/L, P=0.024). In addition, the number of patients with AERD was significantly larger in the OT group than in the STC group (30.6% vs 11.3%, P=0.019). Smoking status, associated comorbidities, and allergic disease were not significantly different between the 2 groups (Table 1).

Therapeutic effect and safety of omalizumab

The proportion of patients having reduced asthma exacerbation was significantly higher in the OT group than in the STC group (53.2% vs 35.5%, P=0.015) (Fig. 2A). The number of responders during the outcome period was larger in the OT group than in the STC group (67.7% vs 41.9%, P=0.007) (Fig. 2B). The mean number of exacerbation per patient during the outcome period was lower in the OT group than in the STC group (-0.6±1.5 vs 0.0±1.0, P=0.006) (Fig. 3A). Moreover, the numbers of hospitalization and hospitalization days were

Table 1. Clinical characteristics of the subjects at baseline

Variables	Control (n=62)	Omalizumab (n=62)	*P* value
Age (year)	46.3±16.6	44.5±13.1	0.492
Female	27 (43.5)	36 (58.1)	0.150
Smoking status			0.621
Never smoker	39 (62.9)	43 (69.4)	
Ex-smoker	12 (19.4)	12 (19.4)	
Current smoker	11 (17.7)	7 (11.2)	
Duration of asthma (year)	5.8±6.3	10.0±7.7	0.001
Medium/high-dose ICS	35/27	33/29	0.718
Chronic SCS use	14 (22.6)	21 (33.9)	0.163
History of ED visit	16 (25.8)	12 (19.4)	0.390
Total IgE (kU/L)	532.7±882.9	538.8±766.6	0.974
Specific IgE to Dp (kU/L)	15.0±18.7	6.7±15.6	0.061
Specific IgE to Df (kU/L)	20.9±26.0	8.0±17.7	0.024
Blood eosinophil (×10^6/L)	605.2±420.2	470.9±443.1	0.093
Sputum eosinophil (%)	42.4±29.5	48.6±33.9	0.520
FEV1/FVC ratio	0.77±0.13	0.79±0.12	0.470
FEV1 (%)	65.1±29.3	57.3±20.7	0.558
Airway reversibility*	23 (37.1)	30 (48.4)	0.204
PC20 value (mg/mL)*,†	3.6±5.3	8.7±10.0	0.027
Comorbidity			
Allergic rhinitis	47 (75.8)	47 (75.8)	1.000
Chronic rhinosinusitis	30 (48.4)	35 (56.5)	0.472
Nasal polyp	6 (9.7)	13 (21.0)	0.133
Old tuberculosis	5 (8.1)	2 (3.2)	0.439
AERD	7 (11.3)	19 (30.6)	0.019
Atopy			
House dust mite	36 (58.1)	36 (58.1)	1.000
Animal dander	12 (19.4)	4 (6.5)	0.058
Pollen	26 (41.9)	18 (29.0)	0.189
Mold	11 (17.7)	7 (11.9)	0.150

Values given are the mean±standard deviation or number (%).
ICS, inhaled corticosteroid; SCS, systemic corticosteroid; ED, emergency department; IgE, immunoglobulin E; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; AERD, aspirin-exacerbated respiratory disease.
*The pulmonary function test which was performed at the initial visit was adopted; †PC20 value means the concentration of methacholine needed to decrease a 20% of FEV1 from baseline.

smaller in the OT group than in the STC group (-0.3±1.0 vs +0.2±1.2, *P*=0.009 (Fig. 3B); -2.5±6.5 vs 1.3±1.2 days, *P*=0.006). In the outcome period, the mean daily dose of SCS per patient was reduced from 4.4±4.4 to 3.4±5.1 mg/day in the OT group, while it was increased from 3.4±1.9 to 3.6±1.2 mg/day in the STC group. The difference in the daily SCS dose (mean value of daily dose of SCS required for 6 months of study period) between the baseline and outcome periods was statistically significant in the OT and STC groups (-1.0±3.7 vs 0.2±1.3 mg/day,

