

Clinical efficacy of omalizumab in an elderly veteran population with severe asthma

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ABSTRACT

Severe asthma in elderly patients is underdiagnosed, difficult to treat, and often accompanied by atopy. This study was designed to compare clinical outcomes of omalizumab therapy in an elderly veteran population with severe allergic asthma. A retrospective, observational data analysis was performed over 2 years. Cohort outcome measures 1 year before omalizumab therapy were compared with 1 year of active treatment. Statistical analysis included two sample t-tests. The total number of patients enrolled was 17 with median age of 60 years. Omalizumab therapy was associated with a significant reduction in acute asthma exacerbations requiring prednisone treatment ($p < 0.01$), a significant improvement in forced expiratory volume in 1 second of 0.28 L ($p < 0.01$), and significantly higher Asthma Control Test (ACT) scores at 3 ($p = 0.043$), 6 ($p = 0.039$), and 12 months of therapy ($p < 0.01$). Two of five patients on daily prednisone for >6 months were able to discontinue systemic steroid use within 3 months of omalizumab treatment. Our study suggests elderly patients with severe atopic asthma show a significant positive clinical response to omalizumab.

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Asthma is a classically defined chronic medical condition impacting 20 million people in the United States.¹ Allergic asthma investigation has primarily focused on the pediatric and young adult population.² The growing elderly population maintains a less clear definition of asthma. Comorbidities including cardiovascular disease and other obstructive lung disease obscure the impact of asthma on geriatric health. It has been estimated the prevalence of asthma in the elderly population in the United States is between 4 and 7%.^{3–5} Subcategories of severe persistent asthma and atopic asthma have been poorly defined in this population.^{3–5}

Previous studies show a correlation with asthma and elevated IgE levels in elderly patients.^{3,6} As such, asthma and reactive airway disease is often underdiagnosed and categorized as moderate to severe.⁴ Treatment for moderate-to-severe asthma in this group of patients is based on the National Asthma Education and Prevention Program's Expert Panel Report 3 and the Global Initiative for Asthma guidelines and consists of traditional step-up therapy with inhaled corticosteroids, long-acting β -agonists, leukotriene modifiers, theophylline, etc.^{7,8} Without age distinction, guidelines also recommend consideration with omalizumab.^{7–11}

Omalizumab is a recombinant, humanized, monoclonal anti-IgE antibody. Omalizumab binds the Fc portion of free circulating IgE thereby clearing it from the systemic circulation. Secondary effects include IgE receptor blockade on mast cells and basophils.¹² The reduction of antigen binding to Fc- ϵ -RI (high affinity IgE receptor) results in a reversible decrease in the Th2 cytokine production of IL-4, IL-8, and IL-13.¹² Omalizumab decreases the amount of local IgE in the airway mucosa. An associated reduction in local cytokine production decreases airway eosinophilia.^{5,13,14} Alternatively, omalizumab has been shown *in vitro* to not cross-link the Fc- ϵ -RI and to not release histamine.¹⁵

Clinically, omalizumab is effective for those patients with moderate-to-severe atopic asthma not controlled on conventional therapy. It has been shown to decrease asthma exacerbations^{16–18} $>50\%$ ¹⁹ as well as decrease emergency visits by nearly one-half.²⁰ Quality of life scores among asthma patients are significantly improved with omalizumab therapy.²¹ Forced expiratory volume in 1 second (FEV₁)^{22,23} is increased and inhaled steroid dosages are decreased with omalizumab therapy.^{18,19,24,25} Other studies have shown effective tolerability and cost-effectiveness.^{26,27}

The majority of omalizumab studies are organized to include younger populations to show efficacy. With the recent exception of a German prospective postmarketing surveillance trial,²⁸ previous studies primarily used pooled geriatric data to show a reduction in asthma exacerbations, improved symptoms, and reduction in rescue inhaler use.²⁹ The current study uniquely evaluates 5 years of omalizumab therapy outcomes in an elderly VA population with severe asthma.

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METHODS

Study Population

The study was conducted as a retrospective, observational data analysis. An exemption and waiver of consent was approved by our institution's Institutional Review Board committee. Patients with moderate-to-severe asthma regularly followed in the Allergy and Immunology clinics at the VA Greater Los Angeles Healthcare System initiated on treatment with omalizumab from January 2005 to May 2009 were eligible for this review. Data from patient visits, pharmacy records, and laboratory reports included in the Computerized Patient Record System was reviewed and analyzed from January 2004 to May 2010. This allowed cohort outcome measures from 1 year before initiation of omalizumab to be compared with 1 year of active treatment.

Statistical Analysis

SAS Version 9.2 (SAS Institute Inc., Cary, NC) was used to conduct all statistical analyses. Mean values of the primary and secondary outcome measures (number of asthma exacerbations requiring steroids; Asthma Control Test [ACT] scores; FEV₁; and number of asthma controllers, emergency department [ED] visits, and hospitalizations) were calculated. The two sample *t*-tests for means were used to compare the mean outcome measures before and after treatment with omalizumab. A value of $p < 0.05$ was used to determine statistical significance.