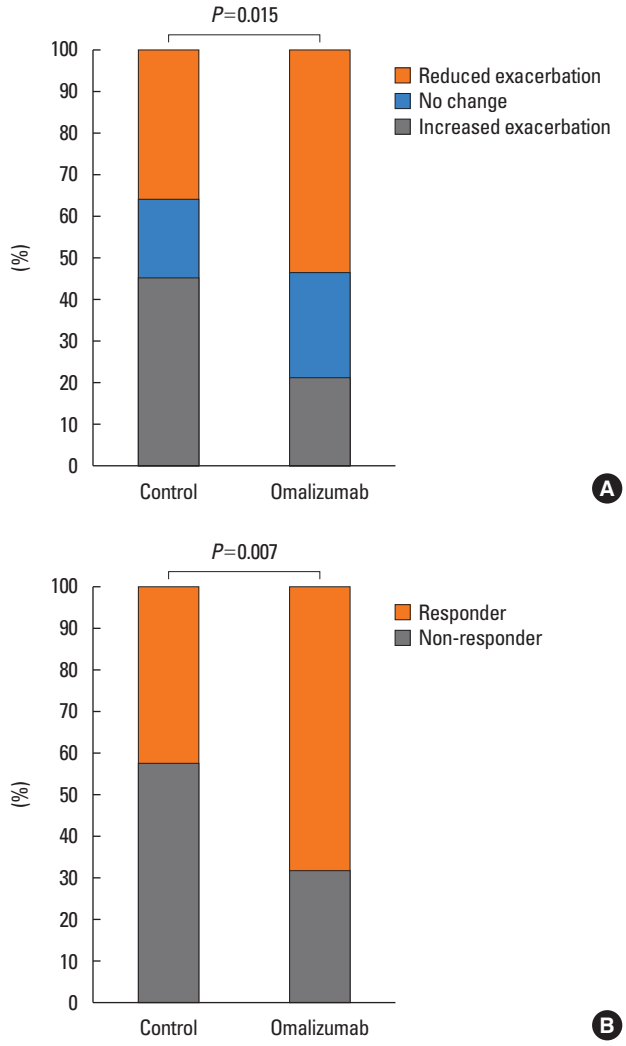

Fig. 2. Response to omalizumab between the 2 groups was presented in 2 ways: according to the number of asthma exacerbation during the outcome period compared to the baseline period (A), and the proportion of responders (B). A response to omalizumab was defined as >50% reduction in AE or SCS requirement during the outcome period. *P* values were estimated from Fisher's exact test. AE, acute exacerbation; SCS, systemic corticosteroids.

P=0.027) (Fig. 3C). There were no significant differences in changes in FEV1 (% predicted) level between the OT and STC groups (57.3%±20.0% to 66.0%±20.9% vs 65.1%±29.3% to 70.2%±31.7%, *P*=0.576) (Fig. 3D). Percentage of sputum eosinophils was similar at baseline between the treatment and control groups (48.6%±33.9% vs 42.4%±29.5%); however, it was significantly lower after omalizumab treatment in the OT group than in the STC group (-28.4%±21.8% vs -3.6%±22.9%, *P*=0.031) (Table 2).

Two adverse events were reported during the outcome period: one benign paroxysmal positional vertigo and one generalized itching, which were not considered to be related with omalizumab. No patient stopped omalizumab treatment due to adverse events.