Inclusion Criteria

1. Age ≥ 49 years but < 90 years at the initiation of omalizumab therapy
2. Moderate-to-severe asthma with multiple steroid bursts per year or on chronic oral steroids for asthma
3. Followed in the Allergy/Immunology clinics at the VA West Los Angeles for at least 1 year before the initiation of omalizumab
4. Followed in the Allergy/Immunology clinics at the VA West Los Angeles for at least 1 continuous year of omalizumab therapy after initiation
5. Documented specific IgE to at least one aeroallergen by skin-prick test or blood test
6. Compliant with maximal controller medications for asthma before the initiation of omalizumab as determined by pharmacy records
7. Serum IgE level of > 30 IU/mL
8. Completion of ACT questionnaire before the prescribing of omalizumab and during the 1st year of therapy.

Exclusion Criteria

1. Ever been on omalizumab therapy before being initiated at the Allergy/Immunology clinics at the VA West Los Angeles
2. Interrupted omalizumab therapy after initiation

Primary and Secondary Outcome Measures

Primary outcome measure was acute asthma exacerbations requiring systemic steroid therapy. Secondary outcome measures included ACT scores, FEV₁, number of hospitalizations and ED visits for asthma, number of daily asthma controller medications used, and adverse drug reactions attributed to omalizumab.

RESULTS

Study Population Demographics

Twenty-six patients (median age, 61 years old) met the eligibility requirements. However, after the inclusion and exclusion criteria were applied, a total of 17 patients (median age, 60 years old) were included in this review. The age range was 49–85 years old at the time of initiation of therapy with omalizumab. Sixteen patients were men and one patient was a woman. All patients were sensitized to at least one perennial aeroallergen. One patient was an active tobacco smoker (Table 1).

Primary Outcome Measure

As a group, the total number of asthma exacerbations requiring systemic steroids were reduced from 48 to 9 when comparing the 1 year before initiation of omalizumab to the 1 year of active treatment with omalizumab ($p < 0.01$) (Fig. 1). The distribution of reduction in systemic glucocorticoid therapy is outlined in Table 2.

Secondary Outcome Measures

ACT scores improved with omalizumab. This effect was seen at 3 months after initiation of omalizumab ($p = 0.043$), and persisted at 6 months ($p = 0.039$) and 12 months of therapy ($p < 0.01$) (Fig. 2, Table 3). Two of the five patients requiring daily oral steroids achieved steroid-free therapy within 3 months of starting omalizumab. Pulmonary function testing showed an improvement in FEV₁ of 0.28 L ($p < 0.01$) (Fig. 3).

Pharmacy data revealed that all patients were maintained on an inhaled corticosteroid, a long-acting β -agonist, and a leukotriene modifier agent before initiating omalizumab therapy. Additional asthma therapy included oral theophylline for 2 patients, anticholinergic metered dose inhalers for 11 patients, and daily oral steroid therapy for 5 patients. Fifteen patients were concomitantly treated for gastroesophageal reflux dis-

Table 1 Study population characteristics

No. of Patients	17
Median age (yr)	60
Age range (yr)	49–85
Age (yr)	
49–54	6
55–64	4
>64	7
Sex	
Females	1
Males	16
Race	
Black	6
White	6
Hispanic	3
Other	2
Mean IgE (IU/mL)	921
Mean dosing weight (kg)	92
Aeroallergen sensitivity (no. of patients)	
Dust mite	10
Molds	9
Animal dander	12
Pollen	15
Concomitant COPD (no. of patients)	3
Concomitant GERD (no. of patients)	16

COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.

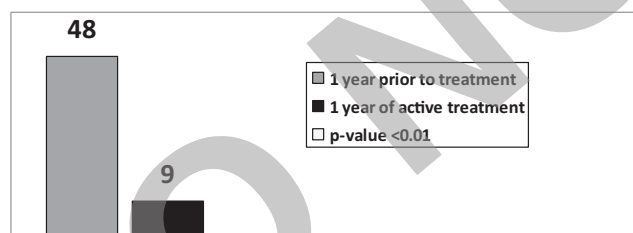


Figure 1. Asthma exacerbations requiring systemic glucocorticoids before and after omalizumab therapy.

Table 2 Distribution of reduction in systemic prednisone therapy before and after omalizumab therapy

No. of Prednisone Bursts	1 yr before Omalizumab (no. of patients)	Active Treatment Year (no. of patients)
0	3	12
1–2	5	4
3–4	4	1
>4	5	0

ease with omeprazole. The total number of daily asthma controller medications (average, 3.00) was not able to be decreased after omalizumab (average, 3.06).