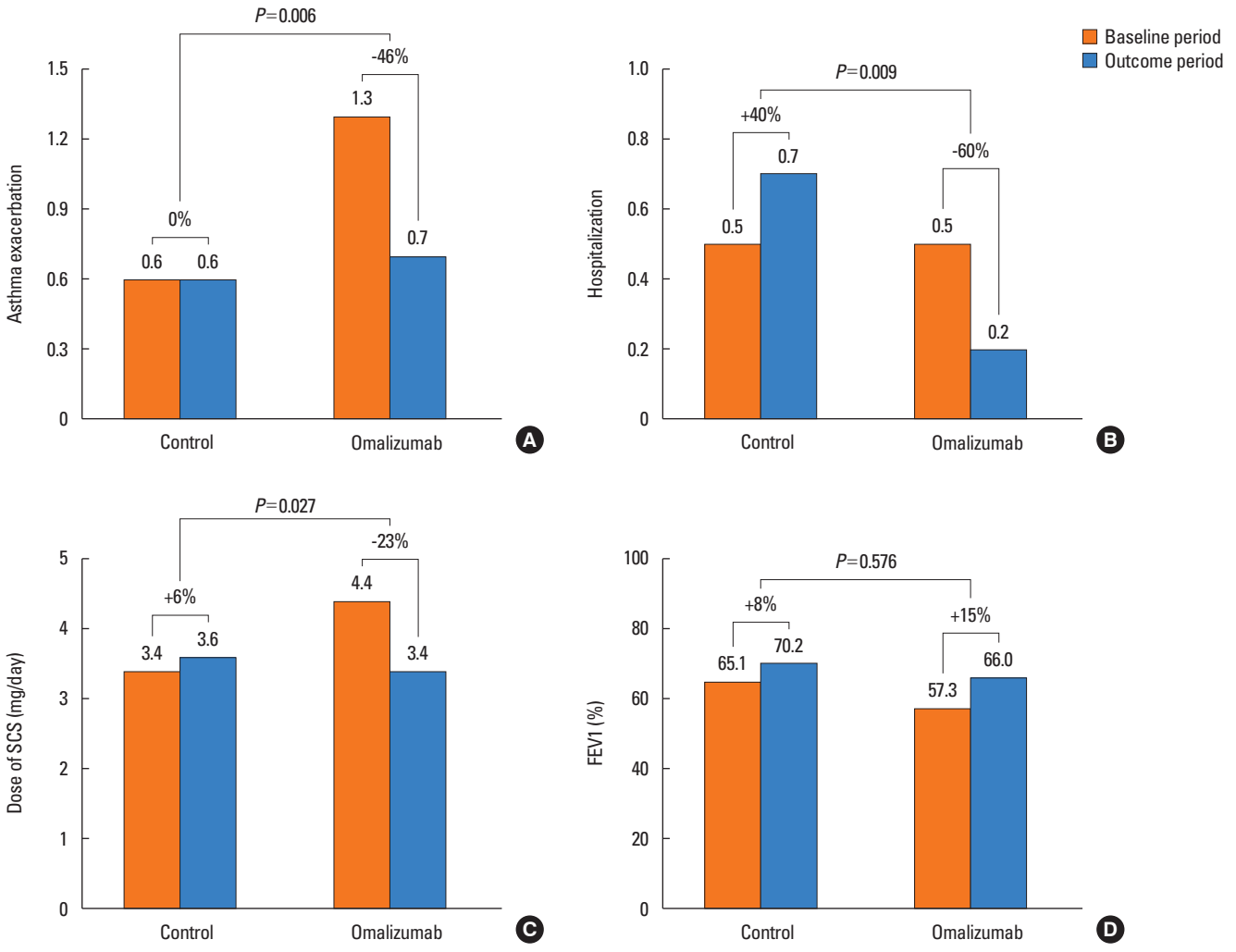

Fig. 3. Changes in clinical parameters during the baseline and outcome periods in the omalizumab treated and control groups in terms of asthma exacerbation (A), hospitalization (B), daily dose of SCSs (C), and FEV1% level (D). SCS, systemic corticosteroid; FEV1, forced expiratory volume in one second.

Table 2. Changes in laboratory parameters between the baseline and outcome periods

Variables	Mean difference*		
	Control	Omalizumab	*P* value
Total IgE (kU/L)	62.1±266.4	39.3±573.1	0.871
IgE to Dp (kU/L)	4.5±18.4	-3.1±5.5	0.204
IgE to Df (kU/L)	2.7±19.6	-5.6±7.1	0.199
Blood eosinophil (×10^6/L)	-212.4±357.9	-145.7±443.4	0.496
Sputum eosinophil (%)	-3.6±22.9	-28.4±21.8	0.031

Values given are the change from baseline mean±standard deviation.
IgE, immunoglobulin E; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.
*These figures were calculated by the difference between the 2 periods in each group.

Predictive factors for responses to omalizumab

To determine predictive factors for responders, baseline demographics including smoking status, duration of asthma, ICS dose, chronic SCS use, history of emergency department visit, associated diseases, and laboratory variables including total IgE, specific IgE to house dust mite, sputum eosinophil, blood eosinophil, FEV1/forced vital capacity (FVC) ratio, FEV1 (%), airway reversibility, PC20, and sensitized allergens were compared in the OT group. There were no factors for significant differences between responders (n=42) and non-responders (n=20) (Table 3).

Comparison of therapeutic effect of omalizumab between atopics and nonatopics

Subgroup analysis of the OT group was conducted to determine whether the therapeutic effect of omalizumab is different between atopics (n=44) and nonatopics (n=18). The decrease in exacerbation was similar between atopics and nonatopics (-0.6±1.5 vs -0.5±1.5, *P*=0.848). Moreover, improvement in the other outcomes, such as number of hospitalization, hospi-

Table 3. Evaluation of baseline predictive factors for favorable response in patients treated with omalizumab

Variables	Responders* (n=42)	Non-responders (n=20)	*P* value
Age (year)	42.7±13.9	48.2±10.9	0.131
Female	23 (54.8)	13 (65.0)	0.584
Ever smoker	13 (31.0)	6 (30.0)	1.000
Duration of asthma (year)	8.6±7.0	12.9±8.3	0.055
Medium/high-dose ICS	22/20	11/9	0.847
Chronic SCS use	16 (38.1)	5 (25.0)	0.308
History of ED visit (%)	10 (23.8)	2 (10.0)	0.198
Total IgE (kU/L)	534.8±772.8	549.2±783.9	0.957
Specific IgE to Df (kU/L)	10.2±20.3	2.1±1.5	0.247
Sputum eosinophil (%)	50.0±34.9	43.3±35.8	0.774
Blood eosinophil (×10^6/L)	496.2±469.2	418.9±390.0	0.526
FEV1/FVC ratio	0.81±0.13	0.76±0.10	0.136
FEV1 (%)	55.9±21.1	65.5±10.0	0.459
Airway reversibility†	18 (42.9)	12 (60.0)	0.207
PC20 value (mg/mL)†,‡	8.3±10.9	9.9±8.0	0.702
Atopy	31 (73.8)	13 (65.0)	0.554
House dust mite	25 (59.5)	11 (55.0)	0.788
Pollen	14 (33.3)	4 (20.0)	0.375
Animal	3 (7.1)	1 (5.0)	1.000
Mold	4 (9.5)	4 (20.0)	0.418
Associated disease			
Allergic rhinitis	33 (78.6)	14 (70.0)	0.532
Chronic rhinosinusitis	25 (59.5)	10 (50.0)	0.586
Nasal polyp	11 (26.2)	2 (10.0)	0.192
AERD	16 (38.1)	4 (20.0)	0.245

Values given are the mean±standard deviation or number (%).
ICS, inhaled corticosteroid; SCS, systemic corticosteroid; ED, emergency department; IgE, immunoglobulin E; Df, *Dermatophagoides farinae*; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; AERD, aspirin-exacerbated respiratory disease.
*Patients having more than 50% reduction of asthma exacerbation or systemic steroid requirement during the outcome period compared to the baseline period; †The pulmonary function test which was performed at the initial visit was adopted; ‡PC20 value means the concentration of methacholine needed to decrease a 20% of FEV1 from baseline.

talization days, requirement of SCS, blood eosinophil count, and FEV1% value, were observed to be higher in atopics compared with nonatopics; however, the differences were not statistically significant (Table 4).

Therapeutic effect of omalizumab in terms of season

Approximately 47.4% of the total patients were classified as responders. The proportion of responders was analyzed in terms of the 4 seasons in the OT and STC groups. Initiating treatment in the winter season was strongly associated with response to omalizumab (OR, 4.29; 95% confidence interval [CI], 1.13-16.31), followed by spring (OR, 3.50; 95% CI, 0.43-28.45) (Fig. 4).