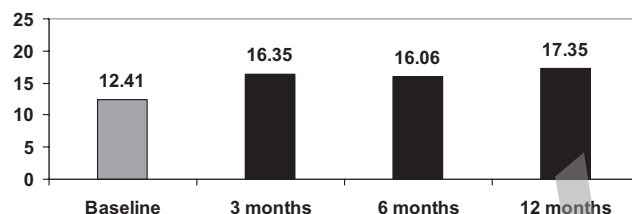


Figure 2. Mean Asthma Control Test (ACT) scores at different intervals of active treatment.

Table 3 Distribution of Asthma Control Test (ACT) scores before and after omalizumab therapy

Average ACT Score Range	1 yr before Omalizumab (no. of patients)	Active Treatment Year (no. of patients)
<10	6	1
10–19	11	11
>19*	0	5

*ACT scores of >19 indicate “well-controlled asthma.”

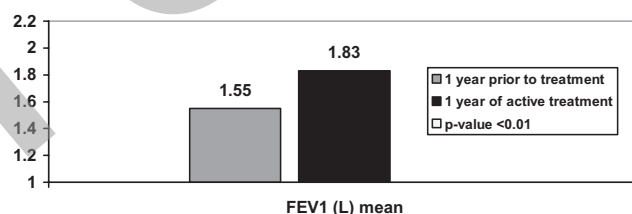


Figure 3. Mean forced expiratory volume in 1 second (FEV₁) (in Liters) before and after omalizumab therapy.

The number of ED visits and hospitalizations for asthma was no different before or after omalizumab treatment. No major adverse reactions to omalizumab were observed.

Omalizumab Dosing

The dose of omalizumab was based on the manufacturer’s dosing chart and schedule. The average IgE level for the cohort was 921 IU/mL, and five patients were above the recommended range of 30–700 IU/mL. The average dosing weight for the cohort was 92 kg, and all patients were under the maximal dosing weight of 150 kg. However, 7 of the 17 patients’ prescriptions did not fall within the manufacturer’s standard dosing parameters. Therefore, off label dosing was used, and these patients were considered to be underdosed. The most common starting dose of omalizumab was 300 mg every 2 weeks.

DISCUSSION

Asthma is a chronic disease with an increasing social and economic burden. Eagan and colleagues showed a trend toward an increase of asthma incidence in the adult population.³⁰ Elderly asthma patients with co-

morbid conditions are responsible for the highest asthma mortality^{31,32} and present unique treatment challenges. Daily systemic glucocorticoid therapy remains a poor alternative for this population. Hyperglycemia and abnormal bone mineralization are two of numerous adverse effects known to such therapy. Severe asthma in the elderly population is thus relegated to alternative viable treatment options including omalizumab. Omalizumab therapy in geriatric lung disease is studied infrequently. A single recent German study analyzed patients >50 years old, indicating clinical efficacy in several clinical parameters.²⁸

Our retrospective, observational review of elderly VA asthma patients treated with omalizumab shows similar efficacy. The number of asthma exacerbations requiring systemic steroids was significantly reduced and two patients were able to discontinue daily oral steroids. Although patients were not able to be stepped down from maximal asthma controller therapy with the addition of omalizumab, the significant decrease in systemic glucocorticoid use for almost all patients validated its use. A small but significant improvement in FEV₁ after omalizumab treatment was also noted. ACT questionnaires revealed an improvement in patient observed symptoms within 3 months of therapy. This effect persisted for 12 months after initiation of therapy. Although the mean ACT score on treatment was <19, five patients did improve to a score of >19. No patients scored >19 before omalizumab therapy initiation. We know from previously collected data that our clinic's average ACT score for all follow-up patients with asthma is 17.52 and for "well-controlled" patients it is 17.61. Therefore, we consider the ACT score improvements in this omalizumab cohort clinically meaningful. Importantly, there were no major adverse side effects observed.

There are several limitations of this study. The small sample size limits clinical extrapolation. It is a retrospective, observational data analysis. Given that the study focused on a veteran population, only a single woman was in the study group. The short duration of the study following patients for 1 year of active treatment may not allow for adequate interpretation of long-term side effects from omalizumab. Although a prospective study with a large number of patients with severe asthma who were >65 years old would be ideal, this population would be difficult to recruit.

Our study findings support the role of IgE-mediated inflammation in elderly patients with severe asthma. ACT scores, which are both reliable and valid,^{33–36} can be an important tool to assess an early response to omalizumab. ACT scores increased within 3 months of starting treatment whereas more objective measures did not improve until later. Patients who showed benefit in this group maintained unique baseline characteristics including sensitization to a wide variety of

indoor and outdoor allergens. Elevated IgE levels and body weight variations require alternative pharmaceutical dosing of omalizumab, and these study outcomes were obtained despite 7 of the 17 patients not falling into standard dosing parameters and resultant underdosing. Therefore, we recommend considering a 3-month trial of omalizumab therapy for inadequately controlled elderly patients with severe allergic asthma not improving with traditional therapy. In conclusion, omalizumab showed a significant positive clinical response in this elderly group of VA patients with severe atopic asthma by reducing asthma exacerbations requiring systemic steroids, improving lung function, and improving subjective asthma perception scores.

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