Table 4. Comparison of outcomes between nonatopic and atopic patients after treatment with omalizumab

Variables	Mean difference		
	Nonatopics (n=18)	Atopics (n=44)	*P* value
Asthma AE	-0.5±1.5	-0.6±1.5	0.848
Hospitalization	-0.1±0.5	-0.3±1.2	0.272
Hospitalization days	-1.3±3.8	-3.0±7.3	0.357
SCS use (mg/day)	-0.6±2.7	-1.0±4.0	0.707
Total IgE (kU/L)	58.5±98.1	26.9±741.3	0.901
Blood eosinophil (×10^6/L)	-14.3±276.6	-198.3±491.0	0.330
FEV1 (%)	2.5±4.3	9.3±11.2	0.204

AE, acute exacerbation; SCS, systemic corticosteroid; IgE, immunoglobulin E; FEV1, forced expiratory volume in 1 second.

Therapeutic effect of omalizumab in AERD patients

Nineteen patients with AERD were enrolled in the OT group, and 7 in the STC group. When subgroup analysis was performed to evaluate whether omalizumab treatment as an add-on therapy has a beneficial effect on AERD patients, exacerbation frequency (-0.4±1.6 vs 0.0±1.2, P=0.534), hospitalization (-0.4±1.0 vs 0.3±1.0, P=0.134), hospitalization days (-2.9±6.6 vs 1.3±5.0 day, P=0.143), blood eosinophil count (-279.1±318.8 vs -54.3±264.6×10^6/L, P=0.199), and SCS use (-0.4±2.5 vs 0.0±1.6 mg/day, P=0.633) were noticeably decreased in the OT group compared to the STC group, although the differences were not statistically significant. In the OT group, 15 (78.9%) of the 19 AERD patients were responders.

DISCUSSION

In the present study, omalizumab treatment significantly reduced the number of asthma exacerbation, hospitalization, hospitalization days, daily dose of SCS, and sputum eosinophils with rare adverse events in patients with severe asthma from Korea. There were no significant differences in response of omalizumab in terms of the presence of comorbid conditions like allergic rhinitis, chronic rhinosinusitis (CRS)/nasal polyps, history of pulmonary tuberculosis, AERD, and smoking status. No predictive factors for favorable response to omalizumab were found. The effect of omalizumab was not different between atopics and nonatopics. The benefit of omalizumab was found to be more prominent during winter season. Patients with AERD may benefit from omalizumab treatment. These findings confirmed the beneficial effects of omalizumab on severe exacerbation in patients with severe asthma whether they are atopic or nonatopic types in the real-world practice.

Previous real-world studies demonstrated that a mean reduction rate of asthma exacerbation after omalizumab treatment was 52.9% for a year and 61.0% for 6 months.[16,17] The proportion of responders ranged from 69.6% to 86.4% after 16 weeks of the

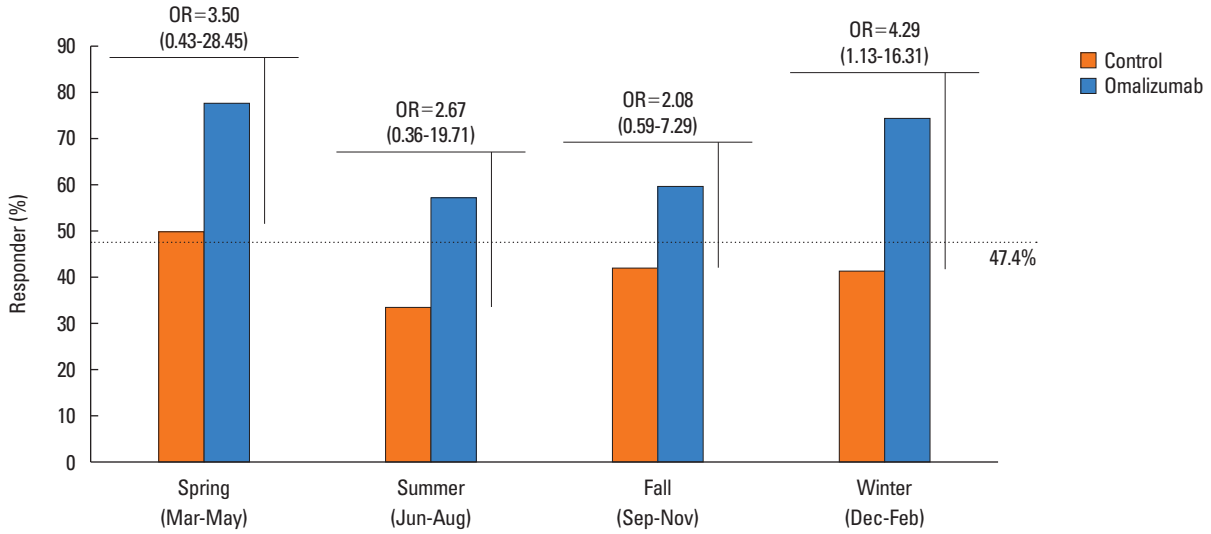

Fig. 4. Seasonal effects of omalizumab. The treatment season was determined based on the index date. The number of subjects assigned to each season was as follows: 8, 6, 31, and 17, respectively, in the control group; and 9, 14, 15, and 24, respectively, in the omalizumab treated group to spring, summer, autumn, and winter. Logistic regression was applied to find the seasonal effect. OR was presented with 95% CIs. The proportion of the responders among all the subjects was 47.4%, which was represented as a reference line. OR, odds ratio; CI, confidence interval.

treatment.[13,18,19] In the present study, the mean exacerbation reduction rate was 46% and the proportion of responders were found to be 67.7%. Previous observational studies demonstrated that the mean number of hospitalization was decreased by 1.6 for 6 months after the omalizumab treatment, and 0.3 and 3.2 for 12 months, respectively.[17,20,21] The mean daily dose of SCS was decreased by 29.2%-62.3% for 6 months in previous studies.[17,22] In the present study, the number of hospitalization was decreased by 0.3 (from 0.5 to 0.2) for 6 months. The dose of SCS used was reduced by 22.7% during the outcome period. It is speculated that the lower reduction rate of outcomes may have been attributed to the differences in the study subjects, as selected patients were from various phenotypes of severe asthma, including nonatopic asthmatics, smokers, and AERD patients in a real-word study setting. In addition, definition criteria of responders were quite variable in each study.[23]

Omalizumab could reduce eosinophilic inflammation, which is evidenced by robust clinical and laboratory data. The number of eosinophils in blood and sputum has previously been shown to significantly decrease by omalizumab treatment, which correlated with clinical benefits in terms of asthma exacerbation and lung function.[24-26] Omalizumab can reduce eosinophilic inflammation by inhibiting release of cytokines and chemotactic factors for eosinophil activation from mast cells/basophils as well as antigen presentation by dendritic cells.[24] Eosinophilic inflammation is proportionally associated with asthma severity.[27] In the present study, sputum eosinophil count was significantly decreased after omalizumab treatment. These finding suggest that omalizumab can be effective in controlling eosinophilic inflammation in the airway of patients with severe asthma.

A RCT reported that total IgE is a predictor of responder because patients with a low total IgE level do not benefit from omalizumab treatment.[28] In contrast Costello *et al.*[17] showed that treatment response is not associated with serum total IgE level. Hanania *et al.*[29] demonstrated that patients with high levels of fractional exhaled nitric oxide, blood eosinophil, and serum periostin have greater improvement from omalizumab treatment compared to those with low levels of the 3 biomarkers. Bousquet *et al.*[30] reported that omalizumab has more beneficial effects in patients with high-dose ICS use, low FEV1 level, and history of emergency treatment. In the present study, we found similar results as patients with a history of emergency department visit or low FEV1 level tended to show more favorable responses, although it did not reach statistical significance. Further prospective larger cohort studies are needed to investigate useful factors predicting favorable responders by applying various biomarkers and phenotypes of severe asthma.

Nonatopics as well as atopics with severe asthma showed similar effect of omalizumab treatment in this study, which is in agreement with those of recent studies reporting that patients with nonatopic asthma improve in terms of exacerbations, asthma symptoms, and FEV1 level.[31,32] Mechanisms by which omalizumab has beneficial effects in nonatopic asthmatics remain elusive. However, recent findings suggest that IgE localized in target tissues may play an important role in patients with severe nonatopic asthma, because the expression of high-affinity IgE receptor on blood basophils and plasmacytoid dendritic cells, as well as the number of total bronchial mucosal IgE-positive cells were reduced in bronchial biopsy specimens after omalizumab treatment.[32,33] Furthermore, it is still challenging to define atopic status using the SPT results and specif-

ic IgE to common inhalant allergens used in most studies. IgE against respiratory viruses and staphylococcal enterotoxins have been found to be associated with asthma development.[34,35] Therefore, nonatopic patients with severe asthma may respond to omalizumab treatment, although more evidence needs to be collected.

Childhood and adolescent asthma tend to exacerbate more frequently in fall, while adult asthma is prone to exacerbate in winter.[36,37] These patterns of seasonal variation in asthma exacerbation represent the implication of respiratory viral infection which is commonly involved in fall and winter, such as rhinovirus, influenza virus, and respiratory syncytial virus.[38] Childhood asthma studies have reported that asthma exacerbation occurring in fall could be effectively prevented by omalizumab.[10,39] However, this effect was not proved in adult asthma, even though respiratory viral infections are the most prevalent causes of exacerbation in adult asthmatic patients. In the present study, the effect of omalizumab was more prominent in winter season indicating that omalizumab can attenuate frequent exacerbation occurring during winter season. IgE seems to mediate interaction between viral infection and airway inflammation.[40] In addition, interferon-alpha responses that play a pivotal defensive role in viral infections are found to recover after omalizumab treatment.[10] Therefore, it is suggested that omalizumab may have preventive effects on asthma exacerbation triggered by respiratory virus infections in adult patients with severe asthma.

AERD is recognized as a severe asthma subtype accompanying elevated mast cells and eosinophilic inflammation, with a higher prevalence of up to 25% in severe asthma than in non-severe asthma, and may be found in both atopics and nonatopics.[41,42] Total IgE tend to be high not only in atopics, but also in nonatopics with AERD.[43] In other case series and a study based on a small population, omalizumab reduced exacerbation, hospitalization, SCS use, and blood eosinophils in patient with AERD,[11,44] comparable to the results obtained in the present study. An *in vitro* study has demonstrated that omalizumab can dissociate pre-bound IgE on mast cells and basophils, and reduce the IgE-dependent phosphorylation pathway, resulting in a decrease in leukotriene synthesis.[45] In addition, key inflammatory mediators in AERD, urinary leukotriene E_4, and prostaglandin D_2 metabolite are significantly decreased after omalizumab treatment.[11] In the present study, omalizumab could not show definite therapeutic effect on AERD. However, it needs to consider small number of AERD patients in both groups and more favorable outcomes of AERD patients after omalizumab treatment. Therefore, omalizumab can be a suitable option for the treatment of AERD, though more evidence is still needed to verify the effect of omalizumab in AERD patients through prospective RCTs.

Adverse events of omalizumab were noted in recent systematic reviews.[13] Substantial variations were observed between real-world studies, where any adverse events reported ranged from 6.7% to 55.6% and withdrawal rate due to adverse events were found to be range from 0% to 12.0%. In the present study, adverse event rate was 3.2%, with 0% of withdrawal rate, as a few studies reported 0% of serious adverse event.[19] This discrepancy seems to be attributable to differences in study subjects and design (prospective or retrospective, where it may be underreported in retrospective studies).

The strength of the present study is that this is a real-world study matched with the control group by applying propensity score matching method. This helps clarify the effect of omalizumab in various phenotypes of severe asthma, including nonatopics, smokers and AERD and comorbid conditions. This study also has several limitations. First, the outcome period was not long enough to evaluate the effect of asthma exacerbation and other outcome parameters. Secondly, the number of study subjects is not large enough. Further long-term investigations will be extended in a larger cohort, including various populations.

In conclusion, omalizumab is an effective option for the treatment of severe asthma in the real-world practice. Good tolerability profile of omalizumab is similar to that reported in previous studies.

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